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Contact allergy to isothiazolinones epidemic: Current situation

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Abstract

Background: Since 2009, an increasing number of published cases of allergic contact dermatitis (ACD) from isothiazolinones in Europe was observed, amounting to an epidemic. However, only few studies have assessed the current situation after changes in European regulation.

Objectives: To analyze the incidence of isothiazolinone-related ACD in our area in the last decade.

Methods: A retrospective study analyzed all patients patch tested in the allergy unit in a tertiary hospital in Spain between January 2010 and June 2019. Positive patch-test reactions to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and/or MI alone were recorded.

Results: A total of 243 patients (9.55%) with positive patch-test reactions to MCI/MI and/or MI alone among 2544 consecutively patch-tested patients were recorded. An initial increase in the prevalence of MCI/MI allergy was observed, from 4.5% in 2010 reaching a peak in 2015, which was followed by a significant decrease until July 2019 with 3.1% prevalence in 2019.

Conclusions: As shown in our data, regulatory interventions have resulted in a dramatic decrease in the prevalence of MCI and MI ACD, reaching a pre-epidemic level of 3.1% in 2019.

KEYWORDS

contact allergy, epidemic, isothiazolinones, methylisothiazolinone

1 | INTRODUCTION

Isothiazolinones, namely methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI), are commonly used preservatives (biocides) in household and industrial products, as well as in cosmetics. Since 1980 a fixed combination of MCI/MI (3:1; eg Kathon CG) had been used.¹ Subsequently, there has been a European epidemic of allergic contact dermatitis (ACD) caused by MCI/MI with sensitization prevalences of up to 5%. As a result, in 1990 maximum authorized concentrations of 7.5 and 15 ppm were recommended for “leave-on”

and “rinse-off” products, respectively. Despite these restrictions, sensitization prevalences remained at 2% to 4%. From 2000 onward, after the epidemic and subsequent prohibition of methylchloroisothiazolinone (Euxyl K 400), MI was introduced in industrial products – owing to its weaker biocide effect, at higher concentrations.² Despite the first descriptions of ACD in an occupational setting in 2004 and 2006, the following year MI alone was allowed in cosmetic products at a maximum level of 100 ppm (Cosmetic Directive 2005/42/EC). In 2010, the first cases of ACD due to the use of MI in cosmetic products were reported.¹

Since 2009, an increasing number of published cases of ACD from isothiazolinones in Europe were observed, finally amounting to an epidemic. Alerts by dermatologists have led the European Commission to intervene and to re-evaluate risk management measures.³ However, only few studies have assessed the current situation after subsequent changes in regulation.

The main objective of our study is to analyze the incidence of isothiazolinone (MCI/MI and MI, respectively) ACD in our area in the last decade. As a secondary objective, patients' clinical characteristics were evaluated.

2 | METHODS

We report a retrospective study conducted at our Allergy Unit in the Dermatology Department of the General University Hospital of Valencia, Spain. A database of patients undergoing standard patch testing with the Spanish Society of Cutaneous Allergy baseline series from January 2010 to June 2019 was analyzed.

All patients were patch tested according to International Contact Dermatitis Research Group guidelines, with readings taken on day (D) 2 and D4. Positive patch-test reactions to MCI/MI (0.02% aq.) and MI alone (0.2% aq.) were recorded. A descriptive statistical analysis of all variables was performed, using the mean and the SD for quantitative variables and percentages for qualitative variables. The χ^2 test or Fisher's exact test was used for statistical testing as indicated. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM, Armonk, New York), with $P < .05$ used as the cutoff for significance.

3 | RESULTS

A total of 243 patients (9.55%) with positive patch-test reactions to MCI/MI and/or MI alone among 2544 consecutively patch-tested patients were recorded. The male, occupational, atopic, hand, leg or face dermatitis and age >40 (MOAHLFA) index of patients reacting

positively to isothiazolinones in patch tests is shown in Table 1. An initial increase in the prevalence of MCI/MI allergy was observed, from 4.5% in 2010 to reaching a peak in 2015 (18.9%), followed by a significant decrease until July 2019 (prevalence in 2019, 3.1%; Figure 1). Among the 243 patients with isothiazolinone allergy, 59.7% ($n = 145$) showed a positive patch to both MCI/MI and MI alone, whereas 17.3% ($n = 42$) were positive to MI alone, with 34 of these recorded in 2015.

