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Methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone contact allergy: A 24-year, single-center, retrospective cohort study from Turkey

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Abstract

Background: Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and MI allergy caused a global epidemic during the period 2010 to 2015, reaching its peak in 2013/14.

Objective: To investigate the characteristics of MCI/MI and MI allergy in Turkey over 24 years.

Methods: A total of 2310 patients patch tested between 1996 and 2019 with MCI/MI 0.01% aq. or MCI/MI 0.02% aq., with or without MI 0.2% aq., were analyzed.

Results: The overall prevalence of contact sensitization was 3.3% (n = 77) with a peak level of (16.4%) in 2015. The prevalence gradually decreased thereafter, but was still high (6.5%) in 2019. Seventy-three patients had clinically relevant sensitizations. MI could detect clinically relevant sensitizations in all seven patients with a negative patch test reaction to MCI/MI 0.02%. Non-occupational allergic contact dermatitis (ACD) was most frequently seen, mainly in women, with hand/face eczema from rinse-off or leave-on cosmetics, such as wet wipes. Occupational ACD was mainly seen among men with airborne eczema from wall paints in house painters, or with hand eczema from hair gel/wax in men's barbers.

Conclusions: The prevalence of MCI/MI and MI sensitization in Turkey following the peak in 2015 is still high. This is probably due to the currently allowed level of 100 ppm for MI in rinse-off cosmetics. This needs to be urgently reduced.

KEYWORDS

allergic contact dermatitis, cosmetics, epidemiology, methylchloroisothiazolinone, methylisothiazolinone, non-occupational, occupational, paint, patch test, prevalence

1 | INTRODUCTION

The mixture of methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) in a 3:1 ratio (Kathon CG) and MI alone are isothiazolinone preservatives that are mainly used in cosmetics, household and personal care products, or 'slime', ie, a novel hobby material, as well as occupational products such as water-based paints, glues, metalworking fluids, and ultrasound gel, for their bactericidal, fungicidal and algicidal

properties.¹⁻⁴ Following the first epidemic of allergic contact dermatitis (ACD) in the 1980s⁵ due to MCI/MI mainly in leave-on cosmetics, the allowed concentration of MCI/MI in cosmetics was reduced from 30 to 15 ppm in 1990.⁶ A novel global epidemic due to MCI/MI and MI occurred during the period 2010 to 2015, reaching its peak in 2013/14, mainly in Europe,⁷⁻¹² the USA,¹³ Canada,¹⁴ Australia,¹⁵ and Asia.¹⁶ During the novel epidemic, the permitted concentration in leave-on and rinse-off cosmetics in European countries was 15 ppm for MCI/MI and

100 ppm for MI.^{17,18} Using MI alone and in higher concentrations in leave-on and rinse-off cosmetics from 2005, was regarded as the main cause of the epidemic.^{1,10,19}

In 2013, MI was named “allergen of the year” by the American Contact Dermatitis Society,²⁰ and it was added to the European baseline series.²¹ Consequently, the use of MCI/MI and MI in leave-on cosmetics was prohibited in Europe in 2016 and 2017, respectively,^{22,23} and in 2018 the concentration of MI in rinse-off cosmetics was reduced by the European Commission to the same level as MCI/MI, ie, 15 ppm.²⁴ The introduction of similar legislative measures around the world led to an observable decrease in the incidence of non-occupational ACD due to isothiazolinones, mainly from cosmetic products,^{12,16,25,26} while an increase in occupational ACD was observed in some countries after the epidemic due to the lack of legal restrictions of the use of isothiazolinones in industrial products.²⁶

There are only limited data on ACD from MCI/MI and MI in Turkey,^{27,28} where MCI/MI and MI up to 15 ppm and 100 ppm, respectively, are currently allowed only in rinse-off cosmetics.^{29,30} We aimed to investigate the rate of sensitization to MCI/MI and MI, and the characteristics of occupational and non-occupational ACD from these allergens, in a relatively large group of patients in Turkey over a 24-year period.

