

Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit?

Johannes Geier¹, Holger Lessmann¹, Axel Schnuch¹ and Wolfgang Uter²

¹Information Network of Departments of Dermatology, University of Göttingen, 37075 Göttingen, Germany and ²Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nuremberg, 91054 Erlangen, Germany

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Summary

Background. The frequency of sensitization to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) observed in the Information Network of Departments of Dermatology (IVDK) was constantly around 2.1% from 1998 to 2009. After that, it increased to 3.9% in 2011, paralleled by an increase in the frequency of allergic reactions to MI in the preservative series from 1.9% in 2009 to 4.4% in 2011. MI without MCI has increasingly been used as a preservative in cosmetics and skin care products in recent years.

Objectives. To epidemiologically investigate the possible reasons for this development and to analyse concomitant reactions to MCI/MI and MI.

Methods. A retrospective analysis of IVDK data from 2009 to 2011 was performed.

Results. Stratified data analysis revealed pronounced increases in reactivity to MCI/MI and MI in females, face dermatitis patients, and patients tested because of suspected cosmetic intolerance. The proportion of MI-positive patients among those reacting to MCI/MI increased from 43% to 59% between 2009 and 2011.

Conclusion. More widespread consumer exposure has most likely led to the increase in primary sensitization to MI and subsequently to a rise in MCI/MI reactions resulting from immunological cross-reactions. A reduction in the maximum use concentration of MI seems advisable. MI should be patch tested in the baseline series.

Key words: biocides; CAS 26172-55-4; CAS 2682-20-4; CAS 55965-84-9; contact allergy; cosmetics; epidemiology; methylchloroisothiazolinone; methylisothiazolinone; occupational; preservatives.

Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) have been used as preservatives/biocides in a fixed combination (MCI/MI at a ratio of 3:1, e.g. Kathon[®] CG) for a long time. However, for a number of

years, MI has also increasingly been used alone, without MCI, or in combination with other preservatives (1–3). Both MCI/MI and MI alone are used in cosmetics and skin care products, as well as in household products and industrial products, that is, occupational contactants (1, 2). The maximum permitted use concentrations in cosmetic products in the EU are 15 ppm for MCI/MI and 100 ppm for MI (4). Contact allergy to both compounds is well known, with MCI being regarded as the stronger allergen (5). Sensitization to MI is mainly thought to be acquired as an immunological cross-reaction after sensitization to MCI. However, isolated sensitization to MI also occurs (1, 2, 6).

Correspondence: Johannes Geier, Information Network of Departments of Dermatology (IVDK), University of Göttingen, von Siebold Str. 3, 37075 Göttingen, Germany. Tel: +49 (0) 551 39 89 84; Fax: +49 (0) 551 39 60 95. E-mail: jgeier@gwdg.de

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After the 'epidemic' of contact allergy to MCI/MI had subsided in the mid-1990s, the prevalence of sensitization to this preservative mixture remained stable at a comparably low level for years (7). In the Information Network of Departments of Dermatology (IVDK) in Germany, Switzerland, and Austria, the age and sex-standardized frequency of sensitization to MCI/MI patch tested in the baseline series of the German Contact Dermatitis Research Group (DKG) was in a narrow range of 2.0–2.3% from 1998 to 2009 (1, 8). However, a significant increase in MCI/MI sensitization in patients <40 years of age with occupational dermatitis was noted (9). In 2010, the age and sex-standardized prevalence of MCI/MI contact sensitization rose to 3.1% (10).

Since the autumn of 2008, MI 500 ppm aq. (0.05% aq.) has been part of the DKG preservative series and the DKG industrial biocide series, eliciting a considerable number of positive reactions (1).

Considering the change in exposure to MCI and MI, that is, the increased use of MI without MCI on the one hand, and the observed increase in allergic reactions to MCI/MI on the other, as well as the fact that we now can survey 3 years of patch testing with MI, we intended to analyse the IVDK data of 2009–2011. Our questions were:

- Is there a significant increase in allergic reactions to MCI/MI and/or MI generally, or only in particular subgroups of patients?
- Do concomitant reactions to MCI/MI and MI reflect the changing exposure and/or explain the increase in MCI/MI reactions?

