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Evolution of methylisothiazolinone sensitization: A Belgian multicentric study from 2014 to 2019

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Abstract

Background: In the 2010s an epidemic of allergic contact dermatitis to methylisothiazolinone (MI) occurred in Europe. European authorities banned the use of methylisothiazolinone in leave-on cosmetics in 2017 and limited its use in rinse-off products in 2018.

Objectives: To investigate the sensitization rate to MI in Belgium between January 2014 and December 2019, and to assess cosensitizations to octylisothiazolinone (OIT) and benzisothiazolinone (BIT) in MI-sensitized patients.

Methods: A retrospective study of patch test results with MI, OIT, and BIT observed in patients attending five Belgian hospitals.

Results: Overall, 560 of 10 029 patients (5.58%) had a positive patch test reaction to MI, and its sensitization rate decreased from 7.9% in 2014 to 3.1% in 2019. Rinse-off cosmetics, paints, and detergents were the most prevalent sensitization sources in recent years. Simultaneous reactions readily occurred to OIT, and, surprisingly, and increasingly, also to BIT.

Conclusions: Contact allergy to MI in Belgium has reached a pre-epidemic level, reflecting the impact of recent regulatory measures. Leave-on cosmetics, in contrast to rinse-off products, have almost disappeared as sensitization sources in Europe. Paints and detergents also remain problematic. The remarkably high number of patients (co)sensitized to BIT should be a focus of future research.

KEYWORDS
allergic contact dermatitis, benzisothiazolinone, cosmetics, cross-reaction, detergents, epidemic, legislation, methylisothiazolinone, octylisothiazolinone, paints

1 | INTRODUCTION

Methylisothiazolinone (MI) is a biocide with strong bactericidal and fungicidal properties frequently used in cosmetics, household, and chemical (industrial) products, the latter including detergents, water-based paints, glues, and metalworking fluids.[1] Initially, MI was used as part of the methylchloroisothiazolinone (MCI)/MI mixture (ratio 3:1), a preservative responsible for an epidemic of allergic contact dermatitis (ACD) in the 1980s. In the 2000s, soon after the use of MI as a standalone preservative in both noncosmetic and cosmetic products, a dramatic outbreak of sensitization to MI occurred in Europe, and beyond. The first case of occupational ACD from MI was described in a patient exposed to wallcovering glues in 2004,[2] followed by, in 2010, the first consumers sensitized to MI in cosmetics.[3] Since then, many more cases have been reported, eventually causing yet another epidemic of ACD from a preservative in Europe.[4-6] In 2013, MI was added to the European baseline series,[7] and also elected as the Allergen of the Year by the American Contact Dermatitis Society.[8] Because of the increased prevalence of ACD caused by MI, the European authorities re-evaluated its safe use in cosmetics and implemented new regulations in February 2017 banning the use of MI in leave-on cosmetics

(EU 1223/2009),[9] and in 2018 limiting its use in rinse-off products to 15 ppm.[10]

The primary aim of this study was to evaluate the impact of these recent regulatory measures on MI sensitization in Belgium by analysing the results of patch tests to MI performed in five Belgian centres from 2014 to 2019. Secondarily, we also focused on the occurrence of cosensitization to octylisothiazolinone (OIT) and benzisothiazolinone (BIT) in MI-sensitized patients.

2 | MATERIALS AND METHODS

Using a standardized data collection form, we retrospectively analysed the patch test results to MI, obtained during the period from January 1, 2014, to December 31, 2019, in five contact allergy units in Belgium: three in Brussels (Cliniques Saint-Jean, Cliniques Saint-Pierre, and Cliniques universitaires Saint-Luc), one in Antwerp (University Hospital), and one in Leuven (University Hospitals). From Leuven, only data from 2014 and 2017 could be included and, for Cliniques Saint-Pierre, Brussels, only those from 2014 to 2018 could be included.

