

Methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone hypersensitivity in 1122 patients: A national multicenter study organized by the Hungarian Contact Dermatitis Group

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The preservative Kathon CG, containing chloromethylisothiazolinone (MCI) and methylisothiazolinone (MI) in a 3:1 ratio, has been widely used because of its antimicrobial effectiveness. Its sensitizing effect in cosmetics is documented since 1985,¹ later confirmed by European studies finding average sensitization prevalences of 3%.²⁻⁴ MI alone was introduced as a preservative at the beginning of the 21st century for industrial and later for cosmetic use. An epidemic of MI sensitization in Europe, the USA, and Asia with various clinical symptoms has been reported. Among the products causing MI hypersensitivity, cosmetics are most important, including hair care products.⁵⁻¹⁵

Because MI constitutes only 25% of the total MCI/MI test material, the earlier prevalence of hypersensitivity to MI cannot be determined exactly by MCI/MI routinely tested in the baseline patch series: for instance, MCI/MI did not detect 27.3% of MI allergy in a previous study.⁸ For this reason, inclusion of MI in the baseline patch test series was recommended, using MI 2000 ppm (0.2%) aq.^{16,17}

METHODS

The Hungarian Contact Dermatitis Group patch tested MI 0.2% aq. (allergEAZE, Brial allergen, Germany) between January 2015 and January 2016 along the standard environmental allergen series (allergEAZE), thus simultaneously with MCI/MI 0.01% aq. In six dermatological centers in Hungary, 1122 patients were tested prospectively. The haptens were applied on the back and occluded for 48 h. Evaluation of the test was performed 1 h

after ending occlusion, and on day (D) 2, and on D3, D4, and D7. Reactions were regarded as positive if + or stronger. Exclusion criteria for the patch tests were medication with local steroids 1 week prior to the examination, taking antihistamines 1 week prior to and during the examination, or undergoing systemic steroid treatment, received ultraviolet radiation 6 weeks prior to the examination, or presence of acute or active skin symptoms, active rhinitis, pregnancy, and lactation.

RESULTS

The mean age of the tested patients was 47 years (13-92 years). There were 268 men (mean age: 48.5 years, age range: 14-84 years) and 854 women (mean age: 46.5 years, age range: 13-92 years). Overall, 28/1122 (2.5%) patients were sensitized only to MI with a mean age of 42.4 years (17-76 years), including five males (mean age: 48.6 years, age range: 40-58 years) and 23 females (mean age: 41.1 years; age range: 17-76 years). In comparison, 18 patients were sensitized solely to MCI/MI (1.6%) with a mean age of 51.7 years (22-75 years), including two men (51 and 53 years respectively) and 16 women (mean age: 51.7 years, age range: 22-75 years). Finally, concomitant MI and MCI/MI sensitization was found in 36 patients (3.2%) with a mean age of 49.8 years (22-77 years): seven men (mean age: 51.3 years, age range: 32-75 years) and 29 women (average: 49.8 years, age range: 21-77 years). Thus, in total, there were 82 (7.3%) patients sensitized to MI and/or MCI/MI and the frequency of MI sensitization was 5.7%

TABLE 1 Distribution of the sensitizing allergens by diagnoses (82 total positive; M: Male, F: Female)

Diagnosis	MI sensitization n = 28			MCI/MI sensitization n = 18			MI and MCI/MI sensitization n = 36		
	n	M	F	n	M	F	n	M	F
Allergic contact dermatitis	21	5	16	14	2	12	22	4	18
Irritative contact dermatitis									
Atopic dermatitis	4		4	1		1	3		3
Dyshidrosis				1		1	2	1	1
Seborrheic dermatitis				1		1	1		1
Microbial eczema									
Stasis dermatitis	1		1	1		1	5	1	4
Psoriasis	1		1				3	1	2
Other ^a	1		1						
Total	28	5	23	18	2	16	36	7	29

Abbreviations: MCI, chloromethylisothiazolinone; MI, methylisothiazolinone.

^aContact urticaria n = 1.