2 | METHODS

This was a single-center, retrospective cohort study based on the analysis of the files of patients who were consecutively patch tested with a baseline series, including MCI/MI with or without MI, in our allergy unit for clinically suspected ACD between June 1996 and December 2019. A total of 2310 patients were enrolled in the study comprising 1779 patients who were patch tested with MCI/MI 0.01% aq. between 1996 and 2014, and 531 patients who were patch tested with 0.02% aq. between 2015 and 2019. Between 2016 and 2019, 446 patients were additionally patch tested with MI 0.2% aq. Patch testing was performed after verbal or written consent of the patients, or legal guardians in the case of children, was obtained. Patients were asked not to take antihistamines, nonsteroidal anti-inflammatory drugs, or immunosuppressive agents, and not to use topical or systemic corticosteroids for at least 1 month before and during patch testing. Pregnant or lactating women were not tested. Test allergens were supplied by Chemotechnique Diagnostics (Vellinge, Sweden) and Brial Allergen (Greven, Germany), and in the earlier period by Hal-Brial (Leiden, The Netherlands). The allergens were applied in IQ Chambers (Chemotechnique Diagnostics) to the upper back for 48 hours. Patch tests were occluded with Hypafix tape (BSN Medical, Hamburg, Germany). Test sites were evaluated at day (D) 2, D3, and D4 in patients who were patch tested between 1996 and 2009 ($n = 1338$), and additionally at D7 in 972 patients who were patch tested in 2010 and later, according to the ESCD patch test guideline.³¹ All patients were additionally tested with supplemental series, ie, a cosmetic series including preservatives and emulsifiers ($n = 50$), fragrance series ($n = 7$), rubber series ($n = 10$), metalworker series ($n = 5$), hairdresser series ($n = 4$), and with their own material ($n = 15$). Patients' own materials, such as

leave-on cosmetics (wet wipes, hair gel, ultrasound gel, moisturizing cream), were patch tested “as is”. Rinse-off cosmetics, household products, and industrial products, such as paints, were not tested to avoid irritant patch test reactions. Metalworking fluids were patch tested in serial dilutions (cutting/cooling fluids as clean and used samples up to 5% aq. and 8% aq., respectively). Patients' files were evaluated with regard to demographic features (gender, age, atopy), patch test findings (concomitant or isolated positive reactions to MCI/MI and MI, the strength of reaction, late positive reactions), the clinical/occupational relevance, and characteristics of patients with non-occupational and occupational ACD. The temporal changes in these findings over the years were analyzed, and the male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, age >40, and at least one positive patch test reaction to baseline series (MOAHLFAP) Index³² was calculated. The clinical/occupational relevance was determined according to history, clinical findings, Mathias criteria³³ (for occupational relevance), additional patch testing with suspected products, if appropriate, and reading of the product labels or material safety data sheets, if available.

Data were stored and assessed using SPSS statistics, version 22 (IBM, Armonk, New York). The chi-square or Fisher's exact test were used for comparisons. A two-tailed P -value < .05 was regarded as a statistically significant difference. This study was approved by the ethics committee of Istanbul University, Istanbul Faculty of Medicine (approval number: 2019/651) and conducted in accordance with the Declaration of Helsinki.

3 | RESULTS

A total of 77 patients (3.3%) showed positive patch test reactions to MCI/MI and/or MI (Table 1). The share of sensitization to MCI/

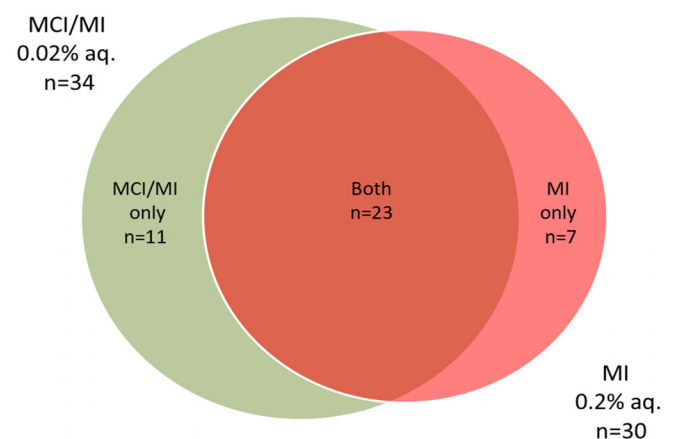


FIGURE 1 Venn diagram showing the distribution of isolated and concomitant positive patch test reactions to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) 0.02% aq. and MI 0.2% aq. in patients who were simultaneously tested with these allergens in 2016 and later

TABLE 1 Characteristics of patients with positive patch test reactions to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and MI

