

ORIGINAL ARTICLE

Ten-year trends in contact allergy to formaldehyde and formaldehyde-releasers

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Background: Preservatives such as formaldehyde and formaldehyde-releasers are common causes of contact allergy.

Objectives: To examine trends in contact allergy to formaldehyde and formaldehyde-releasers in patch tested patients in Denmark over a 10-year period (2007-2016), and to investigate relevant sources of formaldehyde among the patients.

Methods: A cross-sectional registry study on patch test data from patients tested with formaldehyde and formaldehyde-releasers ($N = 8463$) was performed. The presence of released formaldehyde in products from formaldehyde-allergic patients was identified with chemical analyses (chromotropic acid or acetylacetone test).

Results: The prevalence of contact allergy to formaldehyde 1% was 1.5%, and ranged between 0.97% and 2.3%, with a decreasing trend in this 10-year period. Contact allergy to formaldehyde 2% was found in 2.4%, and no significant trend was observed. Quaternium-15 was the formaldehyde-releaser most often positive (0.86%). Patients allergic to formaldehyde often had simultaneous positive patch test reactions to formaldehyde-releasers (36%). Almost 63% of the patients with formaldehyde allergy used products that released formaldehyde; cosmetics were the most common sources.

Conclusions: Although contact allergy to formaldehyde 1% decreased in this 10-year time period, contact allergies to formaldehyde and formaldehyde-releasers overall remain frequent in patients. In most cases, formaldehyde-allergic patients are exposed to ≥ 1 products containing formaldehyde. Improved regulation on permitted amounts of free formaldehyde in cosmetics is still warranted, including direct labelling of formaldehyde when it is present in small but relevant amounts.

KEYWORDS

chromotropic acid test, consumer products, contact allergy, formaldehyde, formaldehyde-releaser

1 | INTRODUCTION

Cosmetic products and toiletries are used daily by most people. Formaldehyde is a preservative that is commonly used in water-based cosmetics to prevent microbial growth.¹ During the 1950s, formaldehyde became a popular preservative because it was efficient and cheap. As a consequence, an increased incidence of contact allergy to formaldehyde was observed (3.9%) in patients from both Western Europe and North America.^{2,3} More recent studies have shown that the

prevalence of formaldehyde allergy is approximately 2% to 3% among patch tested patients in Europe.^{1,4,5} Formaldehyde can be found in products containing formaldehyde-releasers,^{2,6} which release formaldehyde in the presence of water.⁵ The recommended patch test concentration of formaldehyde in the baseline series has been discussed for decades, and has gradually been reduced from 4% to 1%.⁷ However, clinical studies later showed that patch testing with formaldehyde 2% detects significantly more cases than testing with formaldehyde 1%.^{8,9} It is of note that a repeated open application test was

used to evaluate the significance of contact allergy to formaldehyde 2%, and showed it to be clinically relevant.¹⁰

Chemically, formaldehyde-releasers are linear or cyclic reversible polymers of formaldehyde. An allergic reaction can be caused by the entire molecule of a formaldehyde-releaser or the released formaldehyde.¹¹ The amount of free formaldehyde depends on the specific formaldehyde-releaser, and its concentration and pH, and other components of the product.⁵ A previous study from our clinic covering the time period 1985 to 2008 showed that contact allergy to formaldehyde was more prevalent than contact allergy to formaldehyde-releasers; the prevalence of contact allergy to quaternium-15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol varied between 0.6% and 1.6%.⁴

In general, preservatives in cosmetics must be declared in the list of ingredients. Moreover, products containing >500 ppm formaldehyde (equivalent to 0.05%) must be labelled with "contains formaldehyde".¹² Despite this, it is difficult for an allergic patient to completely avoid formaldehyde or formaldehyde-releasers, and previous studies have shown that hidden sources of formaldehyde in cosmetics can cause chronic allergic eczema.^{1,6,10} In this study, we investigated trends in contact allergy to formaldehyde and formaldehyde-releasers in Denmark over a 10-year period. We also examined the types and the number of products that contain formaldehyde used by formaldehyde-allergic patients.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was a registry study on patch test data from patients tested with the European baseline series and an extended baseline series at Gentofte University Hospital between January 1, 2007 and December 31, 2016 (10 years). All patients were adults (>18 years) who underwent patch testing with formaldehyde and formaldehyde-releasers. In the course of 8745 consultations, 241 patients were patch tested twice, 19 patients were tested 3 times, and 1 patient was tested 4 times. In cases of multiple consultations, the first positive test result for formaldehyde was used for analysis, resulting in a study population of 8463 patients. However, 1 patient reacted positively to formaldehyde in the first consultation and to formaldehyde-releasers in the second consultation, which is why the final dataset includes 8464 consultations.

