

ORIGINAL ARTICLE

Methylisothiazolinone contact allergy in Croatia: Epidemiology and course of disease following patch testing

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Email: suzana.ljubojevic@gmail.com**Background:** Methylisothiazolinone (MI) caused an epidemic of contact allergy in Europe, as shown by data from many countries, but no studies from Croatia exist. Also, data are lacking on the severity of allergic contact dermatitis (ACD) caused by MI, and its impact on quality of life and prognosis.**Objectives:** To determine the frequency of MI contact allergy among Croatian dermatitis patients, identify causative exposures, assess the impact of disease, and study the prognosis.**Methods:** Data were collected for consecutive dermatitis patients with MI contact allergy patch tested in Croatia between November 2, 2015 and November 3, 2016.**Results:** MI contact allergy was diagnosed in 13.2% of 798 tested patients. The most frequent dermatitis locations were the hands (76%) and face (61%). In 89.3% of patients, MI contact allergy was found to be of current relevance. Considerable severity and impact on daily life of disease was found at the first consultation, but this significantly decreased until follow-up 3 months later.**Conclusions:** Patch testing is the standard method for the diagnosis of ACD, and it has been shown to have an important beneficial effect on prognosis. The severity of MI ACD and the impact on daily life emphasize the need for prevention.

KEYWORDS

education, exposure, follow-up, methylisothiazolinone, patch test

1 | INTRODUCTION

Methylisothiazolinone (MI) has recently been added to the European baseline series.¹ An unprecedented rise in MI contact allergy was seen, primarily attributable to leave-on cosmetic products, but also resulting from other exposures, such as paints and soaps.^{2–5} Data have been collected from many countries, but not from Croatia, where patch testing with MI has been performed since March 2015. Many studies on MI contact allergy have been published in recent years, but none of these has included severity assessments, impact on quality of life (QoL), or prognosis. The aim of the present study was to identify current and causative exposures to MI in Croatian patients with MI allergy, and to qualify reaction patterns and the course of disease.

2 | PATIENTS AND METHODS

Consecutive dermatitis patients who were patch tested in the Department of Dermatology and Venereology, University Hospital Centre Zagreb between November 2, 2015 and November 3, 2016 were eligible for inclusion in the study, provided that they were diagnosed with MI contact allergy (see below). At inclusion, basic characteristics of the patients, such as sex, age, occupation, site of dermatitis, history of atopic dermatitis, previous patch test results, and onset of dermatitis, were documented. Furthermore, the dermatologist graded the severity of the dermatitis on a visual analogue scale (VAS) from 0 (no dermatitis) to 100 (very severe dermatitis), in terms of a physician's global assessment. Patients were asked to indicate how much their skin disease had influenced their daily life negatively, by thinking

of the past week, on a VAS scale from 0 (no influence) to 100 (could not be worse), to provide the patient's own global assessment.

All patients were patch tested with the Croatian baseline series (Imunološki zavod, Zagreb, Croatia; and Chemotechnique, Vellinge, Sweden) with 8-mm Finn Chambers (Epitest, Tuusula, Finland) on Scanpor tape (Norgesplaster, Vennesla, Norway) applied to the upper back and left in place for 2 days. A micropipette was used to apply 15 µL each of methylisothiazolinone (MI) 0.2% aq. and MI/methylisothiazolinone (MCI) 0.01% aq. to the filter paper in a Finn Chamber. Patches were read on day (D) 2, D3 and D7 according to the ESCD guideline on patch testing.⁶ A positive response was defined as a +, + or +++ reaction.

On D7, patients with a positive reaction to MI 0.2% were asked to bring all of their cosmetics, cleaning products, and other types of relevant products, including from the workplace. The ingredient labels

of all products were examined for the presence of MI or MCI/MI, and the results were documented in terms of the numbers of products in different product categories (Table 1). If ≥ 1 of these products were regarded as the cause, or a cause, of the current dermatitis, more product details were retrieved. Moreover, it was recorded whether the patients had experienced symptoms in newly painted rooms. A follow-up visit 3 months after patch testing was arranged, during which patients and physicians were asked again to give their global assessment concerning the severity of dermatitis and the negative influence of dermatitis on daily life, respectively, using instruments identical to those used at the initial visit.