Patient characteristics	Patients allergic to MCI/MI and/or MI (n = 77)
Gender, male/female, n (ratio)	36/41 (1:1.1)
Age (years), range (median)	9–72 (37)
Atopy, n	
None	41
Unknown	13
Allergic rhinoconjunctivitis	18
Atopic skin diathesis	4
Atopic dermatitis	1
Overall prevalence of sensitization to MCI/MI and/or MI % (n)	3.3% (77/2310)
Positive patch test reaction to, n	
MCI/MI	69
MI	30
From 2016 onwards when MCI/MI 0.02% aq. and MI 0.2% aq. were simultaneously tested	
MCI/MI only	11
MI only	7
Both	23
Degree of positive patch test reaction to MCI/MI, n	
+	38
++	28
+++	3
Degree of positive patch test reaction to MI, n	
+	15
++	14
+++	1
Late positive patch test reaction to MCI/MI on day 7, n	2
Additional positive patch test reactions (most frequent), n	
Nickel/other metals	18
Thiuram/carbamate/other rubber	12
Formaldehyde/formaldehyde releasers	12
Thimerosal	8
Fragrance mix/fragrance mix II/Myroxylon pereirae/other fragrances	5
Methyldibromo glutaronitrile	3
Benzisothiazolinone	1
Clinical relevance, n	
Current	73
Unknown	4
Demographic features of patients with confirmed clinical relevance (n = 73)	
Gender, male/female	33/40
Age, range (median), years	9–72 (35)
Duration of disease, range (median), months	1–431 (24)
Patients <18 years, n (%)	8 (10.4)
Non-occupational relevance, n, patients' outcome ^a	58 (+ 1) ^b
Relevant topical non-occupational contact material	
Cosmetics and personal careproducts: rinse-off products, ie, liquid soap/shampoo/bath gel	45
Leave-on products, ie, wet cleaning wipes	4
Moisturizing hand/face cream	2
Household products: floor, washing machine, and dishwasher detergents	7
Domestic products/imported products (mainly from Europe or United States) ratio	2:1
Occupational relevance, n, patients' outcome ^c	14 (+ 1) ^b
Relevant occupational contact material	
Water-based wall paint in house painters	5
Hair gel/wax in men's barbers	4
Shampoos and hair cosmetics in women's hairdressers	2
Metalworking fluids in a metalworker	1
Ultrasound gel in a perinatologist	1

(Continues)

TABLE 1 (Continued)

Patient characteristics	Patients allergic to MCI/MI and/or MI (n = 77)
Dishwasher detergent in a restaurant dishwasher	1
Surface cleaner and rust remover in a tramline ^b worker ³⁴	1
Localization of allergic contact dermatitis (n = 73)	
Hands total	66
Hands only	54
Hands/face/other	12
Face/periorbital only	5
Trunk/extremities	2
Specific pattern (n = 7)	
Generalized	1
Airborne	6
MOAHLFAP index (%)	46.8-19.5-6.5-85.7-0-22.1-45.5-100

Abbreviations: MOAHLFAP, Male-occupational dermatitis-atopic dermatitis-hand eczema-leg eczema-face eczema-age ≥ 40 years-at least one positive patch test reaction to baseline series.

^aEczema improved in 16 patients following avoidance of contact to MCI/MI and MI-containing products. A long-term follow-up was missing.

^bOne tramline worker had both occupational and non-occupational ACD from surface cleaner and rust remover at work, and from detergents/shampoo/liquid soap/moisturizing cream/water-based wall paint at home³⁴.

^cEczema improved in two house painters, one barber, the tramline worker, and the perinatologist following avoidance of contact to MCI/MI and MI-containing products and/or quitting their job.

TABLE 2 Temporal changes in characteristic features of patients with positive patch test reactions to methylchloroisothiazolinone (MCI) / methylisothiazolinone (MI) and MI over years

Patient characteristics	Temporal changes
Demographic features	The total number of patients between 1996 and 2013 (n = 19) increased to threefold (n = 58) between 2014 and 2019 including the peak in 2015 without a significant impact of gender and age.
Range of contact sensitization rate to MCI/MI or MI %	
1996-2007	0-1.2
2008-2014	2.1-6.2
2015 (peak level)	16.4
2016-2019 (gradual decrease)	10-6.5
Non-occupational ACD	The number of patients increased to 3.1-fold since 2014 with a prominent increase in the number of male patients (to 5.7-fold) vs female patients (to 2.5-fold). The difference was statistically not significant.
Occupational ACD	The number of patients increased to 2.8-fold since 2014, exclusively consisting of male patients. Occupational ACD in house painters were exclusively diagnosed during and after 2014. Most of the hairdressers/barbers (66.7%) were diagnosed before 2014. No new cases of occupational ACD from hair gel were seen since 2016.

