

Methylisothiazolinone contact allergy – are rinse-off cosmetics and household products relevant sources of exposure?*

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doi:10.1111/cod.12595

Key words: allergic contact dermatitis; cosmetics; household products; methylchloroisothiazolinone; methylisothiazolinone; CAS no. 2682-20-4.

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*Part of the results have been previously published in *G Ital Dermatol Venereol*. 2016 Mar 16. [Epub ahead of print].

Methylisothiazolinone (MI) is a biocide used in industrial, household and cosmetic products, either alone or in combination with methylchloroisothiazolinone (MCI). In 2005, approval was given for its use as a stand-alone preservative in cosmetic products at a maximum concentration of 100 ppm, that is, considerably higher than the concentration allowed when it is combined with MCI. An

Table 1. Comparison of the MOAHLFA index [numbers (percent) in subgroup] in four subgroups

MOAHLFA	A: patients negative to both MCI/MI and MI	B: 28 patients positive to MI only	C: 74 patients positive to MCI/MI only	D: 78 patients positive to both MCI/MI and MI	p-Value
Male	525 (28.4)	15 (53.6)	25 (33.8)	19 (24.4)	0.023*
Occupational	45 (2.4)	0 (0)	3 (4.1)	3 (3.8)	0.49
Atopic dermatitis	208 (11.3)	6 (21.4)	4 (5.4)	10 (12.8)	0.12
Hands	516 (27.9)	6 (21.4)	38 (51.4)	39 (50)	< 0.001†
Leg	138 (7.5)	3 (10.7)	7 (9.5)	9 (11.5)	0.37
Face	417 (22.6)	8 (28.6)	16 (21.6)	30 (38.5)	0.015‡
Age >40 years	1177 (63.7)	19 (67.9)	47 (63.5)	39 (50)	0.10

Fisher's exact test was used to statistically compare the MOAHLFA frequency in the four groups. Each group was compared with the others in a pair (e.g. A versus B) and *p*-values were adjusted for multiple comparisons using the false discovery rate approach.

Significant differences were found for *Gender, †Hands and ‡Face.

*Significant differences comparing B vs. A (*p* = 0.026) and B vs. D (*p* = 0.026), but not B vs. C (*p* = 0.15).

†Significant differences comparing C vs. both A (*p* < 0.001) and B (*p* = 0.015) and D vs. both A (*p* < 0.001) and B (*p* = 0.02).

‡The only significant difference is between A and D (*p* = 0.014).

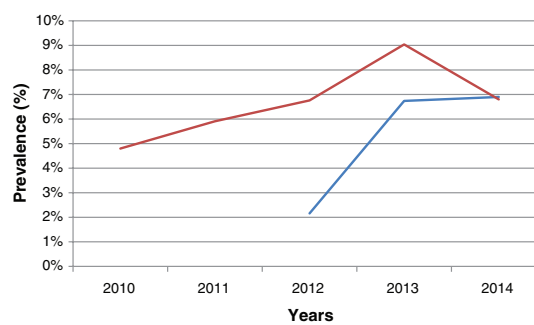
Table 2. Sources of certain, likely or possibly relevant exposure to MI and trend over time in 94 patients that were patch test positive to MI, either alone or in association with MCI/MI

Sources of exposure to MI	2012 N (%)	2013 N (%)	2014 N (%)	Chi-square for trend (<i>p</i> -value)
Leave-on cosmetics	11 (48)	26 (46)	27 (47)	0.99
Rinse-off cosmetics	9 (39)	23 (41)	14 (25)	0.10
Household products	2 (9)	6 (11)	15 (26)	0.022
Industrial products	1 (4)	1 (2)	1 (2)	0.55
Total products	23	56	57	

alarming epidemic of contact allergy to MI ensued (1, 2). In December 2013, the Scientific Committee on Consumer Safety of the European Commission recommended that the use of MI in leave-on products should be banned, and that its use concentration in rinse-off products should be limited to 15 ppm. Thereafter, the European legislators decided to prohibit the use of MCI/MI in leave-on cosmetics, and to lower its maximum allowed concentration to 15 ppm in rinse-off products. This rule became fully operational in 16 April 2016 (3). However, no decision was made regarding the use of MI alone in cosmetic products, or concerning the permissible concentration of isothiazolinones in household products (4).

