

Formaldehyde in cosmetics in patch tested dermatitis patients with and without contact allergy to formaldehyde

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doi:10.1111/cod.12493

Summary

Background. Formaldehyde is a well-known contact sensitizer. Formaldehyde releasers are widely used preservatives in cosmetics.

Objectives. To survey the release of formaldehyde in cosmetics brought by patients investigated because of suspected allergic contact dermatitis, to compare it with information given by the manufacturers on the packages, and to investigate whether formaldehyde-allergic patients are potentially exposed to more cosmetics releasing formaldehyde than dermatitis patients without contact allergy to formaldehyde.

Patients/methods. Cosmetics from 10 formaldehyde-allergic and 30 non-allergic patients (controls) matched for age and sex were investigated with the chromotropic acid spot test, which is a semiquantitative method measuring the release of formaldehyde.

Results. Formaldehyde was found in 58 of 245 (23.7%) products. Twenty-six of 126 (20.6%) leave-on products released formaldehyde, and 17 of 26 (65.4%) of these were not declared to contain formaldehyde or formaldehyde releasers. Among the rinse-off products, there were 32 of 119 (26.8%) formaldehyde-releasing products, and nine of 32 (28.0%) of these were not labelled as containing formaldehyde or formaldehyde releasers. Five of 10 formaldehyde-allergic patients brought leave-on products with ≥ 40 ppm formaldehyde, as compared with 4 of 30 in the control group ($p = 0.029$).

Conclusions. Cosmetic products used by formaldehyde-allergic patients that are not declared to contain formaldehyde or formaldehyde-releasing preservatives should be analysed.

Key words: baseline series; chromotropic acid method; concentration; cosmetics; formaldehyde releasers; relevance.

According to EU regulations, cosmetics consist of a wide range of products: from everyday hygiene products such as soap, shampoo, deodorant, and toothpaste, to luxury beauty items including perfumes and makeup (1). Cosmetics are thus used by most individuals on a daily basis.

As most of these products contain water, preservatives are required to prevent the growth of microorganisms. Preservatives are some of the most common causes of contact allergy and allergic contact dermatitis (2). Contact dermatitis caused by preservatives can be difficult to suspect exclusively on the basis of the patient's history, as preservatives are present in many products that come into daily contact with the skin.

Among the most problematic preservatives are formaldehyde and formaldehyde-releasing agents. The use of free formaldehyde has been reduced as a result of its reputation as a sensitizer, and a potential carcinogen, and formaldehyde-releasing preservatives, that is, chemicals releasing formaldehyde, are used instead. They

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Conflict of interests: The authors declare no conflict of interests.

Accepted for publication 21 September 2015

are widely present in products used on a daily basis, including household products, cosmetics, and topical medicaments (3).

Formaldehyde is a well-known contact sensitizer. The prevalence of formaldehyde allergy has been reported to be 2–3% in European countries and 8–9% in the United States in patients investigated because of suspected allergic contact dermatitis (4). The recommended patch test concentration (1.0%) has been discussed, owing to false-positive and false-negative reactions (5, 6). However, on the basis of the results of recent studies (7–10) and recommendations by the European Society of Contact Dermatitis, the formaldehyde concentration has been increased to 2.0% (0.60 mg/cm²) (11). The new information on formaldehyde contributed to formaldehyde being the American Contact Dermatitis Society 'Contact Allergen of the Year' for 2015 (12).

A semiquantitative method, based on the reaction of formaldehyde with chromotropic acid (CA), can be used to detect formaldehyde release from cosmetics (13). This method does not show the total content of formaldehyde in the product, but the release of formaldehyde. In this study, these terms are often used as synonyms. We examined formaldehyde release by using the CA spot test on cosmetics brought by patients investigated because of suspected allergic contact dermatitis. The statement by the manufacturers on the packages regarding the presence of formaldehyde or formaldehyde releasers was compared with whether there was actually release of formaldehyde from the products. Furthermore, we investigated whether there were any differences in potential exposure to cosmetics containing formaldehyde in patch tested dermatitis patients with and without contact allergy to formaldehyde, on the basis of the products brought by the patients.

Materials and Methods

Study design

The process for investigation of the skin care products is shown in Fig. 1. All individuals had been patch tested at our department because of suspected allergic contact dermatitis during the period 1 October 2012 to 31 January 2013. During this period, all individuals received written information before coming to the investigation, in which they were asked to bring all cosmetics that they had used on the skin recently. We specified that these should be cosmetics containing water, such as moisturizers and liquid soap, but not dry products, such as eye shadow. We asked the patients to bring all products in their original containers, so that we could read the printed declaration.