Abbreviation: ACD, allergic contact dermatitis.

[Correction added on 18 September 2020, after first online publication: Tables 1 and 2 data have been corrected in this current version.]

MI and MI was (2.9%) (69/2310) and 6.7% (30/446), respectively. A Venn diagram shows isolated and concomitant positive patch test reactions between 2016 and 2019, when MCI/MI (0.02% aq.) and MI were simultaneously tested (Figure 1). The characteristic features of the patients are shown in Table 1. There was no statistically significant difference between MI and MCI/MI sensitization regarding gender, age, and clinical features, including localization of dermatitis and occupational/non-occupational nature of eczema.

The temporal changes in the rate of contact sensitization to MCI/MI and MI are shown in Tables 2 and 3, and Figure 2. An upward trend started in 2012, and the share of positive reactions increased to

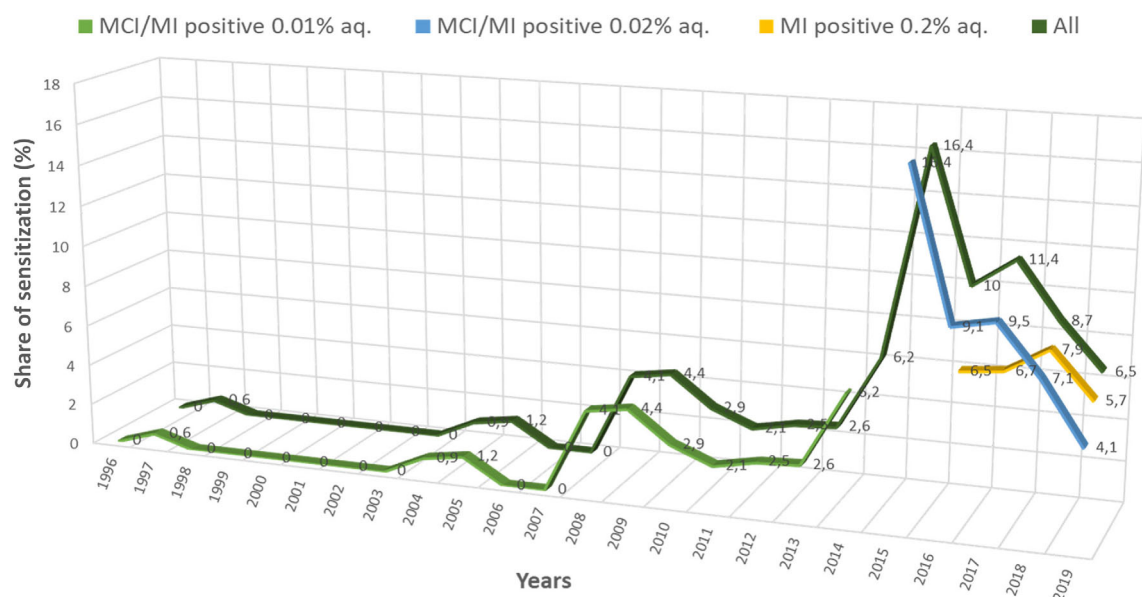
more than twofold from 2013 to 2014, when the test concentration of MCI/MI was still 0.01% aq. Then, there was a peak in reactions of 16.4% in 2015, corresponding to the year the test concentration of MCI/MI was changed from 0.01% aq. to 0.02% aq. in our patch test battery.

Among 73 patients with confirmed clinical relevance, 58 had non-occupational and 14 occupational ACD only, whereas one patient had both non-occupational and occupational ACD (Table 1). A total of 59 (80.8%) patients had non-occupational ACD, mainly from rinse-off cosmetics and personal care products (Table 1). Non-occupational ACD was significantly more frequent among female patients (chi-

TABLE 3 Share of contact sensitization to methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) and/or MI between 1996 and 2019