Our hypothesis was that increased exposure to MI may lead to an increased number of patients with primary sensitization to MI, of whom a certain proportion cross-reacts to MCI.

Material and Methods

The IVDK is a surveillance system on contact allergy with 56 departments of dermatology in Germany, Switzerland and Austria participating. Its operating principles and quality control are described in detail elsewhere (11). Briefly, patch test results, as well as clinical and history data of all patch tested patients are documented in a standardized way in the participating departments of dermatology. These data are transferred to the IVDK central office at the University of Göttingen, where they are subjected to standardized quality control and then added to the central IVDK database (11, 12). Among other items, the suspected allergen source is documented in a standardized way. The definition of 'cosmetics and

skin care products' in this context meets the criteria of the EU cosmetic directive (4). All participants of the IVDK are members of the DKG. Patch tests are performed and read according to international guidelines that have been further refined by the DKG (13). Patch test substances were purchased from Almirall-Hermal (Reinbek, Germany). For data analysis, patch test reactions at D3 were selected. Reactions at D4 were chosen in a few exceptional cases, when no reading was performed at D3, but a reading was performed at D4 instead. Positive reactions were summarized from all reactions categorized as +, ++, or ++++. Data analysis was performed with the statistical software package SASTM 9.3 (SAS Institute, Cary, NC, USA). Proportions of positive reactions were calculated with accompanying exact 95% confidence intervals (CIs).

IVDK data of the years 2009, 2010 and 2011 formed the basis of the present data analysis. In these years, 12 427, 12 802 and 12 575 patients, respectively, were patch tested (quality-controlled data). MCI/MI 100 ppm aq. was patch tested as part of the DKG baseline series in 88%, and MI 500 ppm aq. was patch tested in 56% of all patients tested in these years (for detailed patient counts, see Table 3).

First, we analysed annual reaction frequencies in subgroups of patients defined by the MOAHLFA Index (14). On the basis on these results and according to the use of MCI/MI and MI as preservatives, we performed additional data analyses in subgroups of patients defined in the same manner as in our recent long-term trend analysis of MCI/MI contact sensitization (9). The first subgroup (cosmetic subgroup) comprised patients patch tested because of suspected contact allergy to ingredients of cosmetics or skin care products; occupational cases were excluded. The second subgroup (occupational subgroup) included patients with occupational dermatitis in whom cosmetics or skin care products were not suspected as allergen sources. We are aware that some cases of occupational dermatitis are caused by skin care products used at work. In order to ensure that cases of contact dermatitis caused by skin care products are strictly separated from those caused by occupational material handled at work, we chose these restrictive subgroup definitions, excluding 'overlap' cases from both subgroups. Hence, both subgroups were disjunct. Both subgroups, as well as all patients tested, were further divided in two age groups (<40 years of age; ≥40 years). In all of these subgroups, we analysed frequencies of reactions to MCI/MI and MI, respectively, and concomitant patch test reactions to MCI/MI and MI. Differences in prevalence were statistically tested with Fisher's exact test. The significance level was set to $p = 0.05$.

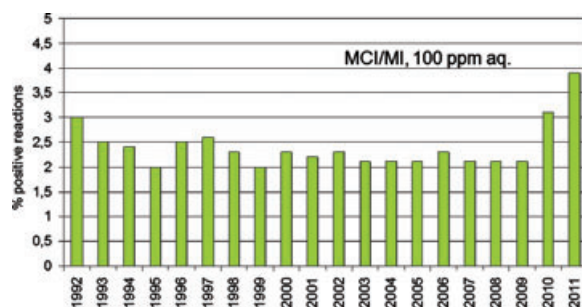


Fig. 1. Information Network of Departments of Dermatology, 1992–2011: age and sex-standardized frequency of sensitization to methylchlorisothiazolinone (MCI)/methylisothiazolinone (MI) patch tested in the baseline series.