A total of 8413 dermatitis patients were patch tested with formaldehyde 1% aq., and 5639 were tested with both 1% aq. and 2% aq., as the 2% concentration had only been tested since 2011. Moreover, 8414 patients were tested with quaternium-15, 8391 patients with imidazolidinyl urea, 8388 patients with diazolidinyl urea, 8395 patients with DMDM hydantoin, and 8393 with 2-bromo-2-nitropropane-1,3-diol. A flow chart of the population is shown in Figure S1.

The MOAHLFA index (Male; Occupation; Atopic dermatitis; Hand eczema; Leg eczema; Facial eczema; Age >40 years)¹³ and information on the clinical relevance of positive reactions to formaldehyde and formaldehyde-releasers were available for all patients in the study. Clinical relevance was noted if the detected exposures to

formaldehyde or formaldehyde-releasers could partly or fully explain the current dermatitis.

2.2 | Patch testing

Patch testing was performed with the European baseline series and a supplemental series, by the use of Finn Chambers (8 mm; Epitest, Tuusula, Finland) on Scanpor tape (Norgesplaster Alpha, Vennesla, Norway). Contact allergens from Trolab were provided by Almirall Hermal (Reinbek, Germany), and applied with a micropipette (15 µL) to filter paper in the Finn Chambers. For pet.-based allergens, 20 mg in pet. was dosed directly into the test chambers. The following test concentrations were used: formaldehyde 1% aq. (0.30 mg/cm²); formaldehyde 2% aq. (0.60 mg/cm², only included since January 1, 2011); quaternium-15 1% pet.; diazolidinyl urea 2% pet.; imidazolidinyl urea 2% pet.; DMDM hydantoin 2% aq.; and 2-bromo-nitropropane-1,3-diol 0.5% pet.

The patch tests were applied to the upper back for 2 days. Readings were performed on day (D) 2, D3, or D4, and on D7 according to the ESCD guidelines.¹⁴ Correspondingly, homogeneous erythema and infiltration in the entire test area was the minimum criterion for a positive reaction (+). Homogeneous erythema, infiltration and vesicles in the test area were the criteria for a strong reaction (++), and homogeneous erythema, infiltration and coalescing vesicles in the test area were the criteria for a very strong reaction (+++). In the analysis, +, ++ and +++ reactions were classified as positive allergic reactions. An irritant response or a doubtful, follicular or negative reading was interpreted as a negative response. Patients are usually not retested with formaldehyde if they have been shown to have formaldehyde allergy by patch testing in the past in our clinic. The formaldehyde patch test results for these patients (N = 37) were classified as missing if the original patch test was not performed in the study period. This was done to minimize bias.

2.3 | Formaldehyde exposure analyses

Formaldehyde exposure analysis is a routine investigation at our clinic that is offered to patients with positive patch test reactions to formaldehyde. Generally, it is performed only if formaldehyde or formaldehyde-releasers are not present in the list of ingredients. However, the data from formaldehyde exposure analysis, performed during 2007 to 2016, were not systematically compared with ingredient labelling, which is why information regarding labelling is lacking in this study design. Data on formaldehyde exposure analysis were available for 183 patients. The products from the formaldehyde-positive patients were placed into 4 categories: "cosmetics", "household products", "occupational products", and "other". The existence of formaldehyde or free formaldehyde released from formaldehyde-releasers in the products was primarily verified with the chromotropic acid test. In cases in which the chromotropic acid test was discoloured, the acetylacetone test was used.

A standard solution with, separately, 2.5, 5 and 10 ppm formaldehyde (Sigma, Søborg, Denmark) plus a negative control containing demineralized water were included in both tests. The results were scored as +, ++, +++, traces, or negative. The +, ++, and +++ results

