

ORIGINAL ARTICLE

Contact allergy in Danish children: Current trends

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Background: Contact allergy is common in children, but may be underdiagnosed. Importantly, the clinical relevance of specific allergies is subject to constant change, and it is therefore important to continuously monitor the trends and changes of contact allergies in the paediatric population.

Objectives: To identify possible changes in contact allergy and allergic contact dermatitis among Danish children referred for patch testing.

Methods: A retrospective study was performed based on patch test data from the Danish National Database of Contact allergy. The current data were compared with previously published data on Danish children referred for patch testing.

Results: Between 2012 and 2016, 1573 children and adolescents were patch tested. Overall, 385 (24.5%) had at least 1 positive patch test reaction. The overall prevalence was similar in boys and girls, across age groups, and in patients with and without atopic dermatitis. Statistically significant increases in contact allergy to fragrances and isothiazoliones were seen, whereas a decrease in nickel allergy was found.

Conclusion: Allergic contact dermatitis continues to be a common disease in children, and is even significantly increasing for some allergens.

KEYWORDS

allergic contact dermatitis, children, contact allergy, epidemiology, patch testing

1 | INTRODUCTION

Several studies have confirmed that allergic contact dermatitis is common in children.^{1–3} Recent evidence indicates that the prevalence of contact allergy and allergic contact dermatitis in children is increasing,^{4,5} which is thought to be attributable to increased

exposure to allergens at a younger age, in addition to improved recognition of contact allergy, including increased patch testing of children.⁶ However, contact allergy may still be underdiagnosed.⁵

Allergic contact dermatitis acquired in childhood has important repercussions. It may affect the child's quality of life,^{7,8} interfere with play, sport, school, and family and social relationships,⁸ and affect

decisions regarding future occupation in adulthood.⁹ Resolution of allergic contact dermatitis depends on the ability to avoid repeated or continued exposure to the causative allergen. As the patient may experience chronic or recurrent episodes of dermatitis if the allergen source is not correctly identified, it is very important for specific contact allergy to be diagnosed as early as possible.^{9,10}

The clinical relevance of specific allergies is subject to constant change, being influenced by consumer preferences, current trends, product formulations, and legislation.¹¹ It is therefore important to continuously monitor the trends and changes of contact allergies in the paediatric population to be able to provide the most optimal and targeted patch test and preventive initiatives.

We have previously published data on children and adolescents patch tested in Denmark during 2003 to 2011.¹² The overall prevalence of contact allergy was 25.1%, and 16.7% of the patch tested children suffered from allergic contact dermatitis. The most frequent allergens from the European baseline series were nickel, cobalt, *p*-phenylenediamine (PPD), fragrance mix I, and colophonium. In this study, we examined possible changes in contact allergy and allergic contact dermatitis among Danish children referred for patch testing since the first data analysis, as well as current trends in causative allergens.

2 | METHODS

This was a retrospective study based on the Danish National Database of Contact allergy. This database contains information on all patients patch tested in 12 different dermatology clinics throughout Denmark (the Danish Group for Contact Dermatitis). These clinics are estimated to perform approximately one fifth of patch test procedures in Denmark. Patient details, clinical characteristics and the detailed information and outcome of patch testing are entered into the database. Characteristics according to the MOAHLFA index (Male, Occupational dermatitis, Atopic dermatitis [current or previous], Hand dermatitis, Leg dermatitis, Facial dermatitis, Age > 40 years) were registered for each patient. The clinical relevance of all positive reactions was evaluated, and designated as having current, past or unknown relevance to the present skin symptoms.

The children referred, aged <18 years, were patch tested with the European baseline series. The patch tests were performed with either single allergens in Finn Chambers or with the TRUE Test supplemented with single allergens in Finn Chambers. Allergens were obtained from either AllergEAZE/SmartPractice Denmark (Hillerød, Denmark), Chemotechnique Diagnostics (Vellinge, Sweden), or Almirall Hermal (Reinbek, Germany). From March 1, 2014 and June 10, 2014, respectively, 2 of the hospital departments changed the patch test methodology, and used a special paediatric series of allergens (Table S1). Patch tests were removed on day (D) 2. Readings were performed according to ICDRG/ESCD guidelines^{11,13} at least on D3 or D4, and often also on D2 and D7. Patch test reactions scored as +, ++ or +++ were regarded as positive. An irritant reaction, a doubtful reaction or a negative reading was interpreted as a negative (non-allergic) response. Relevance of the positive reactions was evaluated according to national guidelines,¹⁴ based on patient history, product labels, spot

tests, etc. The primary dichotomous outcome variables were "contact allergy", that is, a positive vs a non-positive patch test reaction, and "relevant reaction", that is, a positive patch test reaction that was also found clinically relevant or not.