If the product lacked the declaration, we found it on the internet.

All products were collected, and the original packages, including the labelling, were photographed. A sample of each product was kept in a disposable plastic container, and stored at room temperature during the period of the investigation. Plastic containers without samples were analysed with the CA method for release of formaldehyde. The products from the formaldehyde-allergic individuals were analysed monthly with the CA method. For each formaldehyde-allergic individual, 3 age-matched and sex-matched formaldehyde-allergic individuals were randomly chosen from the patients patch tested during the same period (± 1 month), and products brought by these individuals were analysed simultaneously. The products brought to the clinic by formaldehyde-allergic individuals after the formaldehyde allergy had been established were not included in the study. We continued the study until we had 10 formaldehyde-allergic patients, and thus 30 controls.

Study groups

There were two groups in the study: the formaldehyde-allergic individuals, and individuals without contact allergy to formaldehyde. These groups are hereafter termed the 'test group' and 'control group', respectively. The test group consisted of 10 individuals (mean age 37.2 years; range 14–55 years; 10 females) who were positive for formaldehyde 1.0% and/or 2.0% and positive/negative for formaldehyde releasers in our baseline patch test series. The control group consisted of 30 age-matched females (aged ± 6 years, mean age 38.1 years, range 16–57 years) without contact allergy to formaldehyde and formaldehyde releasers in our baseline series.

Chemicals

Formaldehyde 37% (wt/wt) aq. was obtained from Acros Organics (Geel, Belgium), and used to prepare the formaldehyde patch test solutions [1.0% and 2.0% (wt/wt) aq.] at our department. The following formaldehyde releasers were included in our baseline patch test series: quaternium-15 [1.0% (wt/wt) pet. and (wt/vol) aq.], diazolidinyl urea [2.0% (wt/wt) pet. and (wt/vol) aq.], imidazolidinyl urea [2.0% (wt/wt) pet. and (wt/vol) aq.], and DMDM hydantoin [2.0% (wt/wt) pet. and (wt/vol) aq.]. DMDM hydantoin was obtained from Chemotechnique Diagnostics AB (Vellinge, Sweden), and quaternium-15, imidazolidinyl urea and diazolidinyl urea were obtained from Sigma-Aldrich Chemie GmbH (Stenheim, Germany). These substances were used at our

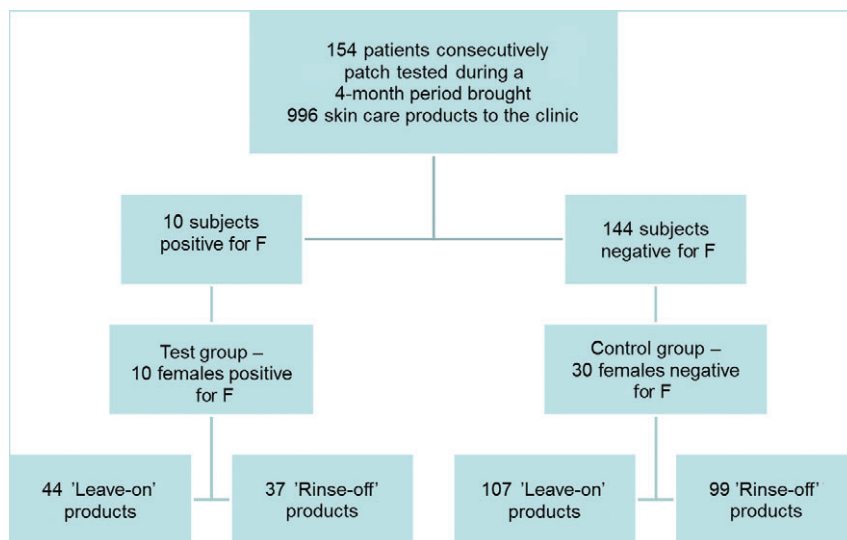


Fig. 1. Flowchart of study. F, formaldehyde.

department to prepare both pet. and aqueous patch test preparations. CA was obtained from Merck (Darmstadt, Germany), and sulfuric acid was obtained from Sigma-Aldrich Chemie GmbH.