(64 patients). An immediate reaction appeared after 60 min only in one patient 1 h after ending occlusion. Irritant reactions were seen for both MI alone and MCI/MI in five patients each (0.4%).

Among the sensitized patients, allergic contact dermatitis was found most frequently (Table 1). In a few cases sensitization was not clinically relevant, and atopic dermatitis and stasis dermatitis were diagnosed. Skin symptoms were localized typically on the hands, face and eyelids, and the trunk. Generalized symptoms were observed only in MI-sensitized patients (6.2%; Figure S1). According to the MOAHLFA index, hand and face dermatitis was common (Table S1).

Among the sensitizing products, shower gels and liquid soaps, hair shampoos, moist cleaning wipes, and household products were the most common (Table 2). Concomitant sensitization to fragrance mix I and II, wood tar mix, and *Myroxylon pereirae* (balsam of Peru) was seen, possibly explained by fragrances used in the same products (Table S2). Concerning occupational allergens, we detected MI sensitization in two patients, and concomitant MCI/MI and MI sensitization in four of these patients. The sources of allergens in these patients were mostly liquid soaps used at their workplace (Table S3).

DISCUSSION

The Hungarian Contact Dermatitis Group evaluated the test results of 1122 patients from six dermatological centers obtained during 1 year. A clinical study in Hungary,¹⁸ performed at the Department of Dermatology, Venerology and Dermato-Oncology of Semmelweis University, showed a prevalence of MI hypersensitivity of 4.8%. Our present national result of MI sensitization (5.7%) fits to the European data,^{19–30} albeit on the lower end. Our patients are predominantly female and affected mostly in their 40s. The clinical symptoms appeared mainly on the patients' hands and face. The most frequent provoking products were liquid shower gels and soaps, shampoos, and household products. According to our data, MI sensitization is associated typically with multiple contact hypersensitivities, mostly with fragrances. This confirms the former experience that MI allergy is a risk factor in the development of polysensitization. This observation and the possibility of cross-reactions between MI, MCI, and other isothiazolinones render this topic important also in the future.^{31–35}

TABLE 2 Products eliciting dermatitis in patients sensitized to MI and/or MCI/MI (n = 82)

	MI positive (n = 28)			MCI/MI positive (n = 18)			MI and MCI/MI positive (n = 36)		
	+n	M	F	+n	M	F	+n	M	F
Liquid soaps, shower gels	15	4	11	4	1	3	21	5	16
Hair shampoos	8		8	6	1	5	7		7
Hair dyes	1		1	1		1			
Body lotions	1		1	1		1	4		4
Cosmetics, face creams	2		2	1		1	3		3
Deodorants	2		2	1		1	1		1
Moist cleaning wipes	8	2	6	1		1	1		1
Oils, coolants	2	1	1	2	2		3	2	1
Household products	10	2	8	8	1	7	24	5	19