Results

In 2011, the age and sex-standardized prevalence of MCI/MI contact sensitization rose to 3.9% (Fig. 1). When patch tested in the DKG preservative series, MI elicited 1.9% positive reactions in 2009, 3.4% in 2010, and 4.4% in 2011. This increase was not paralleled by other preservatives, e.g. iodopropynyl butylcarbamate or 2-bromo-2-nitropropane-1,3-diol (Fig. 2); hence a selection bias in terms of a stricter indication for patch testing with the preservative series can probably be excluded. As part of the DKG industrial biocide series, MI was patch tested in ~400 patients per year, and the reaction frequencies were 3.8% (2009), 5.6% (2010), and 5.2% (2011), respectively.

In Table 1, percentages of positive reactions to MCI/MI and MI, respectively, in subgroups of patients defined by the items of the MOAHLFA Index, including sex, are presented. In all subgroups, except for leg dermatitis

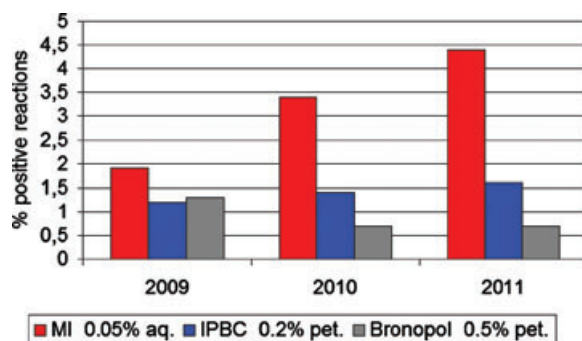


Fig. 2. Information Network of Departments of Dermatology, 2009–2011: frequency of sensitization to methylisothiazolinone (MI), iodopropynyl butylcarbamate (IPBC), and 2-bromo-2-nitropropane-1,3-diol (bronopol) when patch tested in the German Contact Dermatitis Research Group preservative series.

patients, there were significant increases in sensitization to MCI/MI and MI from 2009 to 2011. The frequency of MCI/MI sensitization almost tripled in face dermatitis patients, whereas in females and atopic dermatitis patients, the increase was ~80%, relative to the status in 2009. At a higher level (not directly comparable with MCI/MI, which was tested in consecutive patients), the same pattern was seen with MI. Notably, the increase in MI sensitization in women was much higher than that in men (+188% versus +54%).

Table 2 shows the results of the age-stratified analysis of the prevalence of allergic reactions to MCI/MI and MI, respectively, in the total study group, and in the cosmetic subgroup and the occupational subgroup of patients defined as described above. From 2009 to 2011, there was a constant increase in positive reactions to MCI/MI in the total study groups, as well as in all of these subgroups of patients, except for patients with occupational dermatitis >40 years of age. In the total study group and in the cosmetic subgroup, differences in the prevalence of sensitization to MCI/MI between 2009 and 2011 were statistically significant. In the cosmetic subgroup, the increase in reactions to MCI/MI was much higher than in the occupational subgroup (+68% versus +34%, relative to the 2009 status). Generally, increases in frequencies of reactions to MCI/MI were more pronounced in younger patients. Similar findings were obtained with MI. Here, too, a significant increase in positive reactions from 2009 to 2011 was found in the total study group and in the cosmetic subgroup, but not in the occupational subgroup, which, however, showed a higher prevalence than the cosmetic subgroup throughout. As with MCI/MI, the increase was more pronounced in the cosmetic subgroup than in the occupational subgroup (+188% versus +65%) and in younger patients than in older ones.