All patients had been patch tested with a baseline series (Chemotechnique Diagnostics, Vellinge, Sweden, and TROLAB, Almirall Hermal, Reinbek, Germany) containing MI (0.05% and/or 0.2% aqua [aq.]) and MCI/MI (0.01% and/or 0.02% aq.). At Cliniques Saint-Pierre, MI was tested at 0.05% aq. in 2014 and was tested at 0.2% aq. in the following years. Except for Antwerp, where only MI 0.2% aq. was routinely used, in the other centres both concentrations (0.05% and 0.2% aq.) were used for three years. All MI-sensitized patients were also tested with BIT (0.05% or 0.1% pet.) and OIT (0.1% pet.) containing in European baseline serie (Chemotechnique Diagnostics, Vellinge, Sweden, and Trolab, Almirall Hermal, Reinbek, Germany).

The patch tests were applied on the upper back and occluded for 2 days, after which they were read on day (D)2 and D4. Positive reactions were scored as +, ++, or +++, according to the guidelines of the ICDRG.[11] Irritant and doubtful reactions were considered as negative.

For patients who showed a positive reaction to MI, the following additional clinical data (if available from the records) were also collected and analysed: age, sex, localization(s) of the dermatitis, occupation, relevance of the positive patch test to MI, and cosensitizations to OIT and BIT. Moreover, the occurrence of airborne dermatitis, photoaggravation, and respiratory symptoms, if documented in the patient files, were equally included.

The demographic data and percentages of positive patch tests were analysed using the descriptive method. The prevalence was calculated as the proportion of positive patch tests among all patch tested patients. Statistical analyses and descriptive analyses, with anonymized data, were performed with JMP Pro 15.2.0 (SAS Institute, Cary, NC). A P value <.05 was considered significant. The chi-square, Fischer exact test, and Cochran–Armitage trend test were used for comparisons.

This study was conducted with the approval of the Institutional Ethics Committee, Commission d'ethique biomédicale Hospitalo-Facultaire de L'Université catholique de Louvain (ref no. 2017/16MAI/276 and 2020/6MAR/140).

3 | RESULTS

Of the 10 029 patients patch tested with MI during the 6-year study period, 560 (5.6%) showed a positive reaction. The majority (73%) were women and the sex ratio remained relatively stable over time. The median age of all patients was 49 years (range 3-88), and it is noteworthy that less than 5% (n = 26) were children (<18 years old). Nevertheless, a slight but nonsignificant increase ($P = .34$) in the proportion of children affected could be observed, mainly in 2018 and 2019. Table 1 summarizes the evolution of the characteristics of patients with positive patch test reaction to MI.

An overall decrease in the rate of sensitization to MI was observed every consecutive year, with a significant decrease for the entire study period (chi-square and Cochran–Armitage trend test; $P < .05$), in particular from 7.9% in 2014 to 3.1% in 2019 (Figure 1.).

The most frequently affected sites were the hands (n = 228) and the face (n = 195, especially the eyelids, n = 80), followed by generalized dermatitis (n = 98).

The main sensitization sources were rinse-off cosmetics (ie, shampoos and soaps: 37.8%, 212 cases); leave-on cosmetics (ie, moisturizing creams and sun creams; 26.9%, 151 cases); detergents and other household products (15.5%, 87 cases); and water-based paints (5.5%, 22 cases). In 36% of cases, the relevant source of MI exposure could not be identified. The evolution of the sensitization sources over the years is represented in Table 1. Although the proportion of sensitization caused by leave-on cosmetic products was relatively stable during the first 3 years of the study, a clear decrease was observed from 2017, whereas no cases occurred in 2018. In 2019, only one patient presented a relevant sensitization caused by a leave-on cosmetic (a body lotion). Conversely, an increase of sensitization caused by rinse-off cosmetic products was noticed.

The most striking atypical clinical presentation, observed in 95 of 560 patients (17%), was the occurrence of airborne contact dermatitis, attributed to water-based paints in almost half of the patients involved (45/95; 47.4%),[12] as well as to household detergents (15/95; 15.8%). Only five of these patients also developed respiratory symptoms from paints (n = 3), and household products (n = 3), with one patient considered to have experienced ACD from MI contained in both allergen sources. Possible photoaggravation was also occasionally reported.[13] This phenomenon was observed in three patients only, in two of them linked to the use of sun care products.

