

Formaldehyde exposure and patterns of concomitant contact allergy to formaldehyde and formaldehyde-releasers

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Background: Formaldehyde and formaldehyde-releasers are widely used in consumer products and may often cause contact allergy.

Objective: To investigate the prevalence of concomitant contact allergy to formaldehyde and formaldehyde-releasers in dermatitis patients, and to determine the sources of formaldehyde exposure based on personal and occupational products obtained from dermatitis patients.

Methods: Patch test data from referred dermatitis patients with a positive patch test reaction to formaldehyde or formaldehyde-releasers were analysed. For the period 2000–2008, the formaldehyde content in products obtained from formaldehyde-allergic patients was analysed by chromotropic acid test and/or acetylacetone test.

Results: Patients allergic to a formaldehyde-releaser often had simultaneous contact allergy to formaldehyde. Other combinations were also prevalent. In patients who reacted to more than two formaldehyde-releasers, nearly all reacted simultaneously to formaldehyde. Seventy-five percent of the formaldehyde-allergic patients used a product that contained formaldehyde. The main source of formaldehyde exposure was cosmetics (78%).

Conclusions: Concomitant contact allergy to formaldehyde and formaldehyde-releaser remains common. Furthermore, contact allergy to a formaldehyde-releaser was nearly always concomitant with another formaldehyde-releaser. Formaldehyde was commonly found in personal products used by formaldehyde-allergic patients.

Key words: consumer products; contact allergy; cosmetics; formaldehyde; formaldehyde-releaser. © John Wiley & Sons A/S, 2010.

Conflict of interests: The authors have no conflict of interest.

Accepted for publication 25 March 2010

Preservatives, such as formaldehyde and formaldehyde-releasers, are used in consumer and occupational products to prevent microbial contamination (1–3). A contact allergy epidemic caused by formaldehyde in cosmetics was observed during the 1960s in Western countries (4). Since then, the use of formaldehyde has decreased markedly in cosmetics but at the same time, the use of formaldehyde-releasers in these products has increased (1, 5). Today, the prevalence of formaldehyde allergy remains stable at 2–3% in European countries (2, 6). The prevalence of contact allergy to the formaldehyde-releasers quaternium-15, diazolidinyl

urea, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol (bronopol) is slightly lower and ranges between 0.5% and 2% (2, 6). An allergic reaction to a formaldehyde-releaser can be caused either by released formaldehyde or by the formaldehyde-releaser itself. de Groot et al. have recently reviewed the relationship between formaldehyde contact allergy and formaldehyde-releasers in cosmetics (7).

Skin exposure to formaldehyde or to one of 35 different formaldehyde-releasers may derive from contact with household products, occupational products, or cosmetics (2). According to European (EU)

legislation, only a few formaldehyde-releasers are permitted in cosmetic and household products. Preservatives in cosmetics and household products must be labelled, and products that contain more than 500 ppm formaldehyde must be labelled 'contains formaldehyde' (8, 9). Nevertheless, studies have shown that formaldehyde is not always declared in formaldehyde-containing creams and that repeated skin exposure to a formaldehyde-releaser in low concentrations may elicit allergic contact dermatitis in formaldehyde-allergic patients (10, 11).

This study investigated the prevalence of concomitant contact allergy to formaldehyde and formaldehyde-releasers in Denmark over a 24-year period. In addition, we investigated the proportion and types of products that contained formaldehyde used by formaldehyde-sensitized dermatitis patients at the time of diagnosis.

Materials and Methods

Study population

A total of 18 179 dermatitis patients aged 4–99 years underwent routine patch testing with the European baseline series and a supplemental series at Gentofte University Hospital between 1 January 1985 and 31 December 2008. All patients were patch tested with formaldehyde and quaternium-15, 11 270 patients with diazolidinyl urea, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol and finally, 1946 patients with DMDM hydantoin. For the formaldehyde exposure study, products obtained from dermatitis patients with positive patch test reactions to formaldehyde for the period 1 January 2000 to 31 December 2008 (9 years) were included.

Patch testing

Patch testing was performed with the European baseline series and a supplemental series using Finn Chambers® (8 mm Epitest Ltd, Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alfarma, Venesla, Norway). The following test concentrations were used: formaldehyde 1% aq., 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 and were occluded for 2D. Readings were performed on D2, D3 or 4, and on D7 according to the recommendations from the International Contact Dermatitis Research Group (12). Thus, homogeneous redness and infiltration in the entire test area was scored as a 1+ reaction. Homogeneous redness, infiltration, and vesicles in the test area was scored as a 2+ reaction, and homogeneous redness, infiltration, and

coalescing vesicles in the test area as a 3+ reaction. A 1+, 2+, or 3+ reading was interpreted as a positive response. An irritant response, a doubtful (+?), or a negative reading was interpreted as a negative response.