Year	Positivity to MCI/MI 0.01% aq. (positive reaction/tested patients) % (n)	Positivity to MCI/MI 0.02% aq. (positive reaction/tested patients)	Positivity to MI 0.2% aq. (positive reaction/tested patients)	Positivity to MCI/MI or MI (positive reaction/tested patients)
1996	0 (0/144)	NT	NT	0
1997	0.6 (1/163)	NT	NT	0.6 (1/163)
1998	0 (0/122)	NT	NT	0
1999	0 (0/123)	NT	NT	0
2000	0 (0/80)	NT	NT	0
2001	0 (0/35)	NT	NT	0
2002	0 (0/27)	NT	NT	0
2003	0 (0/103)	NT	NT	0
2004	0.9 (1/106)	NT	NT	0.9 (1/106)
2005	1.2 (1/81)	NT	NT	1.2 (1/81)
2006	0 (0/92)	NT	NT	0
2007	0 (0/95)	NT	NT	0
2008	4.1 (5/122)	NT	NT	4.1 (5/122)
2009	4.4 (2/45)	NT	NT	4.4 (2/45)
2010	2.9 (2/69)	NT	NT	2.9 (2/69)
2011	2.1 (2/94)	NT	NT	2.1 (2/94)
2012	2.5 (2/81)	NT	NT	2.5 (2/81)
2013	2.6 (3/116)	NT	NT	2.6 (3/116)
2014	6.2 (5/81)	NT	NT	6.2 (5/81)
2015	NT	16.4 (11/67)	NT	16.4 (11/67)
2016	NT	9.1 (10/110)	6.5 (6/92)	10 (11/110)
2017	NT	9.5 (10/105)	6.7 (7/105)	11.4 (12/105)
2018	NT	7.1 (9/126)	7.9 (10/126)	8.7 (11/126)
2019	NT	4.1 (5/123)	5.7 (7/123)	6.5 (8/123)

Abbreviation: NT, not tested. The bold type highlights the peak year of MCI/MI allergy in our series.

**FIGURE 2** Share of contact sensitization to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) 0.01% aq., 0.02% aq., and MI 0.2% aq. according to the years between 1996 and 2019

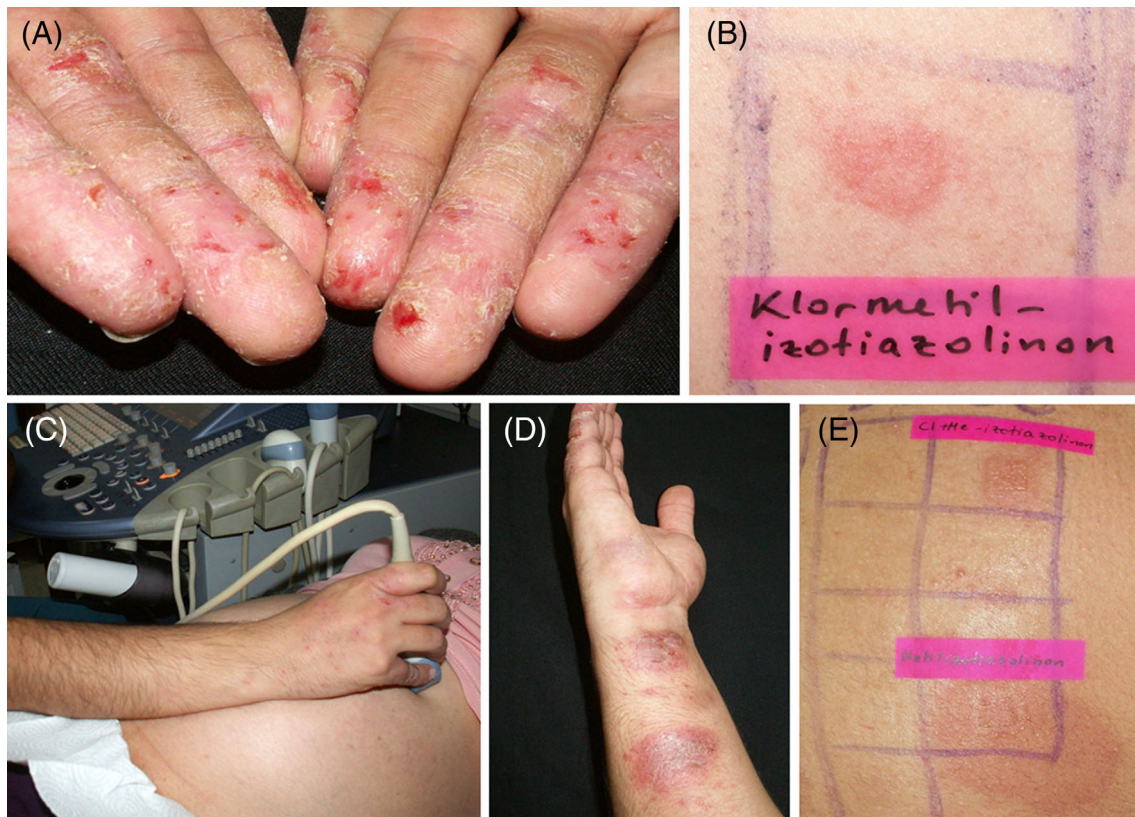


FIGURE 3 (A) Occupational allergic contact dermatitis (ACD) on the hands of a men's barber from methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in a hair gel, (B) ++ positive patch test reaction to MCI/MI (0.01% aq.) on day 3, (C,D) occupational ACD in a perinatologist from ultrasound gel containing MCI/MI, (E), ++ positive patch test reaction to MCI/MI (0.02% aq.) and MI (0.2% aq.) on day 2