Chromotropic acid (CA) method

The release of formaldehyde from the cosmetics was analysed with the CA method (13). The CA method is a semiquantitative method, based on the reaction of formaldehyde with CA, which causes a change in colour from colourless to violet in the presence of formaldehyde. To 25-ml glass sample bottle with ground-glass stoppers, 1.0 ml of standard solutions of formaldehyde (40.0, 20.0, 10.0 and 2.5 µg/ml) was added. A sample bottle with 1.0 ml of purified water was used as a blank. Cosmetics were prepared by weighing 1.0 g of each cosmetic product and placing this in a sample bottle. In each of the sample bottle (standard, blank, and sample), a 1.0-ml glass tube containing 0.5 ml of freshly prepared CA in concentrated sulfuric acid (4 mg/ml) was placed. The sample bottle were kept in the dark, and the colour was observed after 2 days. If formaldehyde was present in a sample, a violet colour of the reagent appeared, and this was compared with the violet colour of the reagents in the standard solution jars to obtain a semiquantitative estimation of the formaldehyde content.

When the CA method is used, some products will be discoloured, and these products cannot be assessed for the presence of free formaldehyde. In this study, discoloured products were excluded from the statistical calculations.

Statistical calculations

Fisher's exact two-sided test was used to compare the number of formaldehyde-allergic individuals using

leave-on products containing ≥ 40 ppm formaldehyde with the number of individuals without contact allergy to formaldehyde using the same types of product. It was also used to compare the number of products containing formaldehyde between the leave-on and rinse-off groups. The numbers of products declared and not declared as containing formaldehyde in the leave-on and rinse-off groups were also compared by the use of Fisher's exact two-sided test.

The numbers of products brought by the formaldehyde-allergic individuals and controls were investigated with a Mann–Whitney two-sided test. A *p*-value of < 0.05 was considered to be significant.

Results

The results of the CA analyses are summarized in Table 1. During a 4-month period, 154 consecutively tested patients (37 males and 117 females) brought 996 cosmetic products to the clinic. In this study, 287 products (151 leave-on products and 136 rinse-off products) brought by the test group and control group were investigated with the CA method. Forty-two products (25 leave-on products and 17 rinse-off products) showed discolouration, and were not included in calculations. The percentage of discoloured products was 14.6% (16.0% in the test group and 14.1% in the control group). Calculations were thus performed on 245 products (126 leave-on products and 119 rinse-off products). Formaldehyde was found in 58 of 245 products (23.7%). Twenty-six of 126 (20.6%) leave-on products contained formaldehyde, and 17 of 26 (65.4%) of these were not declared to contain formaldehyde or formaldehyde-releasing preservatives. Among the rinse-off products, 32 of 119 (26.9%) released

formaldehyde, and nine of 32 (28.0%) of these were not declared to contain formaldehyde or any formaldehyde releaser.

The difference between the number of formaldehyde-allergic patients using leave-on products with ≥ 40 ppm formaldehyde and the number of controls using such products was statistically significant (5/10 versus 4/30, $p=0.029$). There were statistically significantly more products not declared to contain formaldehyde among leave-on products than among rinse-off products (17/26 versus 9/32, $p=0.0075$).

There was no statistical difference between the number of products brought by the formaldehyde-allergic individuals (3–13, mean 8.1) and the number brought by controls (3–16, mean 6.9) ($p=0.148$). The formaldehyde releasers labelled on the cosmetics are shown in Table 1. DMDM hydantoin was the most common formaldehyde releaser (21/30), followed by imidazolidinyl urea (10/30), quaternium-15 (3/30), and 2-bromo-2 nitropropane-1,3-diol (1/30). Five of 30 products contained two formaldehyde-releasing preservatives, namely DMDM hydantoin and imidazolidinyl urea.

The CA analysis of plastic containers used for storage of samples gave negative results.

Discussion

This study demonstrates that formaldehyde-releasing preservatives are still widely used in cosmetics. Formaldehyde was found in almost 25% of the products, and slightly more often in the rinse-off products. A majority of the leave-on products and $\sim 25\%$ of rinse-off products were not declared to contain formaldehyde releasers. Studies in Denmark and Sweden in the 1990s showed that formaldehyde was present in $\sim 30\%$ of cosmetic products (14, 15). A similar result regarding formaldehyde content in the products was obtained in the United States one decade later: $\sim 20\%$ of cosmetic products contained formaldehyde releasers, comprising 17% leave-on products and 27% rinse-off products (16). There are two recently published studies on preservatives in cosmetics in Israel and in the United Arab Emirates, and they reported even higher percentages of formaldehyde in products, especially in rinse-off products (17, 18). To the best of our knowledge, there are no more recent comparable data for Europe available.

