

METHYLISOTHIAZOLINONE AS A COMMON AND RELEVANT CONTACT ALLERGEN

Rovira R¹, Gómez I¹, Curto L¹, Espona M², Pujol RM¹, Giménez-Arnau A¹
Departments of Dermatology¹ and Pharmacy², Hospital del Mar. Universitat Autònoma and Universitat Pompeu Fabra. Barcelona, Spain

BACKGROUND

Isothiazolinones are known highly effective preservatives. In 1992, the Cosmetic Ingredient Review Expert Panel concluded that a mixture of methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) at 76.7%/23.3% concentration respectively may be safely used in “rinse-off” products at a concentration not to exceed 15 ppm and in “leave-on” cosmetics products at a concentration not to exceed 7.5 ppm. *In vitro* studies showed MI to be allergenic, cytotoxic and neurotoxic; nevertheless it is allowed as a cosmetic preservative because it is supposed to be a weaker allergen than MCI. In the early 2000s, MI was released as an individual preservative for industrial products and, in 2005, it was permitted for use in cosmetic products. Since then, an increased number of case reports and prevalence studies on isolated MI contact allergy have been published^{1, 2}. According to a report of safety³, cosmetic products formulated with 100 ppm of MI or less are not expected to increase a sensitization risk, considering MCI as a strong sensitizer and MI as a weak sensitizer.

OBJECTIVE. To evaluate the prevalence of MI contact allergy

RESULTS

Seventy-eight patients (4.57%) showed positive patch test at least to MCI/MI. Thirty one of them showed positive patch test reaction just to MCI/MI (1.81%). Thirty-five patients (2.05%) showed MCI/MI and MI positive patch test reaction. Eleven patients (0.64%) showed just MI positive patch test reaction (example [figure 1](#)).

Among those patients with MI and MCI/MI positive patch test (n=35), thirteen (37%) showed a stronger reaction to MI patch test than to MCI/MI patch test.

MI sensitization was demonstrated in forty-six patients (2.69%, 46/1705) aged 16-82 years. This prevalence is slightly higher than the previously published by three European groups⁴ ([table 1](#)). Concomitant positive reactions to MI and MCI/MI were described in 76% (35/46) of MI-allergic patients. Current relevance was certain in 90% of these cases, mostly attributable to cosmetics ([figure 2](#)), being allergic contact dermatitis the most common diagnosis.

Besides trunk eczema (39%, n=18), the anatomical site of dermatitis included the hands (35%, n=16), face (30%, n=14), legs (6%, n=6) and arms and wrists (both 4%, n=2). In one case associated with use of cleaning moist wipes the eruption showed a perianal distribution. The face was the anatomical location more frequently affected in MI isolated allergic patients (54%, n=6).

According to the MOAHLFA index ([table 2](#)), MI isolated contact allergy was significantly more often associated with facial dermatitis (OR 4.8, p = 0.02)

MATERIAL AND METHODS

Over a 4-year period (2010-2013) a thousand seventy hundred and five patients were consecutively patch tested with MCI/MI 100 ppm aq and MI 500 and 2000 ppm aq. Allergens were applied according to the International Contact Dermatitis Research Group recommendations using Finn Chambers®. Patch test exposure time was 2 days. The standard positive outcome of the patch test was defined as a morphological 1+ to 3+ reaction between days 5 and 7.

Patch-testing results were collected along with basic demographic and clinical data. The MOAHLFA (male, occupational dermatitis, atopic dermatitis, hand eczema, leg dermatitis, facial dermatitis, age above 40 years) index was routinely performed and registered. Medical records from patients with MCI/MI and/or MI allergy contact were reviewed retrospectively. A comparative study between patients showing a positive patch test to MI and individuals with negative results was performed using the Fisher's exact test.