Formaldehyde exposure analysis

The names and usages of products were registered prior to formaldehyde analysis. Based on this information, products were divided into four categories for the purpose of this study; 'cosmetics', 'household products', 'occupational products', and 'other'. The last group consisted of products where the name or usage was not clear, or in cases where products could not be categorized.

The presence of formaldehyde was tested with either the chromotropic acid test or the acetylacetone test (13). The acetylacetone test was only used in cases where the chromotropic acid test was discoloured by the product, making interpretation impossible. In both tests, a standard solution with respectively, 10, 5, and 2.5 ppm formaldehyde (Sigma) and a negative control containing demineralized water were included. The results of each analysis was scored with either negative, traces, +, ++, or +++. The +, ++, and +++ correspond to the colour intensity compared to the 2.5, 5, and 10 ppm standard solution. In this study, +, ++, and +++ were all scored as positive. Weak colour development below the 2.5 ppm standard result was in both tests scored as 'traces', and interpreted as a negative result in this study.

Chromotropic acid test. A sample of the product (solid samples were wetted with demineralized water) was placed in a glass test tube with a ground stopper. A smaller test tube containing 2 ml of a mixture of 400 mg chromotropic acid [4,5-dihydroxynaphthalene-2,7-disulfonic acid (Sigma)] and 100 g sulfuric acid 95–97% (Sigma) was placed in the sample test tube. It was sealed and kept in the dark. If formaldehyde was present in the sample, it reacted with the chromotropic acid mixture and formed a violet derivate. Results were collected after 24 and 48 hr (13).

Acetylacetone test. A sample (0.5 g) was placed in a glass test tube, mixed with 2.5 ml of acetylacetone (Gentofte Hospital Pharmacy, Copenhagen), sealed with a glass ground stopper and heated to 60°C for 10 min. Products that contained formaldehyde developed a yellow colour (14).

Results

Concomitant preservative allergy

A total of 3.1% (555) and 1.0% (174) of the 18 179 patch tested patients reacted to formaldehyde and

quaternium-15, respectively. Of 11 270 patients tested to diazolidinyl urea, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol, 1.6% (178), 0.8% (93) and 0.6% (67), respectively, had positive test reactions. Of 1946 patients who were tested with DMDM hydantoin, 0.7% (14) had positive test reactions. All this has previously been published (6). The prevalence of concomitant contact allergy to formaldehyde and the formaldehyde-releasers are presented in Table 1. In formaldehyde-allergic patients, concomitant contact allergy to quaternium-15, diazolidinyl urea, and DMDM hydantoin were found in 23%, 21%, and 19%, respectively, of those tested with both preservatives. In quaternium-15 allergic patients, 74%, 35%, and 36% had a concomitant positive patch test reaction to formaldehyde, diazolidinyl urea, and DMDM hydantoin, respectively. Concomitant patch test reactions to 2-bromo-2-nitropropane-1,3-diol were infrequent (Table 1).

Table 2 shows some of the various combinations of multiple patch test reactions among patients that reacted to more than two preservatives. A total of 0.53% (60/11 270) patients tested with at least five preservatives were allergic to three or more preservatives. Among these, 3 patients were allergic to five of six preservatives; 11 were allergic to four of six preservatives, and the remaining 46 (76%) patients were allergic to different combinations of three preservatives (Table 2). The most frequent combinations of multiple preservative allergy were formaldehyde/quaternium-15/diazolidinyl urea and formaldehyde/diazolidinyl urea/imidazolidinyl urea. Only 3 of 60 cases did not have a positive patch test reaction to formaldehyde.

Sources of formaldehyde exposure

Between 2000 and 2008, a total of 5437 products (340–813 per year) from 314 patients (each brought in 1–64 products) were tested for their formaldehyde content by the chromotropic acid test and/or the acetylacetone test. In 75% (236) of the patients, at least one product tested positive for formaldehyde. Discoloration of the chromotropic acid test was observed in 9.3% (503) cases and hence the acetylacetone acid test was performed. A total of 143 products were scored as containing 'traces' of formaldehyde. The distribution of products tested was: cosmetics 72% (3907), household products 18% (990), occupational products 6.8% (368), and other products 3.2% (172). Seven hundred and fifty different products were tested positive for formaldehyde, 78% (583) were cosmetics, 16% (120) were household products, 3.9% (29) were occupational products, and 2.4% (18) were categorized as 'other'.