In almost one-fifth of the patients (98/560, 17.5%), a clear link between MI sensitization and occupation could be established, with the most common categories being (a) primarily household helpers, cleaners, or launderers (n = 28); closely followed by (b) healthcare personnel (nurses, doctors, physiotherapists) (n = 23); and finally, (c) personal services workers (hairdressers, barbers, beauticians) (n = 16). Sources of occupational sensitization included household detergents in 35/98 (35.7%), industrial soaps in 29/98 (29.6%), and industrial oils in 9/98 (9.2%).

Simultaneous positive patch test reactions were observed with MCI/MI in 370/560 (66%), OIT in 118/560 (21%), and BIT in 42/560 (7.5%) cases. A clear increase ($P < .05$) of simultaneous positive patch

TABLE 1 Evolution, from 2014 to 2019, of characteristic features of patients with positive patch tests to methylisothiazolinone

Characteristic	2014, n (%)	2015, n (%)	2016, n (%)	2017, n (%)	2018, n (%)	2019, n (%)	Total, n (%); 95% confidence interval
Methylisothiazolinone positive patch test	135 (7.9)	117 (6.2)	104 (5.5)	107 (5.6)	60 (4.0)	37 (3.1)	560 (5.6); 5.1-6.0
Children (<18 y)	5 (3.7)	4 (3.4)	4 (3.8)	4 (3.7)	6 (10.0)	3 (8.1)	26 (4.6); 3.2-6.7
Female sex	92 (68.1)	89 (76.1)	81 (77.9)	84 (78.5)	41 (68.3)	24 (64.9)	411 (73.3); 69.5-76.8
Occupational dermatitis	25 (18.5)	27 (23.1)	13 (12.5)	15 (14.0)	11 (18.3)	7 (18.9)	98 (17.3); 14.6-20.9
Airborne dermatitis	20 (14.8)	30 (25.6)	18 (17.3)	16 (14.9)	8 (13.3)	3 (8.1)	95 (16.9); 14.0-20.2
Source of exposure							
Leave-on cosmetics products	60 (44.4)	47 (40.2)	39 (37.5)	4 (3.7)	0 (0)	1 (2.7)	151 (26.9); 23.1-30.4
Rinse-off cosmetics	56 (41.5)	41 (35.0)	28 (26.9)	25 (23.4)	33 (55.0)	29 (78.4)	212 (37.8); 34.3-40.2
Household products	14 (11.1)	28 (23.9)	17 (16.3)	14 (13.1)	10 (16.7)	4 (10.8)	87 (15.5); 12.1-18.0
Water-based paints	0 (0)	9 (7.7)	12 (11.5)	6 (5.6)	4 (6.7)	3 (10.8)	34 (6.1); 3.9-7.7
Main localization affected							
Face	45 (33.3)	49 (41.9)	35 (33.7)	28 (26.2)	20 (33.3)	18 (48.6)	195 (34.8); 30.9-38.8
Hands	56 (41.5)	55 (47.0)	47 (45.2)	40 (37.4)	18 (30.0)	12 (32.4)	228 (40.7); 36.7-44.8
Generalized dermatitis	24 (17.8)	22 (18.8)	17 (16.3)	19 (17.7)	10 (16.6)	6 (16.2)	98 (17.5); 3.9-7.7
Simultaneous sensitization							
Methylchloroisothiazolinone/ methylisothiazolinone	90 (66.7)	82 (70.1)	75 (72.1)	60 (56.1)	41 (68.3)	22 (59.5)	370 (66.1); 62.0-69.8
Octylisothiazolinone	27 (20.0)	25 (21.4)	20 (19.2)	24 (22.4)	12 (20.0)	10 (27.0)	118 (21.1); 17.9-24-8
Benzisothiazolinone	4 (3.0)	6 (5.1)	3 (2.0)	15 (14.0)	7 (11.7)	7 (18.9)	42 (7.5); 5.6-10.0