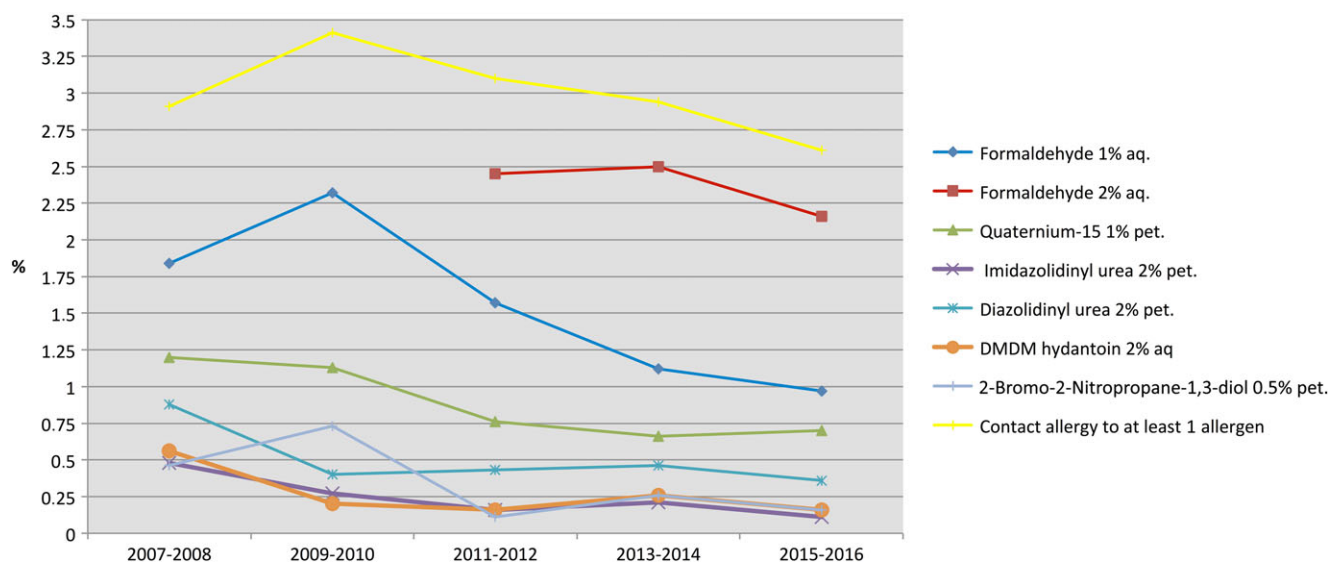


FIGURE 1 Temporal trends of formaldehyde and formaldehyde-releaser allergy in Denmark (2007-2016). Total prevalences during the 10-year period: formaldehyde (1%), 1.5% (minimum 0.97% to maximum 2.3%, $P_{\text{trend}} = .002$); formaldehyde (2%), 2.4% (minimum 2.2% to maximum 2.5%, $P_{\text{trend}} = .57$); quaternium-15, 0.86% (minimum 0.66% to maximum 1.2%, $P_{\text{trend}} = .053$); imidazolidinyl urea, 0.23% (minimum 0.11% to maximum 0.48%, $P_{\text{trend}} = .048$); diazolidinyl urea, 0.49% (minimum 0.36% to maximum 0.88%, $P_{\text{trend}} = .14$); DMDM hydantoin, 0.25% (minimum 0.16% to maximum 0.56%, $P_{\text{trend}} = .10$); 2-bromo-2-nitropropane-1,3-diol, 0.33% (minimum 0.11% to maximum 0.73%, $P_{\text{trend}} = .007$); contact allergy to at least 1 allergen, 3.0% (minimum 2.6% to maximum 3.4%, $P_{\text{trend}} = .36$)

correspond to the colour intensity matched to the 2.5, 5 and 10 ppm standard solution, and were classified as positive results. A weak colour intensity below the 2.5 ppm standard result was classified as a negative result. The test has previously been described in detail.^{15,16}

2.3.1 | Chromotropic acid test

In short, a small sample from the patient's product was placed in a test tube with a ground-glass stopper. A test tube containing 2 mL of a mixture of 400 mg of chromotropic acid (Sigma) and 100 g of sulfuric acid 95% to 97% (Sigma) was placed with the sample test tube, and then kept in the dark for 24 and 48 hours. If formaldehyde was released and present in the patient's product, formaldehyde caused a chemical reaction with the chromotropic acid mixture and resulted in a violet derivative.^{15,16}

2.3.2 | Acetylacetone test

In short, a small sample of the patient's product was placed in a glass jar with a ground-glass stopper, mixed with 2.5 mL of acetylacetone (Gentofte Hospital Pharmacy, Copenhagen), and finally heated at 60°C for 10 minutes. If formaldehyde was present in the product sample, it resulted in a yellow derivative.^{15,16}

2.4 | Statistics

Data management and statistical analyses were performed with SAS software (Version 9.4 for Windows; SAS Institute, Cary, North Carolina). Descriptive statistics are presented as percentages with accompanying 95% confidence intervals (CIs). If the 95% CIs do not overlap, this is equivalent to a significant difference. Comparisons were made by use of the χ^2 test. A Cochran-Armitage trend test was used to evaluate trends across test years; the trend was calculated on the basis of the 2-year prevalence as shown in the figure 1. The level of significance was set at $P < .05$.

