Contact allergy to methylchloroisothiazolinone/methylisothiazolinone in north-eastern Italy: a temporal trend from 1996 to 2016

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Abstract

Background Methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) (Kathon® CG) is a common preservative used in industrial products, owing to its strong biocide effect. Contact allergy to MCI/MI has been reported in different occupations, including mechanics, hairdressers and healthcare workers.

Objective To retrospectively analyse the temporal trend of MCI/MI sensitization in north-eastern Italy and to evaluate the associations with occupations in our geographical area.

Methods From 1996 to 2016, 27 381 patients with suspected allergic contact dermatitis were patch tested in eight departments of Dermatology or Occupational Medicine in north-eastern Italy. Individual characteristics were collected through a standardized questionnaire.

Results The overall prevalence of MCI/MI sensitization was 4.2%, with the highest prevalence found in women and in patients younger than 25 years. MCI/MI sensitization was significantly associated with atopic eczema (OR: 1.34, 95% CI: 1.10–1.70), hand/forearm dermatitis (OR: 1.20, 95% CI: 1.05–1.36) and face dermatitis (OR 1.30, 95% CI: 1.10–1.40). There was a significant association between MCI/MI sensitization and chemical processing workers (OR 1.74, 95% CI: 1.03–2.94), while mechanics and healthcare workers resulted more sensitized to this hapten only in the last 3 years.

Conclusion Sensitization to MCI/MI is rising in the last years in Triveneto region, the 'epidemic' of sensitization to MCI/MI is mainly driven by extra-occupational dermatitis, and sensitization in some occupational groups is emerging only in the last years. A full labelling is compulsory for all products that contain isothiazolinones, to permit to identify the culprit agent.

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Conflicts of interest

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Introduction

Methylchloroisothiazolinone and methylisothiazolinone, both in a 3 : 1 ratio (MCI/MI) and as standalone (MI), have been commonly used as preservatives in household, cosmetics and industrial water-based products since the 1980s, due to their strong bactericide, fungicide and algaecide properties. Their biocide activity also encourages their use in humidifier disinfectant and air conditioning systems.[1]

Following the definite increase in isothiazolinone-associated contact allergy rates in Europe,[2] MCI/MI and MI are forbidden in leave-on cosmetics and allowed in rinse-off cosmetics up to max of 15 ppm. Concerning non-cosmetic products (e.g. paints and glues, but also industrial/chemical products) since 11 March 2016, there is a labelling obligation (CLP regulation) for this type of products that generally contain (MCI/MI) <15 ppm and (MI) <300 ppm, although higher concentrations can sometimes be present. However, legislation regarding concentration limits of industrially used isothiazolinones is still lacking.[3] Hitherto, contact allergy rates across Europe and North America remain high.[4] The recently investigated potential cross-reactivity between isothiazolinones,[5] including MCI/MI, MI, benzisothiazolinone and octylisothiazolinone, and their wide spread of

usage raises concerns. In recent years, besides cosmetics, to which contact allergy might be declining, also non-cosmetic products were often shown to be important sources of MCI/MI and MI, in which, apart from labelling obligations, effective use concentrations are still high.

Occupational contact dermatitis to MCI/MI and MI has been described in different occupations, among which painters, hairdressers, mechanics, machinists, healthcare workers, textile workers and leather workers stand out.[3,6–8]

In the present study, we investigated the prevalence of MCI/MI sensitization in a patch test population in north-eastern Italy, evaluated between 1996 and 2016, in order to analyse the temporal trend of MCI/MI contact dermatitis and its association with occupations.

Patients and methods

Patients

The north-eastern Italian Database has been already described in several publications.[9–12] From 1996 to 2016, 27 381 patients with symptoms and/or signs of suspected allergic dermatitis were patch tested in eight Departments of Dermatology or Occupational Medicine in north-eastern Italy, comprising the North-East Italy Contact Dermatitis Group (NEICDG): Bolzano, Padua (three clinics), Pordenone, Rovigo, Trento and Trieste (Bolzano, Trento and Rovigo participated only from 1998 to 2004). Patients underwent patch testing after receiving a thorough clinical examination and completing a standardized questionnaire.

All patients were assigned to occupational categories, comprised of related job groups (physicians, nurses, physiotherapists and dental assistants were aggregated into the healthcare workers category; hairdressers and barbers were aggregated into hairdressers category; assemblers textile products, assemblers textile machinery, all machine operators fibre/textiles and grinder textile carding machinery were aggregated into textile workers category; mechanics in different sectors, assembler mechanical machinery and metal products, car and truck mechanics, mechanical technicians in various sectors and machine operators of metals when exposed to various oils and cutting fluids were aggregated into mechanics category; machinery workers in chemical industries were defined as chemical processing workers, and all white collar workers were aggregated into clerks category).