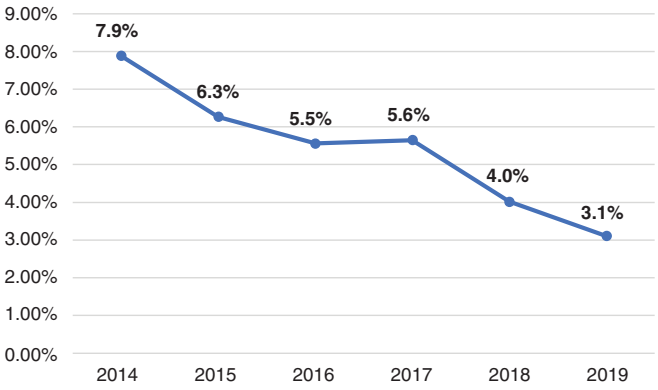

FIGURE 1 Evolution of the sensitization rate to methylisothiazolinone in Belgium between January 2014 and December 2019 (2014-2017, data from five university centres; 2017-2019, data from four university centres; and 2019, data from three university centres)

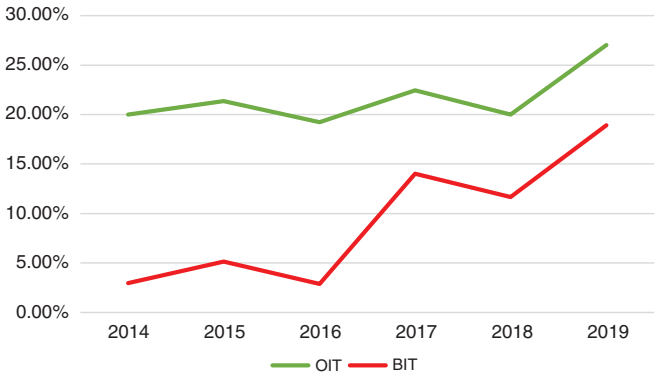

FIGURE 2 Evolution of the simultaneous positive reactions to octylisothiazolinone (OIT) and benzisothiazolinone (BIT) in patients sensitized to methylisothiazolinone from 2014 to 2019

test reactions with MI and OIT was observed, rising from 20% in 2014 to 27% in 2019, and, surprisingly, also a strong and equally significant increase ($P < .05$) of simultaneous positive patch test reactions to MI and BIT, rising from 2.9% in 2014 to 18.9% in 2019 (Figure 2 and Table 1). The proportion of women affected by ACD is quite similar in the case of cosensitization to OIT or BIT: 70% and 73.8%, respectively. For patients cosensitized to OIT, the most frequently affected site was the face in 50/118 (42.3%) patients, while the hands (52.3%) were affected in 22/42 cases of cosensitization to BIT.

4 | DISCUSSION

In 2015, a study carried out in 11 European countries estimated the prevalence of MI contact allergy to be 6.0% (range 2.6%-13.0%).[14] A previous Belgian multicentric study reported an increase of MI sensitization from 3.1% in 2010 to 7.2% in 2013.[6] According to the present study, the prevalence further increased to 7.9% in 2014.

As already demonstrated by other multicentre studies, the European Union (EU) restrictions on the use of MI in leave-on and rinse-off cosmetics seem to have had a direct impact on the prevalence of MI sensitization.[14,15] Similarly, we also observed a significant

decrease in MI sensitization from 7.9% in 2014 to 3.1% in 2019. The sensitization rate observed in Belgium thus returned to pre-epidemic levels (ie, to ~3.1%, as in 2010)[6]; this is unfortunately not yet the case for all (European) countries.[16] The decrease observed in our study can primarily be explained by the ban on the use of MI in leave-on cosmetics, which nowadays is only a negligible source of MI exposure, thus demonstrating the effectiveness of the regulatory changes in this regard. Interestingly, we observed, mainly in 2018 and 2019, an increase in the number of culprit rinse-off cosmetic products (soaps/shampoos), in which, since April 2018 (EU 2017/1224), a maximum concentration of MI of 15 ppm is still allowed.[10] If in the following years rinse-off cosmetics remain or become more important sources of MI contact allergy, then a further refinement of the existing regulations may be necessary (ie, maximum concentration limits re-discussed).