The overall prevalence of contact allergy was calculated, as was the frequency of positive reactions to each allergen. Past or current clinical relevance were combined, and all positive reactions were designated as either relevant or not. To compare age groups, we divided the patients into 4 different age categories (1-4 years, 5-8 years, 9-12 years, and 13-17 years). To adjust for possible confounding, a logistic regression analysis was performed with "positive patch test reaction" (overall and for each allergen) as the dependent variable, and sex, atopic dermatitis and age group as independent, explanatory variables. In some age groups, no positive reactions were observed. The model was then applied with fewer age categories. In the same manner, we examined possible changes in the prevalence of contact allergy over time, by comparing the current data with previous data on Danish children referred for patch testing during 2003 to 2011,¹² again adjusting for sex, atopic dermatitis, and age group.

Data on 100 of the children with atopic dermatitis were reported previously.¹⁵ The data analysis was performed with the statistical software program IBM SPSS version 22 (SPSS, Chicago, Illinois). The reporting of this study conforms to the STROBE statement.

3 | RESULTS

During January 1, 2012 to December 31, 2016, 1573 children and adolescents aged 2 to 17 years (mean age 12.5 years, standard deviation [SD] 4.03) were patch tested. As in the previous investigation, there was a predominance of girls, who constituted 63.9% ($n = 1005$) of the patients. The number of children referred for patch testing increased with age, and significantly more children in the 2 younger age categories were patch tested than in our previous investigation. Of all children, 52.3% ($n = 823$) had a current or previous diagnosis of atopic dermatitis, which was a significantly larger proportion than in our previous investigation (odds ratio [OR] 1.35, 95% confidence interval [CI]: 1.19-1.54). The proportion of children with atopic dermatitis was the same across age groups in both study periods. Table 1 shows an overview of the demographic characteristics in both studies.

Overall, 24.5% ($n = 385$, 95%CI: 22.3-26.5) of children had a positive patch test reaction to at least 1 allergen, and 48.3% of these children ($n = 186$, 95%CI 43.3-53.3) had at least 1 positive reaction that was of current or past relevance. There were 633 positive patch test reactions, and 40.0% ($n = 252$) of these were judged to be clinically relevant. The overall prevalence of contact allergy was the same in girls and boys (adjusted OR 1.02, 95%CI: 0.80-1.20), remained stable during the 2 study periods (adjusted OR 0.98, 95%CI: 0.85-1.14), and was the same across age groups, also when adjusted for sex and atopic dermatitis.

The top 10 allergens in the current study were nickel, cobalt, fragrance mix I, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI), colophonium, chromium, fragrance mix II, PPD, textile dye mix, and MI. Table 2 shows the overall prevalence of contact allergy to each allergen, the share of clinically relevant reactions, and adjusted

TABLE 1 Demographics from the the previous study and the current study

	2003-2011	2012-2016 ^a	OR (95%CI)
Number of patients	2594	1573	
Sex, % (n)			
Girls	65.9 (1710)	63.9 (1005)	1.09 (0.96-1.25)
Boys	34.1 (884)	36.1 (568)	
Mean age (y)	13.2 (SD 3.6)	12.5 (SD 4.0)	
1-4, % (n)	2.9 (76)	5.7 (90)	2.01 (1.47-2.75)
5-8, % (n)	8.8 (227)	13.4 (211)	1.62 (1.32-1.97)
9-12, % (n)	23.0 (579)	22.8 (358)	1.02 (0.88-1.19)
13-17, % (n)	66.0 (1712)	58.1 (914)	0.71 (0.63-0.81)
Atopic dermatitis, % (n)			
Yes	44.8 (1161)	52.3 (823)	1.35 (1.19-1.54)
No	55.2 (1433)	47.7 (750)	
≥1 PPT	25.1 (651)	24.5 (385)	0.98 (0.84-1.12)

Abbreviations: CI, confidence interval; OR, odds ratio; PPT, positive patch test reaction.

^a Data on 100 children has been reported previously (Ref. 15).

ORs. Table 3 shows the comparison of data from 2003 to 2011 and from 2012 to 2016.