Two spot tests are frequently used to detect formaldehyde in various types of product: the CA method and the acetylacetone method. At our department, we prefer to use the CA method. The CA method was first described in 1959 by Blohm (19). It is still used, because of its simplicity and sensitivity. With the CA method, a

low level of formaldehyde emission in the range of 2.5 to ≥ 40 ppm can be detected and semiquantified (13). Sometimes, this spot test cannot be used, owing to discolouration, or there might be a need to confirm and quantify the presence of formaldehyde in the products. In these situations, a high-performance liquid chromatography (HPLC) method based on hydrazine can be used (20). In this study, we decided to determine formaldehyde release only with the CA method, and HPLC was not used at all. The reason for this is the experience in our department over several decades regarding the chemical analysis of formaldehyde in occupational and non-occupational products with the CA and HPLC methods, which generate equivalent results qualitatively (Hauksson, 2012, 17, 18).

The EU Cosmetics Regulation states that all products containing formaldehyde or substances that release formaldehyde must be labelled with the warning 'contains formaldehyde' when the concentration of free formaldehyde exceeds 0.05% (500 ppm) (1).

Currently, formaldehyde at 0.2% (2000 ppm) is allowed in cosmetics and household products in the EU and United States (1). It has been shown that formaldehyde in moisturizers at this concentration can cause allergic contact dermatitis on healthy skin in formaldehyde-allergic individuals (7). It has also been shown that products which, according to the CA method, emit formaldehyde at levels of approximately 10 to ≥ 40 ppm, which are concentrations often found in skin care products, are sufficient to exacerbate an existing irritant contact dermatitis, and can thus not be safely used by formaldehyde-allergic individuals (21).

Formaldehyde-allergic individuals are advised to avoid products containing formaldehyde and formaldehyde releasers as stated on the product labelling and in material safety data sheets. However, undeclared formaldehyde may be present in the products, owing to the addition of formaldehyde in the raw material or release from other chemicals. It has been shown that surfactants, which are used as emulsifiers in cleaners and toiletries, can produce formaldehyde, because of autoxidation, at a level even above 500 ppm, and this process is exacerbated under stress conditions, for example heat and high relative humidity (3, 22). Furthermore, these are also irritants, and it is therefore possible that formaldehyde-allergic patients often have a combination of irritant and allergic contact dermatitis. Another source of formaldehyde contamination may be material used in packaging, such as resins based on formaldehyde and melamine or carbamide (23).

Contact allergy to formaldehyde is almost impossible to suspect exclusively on the basis of the

Table 1. Occurrence and amount of formaldehyde (F) determined with the chromotropic acid method in 'leave-on' (L) and 'rinse-off' (R) products brought in by 40 patch tested dermatitis patients [10 individuals allergic to F and formaldehyde releasers (FRs) in our baseline series, and 30 matched control individuals negative for F and FRs]