Data were recorded anonymously in an online documentation system (SoSci survey; <https://www.soscisurvey.de>), and processed and analysed with the statistical software package R (version 3.4.2, <https://r-project.org>). Besides descriptive statistics, the Wilcoxon

TABLE 1 Number of products containing methylisothiazolinone (MI) or methylchloroisothiazolinone (MCI)/MI and used by the patients (determined from ingredient labelling, materials safety data sheets, contact with manufacturer, or chemical analysis)

Product type	Number of products with MI	Number of products with MCI/MI	Number used in private life	Number used occupationally
Cream/lotion				
Body	3	3	2	0
Face	7	4	6	0
Eyes	3	1	2	0
Hands	16	10	14	1
Feet	1	0	1	0
Sunscreen	3	1	3	0
Self-tanning	0	0	0	0
Deodorant				
Spray	3	2	2	0
Roll-on/stick	5	5	6	1
Make-up				
Face mask	3	2	2	1
Eye make-up	2	0	1	0
Tinted base	0	0	0	0
Make-up remover	9	4	9	1
Wet wipe	34	24	31	6
Hairstyling				
Gel/mousse	3	2	3	0
Spray	2	1	2	0
Nail care	0	0	0	0
Mouth wash	0	0	0	0
Rinse-off cosmetic				
Liquid soap	27	20	24	6
Bath/shower gel	20	13	18	0
Shampoo	27	20	22	0
Conditioner	3	3	3	0
Shaving	1	0	1	0
Cleaning agent	23	17	21	7
Household cleaning spray	17	11	17	4
Dishwashing liquid	23	14	21	2
Paint	4	3	3	0
Glue	1	0	1	1
Cutting oil	1	0	0	1

signed-rank test was used for before and after comparison of the VAS score for the severity and impact of disease. A *P* value of < .05 was considered to be significant.

3 | RESULTS

In total, 798 patients (198 males and 600 females) were tested with the baseline series. Of these, 51 (6.4%) reacted positively to MCI/MI (11 males, and 50 females), and 105 (13.2%) reacted positively to MI (17 males and 88 females). Forty (5%) patients reacted positively to both MI and MCI/MI, and 116 (14.5%) patients reacted positively either to MCI/MI or MI. Of the 105 patients who reacted positively to MI, 75 (11 [14.7%] males and 64 [85.3%]) females were included in the study. Their median age was 42 years. The main occupations were office workers (*n* = 20), student/pensioners (*n* = 12), and housewives (*n* = 4). Five were unemployed, 3 were hairdressers/beauticians, and only 1 was a painter. In total, 22 patients did not want to participate in the study, and 8 patients did not show up after 3 months and did not reply to telephone calls and/or letters.

Eleven patients had atopic dermatitis, current⁷ and/or past.⁵ The onset of disease occurred between 2013 and 2016 in 48 (69%) patients, and in 2015 in most of them (*n* = 23). Only 3 (4%) had a known contact allergy to MI and/or MCI/MI previously proven by patch testing. In total, 69 (92%) patients had ongoing dermatitis at the first consultation; the locations were the hands in 76% (*n* = 57), and the face in 61% (*n* = 46), including 51% (*n* = 38) with periorbital involvement. In 42 (56%) patients, ≥3 anatomical sites (with the categorization chosen) were affected. In the remaining 33 patients, the most common combinations were hands and arms (*n* = 11), hands and feet, and neck and periorbital (*n* = 2 each). In total, 18 (24%) of patients had experienced airborne symptoms, mainly dermatitis (*n* = 15), but rhinitis (*n* = 3), asthma-like symptoms (*n* = 1) and/or conjunctivitis (*n* = 2) were also reported.