Concomitant reactions to MI 500 ppm aq. and MCI/MI 100 ppm aq. were analysed in a similar way, that is, in the total study group, the cosmetic subgroup, and the occupational subgroup. The proportion of patients reacting to MI among those with a positive patch test reaction to MCI/MI showed a constant increase in the total study group (43.3–58.9%) and in all subgroups of aged ≥ 40 years (Table 3). On comparison of reaction frequencies between 2009 and 2011, significant differences could be seen in the total study group, the whole group of patients aged ≥ 40 years, and the subgroup of older patients among the cosmetic subgroup patients, the last of these showing the most prominent increase (37.3–63.1%). As the sample size of patients aged ≥ 40 years within the occupational subgroup was rather small ($n = 27$), leading to wide 95% CIs, the remarkable difference in reaction frequencies between

Table 1. Percentages of positive reactions to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) tested in the baseline series and MI tested in the preservative and industrial biocide series, with 95% confidence intervals, in subgroups of patients defined by sex and items of the MOAHLFA Index, Information Network of Departments of Dermatology, 2009–2011

Subgroup	MCI/MI				MI			
	2009	2010	2011	Increase from 2009 to 2011*	2009	2010	2011	Increase from 2009 to 2011*
Women	2.2 (1.9–2.6)	3.1 (2.7–3.6)	3.9 (3.5–4.4)	+77	1.6 (1.2–2.0)	2.8 (2.4–3.3)	4.6 (4.0–5.3)	+188
Men	2.5 (2.1–3.1)	3.7 (3.1–4.3)	3.8 (3.2–4.4)	+52	2.6 (2.0–3.3)	4.3 (3.6–5.1)	4.0 (3.3–4.8)	+54
Occupational dermatitis patients	4.0 (3.1–5.1)	4.9 (4.0–6.0)	6.2 (5.2–7.4)	+55	3.7 (2.7–4.8)	4.8 (3.8–6.0)	6.4 (5.3–7.7)	+73
Atopic dermatitis patients	2.7 (2.1–3.5)	4.6 (3.8–5.5)	5.0 (4.2–5.9)	+85	2.2 (1.5–3.1)	3.6 (2.8–4.6)	4.7 (3.8–5.8)	+114
Hand dermatitis patients	3.2 (2.6–3.9)	4.8 (4.1–5.6)	5.0 (4.3–5.8)	+56	2.5 (1.9–3.3)	4.2 (3.5–5.1)	5.4 (4.6–6.4)	+116
Leg dermatitis patients	2.1 (1.4–3.0)	1.6 (1.0–2.4)	2.6 (1.8–3.7)	NS	1.5 (0.8–2.6)	1.5 (0.7–2.6)	1.9 (1.0–3.2)	NS
Face dermatitis patients	1.7 (1.2–2.4)	3.3 (2.5–4.2)	5.0 (4.0–6.2)	+194	1.7 (1.1–2.7)	3.6 (2.6–4.8)	5.1 (3.9–6.4)	+200
Patients aged ≥ 40 years	2.6 (2.3–3.0)	3.6 (3.2–4.1)	3.8 (3.4–4.2)	+46	2.0 (1.6–2.5)	3.8 (3.3–4.4)	4.4 (3.9–5.0)	+120

NS, not significant.

*Increase in percent, related to the percentage of positive reactions in 2009, if significant at a 5% level.

It should be noted that the prevalences of reactions to MCI/MI and MI are not directly comparable, as the former were obtained from consecutive patients, whereas the latter were based on a slightly selected subgroup (see text for further explanation).

2009 and 2011 (48.1% versus 68.6%) was not significant in this subgroup.

Looking at concomitant reactions to MCI/MI and MI from the opposite perspective, the proportion of MI-positive patients who also reacted to MCI/MI was 63.5% (95% CI 59.7–67.2%), without any significant time trend or differences in subgroups of patients (data not shown in detail).

The proportion of strong reactions (++ and +++) among the total of positive reactions (+, ++, and +++) to MI 500 ppm was within a range of 36–51% in all subgroups (total, cosmetic subgroup, and occupational subgroup) and in each year. No significant increase or consistent change in this proportion with time was found (data not shown in detail).