Patch tests

All patients were tested with the European baseline series using Finn® Chambers on Scampor® tape (Epitest Ltd, Tuusula, Finland) on aluminium. MCI/MI 0.01% aqueous solution was used (Firma, Firenze, Italy). Substances and clinical protocols did not change over time. Substances were applied on the upper back and removed after 48 h (day 2). The sites were examined upon removal and after 24 h (day 3) or 48 h (day 4), according to ICDRG guidelines.[13]

Statistical analysis

Data analyses were performed using the software STATA™ v.14.0 (Stata Corp., LP, College Station, TX, USA). Categorical data were tabulated in $k \times k$ contingency tables and compared with the chi-square test. The associations between patch test results, occupations and year of patch testing (aggregated in 3-year periods: 1996–1998, 1999–2001, 2002–2004, 2005–2007, 2008–2010, 2011–2013, 2014–2016) were investigated through multivariate logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from the coefficients and the standard errors of logistic regression output. Logistic analysis was performed with correction of results by sex, using white collar workers as a reference group. Trends were analysed using ORs estimated from logistic regression output or Pearson chi-square test, as needed.

Patients with missing data for relevant variables were excluded from analysis.

A P-value of <0.05 was established as the limit of statistical significance.

Results

General characteristics of the population studied are described in Table 1, comparing MCI/MI sensitized with non-sensitized subjects. Sensitization to MCI/MI is lower in man (OR = 0.86; 95% CI: 0.76–0.98) and is associated to hand/forearm dermatitis (OR = 1.20; 95% CI: 1.05–0.1.36) and face dermatitis (OR = 1.30; 95% CI: 1.10–1.40). Occupational dermatitis prevalence is similar in the two groups, and history of atopic eczema is a predisposing factor for MCI/MI sensitization (OR = 1.34; 95% CI: 1.10–1.70).

The overall prevalence of MCI/MI sensitization was 4.2%. Prevalence of MCI/MI sensitization among different age classes is shown in Table 2. The highest prevalence was found in patients younger than 25 years (5.47%, $P < 0.05$), with a

Table 1 Characteristics of patients sensitized and non-sensitized to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (in bold significant results)

	MCI/MI positive *n* (%)	MCI/MI negative *n* (%)	OR	95% CI
Total	1160 (4.2)	26.221 (95.4)		
Men	**340 (29.3)**	**8510 (32.3)**	**0.86**	**0.76–0.98**
Age >40 years	595 (51.3)	565 (48.7)	0.95	0.85–1.10
Atopic eczema	**90 (9.1)**	**1449 (7.0)**	**1.34**	**1.10–1.70**
Occupational dermatitis	91 (7.8)	2008 (7.7)	1.01	0.80–1.30
Hand/forearm dermatitis	**427 (36.8)**	**8085 (30.8)**	**1.20**	**1.05–1.36**
Leg dermatitis	62 (5.3)	1688(6.4)	0.77	0.59–0.99
Face dermatitis	**240 (20.7)**	**4176 (19.9)**	**1.30**	**1.10–1.40**

Table 2 Factors associated to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) sensitization evaluated using the logistic regression

Factors	MCI/MI + (%)	OR	95% CI	*P*
Age (years)				
<25	250 (5.2)	1	–	–
26–35	**232 (3.9)**	**0.75**	**0.63–0.90**	**0.002**
36–45	**217 (4.2)**	**0.81**	**0.67–0.98**	**0.027**
46–55	194 (4.4)	0.85	0.70–1.02	0.091
56–65	**142 (3.9)**	**0.74**	**0.60–0.92**	**0.006**
>65	**125 (3.6)**	**0.60**	**0.55–0.86**	**0.001**
Calendar years				
1996–1998	162 (4.3)	1	–	–
1999–2001	342 (4.4)	1.04	0.85–1.25	0.682
2002–2004	120 (3.2)	**0.74**	**0.58–0.94**	**0.013**
2005–2007	153 (4.4)	1.04	0.83–1.3	0.741
2008–2010	147 (4.2)	0.99	0.79–1.24	0.941
2011–2013	102 (3.8)	0.89	0.69–1.14	0.369
2014–2016	**134 (5.5)**	**1.31**	**1.04–1.66**	**0.023**

Data are reported as OR (odds ratios) and 95% CI (confidence intervals). In bold are reported significant results.

significant decreasing trend in older patients. Looking to calendar years, we observed a reduction in MCI/MI sensitization in 2002–2004 and a significant increase in the last 3 years considered (5.3%: OR = 1.31; 95% CI: 1.04–1.66).