3.1 | Exposures

According to the documentation of products to which the patients had been exposed, 71 were exposed to products containing MI (between 1 product in 16 patients to 11 products in 2 patients; the mean number of products was 3.8). Exposure to products containing MCI/MI was noted in 57 patients (between 1 product in 19 patients to 11 products in 1 patient; the mean number of products was 2.4). Exposure to privately used products was dominant, with a share of 89% (*n* = 67) and a mean number of products of 3.4; occupationally used products were documented for just 27% of patients (*n* = 20). The main product groups in the context of private exposure were wet wipes, liquid soaps, shampoos, bath and shower gels, and hand creams (Table 1). Additionally, liquid laundry detergents (*n* = 21) and fabric softeners (*n* = 14) were frequently identified as containing MI or MCI/MI.

3.2 | Current relevance

In 67 of 75 (89.3%) patients, MI contact allergy was found to be of current relevance. Products were identified that had caused or contributed to the current dermatitis. On average, 2.87 products per

patient were given as being responsible for the dermatitis. The most frequent types of product found to be relevant were dishwashing liquids (36%), laundry detergents, and shampoos (34.7% each) (Table 2).

3.3 | Severity, QoL, and course of disease

Severity was assessed by the physician at the first consultation, when patch testing was planned according to a VAS from 0 (no dermatitis) to 100 (very severe dermatitis), and again at a follow-up visit at least 3 months following patch testing. At the first consultation, the median severity was 40, with 30 and 80 as quartiles; the range was 5 to 100. At the follow-up visit, the median severity was 5, with 0 and 17.5 as quartiles; the range was 0 to 70. This is shown in Figure 1. The improvement in severity was statistically significant (*P* < .001, Wilcoxon signed-rank test).

At the same time, the patients were asked to indicate how much their skin disease had influenced their daily life negatively, by thinking of the past week, on a VAS scale from 0 (no influence) to 100 (could not be worse). At their first consultation, the median negative impact score was 100, with 70 and 100 as quartiles; the range was 15 to 100. At the follow-up visit, the median negative impact score was 5, with 0 and 20 as quartiles; the range was 0 to 100. This is shown in Figure 2, and the improvement was statistically significant (*P* < .001, Wilcoxon signed-rank test).

Twelve patients (16%) had to take sick leave because of their MI contact allergy, 2 (2.7%) were admitted to hospital for treatment, and 4 (5.3%) experienced occupational consequences in terms of job loss or job change.

4 | DISCUSSION

This is the first study to examine the prevalence of MI contact allergy in Croatia. An exceptionally high MI contact allergy prevalence of 13.2% in consecutively patch tested patients, defined by a positive

TABLE 2 The most frequent types of product found to be relevant for the current dermatitis

Product	Number	In % of all relevant products
Dishwashing liquid	27	36
Laundry detergent	26	34.7
Shampoo	26	34.7
Wet wipe	23	30.7
Fabric softener	19	25.3
Cleaning agent	15	20
Shower gel	10	13.3
Liquid soap	8	10.7
Hand cream	7	9.3
Wall paint	4	5.3
Face cream	4	5.3
Conditioner	3	4
Roll-on deodorant	3	4
Make-up remover	2	2.7

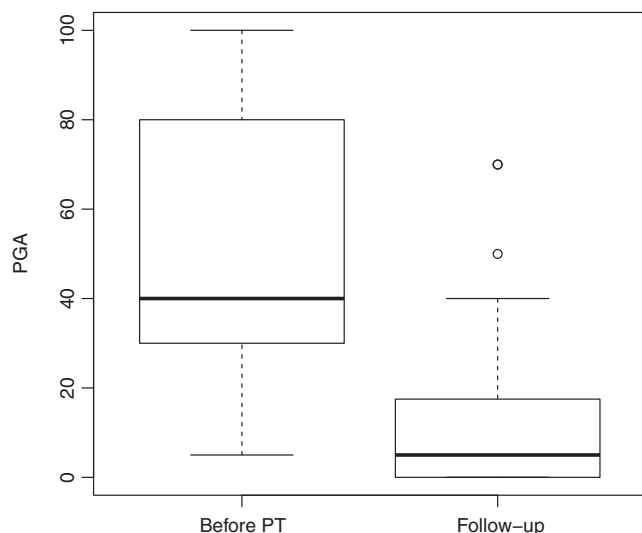


FIGURE 1 Visual analogue scale of severity according to physician's global assessment (PGA) at baseline and at the follow-up visit. PT, patch testing