Discussion

Our data analysis showed that, from 2009 to 2011, (i) the prevalence of sensitization to MCI/MI increased from 2.3% to 3.9%, (ii) allergic reactions to MI in the preservative series increased from 1.9% to 4.4%, and (iii) the proportion of MI-positive patients among those who reacted to MCI/MI increased from 43.3% in 2009 to 58.9% in 2011. All of these observations were pronounced in younger patients, patients with face dermatitis, and, consistent with this, patients tested

because of suspected contact allergy to cosmetic or skin care product ingredients. Although we have no reliable data on the time course of MI usage in cosmetics and skin care products, it is our impression that the use of MI has become more widespread in recent years. This may also be true for some industrial products. In contrast, preservation with MCI/MI has been regulated in the past, and its use concentration in cosmetics and skin care products has been limited to a low concentration that is regarded as safe. Hence, our data seem to support our hypothesis that increasing exposure to MI leads to an increase in primary sensitization to MI, and partly to subsequent immunological cross-reactivity to MCI.

In detail, the following items have to be considered.

MI test concentration, and concentration of MI in MCI/MI

In a previous IVDK data analysis (data of 2008/2009), 134 of 339 MCI/MI-positive patients, that is, 39.5% (95% CI 34.3–45.0%), also reacted to MI 500 ppm aq. (1). This proportion was very similar to that found in a Danish study, covering 2006–2010, when MI 2000 ppm aq. was patch tested as a supplement to the baseline series: of the 40 patients reacting to MCI/MI, 15 also reacted to MI, which corresponds to 37.5% (95% CI 22.7–54.2%) (15). A slightly higher percentage was

Table 2. Information Network of Departments of Dermatology, 2009–2011: age-stratified analysis of proportions of positive patch test reactions to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and MI

	MCI/MI						MI					
	2009			2010			2011			2009		
	Patients tested	% positive (95% CI)	Patients tested	Patients tested	% positive (95% CI)	Patients tested	Patients tested	% positive (95% CI)	Patients tested	Patients tested	% positive (95% CI)	Patients tested
All patients tested												
Total	11 040	2.3 (2.1–2.6)	11 156	3.3 (3.0–3.7)	3.9 (3.5–4.2)	10 922	6789	1.9 (1.6–2.3)	7193	3.4 (3.0–3.8)	7292	4.4 (3.9–4.9)
Age <40 years	3112	1.6 (1.2–2.1)	3066	2.6 (2.0–3.2)	4.0 (3.3–4.8)	2941	1973	1.7 (1.2–2.4)	2095	2.3 (1.7–3.1)	2060	4.4 (3.5–5.3)
Age ≥40 years	7928	2.6 (2.3–3.0)	8090	3.6 (3.2–4.1)	3.8 (3.4–4.2)	7981	4816	2.0 (1.6–2.5)	5098	3.8 (3.3–4.4)	5232	4.4 (3.9–5.0)
Cosmetic subgroup												
Total	4602	2.5 (2.0–3.0)	4419	3.6 (3.0–4.2)	4.2 (3.6–4.9)	4090	3233	1.6 (1.2–2.1)	3287	3.3 (2.7–3.9)	3032	4.6 (3.8–5.4)
Age <40 years	1233	1.5 (0.9–2.3)	1073	2.2 (1.4–3.3)	3.7 (2.6–5.1)	1002	824	1.2 (0.6–2.2)	785	2.0 (1.2–3.3)	732	3.6 (2.3–5.2)
Age ≥40 years	3369	2.8 (2.3–3.5)	3346	4.0 (3.4–4.7)	4.4 (3.7–5.2)	3088	2399	1.8 (1.3–2.4)	2502	3.6 (2.9–4.4)	2300	4.9 (4.0–5.8)
Occupational subgroup												
Total	1297	3.8 (2.8–5.0)	1430	4.6 (3.6–5.8)	5.1 (4.1–6.4)	1483	1014	3.4 (2.3–4.7)	1188	4.8 (3.7–6.2)	1285	5.6 (4.4–7.0)
Age <40 years	594	3.0 (1.8–4.7)	668	3.7 (2.4–5.5)	5.8 (4.1–8.0)	605	459	3.3 (1.8–5.3)	540	2.8 (1.6–4.5)	520	5.6 (3.8–7.9)
Age ≥40 years	703	4.4 (3.0–6.2)	762	5.4 (3.9–7.2)	4.7 (3.4–6.3)	878	555	3.4 (2.1–5.3)	648	6.5 (4.7–8.7)	765	5.6 (4.1–7.5)

CI, confidence interval.