Methods and Results

From January 2012 to December 2014, MI 0.2% aq. was tested, in addition to MCI/MI 0.01% aq., in 2028 consecutive patients patch tested at the Clinica Dermatologica of San Martino University Hospital, Genoa, Italy. Patch tests were performed according to international guidelines (5). The MOAHLFA index (percentage of males, patients with occupational dermatitis, atopic dermatitis, hand, leg, and

**Fig. 1.** Trend of sensitization to methylisothiazolinone (MI) between 2012 and 2014 (blue line) and to methylchloroisothiazolinone (MCI)/MI between 2010 and 2014 (red line). The χ^2 -test for trend for MI sensitization was highly significant (*p* < 0.001); it was also highly significant for MCI/MI sensitization during the study period 2010–2014 (*p* = 0.010).

face dermatitis, and age >40 years) was registered for all patients. Relevant exposures to MI and/or MCI/MI were systematically evaluated. Relevance was scored as certain/probable when MI or MCI/MI was found in the patients' own products, and as possible/doubtful when exposure to MI and/or MCI/MI was likely but could not be proven. The patients with currently relevant positive reactions were followed up to assess their clinical outcome after avoidance of isothiazolinones (6).

The overall prevalences of positive reactions to MI or MCI/MI were 106 of 2028 (5.2%) and 152 of 2028 (7.5%), respectively; 3.8% of patients reacted to both compounds, and 1.4% reacted to MI only. The prevalence of MI sensitization showed a steep increase from 2.3% in 2012 to 6.9% in 2014. Prior to 2013, there was a parallel increase in the prevalence of sensitization to MCI/MI that confirmed a trend already observed in 2010 and 2011 (Fig. 1).

Comparison of the MOHALFA index among MCI/MI-positive and/or MI-positive patients, and patients who did not react to either allergen, showed some significant differences (Table 1). In particular, sensitization to only MI, as compared with sensitization to MCI/MI or to both isothiazolinones, was associated with male sex; sensitization to MCI/MI, alone or together with MI, correlated with hand dermatitis; concomitant sensitization to MI and MCI/MI was associated with face involvement.

Current clinical relevance was found in 150 of 180 (83.3%) patients sensitized to either or both allergens. It was scored as certain/probable in 94 of 180 (52.2%) and as possible/doubtful in 56 of 180 (31.1%). Clinical resolution or improvement after avoidance of isothiazolinones was reported by 91 of 125 (72.8%) patients who were followed up. Twenty-five patients were lost to follow-up. The main categories of relevant exposure to MI and their trend over time are shown in Table 2.

Discussion

This is one of the few large clinical series concerning contact allergy to isothiazolinones in southern Europe (7); it confirms the epidemic of MI contact allergy and the parallel increase in the prevalence of sensitization to MCI/MI reported in other countries. Interestingly, it shows a decrease in the prevalence of MCI/MI sensitization in 2014, after a peak in 2013, whereas the rate of sensitization to MI has remained stable, and does not seem to have been influenced yet by the recommendation of Cosmetics Europe of December 2013 to no longer use MI in leave-on products.

Our data confirm that leave-on cosmetics and female sex are strongly implicated in MI and MCI/MI contact allergy, respectively, with some interesting exceptions that were clarified through the systematic evaluation of the sources of exposure combined with the determination of the patients' clinical outcomes after patch testing.

The prevalence of sensitization to only MI was unexpectedly similar in males and females, and this was partly explained by the presence of MI in low-price brands of shaving products.

Concomitant sensitization to both MI and MCI/MI appeared to be significantly associated with involvement of the face, where contact allergy initiated by MI-containing leave-on cosmetics was often maintained by exposure to MI and/or MCI/MI in rinse-off products, and resolved only after avoidance of these products.

Concerning household products, in particular detergents, it has recently been noted that they may contain high MI concentrations and that they are sometimes mislabelled (4). This makes it difficult to evaluate their possible relevance. However, in our experience, resolution of recalcitrant eczema after careful avoidance of suspected household products confirmed that these were, indeed, relevant exposures. This pertained in particular to patients with hand involvement who reacted to MCI/MI or MCI/MI and MI. Hand involvement was also associated with exposure to MCI/MI in rinse-off cosmetics, frequent hand washing, and insufficient rinsing.

In 2014, the association between contact allergy to the isothiazolinones considered and rinse-off cosmetics seemed to decrease. However, this was not significant, and should thus not be over-interpreted. In contrast, a recent UK survey showed a significant shift in the use of MI from leave-on to rinse-off products, as compared with previous studies (8). It is of note that a significant increase in the number of household products considered to be relevant exposure sources was observed (Table 2).

In conclusion, our study shows that the epidemic of contact allergy to MI is not yet under control, and that rinse-off cosmetics and household products represent relevant sources of exposure. On the basis of our experience, the present legal restrictions on the use of MI in cosmetics are probably insufficient, and household products also need stricter regulation.

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