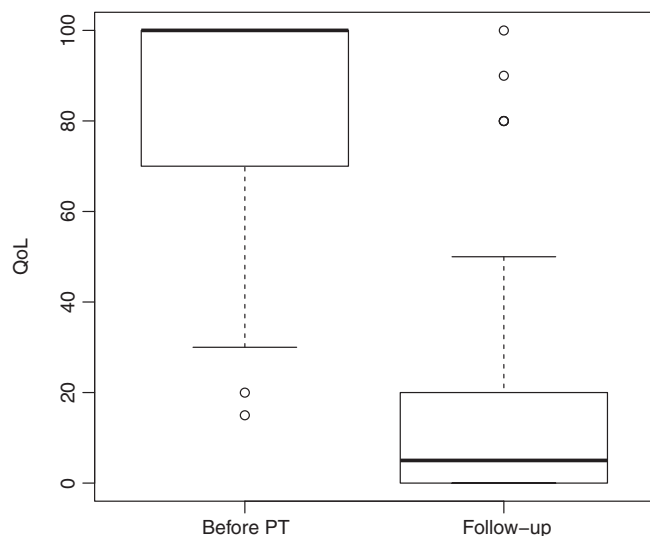


FIGURE 2 Visual analogue scale of quality of life (QoL)/impact on daily life perceived by the patient at baseline and at the follow-up visit. PT, patch testing

patch test reaction, was found. In comparison, 6.0% of consecutively patch tested patients from 8 European countries had a positive patch test reaction to MI in 2015, with a top prevalence of 13.0% (7/54) in Finland, in a special centre for occupational skin disease.⁸ In previous investigations from 2013 in individual countries, high prevalences were found in Portugal, with 10.9% positive patch test reactions to MI,⁹ 11.1% in the British Isles,⁷ and 13.2% in Finland.¹⁰ If the number of patients with positive patch test reactions to MCI/MI are added to those with positive patch test reactions to MI, 1 in 5 patients in Croatia are allergic to isothiazolinones, which were permitted in cosmetic products at the time. In the current investigation, most reactions were caused by consumer products. This is also reflected in the fact that many more females than males were allergic to MI (2.1% males; 11.0% females), which is also seen in other populations.¹¹

The majority (69%) of cases identified in Croatia were incident cases with an onset of dermatitis within the past 3 years, reflecting an ongoing epidemic. In a study from Leeds,¹² trends of MI contact allergy were followed from 2008 to 2015. Even though decreasing prevalences of both MI and MCI/MI contact allergy were seen after 2013, when the first recommendation from the Scientific Committee on Consumer Safety to ban MI in cosmetic products was given,¹³ 11 of 16 patients (69%) had their first symptoms after 2013.¹² In the European multicentre study mentioned above, 68% (86/126) of patients also developed symptoms after 2013.⁸ In this study from Croatia, the most frequent types of product found to be relevant to the dermatitis, that is, considered to be causative, were dishwashing liquids (36%), laundry detergents, and shampoo (34.7% each). Wet wipes as leave-on cosmetics (30.7%) were among the top-ranking causative products, which is interesting, as wet wipes were implicated in the first reported cases of MI contact allergy caused by cosmetics.¹⁴ Hand and facial creams accounted for 9.3% and 5.3% of causative products, respectively, which may reflect the start of an effect of the announced ban regarding leave-on cosmetic products¹⁵; the ban was fully implemented by February 17, 2017, from which date leave-on cosmetics containing MI have not been allowed to be sold in Europe. There is a changing pattern in the product types causing MI contact allergy, from leave-on cosmetics to rinse-off and household products. In a recent Swiss market survey of 1948 consumer products, it was shown that only 7.6% of all cosmetic products were found to contain isothiazolinones. Shampoo was the product category with the highest percentage of isothiazolinones (33.8%), followed by shower gel (13.3%), and wet wipes (11.6%).¹⁶ A higher proportion of detergents (42.7%) than of cosmetics was found to contain isothiazolinones, most often benzisothiazolinone (BIT), in 31.2%, followed by MI in 31.1% and MCI in 9.9%. High concentrations were particularly found in detergents.¹⁶ These results connect well with the patterns of causative products in the current investigation.

