

Concomitant contact allergies to formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, and fragrance mixes I and II

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Summary

Background. Contact allergies to the preservatives formaldehyde and methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) have been reported to appear together at a statistically significant level. Recently, revisions concerning the patch test preparations of MCI/MI, MI and formaldehyde have been recommended for the European baseline series.

Aim. To investigate (i) the number of concomitant contact allergies to the preservatives, (ii) the number of concomitant contact allergies to the preservatives and the fragrance mixes (FM I and FM II) and (iii) gender differences.

Methods. Patients tested with the Swedish baseline series during the period 2012–2014 at the Department of Occupational and Environmental Dermatology in Malmö, Sweden were investigated.

Results. 2165 patients were patch tested with the baseline series (34% males and 66% females). Contact allergies to formaldehyde and MCI/MI and/or MI were significantly associated ($p < 0.001$). The associations between contact allergy to MCI/MI and/or MI and FM I and/or FM II, and between formaldehyde and FM I and/or FM II as well as, were statistically significant ($p < 0.001$).

Conclusion. Contact allergies to formaldehyde and MCI/MI and/or MI are significantly associated, as well as contact allergies to these preservatives and fragrance allergy. Males and females do not differ significantly concerning contact allergy to fragrances.

Key words: contact allergy; fragrances; preservatives; sex.

Recently, the following changes in the European baseline series have been recommended. In 2013, the preservative methylisothiazolinone (MI) was recommended to be included at the patch test concentration of 2000 ppm aq. (1). The patch test concentrations of both methylchloroisothiazolinone (MCI)/MI and formaldehyde have been revised, and the recommended concentrations

are now 200 ppm and 2.0% aq., respectively (2014 and 2013) (2, 3). Moreover, the European baseline series contains two fragrance mixes since 2008 (4). Contact allergies to formaldehyde and to MCI/MI have been reported to be significantly associated (5).

The aim of the present study was to investigate whether the association between contact allergies to formaldehyde and to MCI/MI is still present when the revised patch test concentrations are used routinely. To further elucidate concomitant reactions, the proportions of contact allergies to the preservatives were also compared with the proportions of contact allergies to the fragrance mixes. The exposure to these groups of contact allergens is hypothesized to reflect either consumer behaviour regarding cosmetics, or the composition of products, or both; both

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groups have different functions in the products. Differences between the sexes were also investigated.

Materials and Methods

The patients patch tested with the Swedish baseline series during the years 2012–2014 at the Department of Occupational and Environmental Dermatology at Skåne University Hospital in Malmö, Sweden were included. All patients were patch tested with formaldehyde 2.0% aq., MCI/MI 200 ppm (0.02%) aq., and MI 2000 ppm (0.2%) aq., as well as with both fragrance mixes. The patch test reactions were read on day (D) 3 or D4 and on D7. Finn Chambers® (diameter, 8 mm) were used, and 15- μ l volumes of the solutions were applied with a micropipette (6). For the patch test preparations in petrolatum (the fragrance mixes), 20 mg was applied to the test chambers (7). The fragrance mixes were loaded in the test chambers immediately before application to the back of the patient (8). Formaldehyde 37% (wt/wt) aq. was bought from Acros Organics (Geel, Belgium), and used to prepare the 2.0% formaldehyde patch test solution at our department. Also, formaldehyde was loaded in the test chamber immediately before application to the back of the patient. MI 2000 ppm (wt/vol) aq. and MCI/MI 200 ppm (wt/vol) aq. were bought from Chemotechnique Diagnostics (Vellinge, Sweden), as were the fragrance mixes. SPSS version 22.0 was used as statistical software, and Fisher's exact test for the comparisons. A *p*-value of <0.05 was considered significant. Prevalence ratios were calculated to quantify the risk of formaldehyde allergy given contact allergy to MCI/MI, MI, or MCI/MI and/or MI compared to when these were negative.

Results

2165 patients were patch tested with the baseline series (34% males and 66% females) during the years 2012–2014. The number of patients with contact allergy to MCI/MI was 175 (8.1%), and the number of patients with contact allergy to MI was 153 (7.1%). Overall, 122 (5.6%) patients reacted to both MCI/MI and MI, 53 (2.4%) reacted only to MCI/MI, and 31 (1.4%) reacted only to MI (*p* < 0.001). When these two groups were merged, 206 (9.5%) cases were found with contact allergy to MCI/MI and/or MI.

The comparisons between contact allergy to formaldehyde and MCI/MI, MI, and MCI/MI and/or MI are shown in Table 1. Among all investigated individuals, 23 (1.1%) reacted to both formaldehyde and MCI/MI and/or MI. Contact allergy only to MCI/MI and/or MI was found in 183 (8.5%) individuals, and contact allergy only

to formaldehyde was found in 82 (3.8%) individuals (*p* < 0.001). For all three preparations of preservatives, 288 (13.3%) reacted to one, two or three of the investigated patch test preparations.