square test, $P < .001$; odds ratio: 12.3, 95% confidence interval (CI): 2.53–58.8). The lesions were most frequently localized on the hands followed by the face (Table 1). One male patient had airborne ACD from isothiazolinones in water-based wall paint and from detergents at home, as recently reported.³⁴ Pediatric patients (<18 years) had almost exclusively non-occupational ACD due to rinse-off cosmetics and personal care products. Wet wipes were the eliciting agent in only one child. Slime was not an eliciting agent in any of the children.

A total of 15 (20.5%) patients had occupational ACD, which was significantly more frequent among male patients (chi-square test, $P < .001$; odds ratio: 12.3; 95% CI: 2.53–58.8). Water-based wall paint in house painters was the leading cause ($n = 5$), followed by hair gel/wax as leave-on hair cosmetics in men's barbers ($n = 4$) (Figure 3A,B), and other causes (Figure 3C–E) (Table 1). The lesions were mainly located on hands. Additional airborne eczema on the face/periorbital region was exclusively seen in house painters and a recently reported tramline worker³⁴ (Table 1). Three of 15 patients (20%) with occupational ACD reacted to MI only, all of them being house painters. The temporal changes in non-occupational and occupational ACD are shown in Table 2.

4 | DISCUSSION

Presenting the largest dataset on patch test results with MCI/MI and MI from Turkey, this study highlights some similarities and differences from previous reports on this topic. First of all, many studies on MCI/MI sensitization reported a clear female preponderance^{10,12,16,26,35–37} and a high percentage of patients aged over 40 years.^{26,35,38} The present study, however, shows an almost equal sensitization share in male patients. Further, sensitization was more frequent among those who were <40 years old. Similar findings regarding gender and age were reported in a previous study from Turkey.²⁷ Interestingly, patients < 25 years of age predominated in a multicentre study from Italy.³⁶ A considerable percentage (10.4%) of our patients in the present study were pediatric patients who were <18 years old. Although contact sensitization to MCI/MI and MI is usually less frequent among pediatric patients,^{39,40} recent reports showed high sensitization prevalences up to 11% among children who underwent patch testing.⁴¹ Atopic dermatitis was suggested as a risk factor for MCI/MI sensitization,^{36,38} however, the number of patients with atopic dermatitis or atopic skin diathesis was relatively low in our study.

Eighty percent of the patients in our series had non-occupational ACD that was significantly more frequent among female patients, and

was mainly due to rinse-off and personal care products, and less from leave-on products such as wet wipes and hand creams. This was interesting, as MCI/MI and MI were still present in leave-on products in Turkey until 2015 and 2017, respectively.^{29,30} Leave-on cosmetics such as wet wipes were once among the main sensitizers for MCI/MI and MI-induced non-occupational ACD,^{13,19,37} but these products no longer contain isothiazolinones in most countries,⁴² and lately in Turkey as well. Hands were predominantly affected followed by the face/periorbital area in patients with non-occupational ACD. Similar findings were reported in previous studies during the worldwide epidemic that was significantly associated with non-occupational ACD in women, mainly from leave-on/rinse-off cosmetics, presenting with facial-and/or hand eczema.^{2,12,37,43,44}