Abbreviations: MCI, chloromethylisothiazolinone; MI, methylisothiazolinone; +n, total number positive in subgroup.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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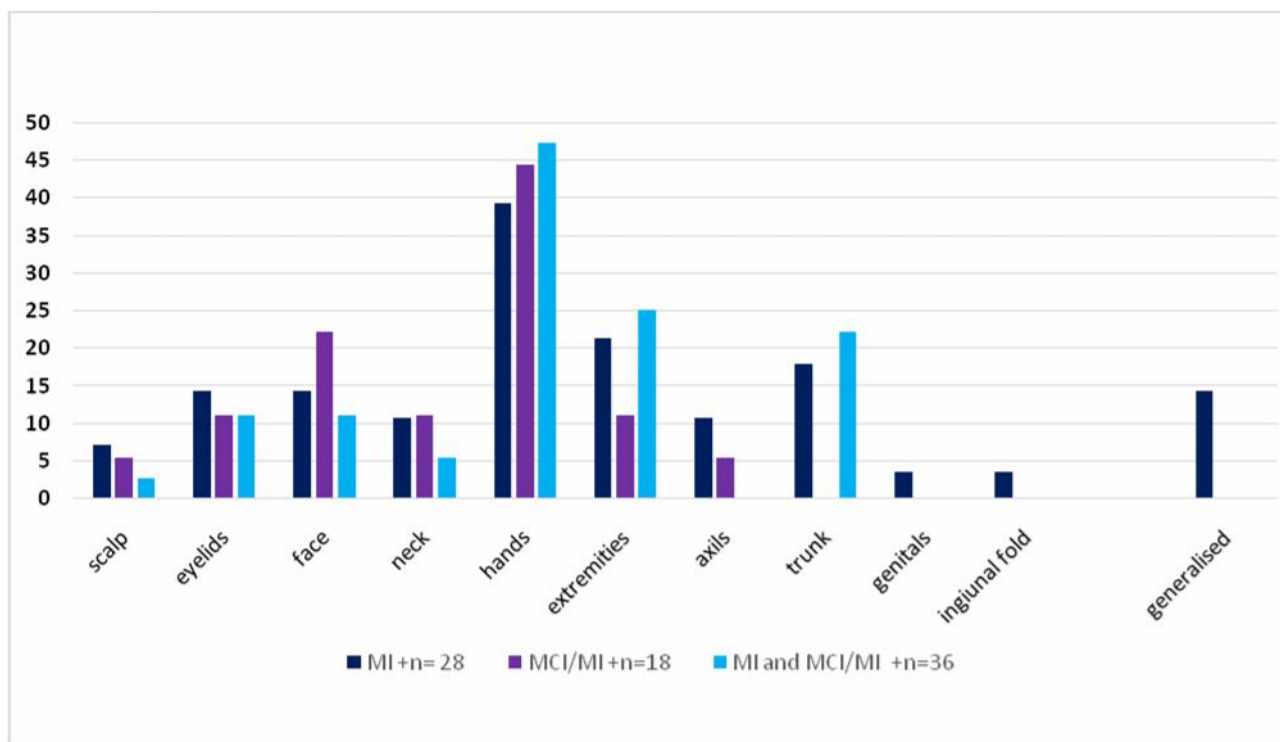
REFERENCES

