

The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicentre study

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doi:10.1111/cod.12249

Summary

Background. The rate of contact allergy and allergic contact dermatitis caused by methylisothiazolinone (MI) is dramatically increasing throughout Europe.

Objectives. To report on methylchloroisothiazolinone (MCI)/MI and MI allergy in Belgium.

Patients and methods. Between January 2010 and December 2012, the medical charts of 6599 patients of the Belgian Contact and Environmental Dermatitis Group were retrospectively reviewed for MCI/MI and MI sensitization by use of a standardized questionnaire. Available data on sensitization in 2081 patients tested in 2013 were also included.

Results. In 2012, the sensitization rate for MCI/MI had increased to 4.5% and that for MI to 6.0%; the latter showed a further increase to 7.2% in 2013. The people mainly affected were women with a median age of 49 years with hand and/or facial dermatitis, most often resulting from the use of cosmetics. Simultaneous reactions to octylisothiazolinone were observed.

Conclusion. A dramatic increase in the rate of contact allergy caused by MI in cosmetics is occurring in Belgium. Notwithstanding the recent recommendation to discontinue the use of MI in leave-on cosmetics, safer use concentrations should also be determined for rinse-off products. Close monitoring of MI sensitization in the near future will be necessary, and the highest test concentrations reported for MI and MCI/MI should be included in the baseline series.

Key words: airborne; allergic contact dermatitis; cosmetics; deodorants; epidemic; generalized reactions; methylisothiazolinone; occupational; paints; wipes.

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Funding: None.

Conflicts of interest: The authors declare no conflict of interests.

Accepted for publication 25 March 2014

Despite the belief that sensitization by methylisothiazolinone (MI; CAS no. 2682-20-4) does not occur easily (1), a significant number of allergic contact reactions caused by this preservative have been reported in Europe, as well as in other parts of the world (2–6). We present here the Belgian experience with MI contact allergy.

Patients and Methods

The medical charts of patients who were investigated between January 2010 and December 2012 at six

university patch test clinics and by three private dermatologists, who are members of the Belgian Contact and Environmental Dermatitis Group (BCEDG), were retrospectively reviewed for methylchlorisothiazolinone (MCI)/MI and MI allergy. All participants reported on the total number of patients who had been tested with MCI/MI and with MI alone, specifying the test concentrations used: for MCI/MI, 100 and/or 200 ppm (both from Chemotechnique, Vellinge, Sweden); for MI, 200 ppm (Chemotechnique) and/or 500 ppm (Trolab, Hermal, Reinbeck, Germany) and/or 1000 ppm (obtained from the Department of Occupational Dermatology in Malmö and tested in Leuven only within the framework of a multicentre study), and/or 2000 ppm (Chemotechnique). All patients were patch tested according to the guidelines of the International Contact Dermatitis Research Group. For the patients who had a positive reaction to MCI/MI and/or MI at D3 or D4, the following data were additionally collected by use of a standardized questionnaire: age and sex, the location of the dermatitis (more than one possible location per patient), the source of the allergen (more than one possible source per patient), the route of exposure (i.e. occupational versus consumer-related), the occurrence of airborne dermatitis, respiratory symptoms or other symptoms, and – if tested – simultaneous reactions to benzisothiazolinone (BIT) 0.05% pet. and octylisothiazolinone (OIT) 0.1% pet. (Chemotechnique or Trolab). The dermatologists were also asked to mention unusual clinical features, if present. Upon additional request, six of nine centres also reported on some available data regarding MCI/MI and MI sensitization in 2013. Statistical analysis, where appropriate, was performed with SPSS 21.0 for Windows™ (SPSS™, Inc., Chicago, IL, USA), and results were considered to be significant when the *p*-value was < 0.05. Continuous variables (age) are

reported as median (minimum–maximum), and categorical variables are reported as numbers (proportions). Differences in age between the 3 years were assessed with the Kruskal–Wallis test. Differences in proportions were compared between the 3 years with a chi-square test or Fisher's exact test when numbers were too small.