3 | RESULTS

3.1 | Overall trends in prevalence from 2007 to 2016

The overall prevalence of contact allergy to formaldehyde 1% or 2% was 2.4%. Figure 1 shows the temporal trends in formaldehyde and formaldehyde-releaser allergy; the prevalence of formaldehyde allergy throughout the 10-year period is shown separately for 1%, ranging between 0.97% and 2.3%, and for 2%, ranging between 2.2% and 2.5% ($P_{\text{trend}} = .002$ and $P_{\text{trend}} = .57$, respectively). The prevalence of contact allergy to quaternium-15 was 0.86% ($P_{\text{trend}} = .053$). The prevalences of contact allergy to diazolidinyl urea and DMDM hydantoin were 0.49% and 0.25%, respectively ($P_{\text{trend}} = .14$ and $P_{\text{trend}} = .10$). The prevalences of contact allergy to the remaining 2 formaldehyde-releasers, imidazolidinyl urea and 2-bromo-2-nitropropane-1,3-diol, showed small but significant decreases, from 0.7% to 0.1% ($P_{\text{trend}} = .048$ and $P_{\text{trend}} = .007$, respectively). Overall, we observed that the prevalence of contact allergy to at least 1 of the investigated allergens did not increase significantly during the study period ($P_{\text{trend}} = .36$). In addition, there was no significant change in occupation-related eczema, age > 40 years or hand eczema among individuals with contact allergy to at least 1 allergen over time ($P_{\text{trend}} = .74$, .052 and .42, respectively).

Prevalences and clinical characteristics of the patient population are shown in Table 1. Patients allergic to formaldehyde were significantly older than patient not allergic to formaldehyde or formaldehyde-releasers. In detail, the age and sex distribution was as follows. Patients allergic to formaldehyde or formaldehyde-releasers had a median age of 52 years (25th-75th percentiles, 41-60 years), and 23.3% were males. Patients not allergic to formaldehyde or

TABLE 1 Demographic and clinical characteristics according to the MOAHLFA index^a of all patients tested in 2007 to 2016, and of patients reacting positively to the respective allergens, as percentages with accompanying 95% confidence intervals (CIs); if CIs do not overlap, this is equivalent to a significantly ($P < .05$) differing prevalence of the factor

	Non-allergic (formaldehyde or formaldehyde-releasers)	Formaldehyde		Quaternium-15 1% pet.	Imidazolidinyl urea 2% pet.	Diazolidinyl urea 2% pet.	DMDM hydantoin 2% aq.	2-Bromo-nitropropane-1,3-diol 0.5% pet.
		Formaldehyde 1% aq.	Formaldehyde 2% aq. (2011-2016) ^b					
Total tested	8350	8413	5652	8414	8391	8388	8395	8393
Prevalence, % (n)	97.0 (8101)	1.5 (127)	2.4 (134)	0.86 (72)	0.23 (19)	0.49 (41)	0.25 (21)	0.33 (28)
M, % (n) (95%CI)	31.5 (2554) (30.5-32.5)	25.2 (32) (17.7-32.8)	22.4 (30) (15.0-29.8)	25.0 (18) (15.0-35.0)	36.8 (7) (15.2-58.5)	29.3 (12) (15.3-43.2)	28.6 (6) (9.3-47.9)	17.9 (5) (3.7-32.0)
O, % (n) (95%CI)	21.5 (1745) (20.7-22.4)	33.1 (42) (24.9-41.3)	28.4 (38) (20.4-36.4)	37.5 (27) (26.3-48.6)	31.6 (6) (10.6-52.5)	26.8 (11) (13.3-42.9)	19.1 (4) (2.3-35.8)	17.9 (5) (3.7-32.0)
A, % (n) (95%CI)	18.9 (1531) (18.1-19.8)	20.5 (26) (13.5-27.5)	18.7 (25) (11.7-25.6)	23.6 (17) (13.8-33.4)	10.5 (2) (0.00-24.3)	19.5 (8) (7.4-31.6)	14.3 (3) (0.00-29.3)	10.7 (3) (0.00-22.2)
H, % (n) (95%CI)	39.2 (3178) (38.2-40.3)	63.0 (80) (54.6-71.4)	50.0 (67) (41.2-58.8)	68.1 (49) (57.3-78.8)	47.4 (9) (24.9-69.8)	61.0 (25) (46.0-75.9)	61.9 (13) (41.1-82.7)	57.1 (16) (38.8-75.5)
L, % (n) (95%CI)	1.9 (154) (1.6-2.2)	1.6 (2) (0.00-3.8)	1.5 (2) (0.00-3.9)	0 (0)	0 (0)	0 (0)	0 (0)	10.7 (3) (0.00-23.2)
F, % (n) (95%CI)	25.7 (2085) (24.8-26.7)	22.8 (29) (15.5-30.1)	32.1 (43) (23.8-40.4)	23.6 (17) (13.8-33.4)	26.3 (5) (6.5-46.1)	31.7 (13) (18.1-48.1)	23.8 (5) (5.6-42.0)	32.1 (9) (14.8-49.4)
A, % (n) (95%CI)	66.8 (5413) (65.8-67.9)	83.5 (106) (75.8-89.5)	73.9 (99) (65.6-81.1)	69.4 (50) (57.5-79.8)	89.5 (17) (66.9-98.7)	90.2 (37) (76.9-97.3)	81.0 (17) (58.1-94.6)	85.7 (24) (67.3-96.0)