No.	Age (years)	No. of products/L products	Reactivity to F ^a	Reactivity to FR ^a				Released F in products (ppm)							
				D	DU	Q15	IU	2.5		10.0		20.0		≥ 40.0	
								L	R	L	R	L	R	L	R
Test group															
1	45	13/5	++	+	++	+	—	1 IU	—	—	—	—	—	1 D	1 D; 1 IU
2	46	9/3	++	—	—	—	—	—	—	—	1 B	—	—	—	—
3	29	8/6	+	—	—	++	—	1 ^b	—	—	—	—	—	—	1 D
4	42	6/3	++	—	—	—	—	—	—	—	—	—	—	—	—
5	55	12/7	+++	+++	—	+++	—	—	—	—	—	—	—	1 Q15	—
6	54	4/0	++	—	—	++	—	—	—	—	—	—	—	—	—
7	18	3/0	+	—	—	—	—	—	—	—	—	—	—	—	—
8	14	9/7	+	—	—	—	—	—	—	—	—	—	—	1 ^c	—
9	36	9/8	+++	+	+	++	—	—	—	—	—	—	—	1 IU; 1 D; 1 ^b	1 ^b
10	33	8/5	+++	—	++	++	—	—	—	—	1 ^b	—	1 ^b	1 ^c	—
Control group															
11	46	8/4	—	—	—	—	—	—	—	—	—	—	—	—	2 D+IU
12	48	8/5	—	—	—	—	—	—	—	—	—	—	—	—	—
13	42	5/5	—	—	—	—	—	1 ^b	—	—	—	—	—	—	—
14	46	6/3	—	—	—	—	—	—	—	—	—	—	—	1 ^b	1 Q15
15	45	8/4	—	—	—	—	—	—	—	1 D	—	—	—	—	1 D
16	50	7/4	—	—	—	—	—	—	1 ^b	1 ^b	—	—	—	—	—
17	32	8/4	—	—	—	—	—	1 ^b	—	—	—	—	—	—	1 D
18	26	5/1	—	—	—	—	—	—	—	—	—	—	—	—	—
19	30	6/4	—	—	—	—	—	—	—	—	—	—	—	1 Q15	—
20	45	4/2	—	—	—	—	—	—	—	—	—	—	—	—	—
21	45	12/8	—	—	—	—	—	—	—	—	—	—	—	—	—
22	44	16/6	—	—	—	—	—	—	1 D	—	—	—	—	—	2 D
23	55	7/2	—	—	—	—	—	—	—	—	—	—	1 D	—	—
24	56	4/2	—	—	—	—	—	—	—	—	—	—	—	1 IU	1 D
25	56	3/0	—	—	—	—	—	—	—	—	—	—	—	—	1 D
26	57	6/3	—	—	—	—	—	—	—	—	—	—	—	—	—
27	49	3/3	—	—	—	—	—	—	—	—	—	—	—	—	—
28	48	4/4	—	—	—	—	—	—	—	1 ^b	—	—	—	—	—
29	19	11/8	—	—	—	—	—	—	—	—	—	—	—	—	1 ^b
30	20	7/2	—	—	—	—	—	—	1 D	—	—	—	—	—	—
31	23	7/5	—	—	—	—	—	—	—	—	—	1 ^b	—	1 ^b	1 IU
32	16	4/2	—	—	—	—	—	—	—	1 ^b	—	—	—	—	—
33	21	14/4	—	—	—	—	—	—	—	—	—	—	—	—	—
34	22	7/4	—	—	—	—	—	—	—	—	—	2 ^b	—	—	2 D+IU
35	33	11/2	—	—	—	—	—	1 ^b	2 ^b	—	—	—	1 ^b	—	—
36	35	5/3	—	—	—	—	—	—	—	—	—	—	1 ^b	—	—
37	35	4/4	—	—	—	—	—	—	—	1 ^b	—	—	—	—	—
38	39	3/2	—	—	—	—	—	—	—	—	—	—	—	—	—
39	30	7/3	—	—	—	—	—	1 ^b	—	1 ^b	—	1 ^b	—	—	1 D; 1 D+IU
40	31	6/4	—	—	—	—	—	—	—	—	—	—	—	—	1 D

B, 2-bromo-2 nitropropane-1,3-diol; D, DMDM hydantoin; DU, diazolidinyl urea; IU, imidazolidinyl urea; Q15, quaternium-15; 1, one product; 2, two products.

^aThe strongest recorded reaction to a pet. or an aq. patch test preparation on D3/4 or D7 is given.

^bNo F or FR was declared on the labelling of the product.

^cThe product was not labelled.

patient's history. Allergic contact dermatitis caused by formaldehyde can often be chronic, as it is difficult to avoid formaldehyde-containing cosmetic products. The low concentrations of formaldehyde, approximately 10–20 ppm, found in the products in the present study and other studies may not be sufficient to induce sensitization or to elicit allergic contact dermatitis on intact skin in formaldehyde-allergic individuals, but exposure to such products can maintain or aggravate an existing dermatitis (21).

The results of the present investigation do not provide any conclusive information on whether dermatitis patients with formaldehyde allergy are more exposed to formaldehyde than those without formaldehyde allergy. Although the allergic patients brought more leave-on products releasing ≥ 40 ppm than the non-allergic patients, we have insufficient knowledge on how much the patients who brought the products were actually exposed to them. Moreover, we have insufficient knowledge on the relative importance of leave-on and rinse-off products, exposure patterns, and the significance of aggregate exposure. Furthermore, possible occupational exposure to formaldehyde from products other than skin

care products or processes was not considered in this study.

Conclusion

Formaldehyde releasers are widely used in skin care products. This study shows that the information on packaging can often be insufficient. It is difficult to determine whether formaldehyde-allergic patients are more exposed to formaldehyde than dermatitis patients without contact allergy to formaldehyde, but our results suggest that this is the case. To assess exposure and clinical relevance in formaldehyde-allergic patients, the patients' skin care products, especially leave-on products, that are not labelled as containing formaldehyde or formaldehyde releasers should be analysed.

Acknowledgements

The authors would like to thank Lena Persson, Monica Andersson, Linda Rosén and Lotta Thorsson for their skilful assistance. The study was supported by the Edvard Welander Foundation and the Skåne county council's research and development foundation.

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