Nickel continued to be the most common allergen, with 7.0% of the patch tested children being sensitized. We observed a significant decrease in contact allergy to nickel from the first to the second study period (adjusted OR 0.69, 95%CI 0.55-0.88). The prevalence of nickel allergy was significantly higher among girls in both study periods, and the observed decrease was significant only in girls. The frequency of positive patch test reactions to cobalt remained stable, whereas there was an increase in contact allergy to chromium, from 1.3% to 2.3% (adjusted OR 1.57, 95%CI: 0.97-2.54). The frequency of positive reactions to nickel was the same across age groups, whereas contact allergy to both cobalt and chromium was associated with younger age.

In the current study, 5.0% of tested children reacted to preservatives. This was mainly attributable to a significant increase in contact allergy to MCI/MI (OR 2.88, 95%CI: 1.67-4.95) and a substantial proportion of positive reactions to MI. Contact allergy to MCI/MI was associated with younger age, but was not related to sex or atopic dermatitis. Overall, the prevalence of contact allergy to fragrance markers increased from 4.7% to 5.7% (adjusted OR 1.32, 95%CI: 1.00-1.75), which was attributable to an increase in positive reactions to fragrance mix I and *Myroxylon pereirae* (balsam of Peru), whereas the frequency of positive reactions to fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde decreased. In 39.8% ($n = 35$, 95%CI: 29.3-50.2) of the children who reacted to a fragrance, contact allergy was clinically relevant. Contact allergy to PPD had decreased since our primary investigation, from 3.5% to 2.3% (adjusted OR 0.68, 95% CI: 0.45-1.05), and was significantly associated with male sex but inversely correlated with atopic dermatitis.

4 | DISCUSSION

The overall prevalence of contact allergy in Danish children referred for patch testing did not change significantly during 2003 to 2011 as compared with 2012 to 2016. The prevalence of 24.5% in the current

study is similar to what has been found in studies from other northern European countries,^{6,9,16-18} whereas studies from other parts of the world have reported higher sensitization prevalences in children.^{3,19-26} Although some authors have reported higher sensitization prevalences among very young children,^{23,25,27} it is generally agreed that the incidence of contact allergy increases with age.^{2,28-32} In the present study, however, we did not find any difference in sensitization frequency across age groups. We believe that this reflects a difference in the threshold for patch testing children according to the child's age; that is, very young children may only be patch tested if the suspicion of allergic contact dermatitis is strong.

The relationship between atopic dermatitis and allergic contact dermatitis is controversial and continues to be debated. Authors of recent review articles have found no overall difference in the prevalence of contact sensitization between patients with atopic dermatitis and non-atopics.^{33,34} In the present study, the overall sensitization prevalence was the same among children with atopic dermatitis as among children without atopic dermatitis, in agreement with recent similar studies.^{5,35,36} However, there is an inherent risk of selection bias in retrospective studies of patients referred for patch testing: As children were patch tested because of either recalcitrant eczema or a clinical suspicion of allergic contact dermatitis, it could be that children without atopic dermatitis were more carefully selected for patch testing, that is, there was a strong suspicion of allergic contact dermatitis, whereas children with atopic dermatitis may be referred for patch testing because of aggravation of the atopic dermatitis. This could lead to an underestimation of the prevalence of contact allergy among children with atopic dermatitis.

Metals were the most common allergens, and this was mainly because of nickel. As in our previous study, it was the most common allergen among those tested. Even though nickel continues to be the most common allergen in children and in adults, we did observe a significant decrease in the prevalence of sensitization to this allergen, with a decrease from 9.7% to 7.0% between the 2 study periods. A similar decrease in the prevalence of nickel allergy among dermatitis patients aged 1 to 16 years in several EU countries was recently reported.⁵ As in our study, nickel allergy is generally more common in females.^{1,37} Even though it was previously suggested that hormonal factors could play a role,^{32,38} this is most likely explained by the higher prevalence of ear piercing among girls and the tendency of girls to wear jewellery at a younger age.³⁹⁻⁴¹ Although girls were still significantly more likely to be sensitized to nickel, we believe that the observed decrease in nickel sensitization could explain why the overall sex difference has evened out.