Methylchloroisothiazolinone/MI sensitization among different occupational groups is shown in Table 3: we found a significant increase in sensitization in chemical processing workers (7.2%; OR = 1.8; 95% CI: 1.1–3.1) compared to clerks, but we did not find any increase in sensitization in textile workers, hairdressers, barbers and beauticians, healthcare workers and mechanics. MOHALFA index permits a better evaluation of the characteristics of MCI/MI sensitization in different occupational groups. Mechanics and chemical processing workers are mainly men, while all the other groups are mainly constituted by women. Occupational contact dermatitis was defined for the 37.5% and the 30% of chemical processing workers and mechanics, respectively. Lower percentages were found for the other professional groups. Hand dermatitis was present in more than 50% of mechanics and by the 46.9% of textile workers. Face dermatitis was present in 23.4% of clerks and in lower percentages in other professional groups.

In Fig. 1, we summarize the temporal trend of sensitization between 1996 and 2016 in clerks and in other professional groups analysed. MCI/MI sensitization increased dramatically for chemical processing workers till 18.2%, healthcare workers and mechanics reached a percentage of sensitization of 8.9% and 9.2%, respectively, in the last 3 years, hairdressers sensitization was between 6% and 7% from 2008 to 2016. Textile workers presented a high variability of sensitization in years considered, reaching the 7.1% in the last 3 years considered.

Characteristics of patch test results to MCI/MI are described in Fig. 2. 45.8% experienced a moderate reaction (++) in the final reading, while strong reactions (+++) involved the 20.8% of cases.

Concurrent sensitization between MCI/MI and other haptens is reported in Table 4. Sensitizations associated with MCI/MI positivity were formaldehyde (OR: 7.6; 95% CI: 6.4–9.1) and other preservatives/disinfectants such as Euxyl K 400, quaternium, parabens, thiurams, carbamates; fragrances mix and Balsam of Perù; stabilizers such as ethylenediamine dihydrochloride 1%; and dyes such as disperse yellow 3, blue mix and *p*-phenylenediamine.

Discussion

Sensitization to isothiazolinones is increasing in Europe,[14] despite the limitations to their use in cosmetic, detergents, glues and paints.[3] Industrially used biocides can contain high MCI/MI concentration and no labelling is required.[3] Moreover, isothiazolinones can be present in many different products and more than 90% of paints can contain MI.[15] Gimenez-Amau *et al.*[14] found a significant increase in MCI/MI sensitization in Europe, from 1–4% in 2009 to 3–11% in 2012, with a mean value of

Table 3 Prevalence of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) sensitization in some occupational groups

Profession	Total, *n*	MCI/MI +	%	OR	95% CI	M *n* (%)	O *n* (%)	A *n* (%)	H	L	F	Age > 40 years
Clerks	6933	286	4.1	1.00		83 (29)	3 (1)	49 (17)	100 (35)	11 (3.8)	67 (23.4)	76 (26.6)
Chemical machinery workers	**223**	**16**	**7.2**	**1.8**	**1.1–3.1**	9 (56)	6 (37.5)	2 (12.5)	7 (43.7)	0	3 (18.5)	6 (37.5)
Textile workers	568	32	5.6	1.3	0.88–1.86	9 (28)	9 (28.2)	4 (12.5)	15 (46.9)	1 (3.1)	4 (12.5)	10 (31.2)
Hairdressers, barbers and beauticians	343	17	5.0	1.3	0.77–2.1	1 (7)	3 (21.4)	3 (21.4)	5 (35.7)	1 (7.1)	3 (21.4)	3 (21.4)
Healthcare workers	2747	131	4.8	1.2	0.95–1.5	20 (1.5)	21 (16)	10 (7.6)	58 (44.3)	6 (4.5)	18 (13.7)	52 (39.7)
Mechanics	1245	50	3.9	1.00	0.73–1.40	34 (68)	15 (30)	6 (12)	28 (56)	0	6 (12)	23 (46)

The ORs and 95% CIs were evaluated with multinomial logistic analysis adjusted for age, with clerks as the reference category. Statistically significant results are in bold. A = atopic eczema; F = face dermatitis; H = hand dermatitis; L = leg dermatitis; M = men; O = occupation, Age >40 years old.
CI, confidence interval; OR, odds ratio.