^a MOAHLFA index: Male, Occupational relevance, Atopic dermatitis (lifetime prevalence), Hand eczema (point prevalence), Leg dermatitis (point prevalence), Facial dermatitis (point prevalence) and Age >40 years.

^b Formaldehyde 2% aq. was tested only in 2011 to 2016.

Bold values indicate significance difference from the group not allergic to formaldehyde or formaldehyde-releasers.

formaldehyde-releasers, but possibly allergic to other allergens, had a median age of 48 years (25th-75th percentiles, 35-61 years), and 31.5% were males.

Generally, patients with formaldehyde and formaldehyde-releaser allergy suffered more often from hand eczema and were significantly older than those without allergies. In detail, 63.0% of the individuals allergic to formaldehyde 1%, and 50.0% of the individuals allergic to formaldehyde 2%, suffered from hand eczema, whereas 68.0% of the individuals allergic to quaternium-15 suffered from hand eczema. In addition to the numbers shown in Table 1, a total of 5639 patients were tested with both formaldehyde 1% and formaldehyde 2% (2011-2016). Of these, 139 (2.5%) patients reacted positively to 1 or both test concentrations. In detail, 50.4% ($n = 70$) of the patients reacted positively only to formaldehyde 2% ($P < .05$), 4.3% ($n = 6$) of the patients reacted positively only to formaldehyde 1%, and 45.3% ($n = 63$) of the patients reacted positively to both formaldehyde 1% and formaldehyde 2%. Of those reacting positively to formaldehyde 2%, only 50% ($n = 35$) had doubtful reactions to formaldehyde 1%.

Occupation-related eczema was more common in patients with contact allergy caused by formaldehyde 1% and quaternium-15 than in patients who were not allergic to formaldehyde or formaldehyde-releasers (33.1% and 37.5%, respectively). In total, 8343 patients were patch tested with all 6 allergens (formaldehyde and 5 formaldehyde-releasers). Of these patients, 2.9% ($n = 241$) were allergic to at least 1 allergen. Figure 2 shows the relationship between allergy to formaldehyde and allergy to formaldehyde-releasers: 51.5% ($n = 124$) of the allergic patients were allergic only to formaldehyde, 19.1% ($n = 46$) patients were allergic only to formaldehyde-releasers, and 29.4% ($n = 71$) patients were allergic to both formaldehyde and formaldehyde-releasers. It follows that 36.4% of all formaldehyde-allergic patients have concomitant allergy to ≥ 1 of the formaldehyde-releasers. In addition to the data shown in Figure 2, 65.3% ($n = 81$) of the patients with allergy to formaldehyde only had extreme (+++) or strong positive (++) patch test responses, whereas 79.4% ($n = 54$) of the patients with allergy to both formaldehyde and formaldehyde-releasers had extreme (+++) or strong positive (++) patch test responses ($P < .05$). The different combinations of patch test reactions among patients reacting to formaldehyde and ≥ 1 formaldehyde-releasers are shown in Table 2. Quaternium-15 was the most prevalent formaldehyde-releaser in combination with formaldehyde, and was involved in 75% of the different combinations (53 of 71). 2-Bromo-2-nitropropane-1,3-diol was the most common formaldehyde-releaser without concomitant contact allergy to formaldehyde. In detail, 85.7% (24 of 28) of the positive patch test reactions to 2-bromo-2-nitropropane-1,3-diol did not show concomitant sensitization to formaldehyde or other formaldehyde-releasers.