Results

Patch test concentrations used for MCI/MI and MI

By the end of December 2012, 6599 patients (2117 in 2010, 2135 in 2011, and 2347 in 2012) had been tested with MCI/MI at 100 ppm (0.01% aq.) as included in the baseline series. MCI/MI 200 ppm was additionally tested in 252 patients (73 in 2010, 92 in 2011 and 87 in 2012), and gave positive results in 6 patients (2.4%) in whom MCI/MI 100 ppm remained negative. In 3 of these patients, a higher test concentration of MI (200 or 500 ppm) gave negative results, indicating that MCI was the culprit allergen. In the remaining 3 patients MI was not tested separately. Moreover, 3923 patients (59.4%, with 587 in 2010, 1473 in 2011, and 1863 in 2012) were tested with MI separately, the majority with 500 ppm (0.05% aq.), that is, 3310 patients (84.4%); 526 in 2010, 1157 in 2011, and 1627 in 2012. In 603 patients (15.4%, i.e. 51 in 2010, 316 in 2011, and 236 in 2012), MI 200 ppm (0.02% aq.) was tested alone, in another 13 patients (2 in 2011 and 11 in 2012) MI 500 ppm was tested as a supplement to MI 200 ppm, and in only 10 patients (0.3%), all in 2010, was MI 1000 ppm (0.1% aq.) tested. Seven patients who did not react to MI 200 ppm did react to MI 500 ppm. Additionally, six of nine centres reported on 2081 patients tested in 2013 with MCI/MI 100 ppm (1474 patients; 70.8%) and/or 200 ppm [tested alone in 607 patients (29.2%); tested as a supplement in

Table 1. Total number of patients tested and their reaction to methylchlorisothiazolinone (MCI)/methylisothiazolinone (MI) and MI*

	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	Total number of tests (4 years)
MCI/MI tests [†]	2117	2135	2347	2081	8680
MCI/MI-positive	77 (3.6)	80 (3.7)	105 (4.5)	111 (5.3)	373
MCI/MI-negative	2040 (96.4)	2055 (96.3)	2242 (95.5)	1970 (94.7)	8307
MI tests [†]	587	1473	1863	2056	5979
MI-positive [‡]	18 (3.1)	47 (3.2)	111 (6.0)	148 (7.2)	324
MI-negative	569 (96.9)	1426 (96.8)	1752 (94)	1908 (92.8)	5655
Total number of patients with a positive test result	82	93	160	174	509

%, percentage of patients in the given year.

*Study period 2010–2013.

[†]Any test concentration of MCI/MI (100 or 200 ppm) and MI (200, 500, 1000 or 2000 ppm).

[‡]Of which patients not reacting to MCI/MI: 5 (in 2010), 13 (in 2011), 55 (in 2012), and 63 (in 2013).

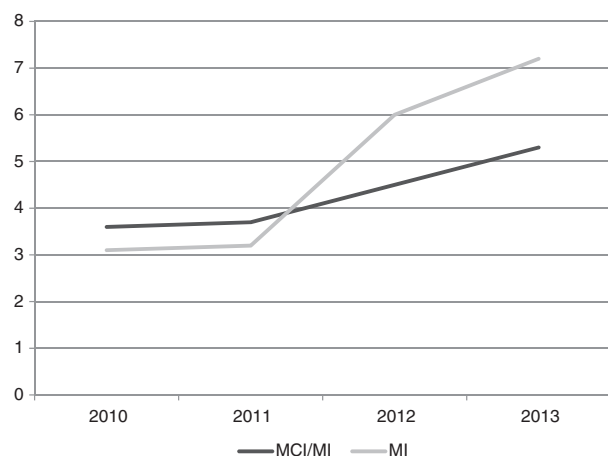


Fig. 1. Rates of sensitization to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and MI in Belgium between January 2010 and December 2013: 2010–2012, data from nine of nine centres; 2013, data from six of nine centres.

314 patients (15.1%)]]. Of 2081 patients, 2056 were also tested with MI 500 ppm (all patients), and in 612 of them it was tested with 2000 ppm as a supplement. One centre (A. Goossens, KU Leuven) reported that, of 17 MCI/MI-allergic patients, 3 (17.6%) were only detected with MCI/MI 200 ppm, and that, of 30 MI-allergic patients, 6 (20%) were only diagnosed with MI 2000 ppm.