For each subgroup, the number of patients tested and the percentage of positive reactions are given, together with 95% CIs. It should be noted that the frequencies of reactions to MCI/MI and MI, respectively, are not directly comparable, as the former were obtained from consecutive patients, whereas the latter were based on a slightly selected subgroup (see text for further explanation).

Table 3. Information Network of Departments of Dermatology, 2009–2011: stratified analysis of proportions of positive patch test reactions to methylisothiazolinone (MI) 500 ppm aq. among patients with a positive reaction to methylchloroisothiazolinone (MCI)/MI 100 ppm aq.

	2009		2010		2011	
	Patients tested	% positive (95% CI)	Patients tested	% positive (95% CI)	Patients tested	% positive (95% CI)
All patients tested						
Total	187	43.3 (36.1–50.7)	274	53.3 (47.2–59.3)	326	58.9 (53.3–64.3)
Age <40 years	36	50.0 (32.9–67.1)	66	48.5 (36.0–61.1)	90	62.2 (51.4–72.2)
Age ≥40 years	151	41.7 (33.8–50.0)	208	54.8 (47.8–61.7)	236	57.6 (51.0–64.0)
Cosmetic subgroup						
Total	78	35.9 (25.3–47.6)	115	60.0 (50.5–69.0)	142	62.7 (54.2–70.6)
Age <40 years	11	27.3 (6.0–61.0)	19	63.2 (38.4–83.7)	28	60.7 (40.6–78.5)
Age ≥40 years	67	37.3 (25.8–50.0)	96	59.4 (48.9–69.3)	114	63.1 (53.6–72.0)
Occupational subgroup						
Total	41	58.5 (42.1–73.7)	58	55.2 (41.5–68.3)	65	64.6 (51.8–76.1)
Age <40 years	14	78.6 (49.2–95.3)	21	52.4 (29.8–74.3)	30	60.0 (40.6–77.3)
Age ≥40 years	27	48.1 (28.7–68.1)	37	56.8 (39.5–72.9)	35	68.6 (50.7–83.1)

CI, confidence interval.

For each subgroup, the number of patients tested and the percentage of positive reactions are given, together with 95% CIs.

observed in a Finnish multicentre study in 2006–2008, in which 97 of 194, that is, 50% (95% CI 42.8–57.2%), of those reacting to MCI/MI also reacted to MI patch tested at 1000 ppm aq. (6).

However, a (short-term) time trend of concomitant reactions had hitherto not been addressed. Our data show, for the first time, an increase in the proportion of MI-positive patients among those who reacted to MCI/MI, which was particularly pronounced in patients tested because of suspected cosmetic intolerance. The patch test preparation MCI/MI 100 ppm aq. (0.01% aq.) contains both chemicals at a ratio of 3:1, that is, 75 ppm MCI, and 25 ppm MI. If it is supposed that concomitant reactions to MI and MCI/MI were exclusively caused by sensitization to MI, and not to MCI, and considering that the test concentration of MI (500 ppm) is 20 times higher than the concentration of MI in MCI/MI (25 ppm), one would expect that patients strongly sensitized to MI, with a correspondingly low elicitation threshold, would react not only to MI 500 ppm, but also to the lower concentration of MI in the MCI/MI mixture. These patients would be expected to have strong reactions to MI 500 ppm and weak reactions to MCI/MI (unless they are co-sensitized to the chlorinated compound). However, our data analysis did not reveal a significant change in the reaction intensity towards more strong positive MI reactions. Hence, the

proportion of highly sensitized individuals among the MI-positive patients, who might react (weakly) to the low MI concentration in the MCI/MI test preparation, apparently remained stable and thus cannot explain the increase in co-reactivity.