3.2 | Sources of formaldehyde exposure in patient products

Between 2007 and 2016, a total of 3679 products from 183 formaldehyde-allergic patients were tested for their formaldehyde content with the chromotropic acid test and/or the acetylacetone test. Formaldehyde was detected in 7.0% of the tested products. The

distributions of tested products are shown in Table 3: cosmetics, 76.3%; household products, 3.9%; occupational products, 7.7%; and "other" products, 2.1%. Regarding the products that tested positive for formaldehyde, 66.8% were cosmetics, 23.4% were household products, 9.0% were occupational products, and 0.8% were categorized as "other". The most frequent cosmetic products releasing formaldehyde were creams (35.1%), shampoos (24.0%), and soaps (12.3%) (Table 4). In total, 62.8% ($n = 115$) of the patients with formaldehyde allergy used a product that released formaldehyde. The formaldehyde exposure data were not compared with the ingredient labelling, and the product categories must therefore be regarded only as indicating frequent sources of exposure among formaldehyde-allergic patients.

4 | DISCUSSION

This study investigated the 10-year trend in contact allergy to formaldehyde and formaldehyde-releasers in Denmark. We found that the prevalence of contact allergy to formaldehyde 1% fluctuated between 0.97% and 2.3% throughout the period. Trends of contact allergy to formaldehyde 1% in Denmark have previously been reported by

TABLE 2 Combinations and numbers of patients allergic to formaldehyde and formaldehyde-releasers

Combinations of formaldehyde and releasers (patients tested with all allergens; $N = 8343$, 137 missing)	No. positive
FORM only ($n = 124$)	124
FORM and releasers ($n = 71$)	
FORM + Q-15	25
FORM + Q-15 + DI	12
FORM + DMDM	8
FORM + IM + DI	6
FORM + Q-15 + DI + DMDM	3
FORM + Q-15 + IM + DI	4
FORM + Q-15 + DMDM	3
FORM + Q-15 + IM + DI + DMDM	3
FORM + Q-15 + BR	2
FORM + DI	2
FORM + BR	1
FORM + IM + DI + DMDM	1
FORM + Q-15 + DI + DMDM + BR	1
Releasers only ($n = 46$)	
BR	24
Q-15	12
IM + DI	4
DI	2
IM	1
DMDM	1
DMDM + Q-15	1
Q-15 + DI	1
Total	241

Abbreviations: BR, 2-bromo-2-nitropropane-1,3-diol (0.5% pet.); DI, diazolidinyl urea (2% pet.); DMDM, DMDM hydantoin (2% aq.); FORM, formaldehyde (1% and 2% aq.); IM, imidazolidinyl urea (2% pet.); Q-15, quaternium-15 (1% pet.).

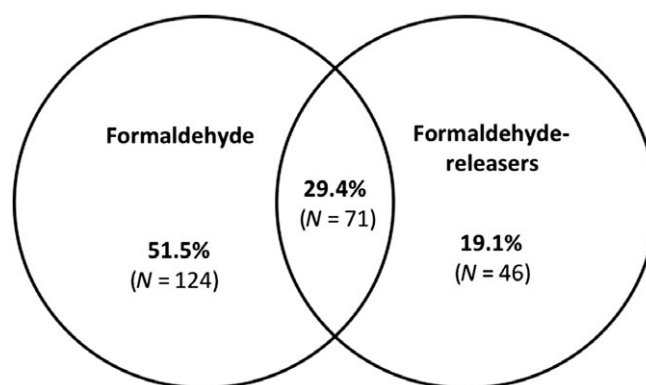


FIGURE 2 One-hundred and twenty-four patients (51.5%) were allergic only to formaldehyde, 46 patients (19.1%) were allergic only to formaldehyde-releasers, and 71 patients (29.4%) were allergic to both formaldehyde and formaldehyde-releasers

Thyssen et al (2010), who found that the prevalence of formaldehyde allergy ranged between 2% and 4% in the time period between 1985 and 2008.⁴ In this article, we report an overall decrease in the prevalence of contact allergy to formaldehyde as diagnosed with 1% aq. between 2007 and 2016. However, there is no evident explanation for the decrease. In contrast, contact allergy to formaldehyde 2% remained stable, with a prevalence ranging between 2.3% and 2.7%, which gives a total prevalence of contact allergy to formaldehyde (1% or 2%) of well above 2%.