- de Groot AC, Liem DH, Weyland JW, Kathon CG: cosmetic allergy and patch test sensitization. *Contact Dermatitis*. 1985;12:76-80.
- Frosch PJ, Lahti A, Hannuksela M, et al. Chloromethylisothiazolinone/methylisothiazolinone (CMI/MI) use test with a shampoo on patch-test-positive subjects. Results of multicentre double-blind crossover trial. *Contact Dermatitis*. 1995;32:210-217.
- Jurcsik Á, Temesvári E. Kathon CG kontakt szenzibilizáció vizsgálata (Kathon CG contact sensitivity). *Bőrgyógy Vener Szle*. 1990;66:9-12.
- Zacharie C, Lerbaek A, Mc Namee PM, et al. An evaluation of dose/-unit area and time as key factors influencing the elicitation capacity of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in MCI/MI- allergic patients. *Contact Dermatitis*. 2006;55:160-166.
- Dillarstone A. Cosmetic preservatives. *Contact Dermatitis*. 1997;37:190.
- Lundov MD, Krøngaard T, Menné TL, Johansen JD. Methylisothiazolinone contact allergy: a review. *Br J Dermatol*. 2011;165:1178-1182.
- Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy - a growing epidemic. *Contact Dermatitis*. 2013;69:271-275.
- Puangpet P, Chawarung A, McFadden JP. Methylchloroisothiazolinone/-methylisothiazolinone and methylisothiazolinone allergy. *Dermatitis*. 2015;26:99-102.
- Garcia-Gavin J, Vansina S, Kerre S, et al. Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis*. 2010;63:96-101.
- Lundov MD, Mosbech H, Thyssen JP, Menné T, Zachariae C. Two cases of airborne contact dermatitis caused by methylisothiazolinone in wallpaint. *Contact Dermatitis*. 2011;65:176-179.
- Lundov MD, Thyssen JP, Zachariae C, Johansen JD. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis*. 2010;63:164-167.
- DeKoven JG, Warshaw EM, Zug KA, et al. North American Contact Dermatitis Group patch test results 2015-2016. *Dermatitis*. 2018;29:297-309.
- Urwin R, Warburton K, Carder M, Turner S, Agius R, Wilkinson SM. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: an occupational perspective. *Contact Dermatitis*. 2015;72:381-386.
- Trokoudes D, Banerjee P, Fityan A, et al. Photoaggravated contact dermatitis caused by methylisothiazolinone. *Contact Dermatitis*. 2017;76:303-304.
- Aerts O, van Dyck F, Dandelooy J, et al. Contact dermatitis masquerading as folliculitis decalvans: methylisothiazolinone strikes again! *Dermatitis*. 2014;25:276.
- Uter W, Aberer W, Armario-Hita JC, et al. Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007-2008. *Contact Dermatitis*. 2012;67:9-19.
- Bruze M, Engfeldt M, Gonçalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series-on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis*. 2013;69:263-270.
- Pónyai G, Németh I, Temesvári E. Methylchloroisothiazolinone/-methylisothiazolinone and methylisothiazolinone sensitivity in Hungary. *Dermatol Res Pract*. 2016;2016:4579071.
- The Editors. The methylisothiazolinone epidemic: is the fire out or is Rome still burning? *Contact Dermatitis*. 2014;70:67-68.
- Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new 'epidemic'. *Contact Dermatitis*. 2013;68:253-255.
- Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. *Contact Dermatitis*. 2014;70:246-247.
- Lammintausta K, Aalto-Korte K, Ackerman L, et al. An epidemic of contact allergy to methylisothiazolinone in Finland. *Contact Dermatitis*. 2014;70:184-185.
- Gameiro A, Coutinho I, Ramos L, Gonçalo M. Methylisothiazolinone: second 'epidemic' of isothiazolinone. *Contact Dermatitis*. 2014;70:242-243.
- Aerts O, Baek M, Constandt L, et al. The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: multicentre study. *Contact Dermatitis*. 2014;71:41-48.
- Johnson GA. The rise in prevalence of contact allergy to methylisothiazolinone in British Isles. *Contact Dermatitis*. 2014;70:238-260.
- Warburton KL, Wilkinson M. Contact allergy to methylisothiazolinone: has there been any change? Experience of a UK centre. *Contact Dermatitis*. 2015;72:398-399.
- Schwensen JF, Uter W, Bruze M, et al. The epidemic of methylisothiazolinone: a European prospective study. *Contact Dermatitis*. 2017;76:272-279.
- Gonçalo M, Goossens A. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis*. 2013;68:257-258.
- Stingeni L, Bianchi L, Foti C, et al. An Italian multicentre study on methylchloroisothiazolinone/methylisothiazolinone contact sensitivity: understanding the structure - activity relationship. *Contact Dermatitis*. 2018;78:287-306.
- Ljubojević Hadžavdić S, Uter W, Ilijanić SM, Johansen JD. Methylisothiazolinone contact allergy in Croatia: epidemiology and course of disease following testing. *Contact Dermatitis*. 2018;79:162-167.
- Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis*. 2013;69:231-238.
- Martin-Gorgojo A, Curto-Barredo L, Rovira-López R, Pujol RM, Giménez-Arnau A. Is methylisothiazolinone contact allergy a risk factor for polysensitization? *Contact Dermatitis*. 2015;72:400-402.
- Andersen KE, Mose KF. Preservatives. In: Johansen JD et al., eds. *Quick Guide to Contact Dermatitis*. Berlin, Heidelberg: Springer-Verlag; 2016.
- Pontén A, Bruze M, Engfeldt M, Hauksson I, Isaksson M. Concomitant contact allergens to formaldehyde, methylchloroisothiazolinone/-methylisothiazolinone, methylisothiazolinone, and fragrance mix I and II. *Contact Dermatitis*. 2016;75:285-289.
- Craig S, Urwin R, Latheef F, Wilkinson M. Patch test clinic experience of potential cross-reactivity of isothiazolinones. *Contact Dermatitis*. 2017;76:299-300.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Online supplemental figure 1. Localisation of skin symptoms by patients sensitized to MI and/or MCI/MI