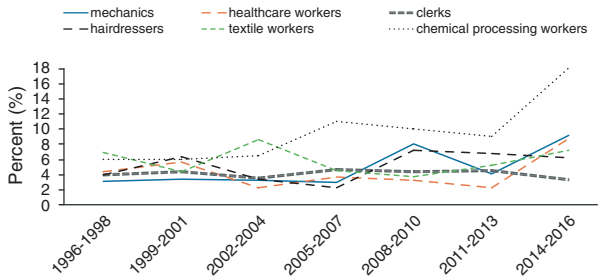

Figure 1 Methylchloroisothiazolinone/methylisothiazolinone sensitization trend in considered years in different professions compared to clerks (%).

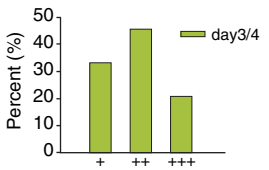

Figure 2 Reactions to patch test obtained for methylchloroisothiazolinone/methylisothiazolinone in day3/4.

Table 4 Concurrent sensitization between methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and other haptens

	MCI/MI + (*n.* 1160)		MCI/MI − (*n.* 26 221)		OR	95% CI
	n	%	*n*	%		
Formaldehyde 1%	183	15.8	628	2.4	7.6	6.4–9.1
Euxyl K400	104	9.0	442	1.7	5.7	4.6–7.2
Quaternium 15 1%	24	2.1	111	0.42	5.0	3.2–7.7
Thiuram mix 1%	67	5.8	382	1.5	4.1	3.2–5.4
Paraben mix 16%	33	2.8	254	0.97	3.0	2.1–4.3
Disperse yellow 3 1%	22	1.9	204	0.8	2.5	1.6–3.8
Fragrance mix 8%	179	15.4	1813	6.9	2.4	2.1–2.9
Balsam of Perù 25%	132	11.4	1502	5.7	2.1	1.7–2.5
Ethylenediamine dihydrochloride 1%	31	2.7	340	1.3	2.1	1.4–3.0
Carba mix 3%	68	6.7	892	3.4	2.0	1.6–2.6
Disperse blue mix 1%	48	4.14	634	2.4	1.7	1.3–2.3
p-phenylenediamine 1%	70	6.0	927	3.5	1.7	1.4–2.2

CI confidence intervals; OR odds ratios; SD, standard deviation.

3.31% when tested at MCI/MI concentration of 0.01% and 4.2% when tested at 0.02%. In another paper by Uter *et al.*,[16] the prevalence of MI sensitization increased from 1.94% in 2009 to 6.02% in 2012, mainly driven by female patients older than 39 years with face dermatitis and regular use of cosmetics. The prevalence of MCI/MI sensitization in North America (tested as 0.01% aqueous solution) increased from 5% in 2011–2012 to 6.3% in 2013–2014.[4]

Substantial differences are reported between countries: in a recent study, Schwensen *et al.*[17] described MI sensitization in eight different nations; Italy had the lowest prevalence of MI sensitization (2.6%), while Finland had the highest (13%). This difference was mainly attributable to occupational contact dermatitis.

The objective of our study was to thoroughly evaluate MCI/MI prevalence in north-eastern Italy in the time period between 1996 and 2016. The overall MCI/MI sensitization prevalence we found was 4.2%; Pesonen *et al.*[7] reported a similar frequency in a large retrospective study on data collected from 11 European countries in 2015. Hadzavdic *et al.*[18] reported a sensitization prevalence of 6.4% in the same period in Croatia and found these preservatives to be present in many patients' cosmetic products. In our study, MCI/MI sensitization increased significantly only in the last 3 years (2014–2016), reaching 5.5% (OR: 1.31; 95% CI: 1.04–1.66), while it remained quite stable in previous years. Italy was previously characterized by a higher sensitization to MCI/MI compared to other countries,[16] with 4.2% in 2007–2008 (tested as 0.01 ppm in aqueous); an increasing in this sensitization was reported to be mainly related to occupation.[19,20]

In our study, sensitization to MCI/MI was significantly related to female sex, as already described in previous studies, as cosmetics can be considered the main inducing agents.[16] We demonstrated and increased risk for young people (<25 years old) and a decreasing trend for older subjects. This result can be explained by young subject's increased exposition risk to products containing isothiazolinones, not only cosmetics.[21] This aspect was also reported by Uter *et al.* in 2012,[16] with an increased trend for occupational dermatitis in workers below 40 years. In 2013, the Scientific Committee on Consumer Safety advised a ban on MI in cosmetics.[22] From April 2016 onwards, MCI/MI was forbidden in leave-on cosmetics and MI was banned from 1 January 2017[3] Since April 2018, MCI/MI and MI are allowed in rinse-off cosmetics up to a max of 15 ppm.[23] However, the most important source of MCI/MI exposure is dishwashing liquid, laundry detergents, shampoos, wet wipes [4] or water-based paints, varnishes, glues, printing inks and toner, and metal-work fluids.[3]

As in other studies,[4,16,17] the most frequently involved sites were hands/forearms and face, because of direct occupational and non-occupational contact (i.e. cosmetics, household products).