A Lithuanian study from 2016 found an increased prevalence of contact allergy to formaldehyde in the period 2006 to 2015 (2.9% versus 4.3%).¹⁷ As pointed out by the authors, this may have been

TABLE 3 The distributions of tested products and products releasing formaldehyde (2007–2016). Formaldehyde exposure data were not compared with the list of ingredients

	Tested, N (%)	Positive, N (%)
Cosmetics	2808 (76.3)	171 (66.8)
Household products	513 (13.9)	60 (23.4)
Occupational products	282 (7.7)	23 (9.0)
Other	76 (2.1)	2 (0.8)
Total	3679 (100)	256 (100)

TABLE 4 Product categories of tested cosmetic products releasing formaldehyde (2007–2016). Formaldehyde exposure data were not compared with the list of ingredients

Cosmetics	Positive, N (%)
Cream	60 (35.1)
Shampoo	41 (24.0)
Soap	21 (12.3)
Makeup	13 (7.6)
Hairstyling	10 (5.9)
Facewash	11 (6.4)
Deodorant	7 (4.1)
Nail products	4 (2.3)
Other	4 (2.3)

attributable to the increase in patch test concentration from 1% to 2% formaldehyde. In our study, we also tested with formaldehyde 2% from 2011, but retained 1% formaldehyde in order to better interpret the patch test reactions. This has given us the unique possibility of looking at these individually and together, and we show that the prevalence of contact allergy to formaldehyde 2% overall was unchanged in the period 2011 to 2016.

In northeastern Italy, the prevalence of contact allergy to formaldehyde was 3.3% (1996-2012, European baseline series), but, as in our study, no significant trend was found over time.¹⁸ Thus, the prevalence of formaldehyde allergy in other parts of Europe still appears to be stable at a high level. This study found that 36.4% of the patients with allergy to formaldehyde also had allergy to ≥ 1 formaldehyde-releasers. Seventy-five per cent of these patients had a combined formaldehyde/quaternium-15 allergy. A similar distribution of concomitant allergy to formaldehyde and quaternium-15 has been observed in previous studies.^{5,19} Quaternium-15 releases the highest amount of formaldehyde among the 5 formaldehyde-releasers,⁵ which could explain the frequent concomitant reactions to formaldehyde and quaternium-15. In line with a previous study on patch test reactivity to DMDM hydantoin,²⁰ we found that patients with combined allergy to formaldehyde and formaldehyde-releasers had stronger positive patch test responses to formaldehyde than patients with formaldehyde allergy only. Therefore, the allergic reaction to quaternium-15 probably depends on the actual amount of released formaldehyde. In addition, 2-bromo-2-nitropropane-1,3-diol showed a separate pattern, as 85.7% of the positive reactions to the releaser occurred without concomitant contact allergy to formaldehyde. This result confirms previous studies showing that contact allergy to 2-bromo-2-nitropropane-1,3-diol as such exists, and only 15% of all reactions to 2-bromo-2-nitropropane-1,3-diol are thought to be caused by a reaction to formaldehyde.⁵

Concerning the temporal trends for the formaldehyde-releasers, contact allergy to imidiazolidinyl urea and 2-bromo-2-nitropropane-1,3-diol showed a small but significant decrease in prevalence. However, caution must be applied in the interpretation of these results, as the total numbers of patients with contact allergy to these 2 compounds were 19 and 28, respectively. Hence, small changes in the numbers of patients with positive patch test reactions to formaldehyde-releasers can affect the trend. In line with this, we did not find a significant trend for contact allergy to quaternium-15 when we analysed the 2-year trend, although the P value can be characterized as "borderline significant" (Figure 1, $P_{\text{trend}} = .053$). Notably, the decreasing trend for contact allergy to formaldehyde 1% was significant irrespective of whether we used the trend test corresponding to a single year or that corresponding to combined years.