Cobalt was the second most common allergen. Authors of recent studies on allergic contact dermatitis in children have reported similar high frequencies of positive patch test reactions to this allergen.^{5,36,42} Cobalt allergy is currently a "hot topic", as it is increasingly being recognized as an independent sensitizer,⁴³ and new sources of exposure have to come to light.^{44,45} Although many occupational exposures to cobalt are well known,⁴⁴ the knowledge regarding causative consumer exposures to cobalt has been limited,⁴³ and this is probably even more pronounced in the paediatric population. Thus, the clinical relevance of positive reactions to cobalt in children is often difficult to assess, highlighting the importance of a continuous search for potential

TABLE 2 Prevalence of contact allergy to, and allergic contact dermatitis caused by, each allergen tested in 2012 to 2016

Allergen	All children			Male sex		Atopic dermatitis		Age 5-8 years		Age 9-12 years		Age 13-17 years	
	≥PTT % (n/N)	≥RPPT % (n _{rel} /n _{pos})	% (n/n _{total})	OR (95%CI)	% (n/n _{total})	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)		
Overall	24.5 (387/1573)	48.1 (186/387)	24.6 (140/568)	1.02 (0.80-1.20)	22.8 (188/823)	0.81 (0.64-1.02)	1.53 (0.85-2.70)	0.91 (0.52-1.57)	1.04 (0.62-1.73)				
Nickel sulfate (5% pet.)	7.0 (107/1540)	39.3 (42/107)	4.5 (25/554)	0.52 (0.33-0.82)	7.3 (59/807)	1.10 (0.74-1.54)	1.32 (0.51-3.46)	0.83 (0.32-2.13)	0.87 (0.36-2.08)				
Cobalt chloride (1% pet.)	3.9 (60/1536)	18.3 (11/60)	4.5 (25/552)	1.22 (0.72-2.08)	3.7 (30/805)	0.88 (0.52-1.48)	0.58 (0.21-1.58)	0.47 (0.19-1.20)	0.34 (0.14-0.81)				
Fragrance mix I (8% pet.)	3.5 (53/1537)	41.5 (22/53)	4.5 (25/553)	1.64 (0.94-2.86)	2.7 (22/809)	0.63 (0.36-1.10)	1.32 (0.26-6.71)	1.49 (0.33-6.77)	1.51 (0.35-6.43)				
Methylchloroisothiazolinone/ methylisothiazolinone (0.01% aq.)	2.5 (38/1539)	57.9 (22/38)	2.5 (14/553)	1.04 (0.53-2.05)	2.2 (18/808)	0.70 (0.37-1.36)	1.05 (0.37-1.36)	0.09 (0.07-0.47)	0.34 (0.12-0.93)				
Colophonium (20% pet.)	2.5 (38/1541)	47.4 (18/38)	2.9 (16/554)	1.43 (0.74-2.77)	1.4 (11/808)	0.38 (0.18-0.77)	Ref.	5.10 (0.62-41.84)	9.13 (1.23-67.47)				
Potassium dichromate (0.5% pet.)	2.3 (35/1537)	37.1 (13/35)	2.0 (11/553)	0.76 (0.37-1.58)	2.9 (23/807)	1.70 (0.84-3.46)	0.38 (0.12-1.21)	0.23 (0.07-0.74)	0.24 (0.09-0.63)				
Fragrance mix II (14% pet.)	2.3 (34/1513)	32.4 (11/34)	3.3 (18/546)	2.20 (1.11-4.38)	1.8 (14/798)	0.64 (0.32-1.28)	Ref.	2.09 (0.42-10.46)	3.87 (0.91-16.48)				
p-Phenylenediamine (1% pet.)	2.3 (29/1291)	62.0 (18/29)	3.8 (17/450)	2.88 (1.35-6.15)	0.9 (6/651)	0.22 (0.09-0.56)	Ref.	0.22 (0.05-0.86)	0.51 (0.02-0.12)				
Textile dye mix (6.6% pet.)	2.2 (10/450)	10.0 (1/10)	1.3 (2/150)	0.56 (0.11-2.72)	0.9 (2/234)	0.23 (0.05-1.14)	Ref.	1.06 (0.09-12.40)	1.22 (0.14-10.57)				