Among isothiazolinone-sensitized patients ($n = 243$), the majority ($n = 178$, 73.3%) were female with a mean (SD) age of 46.5 (18) years. The average age remained stable throughout the years of the study and there were no significant differences between the shares of males and females. Figure 2 shows the incidence of sensitization to isothiazolinones by year stratified for sex. A personal history of atopy was seen in 36.6% of patients ($n = 89$).

The most frequently involved anatomical sites were the hands (33.3%) followed by the face including eyelids (26.3%) and generalized involvement (14.8%). Figure 3 shows the incidence of sensitization to isothiazolinones by years stratified for affected location. Facial dermatitis was more frequent in female patients ($P = .04$), whereas hand dermatitis was more frequent among men ($P = .04$).

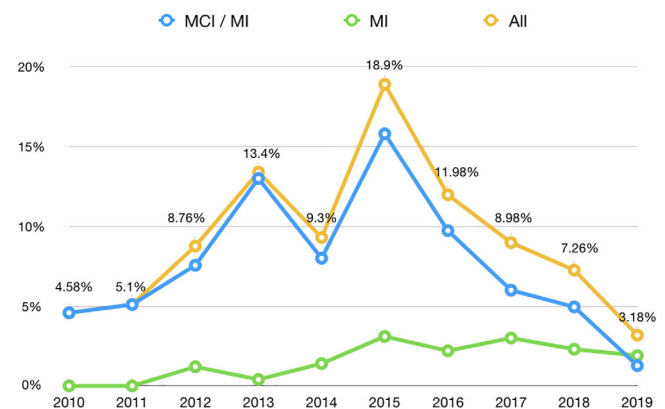


FIGURE 1 Incidence of sensitization to isothiazolinones by year. MCI, methylchloroisothiazolinone; MI, methylisothiazolinone

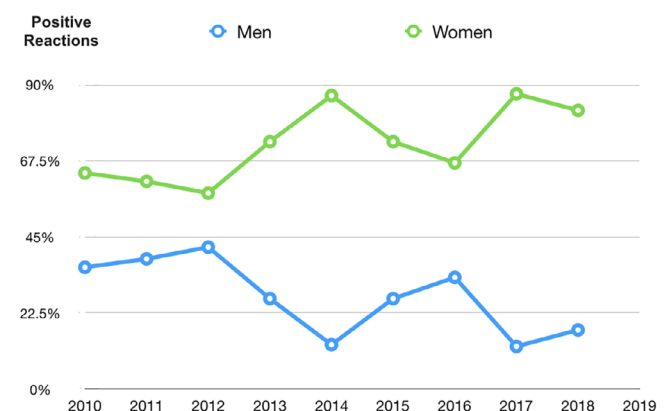


FIGURE 2 Share of sensitization to isothiazolinones by year, stratified for sex

TABLE 1 The MOAHLFA index of patch-tested patients ($n = 2544$) with contact sensitization to MCI/MI and/or MI alone ($n = 243$)

Characteristics	All, n (%)	MCI/MI or MI alone, n (%)	P value
Male	743 (29.2)	65 (26.7)	.3
Occupational	37 (1.4)	11 (4.5)	.03
Atopy	794 (31.2)	90 (37)	.04
Hand	685 (26.9)	94 (38.6)	.006
Leg	172 (6.7)	12 (4.9)	.1
Face	727 (28.5)	85 (34.9%)	.4
Age ≥ 40 years	1634 (64.2)	165 (67.9%)	.3

Note: Significant P -values are set in bold.

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

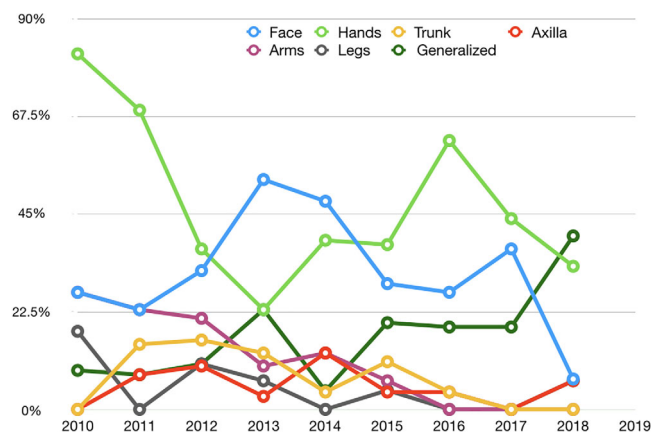


FIGURE 3 Incidence of sensitization to isothiazolinones by year, stratified for affected location

Isothiazolinone-sensitized patients showed an average of 2.3 positive patch tests. Up to 63 different substances were recorded as allergens, with the most frequent concomitant allergen being nickel ($n = 78$), followed by fragrance mix I ($n = 41$) and cobalt chloride ($n = 29$). Concerning the group of allergens and the analysis of their relevance, metals were the most frequent (54.3%; 16.6% of current relevance), followed by fragrances (31.2%; 63.1% of current relevance) and preservatives and antiseptics (50%; 50% of current relevance). Polysensitization, defined as the detection of ACD to three or more unrelated allergens, was recorded in 23% ($n = 56$) of isothiazolinone allergic patients.