Table 1. The prevalence of concomitant contact allergy to formaldehyde and formaldehyde-releasers in dermatitis patients

Concomitant contact allergy to:	Formaldehyde-allergic subjects % (n/n _{total})*	Quaternium-15 allergic subjects % (n/n _{total})	Diazolidinyl urea allergic subjects % (n/n _{total})	DMDM hydantoin allergic subjects % (n/n _{total})	Imidazolidinyl urea allergic subjects % (n/n _{total})	2-Bromo-2-nitropropane-1,3-diol allergic subjects % (n/n _{total})
Formaldehyde	–	74 (128/174)	43 (77/178)	79 (11/14)	34 (32/93)	18 (12/67)
Quaternium-15	23 (128/555)	–	23 (40/178)	79 (11/14)	15 (14/93)	3.0 (2/67)
Diazolidinyl urea	21 (77/361)	35 (40/114)	–	43 (6/14)	90 (84/93)	4.5 (3/67)
DMDM hydantoin	19 (11/57)	36 (11/31)	25 (6/24)	–	13 (2/16)	0 (0/10)
Imidazolidinyl urea	8.9 (32/361)	12 (14/114)	47 (84/178)	14 (2/14)	–	4.5 (3/67)
2-Bromo-2-nitropropane-1,3-diol	3.3 (12/361)	1.8 (2/114)	1.7 (3/178)	0 (0/14)	3.2 (3/93)	–

* (n/n_{total}), number of concomitant reactions/total number of patients tested positive and tested to both compounds.

Table 2. Combinations and actual numbers of patients allergic to at least three of the tested preservatives

Combination	n*	Positive
Form + Q-15 + DI + IM + DMDM	1946	2
Form + Q-15 + DI + IM + BR	11 270	1
Form + Q-15 + DI + IM	11 270	8
Form + Q-15 + DI + DMDM	1946	3
Form + Q-15 + DI	11 270	19
Form + Q-15 + DMDM	1946	4
Form + DI + IM	11 270	20
Q-15 + DI + IM	11 270	2
Q-15 + DI + DMDM	1946	1

*n, number of patients tested to the specific combination of preservatives; BR, 2-bromo-2-nitropropane-1,3-diol; DI, Diazolidinyl urea; DMDM, DMDM-hydantoin; Form, formaldehyde; IM, Imidazolidinyl urea; Q-15, Quaternium-15.

Discussion

This study showed that 75% (236) of 314 formaldehyde-allergic patients were exposed to at least one product that contained formaldehyde. Exposure mainly derived from cosmetics (78%) and household products (16%). These two product groups constituted 90% of tested products and 94% of formaldehyde-positive products. The distribution of analysed products was similar to the outcome of testing, that is, cosmetic products were the main product type investigated and also the main source of formaldehyde exposure observed. Occupational products consisted primarily of gloves and different paper types of which only a few were positive for formaldehyde. The group 'other products' consisted primarily of products that had insufficient registration making it impossible to categorize. A few textiles, that used to be a common source of formaldehyde exposure (15), were included in this group but they were all negative for formaldehyde.

The best method to detect formaldehyde in various products is by high-performance liquid chromatography (HPLC); however, in a clinical laboratory the acetylacetone test and chromotropic acid test are considered sufficient (13, 16). Gryllaki-Berger et al. (16) recommended clinical laboratories to use the acetylacetone test based on 48 different samples. In another study on 1324 products, it was shown that when the chromotropic acid test was modified to include a second reading on D2, the two tests were identical in efficacy (13). The authors recommended to use the test most suitable for the laboratory, and in cases of problems with one method the other would often be successful (13). A standard solution with 1 ppm formaldehyde was negative on D1 and showed 'traces' on D2 in the chromotropic acid test and a weak reaction in the acetylacetone test; this is considered to be the detection limit for the two tests (13). If colour developments were weaker than the 2.5 ppm

standard solution, the result was scored as 'traces'. In this study, 'traces' was registered as a negative result. The detection threshold of 2.5 ppm in the two tests is well below the 370 ppm free formaldehyde that elicited an allergic reaction during repeated exposure (10). However, repeated exposures over a longer period of time, use of several formaldehyde-containing products, or exposure to damaged or sensitive skin may lead to an allergic reaction to products containing even lower concentrations of free formaldehyde.

The EU Cosmetic Directive and the Regulation on Detergents dictate that all preservatives in cosmetics and household products are labelled (8, 9). One would, therefore, expect that avoidance of formaldehyde exposure was straight forward. However, many products contain small amounts of formaldehyde without the manufactures' knowledge, and the formaldehyde content in some products is, therefore, not labelled correctly (11, 17). Furthermore, it may be difficult for patients to read and understand ingredient labels (18). Although preservatives are required in consumer and household products, the frequency of contact allergy and dermatitis could probably be reduced if preservatives were used in lower concentrations (10). It is possible to combine allergenic preservatives with non-allergenic preservatives and take advantage of synergistic or additive effects between the preservatives to reduce the concentration of the allergenic preservative (19).