	MI +n=28		MCI/MI +n=18		MI and MCI/MI +n=36	
Male	5	(17,9)	2	(11,1)	7	(19,4)
Occupational dermatitis	2	(7,1)	6	(33,3)	4	(11,1)
Atopic eczema	4	(14,3)	1	(5,6)	3	(8,3)
Hand dermatitis	11	(39,3)	8	(44,4)	17	(47,2)
Leg dermatitis	2	(7,1)	0		1	(2,8)
Facial dermatitis	7	(25,0)	4	(22,2)	6	(16,7)
Age ≥ 40	14	(50)	13	(72,2)	25	(69,4)

Online supplemental table 2. Distribution of MI and/or MCI/MI sensitive patients (+n=82) according to MOAHLFA index (percent of positive reactions)

MI (+n=14)		MCI/MI (+n=13)		MI and MCI/MI (+n=22)	
male (+n=1)	female (+n=13)	male (+n=1)	female (+n=12)	male (+n=5)	female (+n=17)
●FMI, balsam of Peru, propolis, pix, lanolin, budesonide, tixocortol pivalate	●FMI ●Propylene glycol ●Co ●Pix, Ni, PPD, ●Ni ●Ni ●Ni, Co, propylene glycol ●Pix, FM I, thimerosal, Mercuric chloride ammoniated, - Mercuric chloride ●Quaternium 15	●FM I, FM II	●balsam of Peru ●Phenylbutazone ●FM II ●PPD ●Propylene glycol ●FM I, FM II ●FM I, Ni, Mercuric chloride ammoniated, thimerosal ●Pix ●Lanolin, propylene	●FM II ●Pix, thiuram mix ●Mercuric chloride ammoniated, thimerosal ●colophony, Mercuric chloride ammoniated - thimerosal ●FM I, FM II, formaldehyde, budesonide	●Ni, Co ●FM I, Ni, Co, ●Ni ●Pix, Mercuric chloride ammoniated, ●FM I, Ni, epoxy resin ●FM I, formaldehyde, pix, Ni, PPD ●FM I, FM II paraben mix, lanolin, Ni, Co

●FM II, Ni, thiuram mix, pix ●Sesquiterpene lactone mix,Cr,Ni, Co, FM II ●Ni, Mercuric chloride ammoniated ●Ni, iodochlorhydroxyquin	glycol ●balsam of Peru ●Ni ●FM I, Ni	●balsam of Peru, pix, thiuram mix, Ni, Mercuric chloride ammoniated ●MBT, Co ●Propolis ●thimerosal ●FM I, colophony, pix, budesonide, Cr ●Pix, Ni ●balsam of Peru, PPD, IPPD ●Propolis ●FM II ●neomycin sulphate, Ni, Co, Mercuric chloride ammoniated	Online supplemental Table 4. Associated hypersensitivities by each patients sensitised to MI and/or MCI/MI (Ni: nickel sulfate, Co: cobalt chloride, Cr: potassium dichromate, pix:wood tar mix, FMI: fragrance mix I, FMII: fragrance
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mix II, PPD: *p*-phenylenediamine IPPD: isopropylaminodiphenylamine, MBT: 2-mercaptobenzothiazole

Occupation	MI +n =2			MCI/MI +n=6			MI and MCI/MI +n=4			Sources of allergens
	+n	M	F	+n	M	F	+n	M	F	
hair dresser				1		1				shampoos, hair balm, hair dyes
cleaner	1	1		1		1				cleaning products
medic staff				2		2	1		1	liquid soaps, disinfectants
masseur							1		1	creams, body lotions, liquid soaps
mechanic				1		1	1			liquid soaps, hand cleaners
metal-worker	1	1		1	1		1	1		oils, coolants

Online supplemental table 5. Occupational dermatitis by patients sensitised to MI and /or MCI/MI (n=12, M: male, F: female)