According to our data, the decrease in MI sensitization had already started in 2013 to 2014 (Figure 1), long before the European regulations concerning the use of MI in cosmetics products come into force in 2017 and 2018. Note that in 2013, following the MI–ACD epidemic, Cosmetics Europe (association of the cosmetic industry) and the Scientific Committee on Consumer Safety (SCCS) recommended the prohibition of MI in leave-on cosmetics and in 2015, the SCCS estimated that a maximum MI concentration of 15 ppm could be considered safe in rinse-off cosmetics. The progressive decrease in MI sensitization observed prior to the implementation of the EU regulations in 2017 and 2018 is therefore likely to be related to some preventive action from the cosmetic industry.

Notwithstanding that exposure sources of MI in general are relatively stable, and regardless of the fact that culprit sources could not be identified in more than one-third of cases, it should be stressed that the presence of (high concentrations of) MI in water-based paints and household detergents continues to be a relevant,[17] and often distressing, cause of (airborne) ACD from this preservative. Regulatory action in this particular field is, unfortunately, still lacking.

Hands were always more frequently affected than the face, but only until 2018, when the reverse started to occur. Soon following the ban of MI from leave-on cosmetics, MI became relatively overrepresented in rinse-off cosmetics, such as shampoos and soaps, more commonly affecting the very thin facial (and eyelid) skin, probably explaining the recent emergence of face dermatitis. Indeed, the responsibility of rinse-off cosmetics as sensitizing exposure sources increased from 41.5% in 2014 to 78.5% in 2019. Although the concentration of MI has been limited to 15 ppm in these products over this period, this relatively surprising increase in sensitization requires further analysis and it is legitimate to question whether this is an absolute or relative increase. Interestingly, almost one-fifth (98/560 patients, or 17%) were suffering from generalized dermatitis, which might be an underappreciated, yet troublesome, presentation of ACD in general, and of ACD due to MI, in particular.

An (albeit nonsignificant) increase in the proportion of children affected over time probably reflects changing exposure sources, such as slime toys,[18] nail polish,[19] and also water-based poster paints for children,[20] the latter still regularly causing airborne ACD, which clearly contrasts with previous reports detailing wet wipes as the most frequent paediatric sensitization source.[21]

Among all patients sensitized to MI, about two-thirds (66%) showed a concomitant positive patch test reaction to MCI/MI, a figure that remained relatively stable during the entire study period. Already in 2017, Craig et al[22] reported that as many as 72% of MI-sensitized patients may show simultaneous reactions to MCI/MI. However, as previously reported by Aerts et al[6] in 2014, more than 30% of the patients with an MI contact allergy can be missed if only patch tests with MCI/MI are performed. A recent paper suggested replacing the MCI/MI 0.02% aq. and MI 0.2% aq. patch test preparations by a new mixture, that is, MCI/MI 0.215% aq. (containing MCI 0.015% and MI 0.2%), which could allow for the detection of more MI- and MCI/MI-sensitized patients than either patch test material alone.[23]

Of all 560 patients sensitized to MI, 18 (21%) showed a positive reaction to OIT. The proportion of patients cosensitized to both MI and OIT remained relatively stable over time. Although debated, and initially considered unlikely,[24] clinical studies have suggested that, besides cosensitization through concomitant exposure, cross-reactivity between both these derivatives may also occur.[25] An animal study using a modified local lymph node assay[26] equally supported this hypothesis and, recently, Russo and Aerts[27] confirmed, in vivo, by using the retest model, that humans, at least those strongly sensitized to MI, effectively show cross-reactivity to OIT. This implies that, in daily practice, it is important to counsel patients sensitized to MI to avoid not only MI- but also OIT-containing products.