The number of patients with contact allergy to fragrance mix I (FM I) was 145 (6.7%), and the number of patients with contact allergy to fragrance mix II (FM II) was 62 (2.9%); when these two groups were merged 170 (7.9%) cases were found with contact allergy to one of these mixes, or both. Among all patients, 37 (4.2%) were allergic to both FM I and FM II, 108 (5.0%) were allergic only to FM I, and 25 (1.2%) were allergic only to FM II (*p* < 0.001). The association between the two fragrance mixes was statistically significant within both sexes (*p* < 0.001). However, among females, 13 (0.9%) were allergic only to FM II, and among males, 12 (1.6%) were allergic only to FM II. The results for formaldehyde, MCI/MI, MI, FM I and FM II are shown in Table 2. Differences between the sexes are also given. Contact allergies to the preservatives were also merged into one variable, and so were contact allergies to the fragrance mixes, as described above. There were no significant differences between the sexes for fragrance allergy, but highly significant differences were found for the preservatives, with females having more contact allergies.

The associations between contact allergy to MCI/MI and/or MI and FM I and/or FM II, and between contact allergy to formaldehyde and FM I and/or FM II, were statistically significant (*p* < 0.001).

Contact allergies found each year during the years 2012–2014 are shown in Tables 3 and 4. The study covers only 3 years, but it can be seen that the proportions of men with contact allergy to fragrances might be increasing, and that, in 2014, a slightly larger proportion of patch tested men than of patch tested women had contact allergy to fragrances (Table 3).

Discussion

Although patch test concentrations have been changed for all of the investigated preservatives, the association between contact allergies to formaldehyde and to MCI/MI remains strong. Consecutive patch testing with MI separately has not changed this association. MCI and MI are not chemically related to formaldehyde. The patch test dose/cm² for MCI/MI is 6 μ g, that for MI is 60 μ g, and that for formaldehyde is 600 μ g. A patch test with formaldehyde contains 465 times more molecules than a patch test with MCI/MI, and 40 times more molecules than a patch test with MI. Therefore, even if MCI/MI, by any chance, could be degraded to formaldehyde, it is unlikely that the dose would elicit any reaction caused by formaldehyde,

Table 1. Concomitant contact allergies to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and/or MI, and formaldehyde, within genders and overall

	Formaldehyde					
	Males		Females		All	
	PR (95%CI)	<i>p</i> -value	PR (95%CI)	<i>p</i> -value	PR (95%CI)	<i>p</i> -value
MCI/MI	4.2 (1.5–12.1)	0.017	2.2 (1.4–3.7)	0.002	2.8 (1.7–4.3)	<0.001
MI	4.8 (1.7–13.7)	0.012	2.0 (1.1–3.5)	0.024	2.5 (1.5–4.1)	0.001
MCI/MI and/or MI	3.5 (1.2–9.9)	0.03	2.1 (1.3–3.4)	0.002	2.5 (1.6–3.8)	<0.001

Fisher's exact test (*p*-value).

Prevalence ratios (PRs) are calculated to quantify the risk of formaldehyde allergy when contact allergies to MCI/MI, MI, or MCI/MI and/or MI are found, as compared with when these are not found.

Table 2. Contact allergies to formaldehyde, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI), MI, and formaldehyde, MCI/MI and MI merged (all preservatives), and fragrance mix I (FM I) fragrance mix II (FM II), and fragrances merged (all FM), among 2165 patients patch tested 2012–2014

Allergen	Positive males, n (%)	Positive females, n (%)	Total positive, n (%)	<i>p</i> -value
Formaldehyde	24 (3.3)	81 (5.7)	105 (4.8)	0.015
MCI/MI	32 (4.3)	143 (10.0)	175 (8.1)	<0.001
MI	29 (3.9)	124 (8.7)	153 (7.1)	<0.001
All preservatives	58 (7.9)	230 (16.1)	288 (13.3)	<0.001
FM I	39 (5.3)	106 (7.4)	145 (6.7)	0.069
FM II	19 (2.6)	43 (3.0)	62 (2.9)	0.68
All FM	51 (6.9)	119 (8.3)	170 (7.9)	0.27

p-values refer to comparisons between the sexes (Fisher's exact test).

especially as this is uncommon with reactions to very low patch test doses of formaldehyde.