Figure 1. Patient with MI positive patch test



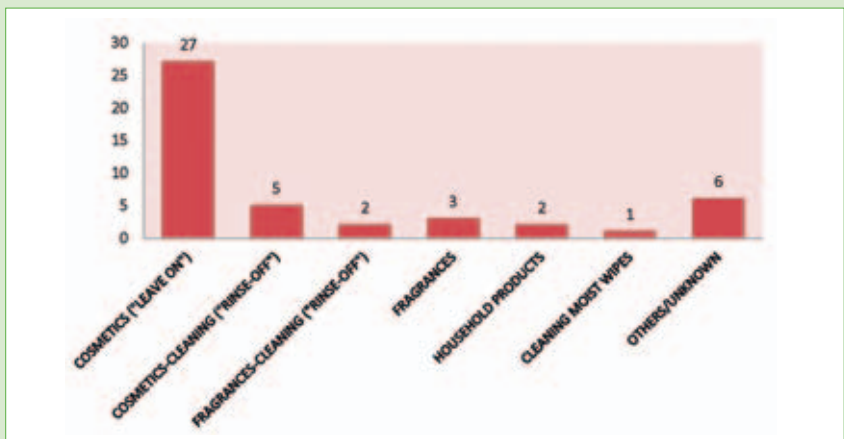
Table 1. Prevalence of MI contact allergy

Country	Years	Prevalence MI pos cases/ n=prev	[MI] patch test	Reference
Denmark	2006-10	37/2536 = 1.5%	2000 ppm (0.2%)	Lundov et al
Germany	2005-9	215/13433 = 1.54%	500 ppm (0.05%)	Schnuch et al
Finland	2006-8	147/10821 = 1.4%	1000 ppm (0.1%) 300 ppm (0.03%)	Ackermann al
Spain	2010-13	46/1705 = 2.69%	500 ppm (0.05%) 2000 ppm (0.2%)	Present report

Table 2. MOAHLFA index among MI/MCI and/or MI patch test positive patients and controls (patch test positive for other substances and MCI/MI and/or MI negative). 2010-2013

	MCI/MI positive (n= 31)	MI-positive isolated (n=11)	MI + MCI/ MI positive (n=35)	MCI/MI + MI positive and MI-positive isolated (n=46)	Control group (n=100)	OR p value (Fisher's Test) CI 95% MI-positive isolated	OR P value (Fisher's test) CI 95% MCI/MI + MI positive and MI-positive isolated
	n (%)	n (%)	n (%)	n (%)			
Male	11 (35%)	5 (45%)	9 (26%)	14 (30%)	23	2.78 0.1 0.779-9.983	1.46 0.22 0.670-3.201
Occupational Dermatitis	4 (13%)	0	2 (5%)	2 (4%)	12	nc	0.3 0.12 0.071-1.554
Atopic dermatitis	7 (22%)	2 (2%)	10 (28%)	12 (26%)	18	1 0.62 0.201-5.809	1.6 0.18 0.699-3.967
Hand dermatitis	10 (32%)	3 (27%)	13 (37%)	16 (35%)	32	0.8 0.52 0.198-3.205	1.13 0.44 0.541-2.370
Leg dermatitis	4 (13%)	1 (9%)	5 (14%)	6 (13%)	11	0.8 0.73 0.094-6.938	1.21 0.45 0.419-3.511
Facial dermatitis	5 (16%)	6 (54%)	8 (23%)	14 (30%)	20	4.8 0.02 1.329-17.332	1.75 0.12 0.789-3.881
Age> 40 years	15 (48%)	5 (45%)	20 (57%)	25 (54%)	68	0.39 0.12 0.111-1.381	0.56 0.08 0.273-1.146

Figure 2. Sources of exposure to MI in MI contact allergy patients



CONCLUSIONS

The prevalence of MI contact allergy (2.69%) is at the same level of other sensitizing preservatives.

MI alone can undoubtedly induce and elicit contact allergic dermatitis.

MI contact allergy was associated with consumer products, especially with cosmetics and should be considered as a potential suspect allergen among patients with suspected cosmetic facial dermatitis.

Concomitant positive reactions to MI and MCI/MI were seen in 76% of MI-allergic patients.

As long as MCI and MI are tested together, and we rarely know what the primary sensitizer is, we cannot answer what is first MCI or MI sensitization; nevertheless, in 37% of the patients with MCI/MI and MI positive patch test, reaction to MI was stronger and this could be attributable to a primary sensitization to MI⁵.

REFERENCES

1. Castanedo-Tardana MP, Zug KA. Methylisothiazolinone. *Dermatitis* 2013; 24:2-6.
2. Lundov MD, Thyssen JP, Zachariae C, Johansen J. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010; 63: 164-167.
3. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol* 2010; 29:187S-213S
4. Lundov MD, Krongaard T, Menné TL, Johansen J. Methylisothiazolinone contact allergy: a review. *Br J of Dermatol* 2011; 165: 1178-1182.
5. Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; 67: 334-341.