Only 20% of our patients had occupational ACD, which was significantly more frequent among male patients presenting with hand/airborne eczema. House painters and men's barbers were the most frequent occupations. Following the first reports on MI-induced occupational ACD from paints and glues in the early- and mid-2000s,^{45,46} MI continued to be an important occupational allergen, especially for painters^{12,44,47-49} as it is a preferred preservative for paints.^{50,51} The painters in the present study were predominantly sensitized with MI. MI and MCI/MI are both well-known causes of airborne eczema from wall paint as they are volatile allergens, and paint-related ACD presented with airborne eczema in all the painters in our series. Apart from painters, MI and MCI/MI were reported to frequently cause occupational ACD in metalworkers, machinists, and welders due to coolants/cutting fluids,^{12,52-54} and in hairdressers/beauticians, healthcare workers, and cleaners, mainly due to rinse-off cosmetics and industrial hand cleansers.^{48,49,52-54} Leave-on hair styling products were another important source of ACD in hairdressers.⁵³ In our series, hair gel/wax was the exclusive cause of occupational ACD in men's barbers. A recent study from Turkey reported a higher percentage of occupational cases (48.8%) mainly consisting of painters and metalworkers, probably due to the close proximity of the testing clinic to industrial areas or to individuals from poor workplace conditions.²⁷ Ultrasound gel as a leave-on non-cosmetic product is another important source of occupational ACD for gynaecologists/perinatologists as it may contain MCI/MI or MI.⁵⁵

The overall prevalence of sensitization to MCI/MI or MI between 1996 and 2019 was 3.3% in our series of 2310 patients from Turkey. Late positive patch test reactions, as previously reported,³⁷ were observed in two patients (2.6%). The number of patients who would be missed if MI 0.2% aq. had not been tested concomitantly was low in our series (9%) and in the recent study from Turkey (8%).²⁷ Previous studies from Europe and the USA reported that up to 51% of patients (32.7%–51%) reacted only to MI and not to MCI/MI. However, this was probably due to the fact that MCI/MI was tested at 0.01% aq. in most of these studies.^{13,47,48} In 2014, MCI/MI was recommended to be tested at 0.02% aq. to avoid false-negative patch test reactions at 0.01% aq.⁵⁶ The low sensitization prevalence of $\leq 1\%$ to MCI/MI in previous reports from Turkey might have resulted from testing this allergen at 0.01% aq. before 2006.^{28,57-59} Since MCI/MI 0.02% aq. and MI 0.2% aq. are

complementary to each other, it is necessary to continue testing with both allergens.

Concomitant patch test reactions were most frequently seen with nickel and other metals, rubber allergens, and formaldehyde/formaldehyde releasers in our study. Nickel,³⁵ fragrances,^{35,36,44,60} and preservatives such as formaldehyde^{36,38,44,60,61} were reported as the main co-allergens, the latter two often coexisting in the same product together with isothiazolinones. Interestingly, fragrance allergens were positive only in a minority of patients in our study. Cross-elicitation might be expected with other isothiazolinones, such as benzisothiazolinone or octylisothiazolinone, mainly from concomitant exposure or cross-reaction.¹²

The legal regulations for cosmetics in Turkey follow the European regulations. During the epidemic in Europe, the allowed concentrations of MCI/MI and MI in all cosmetics in Turkey were the same as in Europe.^{62,63} Our study showed that the rate of sensitization to MCI/MI ranged between 0% and 1.2% until 2008, similar to the pre-epidemic levels in Europe. Then, showing fluctuations between 2008 and 2013, a definite increase (6.2%) was observed in 2014, reaching a peak level of 16.4% in 2015, when the test concentration of MCI/MI was changed from 0.01% aq. to 0.02% aq. in our patch test battery. However, the peak could not be solely attributed to the increase of the test concentration of MCI/MI as a rising trend had already started before 2015.

In 2013–2014, the prevalence of MI or MCI/MI sensitization reached a peak in different European and non-European countries ranging between 2.6% in Italy and 13% in Finland.^{12,13,36,44,64} Higher levels were reached in Spain (18.9%) in 2015.³⁵ The highest prevalence was observed in Australia (20.3%),¹⁵ followed by other non-European countries such as Thailand (18.5%),¹⁶ and Canada (15.3%)¹⁴ in 2015.

Shortly after the epidemic, the Scientific Committee on Consumer Safety of the European Commission (SCCS) advised banning the use of MCI/MI and MI in leave-on cosmetics, as well as reducing the level of MI to a maximum of 15 ppm in rinse-off cosmetics.⁶⁵ The prevalence of contact allergy to MCI/MI or MI definitely decreased in many European countries due to regulatory interventions starting from 2015,²⁶ although the recommended restrictions became effective from 2016–2018 in Europe.²²⁻²⁴ A declining prevalence of contact sensitization to MCI/MI and MI was first reported from the UK in 2015,²⁵ and reached the pre-epidemic level in Spain in 2019.³⁵ Similar legislative measures led to the decrease in the prevalence of MI and MCI/MI allergy in Australia¹⁵ and Thailand.¹⁶ A recent study showed decreasing concentrations of N-methylmalonic acid, a common metabolite of MI and MCI, in the urine samples of the participants following the legal restrictions.⁶⁶ A decreasing tendency in the prevalence of MCI/MI and MI sensitization was obvious in the present study from Turkey as well; however, the prevalence was still high in 2019. A previous study from Turkey on 29 patients with MCI/MI and/or MI sensitization showed similar slow decreasing prevalences of sensitization (from 10.2% to 6.7%) between 2016 and 2018.²⁷ This study was probably conducted shortly after the epidemic, in the “decreasing period” of the prevalence.²⁷