Immunological cross-reactivity

Immunological cross-reactivity between MCI and MI is well known from animal experiments. However, cross-reactions are not obligatory; they occur in only a certain proportion of animals after induction with the respective other compound (16). MCI is the stronger allergen of the two, and it may react not only with free sulfhydryl groups (as MI does also), but also with free amino groups in histidine or lysine side chains (17–21). Hence, a higher percentage of patients primarily sensitized to MI can be expected to have cross-reaction with MCI than vice versa. Because of the special concomitant exposure to MCI and MI in the past, sensitization to the stronger allergen (MCI), which was also present at a higher concentration, was more likely. However, there is now increased exposure to the weaker allergen of the two (MI) at much higher concentrations than before, and often without concomitant exposure to MCI, resulting in an increased proportion of patients with primary

sensitization to MI. These considerations would explain the increase in concomitant reactions (i.e. proportion of MI-positive patients among MCI/MI-positive patients) that we observed from 2009 to 2011.

Sensitization to MI without cross-reactivity to MCI

We found that 63.5% of the patients reacting to MI also reacted to MCI/MI. Therefore, the proportion of MI-positive patients who were not sensitized to MCI was 36.5%, which is similar to the 34% described by Ackermann et al. in Finland in 2006–2008 (6). Lundov et al. found a higher proportion, namely 59%, in Danish patients tested from 2006 to 2010, which may be attributed to the higher patch test concentration (2000 ppm) (15). To our knowledge, no earlier data have been published. In the second half of 2005, some IVDK centres had patch tested MI 500 ppm aq. parallel with the baseline series as part of the IVDK 'monitor series' (unpublished data). Of the 2167 patients tested, 48 (2.2%) reacted to MCI/MI (100 ppm aq.), but only 17 (0.8%) to MI. Only 4 of these 17 patients (23.5%) did not react to MCI. However, because of the very small sample size, the 95% CI is huge, ranging from 7% to 50%. Hence, no significant difference compared to the current data can be seen.

Past sensitization to MCI

As an alternative explanation for the increase in allergic reactions to MI, one might argue that, with the increasing use of MI at higher concentrations in cosmetics and skin care products, some patients who had been sensitized previously (years ago) to MCI, and now have cross-reactivity to MI, develop contact dermatitis. However, we can neither verify nor refute this assumption, because in our data, we found <3% of patients who had been patch tested before.

Conclusion

In our opinion, the results presented here indicate that contact sensitization to MI is generally increasing, probably because of increased consumer and worker exposure, and that this also leads to an increase in MCI/MI reactions

via immunological cross-reactions. Hence, the recent increase in allergic reactions to MCI/MI may – at least partly – be attributable to MI sensitization in general, and particularly in cosmetic users. Therefore, lowering the maximum allowed use concentration of MI in cosmetics and skin care products seems advisable. To further monitor sensitization to MI, to generate a larger database for concomitant reactions to MCI/MI and MI, and to detect relevant cases of sensitization for the benefit of affected patients, we propose the inclusion of MI 500 ppm aq. in the baseline patch test series.

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References

- 1 Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br J Dermatol* 2011; **164**: 1316–1325.
- 2 Lundov M D, Krongaard T, Menné T L, Johansen J D. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011; **165**: 1178–1182.
- 3 Schnuch A, Mildau G, Kratz E-M, Uter W. Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. *Contact Dermatitis* 2011; **65**: 167–174.
- 4 European Commission. Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products