Methylisothiazolinone (0.2% aq.)	1.9 (27/1430)	74.0 (20/27)	1.2 (6/517)	0.49 (0.19-1.23)	1.5 (11/745)	0.54 (0.25-1.19)	1.38 (0.36-5.3)	0.23 (0.04-1.15)	0.33 (0.09-1.21)				
Linolin alcohol (30% pet.)	1.8 (27/1538)	37.0 (10/27)	2.7 (15/552)	2.26 (1.04-4.88)	1.5 (12/809)	0.67 (0.31-1.45)	1.31 (0.26-6.71)	0.56 (0.11-2.96)	0.67 (0.15-3.01)				
Black rubber mix (0.6% pet.)	1.5 (6/405)	50.0 (3/6)	1.3 (2/157)	0.72 (0.13-4.03)	0.4 (1/234)	0.14 (0.02-1.20)	Ref.	1.27 (0.17-9.30)	0.74 (0.10-5.38)				
Carba mix (3% pet.)	1.5 (6/407)	33.3 (2/6)	3.2 (5/157)	9.00 (1.03-78.87)	2.1 (5/235)	4.00 (0.46-34.89)	0.93 (0.08-10.99)	0.35 (0.02-5.99)	0.60 (0.05-7.07)				
Myroxylon pereiirae (balsam of Peru) (25% pet.)	1.4 (22/1535)	40.9 (9/22)	1.6 (9/552)	1.35 (0.57-3.19)	1.0 (8/807)	0.52 (0.22-1.24)	-	Ref.	2.40 (0.88-6.57)				
Sesquiterpene lactone mix (0.1% pet.)	1.3 (19/1522)	52.6 (10/19)	2.0 (11/548)	2.48 (0.99-6.23)	1.4 (11/803)	1.21 (0.48-3.03)	Ref.	0.76 (0.19-3.10)	0.88 (0.28-2.82)				
Ethylenediamine (1% pet.)	1.0 (1/100)	100 (1/1)	2.2 (1/46)	-	1.6 (1/63)	-	-	-	-				
Caine mix III	0.9 (2/221)	0 (0/2)	0 (0/75)	-	0 (0/118)	-	-	-	-				
Methyldibromo glutaronitrile (0.3% pet.)	0.8 (11/1316)	18.2 (2/11)	0.9 (4/461)	1.11 (0.32-3.82)	0.7 (5/673)	0.75 (0.23-2.50)	Ref.	0.30 (0.03-3.36)	0.80 (0.17-3.84)				
Epoxy resin (1% pet.)	0.8 (10/1287)	20.0 (2/10)	0.9 (4/450)	1.20 (0.33-4.31)	0.8 (5/645)	1.02 (0.29-3.56)	Ref.	2.00 (0.21-19.51)	1.20 (0.14-10.12)				
Neomycin sulfate (20% pet.)	0.7 (9/1361)	0 (0/9)	0.6 (3/475)	0.84 (0.21-3.40)	0.4 (3/699)	0.47 (0.12-1.90)	Ref.	1.29 (0.23-7.20)	0.32 (0.05-1.95)				
Thiuram mix (1% pet.)	0.7 (10/1538)	50.0 (5/10)	1.3 (7/553)	4.38 (1.12-17.11)	0.4 (3/807)	0.35 (0.09-1.38)	Ref.	0.23 (0.02-2.22)	0.64 (0.16-2.59)				
Formaldehyde (1% aq.)	0.6 (9/1535)	33.3 (3/9)	0.5 (3/552)	0.95 (0.24-3.85)	0.9 (7/807)	3.18 (0.67-15.44)	1.89 (0.12-30.53)	-	3.25 (0.40-26.70)				
Benzocaine (5% pet.)	0.5 (6/1126)	33.3 (2/6)	1.3 (2/393)	9.80 (1.13-84.74)	0.4 (2/570)	0.43 (0.08-2.41)	3.20 (0.19-52.70)	-	1.91 (0.21-17.30)				
Mercaptobenzothiazole (2% pet.)	0.5 (8/1535)	50.0 (4/8)	0.5 (3/552)	1.04 (0.25-4.40)	0.4 (3/804)	0.53 (0.13-2.23)	Ref.	0.74 (0.10-5.31)	0.58 (0.10-3.20)				
p-tert-Butylphenolformaldehyde resin (1% pet.)	0.5 (8/1535)	37.5 (3/8)	0.4 (2/554)	0.57 (0.11-2.87)	0.4 (3/806)	0.49 (0.12-2.08)	Ref.	0.24 (0.03-2.39)	0.36 (0.08-1.67)				
Diazolidinyl urea (2% pet.)	0.5 (6/1254)	50.0 (3/6)	0.4 (2/463)	0.90 (0.16-4.98)	0.3 (2/649)	0.47 (0.08-2.56)	Ref.	0.76 (0.05-12.30)	1.26 (0.14-11.40)				
Mercapto mix (1% pet.)	0.5 (7/1538)	57.1 (4/7)	0.5 (3/554)	1.26 (0.28-5.72)	0.2 (2/808)	0.35 (0.07-1.83)	-	Ref.	0.52 (0.11-2.33)				
N-isopropyl-N'-phenyl-p- phenylenediamine (0.1% pet.)	0.4 (5/1135)	40.0 (2/5)	0.8 (3/396)	3.04 (0.50-18.38)	0.3 (2/577)	0.62 (0.10-3.74)	Ref.	-	2.26 (0.24-20.43)				
Bronopol (0.5 mg/cm ²)	0.3 (2/586)	50.0 (1/2)	0 (0/222)	-	0.7 (2/299)	-	-	-	-				