The role of MCI/MI as an occupational hapten has been reported by many authors [7,19,20] as MCI/MI can be present as preservative in many products.[3,4,17,20] In our study, we find a significant increased risk of MCI/MI sensitization in chemical processing workers (7.2%; OR: 1.8%, 95% CI: 1.1–3.1), as previously described by Pesonen *et al.*[7] As previously discussed,

these workers were exposed to many chemical agents that can contain isothiazolinones.[18] However, we failed to find a significantly increased sensitization prevalence among other professional groups, such as textile workers, hairdressers, healthcare workers and mechanics. Through an occupation-stratified sensitization trend analysis, we observed that MCI/MI sensitization is increased in all these occupational groups reaching values over 6% in more recent years: healthcare workers and mechanics reached 8.7% and 9.2% of sensitization, respectively, in the last 3 years considered. Healthcare workers can be exposed to ultrasound gel, wet wipes, liquid soap and personal care products.[3,18,24] Mechanics can be exposed to oils and cooling fluids that can contain isothiazolinones as preservatives[3,18] as well as industrial detergents.[4] Thus, it seems that in Triveneto region, the 'epidemic' of sensitization to MCI/MI is mainly driven by extra-occupational dermatitis and sensitization in some occupational group is emerging in the last years.

While for clerks, MCI/MI sensitization in years was stable and around 4%; for some professional groups, the sensitization was increasing. To note that, a diagnosis of occupational dermatitis was defined for the 37.5% of chemical processing workers and for 30% of mechanics, while the percentages were lower for the other professional groups: these rates can be influenced by the fact that MCI/MI sensitization is believed to be an hapten related to cosmetics, while it must be considered and occupational hapten, at least in some occupational groups with exposure to products that can contain isothiazolinones.

Moreover, the percentage of sensitization to this hapten is very high and is one of the most sensitizing agents in Italy, after nickel, cobalt and perfumes.

Through an analysis of concurrent sensitizations, we showed an association between MCI/MI sensitization and other preservatives sensitizations, such as formaldehyde, Euxyl K400, quaternium, thiurams and parabens. The other strong association we found was with fragrances and Balsam of Perù, suggesting that multiple sensitizations to haptens contained in similar products are common. Similar concurrent sensitizations were reported by Schwensen *et al.*,[17] Marrtin-Gorgojo *et al.*[25] and Ponten *et al.*[24] MCI/MI are not chemically related to formaldehyde[26] and there are no data available on cross-reactivity between any fragrance and preservatives; moreover, our study confirms the results obtained by Pontén *et al.*,[24] since the concurrent sensitizations are related to the presence of both haptens in the same products.

Our study has several limitations. Our large sample size derives from patients attending health services for suspected allergic dermatitis; consequently, our results may be affected by selection bias. Our decision to assign patients to occupational categories, to improve the statistical power of our analysis, has probably led to some loss of data. Moreover, the multicentre design of our study may have affected the consistency of our data, though every centre used the same standardized questionnaire. Another limitation is that we have no extensive data on MI sensitization alone that is considered the culprit of the increase in MCI/MI sensitization found in recent years.[27] MI patch test should have permitted to find more patients sensitized to this hapten. However, the aim of our work was to see a long-term trend of sensitization and comprehensive data are available on long term only with MCI/MI.

Another limitation is that we tested MCI/MI at 0.01% for all the period and we did not report data on concentration at 0.02% because the long trend of sensitization was available only for the lower concentration. However, our aim was to verify the trend of sensitization during more than 20 years and this was possible only analysing patch test at 0.01%.

Conclusion

Our study evaluates MCI/MI sensitization and its relationship with occupational groups in north-eastern Italy in a long-time frame and shows an increased trend in the last years, suggesting the need to act from the regulatory point of view to reduce isothiazolinones content in products. Since April 2018, MI is lowered in rinse-off cosmetics to 15 ppm, so we will expect a decreasing of this sensitization in future years. However, they are still used in many household and industrial products, often at higher concentration, and sometime still without an appropriate labelling.[25] To permit the identification of causal product and to prevent the rise of MCI/MI and MI sensitizations, it is compulsory not only to have a complete labelling requirement but also to limit their presence in common household products.

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