MI was already shown to be a sensitizer in humans and guinea-pigs in the mid-1980s (9, 10). The first occupational cases of allergic contact dermatitis caused by MI were reported from our department (11). Since the first report on MI contact allergy related to cosmetics in 2010, there has been an 'epidemic' of contact allergy to MI (12–20). It has been concluded that the risk assessment performed by industry was insufficient prior to the introduction of MI onto the market (21). Although the present study covers a short period, there is a tendency for there to be a larger number of contact allergies to MI diagnosed in 2014 than in 2012 – or, at least, there is no sign of a diminishing number of MI allergies. MCI/MI, MI and formaldehyde are also present in work environments, and sensitization to these can cause occupational contact dermatitis, sometimes by unexpected exposures (20, 22–29).

In the present study, contact allergy to MCI/MI and MI was compared with contact allergy to formaldehyde, but not with contact allergy to formaldehyde-releasing agents, as the aim was to investigate the effect on the association of the revised patch test doses of formaldehyde, MCI/MI, and MI. Also, when more cases are found with the higher patch test dose of formaldehyde, fewer

additional cases might be found by patch testing with formaldehyde-releasing agents in the baseline series. Among these 2165 patients, 1 was recorded as being allergic to quaternium-15, which is present in the European baseline series, but not to formaldehyde. Furthermore, 1 patient was found to have strong allergies to both quaternium-15 and diazolidinyl urea, which is present in the Swedish baseline series, but was suspected to have irritant patch test reactions to formaldehyde, both to 1.0% and to 2.0%. To discern whether the bullous reactions that she had to formaldehyde were allergic or irritant, she was tested with a dilution series, and reacted down to a concentration of 0.1%. She had vesicles and infiltration in response to several concentrations, and was therefore judged to be allergic to formaldehyde. This means that we found only 1 additional patient with contact allergy to any of the formaldehyde-releasing preservatives in the Swedish and European baseline series during these 3 years.

Presumably, fragrances and preservatives are often present in the same consumer products. The association between allergies to these two groups of chemicals might be explained either by the use of a range of products containing different combinations of allergens, or different products with different combinations of allergens being used by the same person. Animal studies concerning

Table 3. Contact allergy to fragrance mix I (FM I), fragrance mix II (FM II), and any or both fragrance mixes (FM I, FM II, all FM) during 2012–2014

	2012			2013			2014		
	M	F	All	M	F	All	M	F	All
FM I	5 (2.2)	30 (6.8)	35 (5.2)	14 (5.2)	44 (8.8)	58 (7.6)	20 (8.4)	32 (6.6)	52 (7.2)
FM II	5 (2.2)	14 (3.2)	19 (2.8)	6 (2.2)	13 (2.6)	19 (2.5)	8 (3.4)	16 (3.3)	24 (3.3)
All FM	10 (4.3)	36 (8.1)	46 (6.8)	16 (6.0)	45 (9.0)	61 (8.0)	25 (10.5)	38 (7.8)	63 (8.7)

F, female; M, male.

Absolute numbers (percentages) are given.

Table 4. Contact allergies to formaldehyde, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI), MI, and formaldehyde, MCI/MI and MI merged (all preservatives)

Allergen	2012			2013			2014		
	M	F	All	M	F	All	M	F	All
Formaldehyde	3 (1.3)	23 (5.2)	26 (3.9)	10 (3.7)	39 (7.8)	49 (6.4)	11 (4.6)	19 (3.9)	30 (4.1)
MCI/MI	10 (4.3)	45 (10.2)	55 (8.1)	9 (3.4)	48 (9.6)	57 (7.5)	13 (5.5)	50 (10.3)	63 (8.7)
MI	9 (3.9)	36 (8.1)	45 (6.7)	6 (2.2)	41 (8.2)	47 (6.1)	14 (5.9)	47 (9.7)	61 (8.4)
All preservatives	14 (6.0)	69 (15.6)	83 (12.3)	20 (7.5)	84 (16.9)	104 (13.6)	24 (10.1)	77 (15.8)	101 (13.9)

F, female; M, male.

Absolute numbers (percentages) are given.

possible cross-reactivity between any fragrances and preservatives have, to the best of our knowledge, not been performed.

Children were not included in this study, but there are several reports on children sensitized to MI (30, 31). An interesting finding is the lack of statistically significant differences between males and females concerning contact allergy to fragrances, but significantly more contact allergy to preservatives being found in females. In an earlier study, females were 1.3 times more likely to be allergic to fragrances (32). Possibly, females use specific products such as wet wipes, which can be regarded as 'leave-on' products and that are containing preservatives, which are more sensitizing than fragrances. MI has also been

present in wet wipes without being disclosed (33–35). To evaluate the findings of this study, the combinations of ingredients in cosmetics and whether they are actually used by females or males need to be studied, as do other possible exposures related to, for example, occupation.

The present study was a single-centre study. The advantages with respect to the specific aim of the present study are that the application and reading of the patch tests were performed by a limited number of trained personnel, and reflect a period when all recent changes in the patch tests were applied simultaneously in all patients. The disadvantages include limited generalizability, owing to the investigated population being from southern Sweden, and a short time period.

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