TABLE 2 (Continued)

Allergen	All children		Male sex		Atopic dermatitis		Age 5-8 years		Age 9-12 years		Age 13-17 years	
	≥PTT % (n/N)	≥RPPT % (n _{rel} /n _{pos})	% (n/n _{total})	% (n/n _{total})	OR (95%CI)	% (n/n _{total})	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (5% pet.)	0.3 (5/1510)	20.0 (1/5)	0.2 (1/543)	0.3 (2/796)	0.71 (0.14-3.72)	0.3 (2/796)	0.14 (0.02-1.14)	Ref.	0.29 (0.02-3.27)	0.45 (0.08-2.52)		
Quaternium-15 (1% pet.)	0.3 (5/1536)	40.0 (2/5)	0.4 (2/552)	0.4 (3/808)	1.29 (0.21-7.78)	0.4 (3/808)	1.38 (0.23-8.29)	-	Ref.	2.86 (0.32-25.80)		
Paraben mix (16% pet.)	0.3 (5/1539)	20.0 (1/5)	0.7 (4/553)	0.2 (2/809)	7.40 (0.82-66.79)	0.2 (2/809)	0.58 (0.10-3.50)	Ref.	0.71 (0.04-11.57)	1.02 (0.10-9.97)		
Budesonide (0.1% pet.)	0.3 (4/1529)	75.0 (3/4)	0.5 (3/550)	0.2 (2/803)	-	0.2 (2/803)	-	-	-	-		
Clioquinol (5% pet.)	0.2 (2/1129)	0 (0/2)	0.5 (2/394)	0 (0/573)	-	0 (0/573)	-	-	-	-		
Imidazolidinyl urea (2% pet.)	0.2 (2/1253)	50.0 (1/2)	0 (0/462)	0.3 (2/649)	-	0.3 (2/649)	-	-	-	-		
Tixocortol 21-pivalate (0.1% pet.)	0.1 (2/1479)	0 (0/2)	0 (0/527)	0.1 (1/777)	-	0.1 (1/777)	-	-	-	-		
Primin (0.01% pet.)	0.1 (1/1322)	0 (0/1)	0.2 (1/462)	0 (0/677)	-	0 (0/677)	-	-	-	-		
Quinoline mix (6.0% pet.)	0 (0/217)	-	-	-	-	-	-	-	-	-		
Hydrocortisone 17-butyrate (1% eth.)	0 (0/349)	-	-	-	-	-	-	-	-	-		
Benzyl alcohol (1% pet.)	0 (0/99)	-	-	-	-	-	-	-	-	-		
Benzyl benzoate (1% pet.)	0 (0/99)	-	-	-	-	-	-	-	-	-		
Triethanolamine (2.5% pet.)	0 (0/100)	-	-	-	-	-	-	-	-	-		
2-Phenoxyethanol (1% pet.)	0 (0/100)	-	-	-	-	-	-	-	-	-		
Dimethyl fumarate (0.01% pet.)	0 (0/97)	-	-	-	-	-	-	-	-	-		

Abbreviations: CI, confidence interval; OR, odds ratio, adjusted for sex, atopic dermatitis, and age; PPT, positive patch test reaction; RPPT, clinically relevant positive patch test reaction. Age group 1-4 years was the reference category for age. In case of no positive reactions in this age group, the next age group was used as reference category. Test concentration of allergen preparations for investigator-loaded systems used, except in cases where only TRUE Test allergens were used (mg/cm²).