Formaldehyde-releasers, such as diazolidinyl urea, imidazolidinyl urea, and quaternium-15, are almost uniquely used in cosmetics, whereas formaldehyde and 2-bromo-2-nitropropane-1,3-diol and other formaldehyde-releasers are mainly used in non-cosmetic products (1, 5). Except for 2-bromo-2-nitropropane-1,3-diol, the prevalence of formaldehyde allergy in formaldehyde-releaser sensitized patients was high (34–79%) (Table 1). We found that the prevalence of formaldehyde-releaser allergy in formaldehyde-sensitized patients was lower than the prevalence of formaldehyde allergy in formaldehyde-releaser sensitized patients (Table 1). Thus, a concomitant positive patch test reaction to quaternium-15 was observed in 23% of formaldehyde allergic patients, whereas 74% of patients with quaternium-15 allergy also were allergic to formaldehyde. Furthermore, 21% of formaldehyde-allergic patients displayed positive patch test reactions to diazolidinyl urea, whereas 43% of patients with diazolidinyl urea allergy also reacted to formaldehyde. Similar distributions of concomitant formaldehyde and quaternium-15 allergy have previously been shown (20–22), whereas the prevalence of concomitant formaldehyde and diazolidinyl urea allergy has generally been lower in previous reports (4.8–11%) (20, 21).

It has been shown that the amounts of formaldehyde released by the formaldehyde-releaser is positively associated with the frequency of formaldehyde allergy (20). Because quaternium-15 releases the highest amount of formaldehyde, it also displayed one of the highest prevalence of concomitant patch test reactions to formaldehyde (Table 1). The same pattern can be seen for DMDM hydantoin, which also releases high amounts of formaldehyde and patients with DMDM hydantoin allergy often have a high prevalence of concomitant formaldehyde allergy (23), whereas diazolidinyl urea and imidazolidinyl urea release less amounts of formaldehyde and in accordance have lower prevalences of formaldehyde allergy. Finally, 2-bromo-2-nitropropane-1,3-diol releases the lowest amounts of formaldehyde (24). This is also illustrated in the low prevalence of concomitant reaction with 2-bromo-2-nitropropane-1,3-diol.

We found that 10 of 14 patients with positive patch test reactions to DMDM hydantoin also reacted to three or more of the six preservatives used for patch testing. This could possibly indicate that patients allergic to DMDM hydantoin may be sensitive to very low levels of formaldehyde. Most patients that were allergic to three or more preservatives reacted to either formaldehyde/quaternium-15/diazolidinyl urea or formaldehyde/diazolidinyl urea/imidazolidinyl urea (Table 2). The high prevalence of formaldehyde/quaternium-15/diazolidinyl urea was also shown by Hectorne and Fransway (25); however, they did not find the strong association between imidazolidinyl urea and diazolidinyl urea allergy shown in this study. Imidazolidinyl urea and diazolidinyl urea share the same chemical backbone. This could explain why 90% of imidazolidinyl urea positive patients react to diazolidinyl urea, and 47% of diazolidinyl urea positive reacts to imidazolidinyl urea. Statham et al. also found a high percentage of concomitant reactions between diazolidinyl urea and imidazolidinyl urea (22).

Currently, it is debated whether patients allergic to formaldehyde and/or a formaldehyde-releaser should avoid contact with the specific allergen alone or also to other formaldehyde-releasers and formaldehyde (2, 7, 20, 26). A recent study showed that 79% of formaldehyde-allergic patients were also allergic to a formaldehyde-releaser (27). Another study showed that among patients who reacted to either formaldehyde or a formaldehyde-releasing preservative, 65% reacted to more than one preservative (26). Furthermore, the threshold concentration of free formaldehyde in cosmetics capable of inducing dermatitis on normal skin is between 200 and 300 ppm, and it is often lower in subjects with sensitive or diseased skin (2). The legislation in the

EU only demands that concentrations of <500 ppm free formaldehyde is labelled with the warning 'contains formaldehyde'. Taken together, these results suggest that formaldehyde-allergic patients should avoid skin contact with formaldehyde-releasers because of the present legislation and the fact that the overall prevalence of concomitant patch test reactions to formaldehyde-releasers is high. Finally, our study showed that formaldehyde remains prevalent in especially cosmetic products and that the majority of formaldehyde-allergic patients were exposed to formaldehyde through cosmetics or household products. This finding suggests that steps should be taken to further protect consumers.

Acknowledgement

We thank Mette Ramm (medical laboratory technologist) for performing the chromotropic acid test and acetylacetone test.

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