Equally interestingly, our data also suggest a strong (7- to 9-fold) increase in the share of MI-sensitized patients that display a concomitant positive (+, ++, or +++) reaction to BIT. This became especially evident since 2017, although it mainly concerned weak BIT (+) reactions. It should also be mentioned that, since 2016, every participating centre also observed an increase in the number of doubtful (? +) patch test reactions to BIT (data on file), considered as negative, and thus not included in the current analysis. This increase in (mainly weak) positive patch test reactions to BIT in individuals sensitized to MI is elusive and several explanations may exist. A first and likely explanation is increased exposure, and thus potential concomitant sensitization to BIT, rather than cross-reactivity. Several arguments are in favour of this: (a) contrary to the derivatives MI, MCI, and OIT, which all have a very similar chemical structure, BIT differs by an additional benzene bicyclic ring, making cross-reactivity less likely; (b) several studies have previously found that less than 10% of MI-sensitized patients coreacted positively to BIT[22,28]; (c) the recent study based on the "retest" model confirmed that, in contrast to OIT, cross-reactivity between MI and BIT is rather unlikely[27]; (d) the main reported sources of exposure to BIT, notably household detergents and water-based paints, are also frequent sources of exposure to MI, rendering concomitant sensitization again more plausible[29,30]; and (e) the possibly increased use of BIT in non-cosmetic products, such as detergents or paints, or even gradual replacement of MI in some of these products, equally favours concomitant sensitization.

Nevertheless, cross-reactivity between MI and BIT may still not be entirely excluded, more-so because the abovementioned studies[26,27] suggested that, especially for the relatively weak sensitizer BIT, higher eliciting concentrations might be required to show cross-reactivity to MI. As such, the mostly weak reactions to BIT might also be an illustration of weak cross-reactivity to MI, at least in some cases.

A third and final explanation may be that an inadequate (too high) patch test concentration, or perhaps less appropriate patch test material, of BIT is currently in use. As reported, the concentration of 0.1% might indeed be more irritant than the 0.05%.[31] However, lower test concentrations might in turn underestimate BIT sensitization.[32] Indeed, the most appropriate patch test conditions for BIT still need to be established. Some participating centres in the current study used BIT concentrations of 0.05% pet. (500 ppm) prior to using the higher test concentration of 0.1% pet. (1000 ppm): among the 560 MI-sensitized patients, 133 were tested with the lower BIT concentration, that is, 33 at the University Hospital Antwerp, until the end of 2014, 60 at Cliniques Saint-Jean, and 40 at Cliniques Saint-Pierre until the end of 2018 (Table 2). It is tempting to speculate that the change of the BIT test concentration from 0.05% to 0.1% explains, at least in some centres, why weaker positive, and potentially false-positive, reactions have been observed. However, in Cliniques universitaires Saint-Luc in Brussels and in the University Hospital in Antwerp, a significant increase ($P < .05$) in cosensitization to BIT was noticed in MI-sensitized patients in more recent years (2017-2019) as compared with previous years (2015-2016), although the same, high (0.1%) BIT patch test concentration had always been used. The latter observation argues against irritancy (which, at the same test concentration, is expected to remain rather stable), and might be indicative of increased, concomitant exposure and sensitization to BIT. Nevertheless, considering the over-representation of weak (+) reactions to BIT, it can probably not be excluded that the intrinsic quality of the BIT patch material might have changed throughout the years, although this remains speculative.

In March 2016, the Committee for Risk Assessment[33] concluded that MI had to be recognized as a skin sensitizer in the 1A, H317 Category (may cause an allergic skin reaction), with a specific concentration limit of 0.0015% (15 ppm). Labelling with EU H208 (contains 2-methylisothiazol-3(2H)-one, may produce an allergic reaction) had to be applied to industrial products, except for paints, which need to be labelled as such since October 2018 and effectively since May 1, 2020. This new limitation will probably lead the paint industry to substitute MI by other preservatives such as OIT or BIT. The appearance of certain ecolabels enables the consumer to learn more about the concentration limits of isothiazolinones in paints, particularly BIT; for example, EU Ecolabel 2014 (BIT 500 ppm with the total biocide level limited to 600 ppm indoors and 3600 outdoors) and Blue Angel 2019 (trace of biocides BIT <10 ppm). However, the sources of exposure to BIT are becoming more diverse and frequent in our environment. Recently, BIT has also been found in a medical liquid soap used for cleaning continuous positive airway pressure masks,[34] and even in a cosmetic soap,[35] despite it being banned by the SCCS from cosmetics since 2012.[36] Therefore, given the apparent increase in