The patch test concentration of formaldehyde has been debated for a long time. Results from a multicentre study suggested that the patch test concentration of 1% was too low and may cause false-negative reactions.²¹ In 2013, The ESCD changed its recommendation to increase the formaldehyde concentration to 2.0%,¹⁴ which has been used at Gentofte Hospital since 2011. Our study shows that 50.4% (70/139) of the formaldehyde-allergic patients had a positive patch test reaction to formaldehyde 2% when formaldehyde 1% did not result in a positive reaction. This indicates that 50% of the

formaldehyde-allergic patients are missed if a test concentration of 1% is used as compared with a test concentration of 2%. On the other hand, half of the patients (50%) who reacted positively to formaldehyde 2%, but did not react to formaldehyde 1%, also reacted to formaldehyde 1%, but with a weaker patch test reaction, classified as doubtful. This was also seen in previous studies,^{8,9} which formed the direct basis for a change in the recommendations, showing that morphologically doubtful patch test reactions to formaldehyde 1% may represent contact allergy to formaldehyde.

Our study also shows that patients with contact allergy to formaldehyde are exposed to various products containing formaldehyde, and that cosmetics are the most prevalent sources of exposure. In line with this, Hauksson et al investigated formaldehyde contents in cosmetics, and found that 23.7% of the 245 products released formaldehyde. Moreover, 44.8% (26/58) of the cosmetic products released formaldehyde despite lacking a declaration of formaldehyde or formaldehyde-releasers in the list of ingredients (65.4% [17/26] of the leave-on products and 28% [9/32] of the rinse-off products).²² In our study, 3679 patient products were chemically tested for formaldehyde release in the time period 2007 to 2016. In total, 7.0% of the products tested positive for formaldehyde release, 66.8% of these products being cosmetic products. It is not possible to estimate the exact proportion of products lacking declarations, as product labelling was not routinely registered in this study. However, products with a declared content of formaldehyde or a formaldehyde-releaser are generally not subjected to chemical testing in our department.

A Danish study from 2010 found that 75% of formaldehyde-allergic patients used at least 1 product containing formaldehyde on a daily basis.¹⁹ In our study, we found that 62.8% of the patients diagnosed with formaldehyde allergy and who had their products investigated in the formaldehyde exposure analysis used ≥ 1 products releasing formaldehyde. The slightly differing results may be attributable to the fact that, in recent years, analyses have not always been performed on products for which formaldehyde or formaldehyde-releasers are declared in the list of ingredients. Formaldehyde contact allergy still represents a significant and relevant clinical problem, and it is generally agreed that it is difficult for allergic patients to avoid exposure to formaldehyde-containing products, as formaldehyde is not directly declared in the list of ingredients, but hidden under complicated names of formaldehyde-releasers.

Although we do not know the exact amount of released formaldehyde that is required to cause an allergic reaction,⁵ a recent study investigating the effect of low concentrations of formaldehyde on irritant contact dermatitis found that a low level of exposure to formaldehyde is sufficient to worsen existing dermatitis.⁶ As it is not obligatory for small amounts of formaldehyde to be declared in the list of ingredients or in the material safety data sheet of the product, the authors suggested that chemical analysis is needed to optimize patient care for formaldehyde-allergic individuals.⁶ We agree with this, and add that the most frequent cosmetic products releasing formaldehyde in our analyses were creams and soaps, which might be contributing to the increased prevalence of hand eczema observed in patients with formaldehyde and formaldehyde-releaser allergy, as these products are applied to the body with the hands.

In conclusion, formaldehyde is still an allergen of high concern, and additional measures must be taken to protect formaldehyde-allergic patients. Patients with allergy to formaldehyde should be advised to avoid products containing formaldehyde-releasers, especially quaternium-15. Although product labelling is mandatory, it remains difficult for allergic patients to avoid formaldehyde in their products, and cosmetics must still be considered to be the main sources of exposure. Meaningful labelling that also indicates the presence of formaldehyde in low but relevant concentrations should therefore be introduced. Hidden sources of formaldehyde can cause chronic allergic eczema, which is why an increased focus on allergy to formaldehyde and formaldehyde-releasers is needed.

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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Total
consultations
N = 8745

Multiple
consultations
N = 282

Tested patients
N = 8463

Formaldehyde
1%
N = 8413
(2007—2016)

Formaldehyde
2%
N = 5652
(2011—2016)

Quaternium-15
N=8414
(2007—2016)

Imidazolidinyl
urea
N = 8391
(2007—2016)

Diazolidinyl
urea
N = 8388
(2007—2016)

Dmdm
hyantoin
N=8395
(2007—2016)

2-bromo-2-
nitropropane-
1,3-diol
N= 8393
(2007—2016)

Formaldehyde
1% and 2%
N = 5639
(2011—2016)