- (consolidated version, 01.03.2010), 2010.
- 5 Gerberick F G, Ryan C A, Kern P S, Schlatter H, Dearman R J, Kimber I, Patlewicz G Y, Basketter D A. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. *Dermatitis* 2005; **16**: 157–202.
 - 6 Ackermann L, Aalto-Korte K, Alanko K et al. Contact sensitization to methylisothiazolinone in Finland – a multicentre study. *Contact Dermatitis* 2011; **64**: 49–53.
 - 7 Thyssen J P, Johansen J D, Menné T. Contact allergy epidemics and their controls. *Contact Dermatitis* 2007; **56**: 185–195.
 - 8 Geier J, Uter W, Krauthaim A, Lessmann H, Schnuch A. Die häufigsten Kontaktallergene der Jahre 2007–2009. Aktuelle Daten aus dem Informationsverbund Dermatologischer Kliniken (IVDK). *Allergo J* 2011; **20**: 93–101.
 - 9 Uter W, Gefeller O, Geier J, Schnuch A. Chloromethylisothiazolinone/methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients over 19 years. *Contact Dermatitis* 2012; doi:10.1111/j.1600-0536.2012.02075.x. [E-pub ahead of print 2012-05-05].
 - 10 Geier J, Uter W, Lessmann H, Schnuch A. Aktuelle Kontaktallergene. *Hautarzt* 2011; **62**: 751–756.
 - 11 Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy* 2012; **67**: 847–857.
 - 12 Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes 'Informationsverbund Dermatologischer Kliniken' (IVDK). *Dermatol Beruf Umwelt* 2005; **53**: 107–114.
 - 13 Schnuch A, Aberer W, Agathos M et al. Durchführung des Epikutantests mit Kontaktallergenen. Leitlinien der Deutschen Dermatologischen Gesellschaft (DDG) und der Deutschen Gesellschaft für Allergie und klinische Immunologie (DGAKI). *J Dtsch Dermatol Ges* 2008; **6**: 770–775.
 - 14 Schnuch A, Geier J, Uter W, Frosch P J et al. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–209.
 - 15 Lundov M D, Thyssen J P, Zachariae C, Johansen J D. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010; **63**: 164–167.
 - 16 Bruze M, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG in the guinea pig. *Acta Derm Venereol* 1987; **67**: 315–320.
 - 17 Alvarez-Sánchez R, Basketter D, Pease C, Lepoittevin J P. Studies of chemical selectivity of hapten, reactivity, and skin sensitization potency. 3. Synthesis and studies on the reactivity toward model nucleophiles of the 13C-labeled skin sensitizers, 5-chloro-2-methylisothiazol-3-one (MCI) and 2-methylisothiazol-3-one (MI). *Chem Res Toxicol* 2003; **16**: 627–636.
 - 18 Alvarez-Sánchez R, Basketter D, Pease C, Lepoittevin J P. Covalent binding of the 13C-labeled skin sensitizers 5-chloro-2-methylisothiazol-3-one (MCI) and 2-methylisothiazol-3-one (MI) to a model peptide and glutathione. *Bioorg Med Chem Lett* 2004; **14**: 365–368.
 - 19 Alvarez-Sánchez R, Divkovic M, Basketter D, Pease C, Panico M, Dell A, Morris H, Lepoittevin J P. Effect of glutathione on the covalent binding of the 13C-labeled skin sensitizer 5-chloro-2-methylisothiazol-3-one to human serum albumin: identification of adducts by nuclear magnetic resonance, matrix-assisted laser desorption/ionization mass spectrometry, and nanoelectrospray tandem mass spectrometry. *Chem Res Toxicol* 2004; **17**: 1280–1288.
 - 20 Gerberick G F, Vassallo J D, Foertsch L M, Price B B, Chaney J G, Lepoittevin J P. Quantification of chemical peptide reactivity for screening contact allergens: a classification tree model approach. *Toxicol Sci* 2007; **97**: 417–427.
 - 21 Mutschler J, Giménez-Arnau E, Foertsch L, Gerberick G F, Lepoittevin J P. Mechanistic assessment of peptide reactivity assay to predict skin allergens with Kathon CG isothiazolinones. *Toxicol In Vitro* 2009; **23**: 439–446.