The slow decrease in sensitization prevalence is probably due to the high allowed level of MI (100 ppm) in rinse-off cosmetics³⁰ in Turkey, as most of the patients' rinse-off cosmetics and personal care items were domestic products.

In contrast to the decrease of ACD from MCI/MI- or MI-related cosmetic products following the cosmetic regulations, an increase was reported in occupational ACD from non-cosmetic occupational products in some European countries,²⁶ probably due to the lack of adequate restrictions of their use and concentration in industrial products. A distinction has been made between a "cosmetic dermatitis pattern" during the epidemic and an "occupational dermatitis pattern" in the pre- and post-epidemic period.²⁶ The "cosmetic dermatitis pattern" during the epidemic was related predominantly to face eczema in female patients from cosmetics, whereas the "occupational dermatitis pattern" in the post-epidemic period was characterized by hand eczema in male patients from industrial products. The particularly affected occupations during the epidemic changed in the post-epidemic period. Sensitizations in house painters continued to increase whereas it decreased in hairdressers and cosmeticians,²⁶ which was in line with our findings. Occupational ACD in painters was diagnosed exclusively during and after the peak in our series. No new cases of occupational ACD from hair gel nor non-occupational ACD from leave-on cosmetics were diagnosed in the present study since 2016 and 2017, respectively. These findings were in temporal accordance with the time of the ban of MCI/MI and MI in leave-on products in our country.^{29,30}

Nearly one-third ($n = 21$; 28.8%) of the patients with occupational or non-occupational ACD in our series were free of lesions following avoidance of contact with MCI/MI or MI-containing products. However, a long-term follow-up was missing, and relapses might be expected due to new exposure to isothiazolinone-containing rinse-off cosmetics, incomplete labelling of some products, and hidden sources, as previously reported.⁶⁷ In 2018, the Committee for Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) in the European Union decided that industrial products, such as paints and detergents, must bear the warning, "Contains methylisothiazolinone. May cause an allergic skin reaction", when they contain more than 15 ppm MI.⁶⁸

The main limitation of our study was its retrospective design. The analysis of a large dataset over a long period of time, based on the standardized forms for the documentation of patch test and clinical findings of each patient, as well as its design, giving the temporal changes in patient's characteristics, and interpreting the causal factors affecting sensitization were the strengths of the study.

5 | CONCLUSION

The global epidemic of MCI/MI and MI contact sensitization during the period 2010 to 2015 with a peak in 2013/14, affected Turkey as well. In 2015, the prevalence reached the peak level of 16.4%, which was higher than the peak level in most other countries. There was a gradual decrease in the prevalence thereafter, but in 2019 it was still

much higher than pre-epidemic at 6.5%. This was probably due to the still high level (100 ppm) of MI permitted in rinse-off cosmetics in Turkey, which were the main eliciting sources in our study. The majority of patients had non-occupational ACD before and after the peak. Hair gel/wax as the exclusive source of occupational ACD in men's barbers fully disappeared following the ban of MCI/MI and MI in leave-on cosmetics. Occupational ACD in house painters from water-based wall paints was exclusively diagnosed during and after the peak. Finally, our findings support the role of concomitant patch testing with MCI/MI 0.02% aq. and MI 0.2% aq. in the baseline patch test series for detecting relevant sensitizations, and the urgent need to reduce the allowed level of MI in rinse-off cosmetics, as well as to regulate the use of isothiazolinones in household and industrial products in our country.

CONFLICT OF INTEREST

There authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Esen Özkaya: Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; visualization; writing-original draft; writing-review and editing. **Sıla Kılıç Sayar:** Conceptualization; data curation; formal analysis; investigation; methodology; software; visualization; writing-original draft; writing-review and editing. **Goncagül Babuna Kobaner:** Conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing-review and editing. **Gizem Pehlivan:** Data curation; investigation; software; visualization; writing-review and editing.

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