TABLE 3 Comparison of data^a from 2003 to 2011 with data from 2012 to 2016

	2003-2011, % (n)	2012-2016, % (n)	OR (95%CI)
Allergen			
Positive patch test reaction to at least 1 allergen	25.1 (651/2594)	24.5 (387/1573)	0.98 (0.85-1.14)
Nickel sulfate	9.7 (252/2587)	7.0 (107/1540)	0.69 (0.55-0.88)
Cobalt chloride	4.4 (114/2593)	3.9 (60/1536)	0.88 (0.64-1.22)
Fragrance mix I	2.5 (64/2592)	3.5 (53/1537)	1.46 (1.01-2.12)
Methylchloroisothiazolinone/methylisothiazolinone	0.8 (21/2593)	2.5 (38/1539)	2.88 (1.67-4.95)
Colophonium	2.4 (62/2593)	2.5 (38/1541)	1.14 (0.76-1.72)
Potassium dichromate	1.3 (34/2592)	2.3 (35/1537)	1.57 (0.97-2.54)
Fragrance mix II	2.4 (43/1823)	2.3 (34/1513)	1.06 (0.67-1.67)
p-Phenylenediamine	3.5 (88/2513)	2.3 (29/1291)	0.68 (0.45-1.05)
Lanolin alcohol	1.0 (26/2592)	1.8 (27/1538)	1.74 (1.01-3.01)
Black rubber mix	5.5 (26/472)	1.5 (6/405)	0.32 (0.13-0.80)
Carba mix	0.6 (14/2451)	1.5 (6/407)	2.11 (0.50-8.87)
Myroxylon pereiarae (Balsam of Peru)	1.0 (27/2591)	1.4 (22/1535)	1.46 (0.83-2.58)
Sesquiterpene lactone mix	0.8 (20/2542)	1.3 (19/1522)	1.35 (0.71-2.56)
Caine mix	3.8 (19/504)	0.9 (2/221)	0.27 (0.06-1.18)
Methyldibromo glutaronitrile	0.6 (14/2451)	0.8 (11/1316)	1.52 (0.69-3.36)
Epoxy resin	0.3 (8/2523)	0.8 (10/1287)	2.54 (1.00-6.48)
Neomycin sulfate	0.5 (12/2592)	0.7 (9/1361)	1.46 (0.61-3.49)
Thiuram mix	0.8 (21/2594)	0.7 (10/1538)	0.86 (0.40-1.84)
Formaldehyde	0.7 (18/2593)	0.6 (9/1535)	0.77 (0.34-1.73)
Benzocaine	0.6 (13/2083)	0.5 (6/1126)	0.92 (0.34-2.43)
Mercaptobenzothiazole	1.0 (26/2592)	0.5 (8/1535)	0.49 (0.22-1.08)
p-tert-Butylphenol formaldehyde resin	0.6 (16/2590)	0.5 (8/1535)	0.87 (0.37-2.05)
Diazolidinyl urea	0.3 (6/2092)	0.5 (6/1254)	1.64 (0.52-5.18)
Mercapto mix	0.9 (23/2593)	0.5 (7/1538)	0.52 (0.22-1.21)
N-isopropyl-N'-phenyl-p-phenylenediamine	0.3 (7/2131)	0.4 (5/1135)	1.38 (0.44-4.37)
Bronopol	0.2 (3/1475)	0.3 (2/586)	1.60 (0.26-9.64)
Hydroxyisohexyl-3-cyclohexene carboxaldehyde	1.1 (27/2429)	0.3 (5/1510)	0.46 (0.20-1.05)
Quaternium-15	0.2 (4/2593)	0.3 (5/1536)	2.12 (0.56-7.99)
Paraben mix	0.5 (13/2593)	0.3 (5/1539)	0.61 (0.22-1.73)
Budesonide	0.6 (12/1980)	0.3 (4/1529)	0.43 (0.14-1.36)
Clioquinol	0.1 (2/2133)	0.2 (2/1129)	1.86 (0.26-13.26)
Imidazolidinyl urea	0.3 (6/2092)	0.2 (2/1253)	0.52 (0.10-2.61)
Tixocortol 21-pivalate	0.2 (3/2009)	0.1 (2/1479)	0.93 (0.15-5.58)
Primin	0.1 (3/2505)	0.1 (1/1322)	0.66 (0.07-6.42)

Abbreviations: CI, confidence interval; OR, odds ratio adjusted for sex, atopic dermatitis and age by logistic regression analysis.

^a Comparison of the prevalence of contact allergy to allergens tested in both periods.

exposure sources. The prevalence of contact allergy to chromium increased between the 2 study periods, although not significantly. Information on chromium exposure sources in children is relatively limited. In children, the most common sources of exposure are thought to be leather shoes, as chromium is a common cause of foot dermatitis.⁴⁶ However, the allergen may also be found in less obvious exposure sources, such as toy make-up.⁴⁷ Another potential source of chromium are mobile phones.^{48,49}

We observed an overall increase in the prevalence of contact allergy to fragrance between the 2 study periods. In the current study, children as young as 3 years were sensitized to fragrance, and the sensitization rate increased with age. Fragrance contact allergy in children is common,^{6,50} and the prevalence is probably increasing because of

the use of cosmetics, perfumes and scented skin care products at a younger age. Supporting this hypothesis, the authors of a large study from the European Surveillance System on Contact Allergies recently reported that the prevalence of contact allergy to fragrance mix is increasing in children across Europe.⁵