In total, 18 (24%) patients had experienced airborne symptoms, mainly dermatitis ($n = 15$), but also rhinitis, asthma-like symptoms, and/or conjunctivitis. Isothiazolinones are used in many water-based paints.^{17,18} MI was found in 55 of 60 (91.7%) paints bought in 5 different European countries in concentrations up to 142 ppm.¹⁸ MI is volatile and can be found for weeks in indoor air after indoor walls have been freshly painted.¹⁹ Airborne contact dermatitis and airway symptoms in MI-allergic children and adults from many countries have been reported.^{2,4,8} There seems to be no effective solution tackling this severe problem.

This is one of the few studies that have investigated the course of disease, the impact on daily life, and the positive effects of being patch tested and informed about a relevant allergy,^{20–24} in this case to MI. A major impact of contact allergy to MI was found. The patients scored the negative impact of their skin disease at the first consultation as “could not be worse”, corresponding to median of 100, on a VAS from 0 to 100. At the same time, the dermatologist assessed the severity of the skin disease on a VAS yielding a median of 40, with 30 and 80 as quartiles, on a 0 to 100 scale. The many sources of MI exposure contribute to the severe state of disease in these patients, along with hidden exposure from products for which there is no ingredient labelling requirement.²⁵

The study also showed a very clear benefit of diagnosing MI allergy by patch testing, informing patients about how to avoid exposures, and treatment. At the follow-up visit after 3 months, the negative impact of disease was scored as 5 points as median by the patients, and so was the severity of disease assessed by the dermatologists. A study from Leeds in the United Kingdom with follow-up 2 months after patch testing showed that patients confirmed as having contact allergy had a subsequent improvement in eczema severity and an improvement in QoL.²¹ A follow-up study on 105 formaldehyde-allergic patients with clinical assessment showed that patients' dermatitis had generally improved as compared with their first visit to the department.²⁰ It was also seen that patients who paid attention to their allergy had significantly fewer rashes than those who did not.²⁰ However, another study, from the United States, found that allergic contact dermatitis (ACD) had an appreciable effect on QoL, especially when it affected the hands or face, or was work-related.²²

It was shown that outcomes in patients with ACD were improved by early diagnosis.²² In the United Kingdom, an audit on the value of patch testing from the patients' perspective was performed. It showed that patch testing was beneficial, especially for those with ACD. Patients' knowledge of the results was good, but education could be improved.²³ In our study, only patients with positive patch test reactions to MI were included; however, in a study from the United States following up 431 patients with suspected ACD, there was significantly better improvement in each patch tested subject concerning QoL than in subjects who had not been patch tested.²⁴

During the current epidemic, many people in the European population have become sensitized. It is of concern that many of these probably do not have access to dermatology care and patch testing. It has been estimated that only 15% to 38% of patients with ACD in Germany²⁶ and 20% to 30% of patients with ACD in Denmark²⁷ are seen by a dermatologist and patch tested. As these countries offer free access to healthcare services, the situation in some other countries may be much worse. This means that patch test data show only the tip of the iceberg, and a large pool of individuals are sensitized but not diagnosed with contact allergy, for example, to MI, and cannot benefit from advice and ingredient labelling. They will continue to have symptoms unless other preventive actions are taken, such as restrictions on or bans of the causative substances. In conclusion, the severity and frequency of ACD caused by MI and its impact on daily life clearly emphasize the need for prevention.

CONFLICT OF INTEREST

W.U. has accepted honoraria for presentations or travel reimbursement from cosmetic industry associations, and lecture fees from dermatology-related sponsors for educational lectures on contact allergy. The other authors declare no potential conflict of interests.

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