TABLE 2 Number of patients tested with benzisothiazolinone (500 or 1000 ppm) among patients sensitized to methylisothiazolinone in the different centres studied and according to the years

	2014			2015			2016			2017			2018			2019		
	BIT+		MI	BIT+		MI	BIT+		MI	BIT+		MI	BIT+		MI	BIT+		MI
Hospitals	500 ppm	1000 ppm	+	500 ppm	1000 ppm	+	500 ppm	1000 ppm	+	500 ppm	1000 ppm	+	500 ppm	1000 ppm	+	500 ppm	1000 ppm	+
Katholieke Universiteit in Leuven	NT	0	35	NT	1	32	NT	0	26	NT	1	27	NT	NT	NT	NT	NT	NT
Cliniques universitaires Saint-Luc in Brussels	NT	2	45	NT	3	29	NT	0	28	NT	4	19	NT	3	12	NT	1	15
University Hospital in Antwerp	1	NT	34	NT	1	34	NT	3	30	NT	10	41	NT	3	33	NT	6	19
Saint-Jean	0	NT	15	0	NT	10	1	NT	14	0	NT	12	1	NT	9	NT	0	3
Saint-Pierre	1	NT	8	1	NT	12	0	NT	6	0	NT	8	0	NT	6	NT	NT	NT

Abbreviations: BIT, benzisothiazolinone; MI, methylisothiazolinone; NT, not tested.

sensitization to BIT in MI-sensitized patients, it seems important to also monitor the sensitization rate of this particular derivative in the general patch test populations, to evaluate and identify relevant sources of BIT exposure, and subsequently, to recommend a refinement of the European legislation concerning its use in industrial or other products.

5 | STUDY LIMITATIONS

Although a large number of patients could be included, the retrospective design of the current study might not have allowed adequate collection of all relevant information present in the patient files. Moreover, two centres were unable to provide data for 2018 and 2019, leading to a smaller study sample during this particular period. It should also be noted that one of the centres was not yet testing MI at 0.2% in 2014, which could have led to a relative underestimation of the number of MI-sensitized patients. Moreover, for BIT, different patch test concentrations were used (0.05% and 0.1%, both pet.) in different centres over time.

6 | CONCLUSION

This Belgian retrospective multicentre study analysed the evolution of the prevalence of sensitization to MI, for which a clear decrease was observed from 7.9% in 2014 to 3.1% in 2019. The exposure sources for MI have equally changed over the years, mainly due to new European regulations in 2017 and 2018 that restricted its use in cosmetic products. Leave-on cosmetics were replaced by rinse-off products as the main current and relevant sensitization sources of MI. Likewise, water-based paints and detergents, for which no regulatory action has been taken yet, remain problematic. Although MI-sensitized patients are often also sensitized to OIT, for whom both concomitant sensitization and cross-reactivity have been demonstrated, a remarkably high and increasing number of patients appear also to be cosensitized to BIT.

Although increased exposure to BIT from its presence in chemical (industrial) products seems likely, false-positive patch test reactions to this derivative cannot be fully excluded; further studies are warranted in this regard.

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AUTHOR CONTRIBUTIONS

Anne Herman: Conceptualization (lead); data curation (lead); investigation (lead); methodology (lead); writing; original draft (lead). **Olivier Aerts:** Resources (equal); supervision (equal); validation (equal); writing; review and editing (equal). **Marie-Claude Jacobs:** Resources (equal); validation (equal); writing; review and editing (equal). **Christel Scheers:** Resources (equal); validation (equal). **Liesbeth Gilissen:** Resources (equal); validation (equal); writing; review and editing (equal). **An Goossens:** Resources (equal); supervision (equal); validation (equal); writing; review and editing (equal). **Marie Baeck:** Conceptualization (equal); methodology (equal); resources (equal); supervision (equal); validation (equal); writing; review and editing (equal).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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