Since our first study in 2013, the prevalence of MCI/MI contact allergy has increased significantly. Furthermore, MI has emerged as a significant allergen in the paediatric population, and is now among the top 5 allergens in children with dermatitis. This has also been observed in similar studies from other European countries.^{6,51} The preservative received increased attention because of an alarming increase in the prevalence of MI contact allergy.⁵² Until recently, it was found in a variety of products used for children, such as wet

wipes, creams, liquid soaps, and shampoos,⁵³ and several reports of severe and widespread dermatitis in children caused by MI have been published.^{54–57} In spring 2017, the European Commission banned the use of MI in leave-on products, but a concentration of 15 ppm in rinse-off products is still allowed.

The prevalence of PPD contact allergy was 3.5% in our first study, and had decreased to 2.3% in the present study population. Children are often sensitized from temporary black henna tattoos, although positive patch test reactions to PPD may also be explained by cross-reactivity with textile dyes present in, for example, shoes.⁵⁸ Cases of connubial dermatitis caused by PPD have even been reported.^{59,60} As sensitization to PPD may cause severe allergic reactions,⁶¹ dermatologists and researchers have warned against the use of black henna tattoos and hair dye in children.⁶² Hopefully, our finding reflects such preventive measures, in which case we expect the prevalence of PPD allergy in children to decrease even further in the future.

The strength of this study is the overall size of the study population. However, a limitation is that data stratification resulted in some subgroups being very small. Thus, caution should be exercised in interpretation of the results; some outcomes are rare, prohibiting strong conclusions. The data used in the study was retrieved from 12 different dermatology clinics throughout Denmark. All clinics used standardized preparations of allergens, and followed the ICDRG/ESCD guidelines with regard to the application and interpretation of patch test reactions. However, some degree of inconsistency is inevitable, given the large number of clinics reporting to the database. The patch test methodology differed in the sense that two thirds of the patch test reactions were evaluated on D3/D4 only, implying a risk of missing late reactions.⁶³ Another limitation is the fact that not all children were patch tested with the same allergens or allergen preparations, which prohibits strong conclusions for some allergens.

5 | CONCLUSION

The prevalence of contact allergy in Danish children referred for patch testing remained stable during 2003 to 2012. However, there has been a change in the causative allergens. Metals continue to be the most common allergens. A significant decrease in the prevalence of nickel allergy was observed, which is possibly a result of both legislation and increased awareness. The prevalence of contact allergy to isothiazolinones and certain fragrance substances increased, and this is probably explained by the increased use of personal care products and cosmetics at a younger age in combination with delayed or missing preventive actions.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary table 1. Paediatric series of allergens.

Nickel sulfate (5.0% pet.)
Cobalt chloride (1.0% pet.)
Potassium dichromate (0.5% pet.)
Fragrance mix I (8.0% pet.)
Fragrance mix II (14.0% pet.)
<i>Myroxylon pereirae</i> (balsam of Peru; 25.0% pet.)
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (5.0% pet.)
Carba mix (3.0% pet.)
Black rubber mix (0.6% pet.)
Mercaptobenzothiazole (2.0% pet.)
Mercapto mix (1.0% pet.)
Thiuram mix (1.0% pet.)
Paraben mix (16.0% pet.)
Formaldehyde (1.0% aq.)
Diazolidinyl urea (2.0% pet.)
Imidazolidinyl urea (2.0% pet.)
Methylchloroisothiazolinone/methylisothiazolinone (0.01% aq.)
Methylisothiazolinone (0.2% aq.)
Quaternium 15 (1.0% pet.)
<i>p-tert</i> -Butylphenol formaldehyde resin (1.0% pet.)
Colophonium (20.0% pet.)
Lanolin alcohol (30.0% pet.)
Sesquiterpene lactone mix (0.1% pet.)
Tixocortol-21-pivalate (0.1% pet.)
Hydrocortisone-17-butyrate (1.0% alc.)
Budesonide (0.1% pet.)
Ethylenediamine dihydrochloride (1.0% pet.)
Benzyl alcohol (1.0% pet.)
Benxyl benzoate (1.0% pet.)
Triethanolamine (2.5% pet.)
Phenoxyethanol (1.0% pet.)
Sorbitan sesquioleate (20.0% pet.)