Causative products were mostly cosmetics (89.3%; $n = 217$), including gels, shampoos, creams, moisturizing lotions, deodorants, and aftershave lotion. Besides cosmetics, household (10.3%, $n = 25$) and industrial (0.4%, $n = 1$) products (especially cleaning agents and wall paints) were the most frequent.

4 | DISCUSSION

Our data show, since 2010, an alarming increase in the prevalence of MCI/MI and/or MI contact allergy to a concerning level of 18.9% in 2015 in patients referred for patch testing. A European epidemic of ACD caused by isothiazolinones has been widely reported, starting between 2009 and 2010, after MI was permitted at higher concentrations in industrial applications and cosmetics with allowed concentrations of up to 100 ppm. As a consequence, risk management measures were adopted between 2013 and 2015 and the Scientific Committee on Consumer Safety of the European Union established that there were no safe concentrations of MI in leave-on products and considered a concentration of 15 ppm as safe in the rinse-off products, finally being regulated in 2017.³

The increasing number of cases of ACD from isothiazolinones published by dermatologists and subsequent regulatory action have enabled a dramatic decrease in the incidence of ACD to isothiazolinones, as reflected in our study. The incidence has markedly decreased since 2015, from a maximum of 18.9% in 2015 to 7.2% in

2018 and 3.1% in 2019. Urwin et al showed a decrease in the incidence of sensitization to MCI/MI or MI from 2013 to 2015.⁴ Recently, Salman reviewed 324 patch-tested patients between January 2016 and June 2018 in Istanbul, and observed a clear decrease in the prevalence of MCI/MI and/or MI sensitization from 10.15% in 2016, 9.25% in 2017, and 6.74% in 2018.⁵ These data are in line with our study including more patch tested patients (282 on average per year), with an incidence of 11.9% in 2016, 8.9% in 2017, 7.2% in 2018, and 3.1% until July 2019.

Occupational and hand dermatitis showed a strong association with isothiazolinone sensitization, but a typical pattern of male patients with ACD related to industrial products (paints, cutting fluids)⁵ has been replaced by a novel pattern of female patients with ACD related to cosmetics. Cosmetics, including rinse-off (gel, shampoos) and leave-on (creams, lotions) products, are still the most frequent causative agents, the ubiquity of which is a striking aspect that has not changed during those years.

Polysensitization may be an important factor among MCI and MI allergic patients. Interestingly, clinically relevant co-sensitizers included fragrances and preservatives, frequent allergens in cosmetics that represent the most common source of contact allergy as reported in several studies.⁶⁻⁸

Through the 1980s, 1990s, and 2000s, MCI/MI has remained one of the most predominant preservative contact allergens with a stable prevalence of around 2% to 4%.¹ In the early 2000s, MI alone was introduced to industrial products and shortly thereafter, occupational cases of ACD were published.⁹ In 2005, MI was permitted in cosmetic products with a maximum concentration of 100 ppm, which led to an alarming epidemic of ACD to MI in Europe; particularly, from 2009 an increase of ACD to MCI/MI was witnessed, identified in around 19% of all patch-tested patients in 2010 when MCI/MI was still the only isothiazolinone patch tested in the baseline series, as demonstrated in our study.¹ Moreover, isothiazolinone allergic patients were significantly more often aged >40 and more often had facial dermatitis related to cosmetic products at home and/or in an occupational setting. The alert raised has led to risk management measures regulating the maximum MI concentration in cosmetic products in the European Union, concluding that no safe concentration in leave-on cosmetic products can be established, and decreasing the maximum permitted level of MI in rinse-off cosmetic products from 100 to 15 ppm.⁴ As shown in our data, regulatory interventions have resulted in a dramatic decrease in the prevalence of MCI and MI ACD (3.1% in 2019), reflecting the rates seen in 1980s, that is, in the pre-epidemic years.

CONFLICTS OF INTEREST

None to declare.

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