Rates of sensitization to MCI/MI and MI

We observed an increase in the rate of contact sensitization to MCI/MI, from 3.6% in 2010, to 3.7% in 2011, and to 4.5% in 2012; this was not statistically significant ($p=0.158$), but showed a clear rising trend. In 2013, MCI/MI sensitization reached 5.3%, and this was statistically significant ($p=0.024$, based on data from six participating centres). The increase in the number of patients reacting to MI alone was even more pronounced: 3.1% in 2010, 3.2% in 2011, and a dramatic increase up to 6.0% in 2012, which was statistically significant ($p=0.006$), and even reaching 7.2% in 2013 ($p<0.001$, again based on data from six centres) (Table 1; Fig. 1). The positive reactions found were increasingly of 'current and certain' relevance (45.1% in 2010, 65.6% in 2011, and 66.2% in 2012; $p=0.002$) (Table 2). Interestingly, the number of reactions that would have been missed if only the mixture of MCI/MI 100 ppm had been tested, calculated as the ratio between (i) the number of patients not reacting to the mixture of MCI/MI and thus only detected by testing MI separately in a given year and (ii) all patients reacting positively to MCI/MI and/or MI in that year, showed a similar increase: 5 of 82

Table 2. Relevance of the reactions to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and/or MI*

Year	Current certain (%)	Current probable (%)	Unknown (%)	Past (%)
2010	45.1	30.5	20.7	3.7
2011	65.6	16.1	16.1	2.2
2012	66.2	14.4	16.9	2.5

*As a percentage of all patients with a positive patch test reaction to MCI and/or MI in the study period 2010–2012.

Table 3. Age and sex distribution of the patients reacting to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and/or MI*

Year	Age (years)			Sex (%)
	Range	Mean	Median	Female/male
2010	12–85	47.7	48.5	68.3/31.7
2011	2–80	45.9	48	72/28
2012	2–90	47.7	49.5	62.5/37.5

%, percentage of patients in a given year.

*Study period: 2010–2012.

(6.1%) in 2010, 13 of 93 (14%) in 2011, and 55 of 160 (34.4%) in 2012, the last of these being again statistically significant ($p<0.001$). In 2013, as observed in six centres, the percentage of missed reactions showed a slight further increase to 36.2% (63 reactions missed out of 174).

Age and sex distribution of patients reacting to MCI/MI and/or MI

Although the median age was 49 years (Table 3), the youngest patient observed was only 2 years of age and the oldest patient was 90 years of age. More females than males (223 versus 112 or 66.6% versus 33.4%, respectively) were affected, with a slight increase (not statistically significant; $p=0.373$) in the male population in 2012 as compared with previous years.

Localization of the dermatitis

The face, including the eyelids, and the hands were the most often reported sites (Table 4), whereas the number of patients presenting with anogenital lesions decreased significantly ($p=0.027$). We noticed an increase in generalized and severe reactions; among these, in 3 cases, the main body folds were affected. Reactions in the axillary region were attributable to the use of deodorants. Exceptionally reported locations included the lips, ears, the peristomal area, around scars, wounds, and

Table 4. Locations of contact dermatitis caused by methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and/or MI*

Location	2010 n (%)	2011 n (%)	2012 n (%)
Face	22 (20.4)	24 (17.9)	47 (20.7)
Eyelids	10 (9.3)	9 (6.7)	22 (9.7)
Hands [†]	21 (19.4)	33 (24.6)	46 (20.3)
Arms	4 (3.7)	10 (7.5)	13 (5.7)
Axillae	3 (2.8)	6 (4.5)	8 (3.5)
Generalized	12 (11.1)	16 (11.9)	35 (15.4)
Anogenital	13 (12.0)	9 (6.7)	13 (5.7)
Scalp	5 (4.6)	1 (0.7)	6 (2.6)
Trunk	5 (4.6)	5 (3.7)	4 (1.8)
Legs	4 (3.7)	5 (3.7)	6 (2.6)
Feet	5 (4.6)	6 (4.5)	8 (3.5)
Neck	2 (1.9)	6 (4.5)	13 (5.7)
Other (exceptional)	2 (1.9)	4 (3.0)	8 (3.5)
Total number of locations	108	134	227
Total number of patients positive for MCI/MI and/or MI	82	93	160

%, the relative percentage of the location with regard to all mentioned locations in a given year.

*Study period: 2010–2012.

[†]One case with pulpitis of the fingers, 1 case superimposed on psoriasis.

prostheses, the buttocks (one a toilet seat distribution and one a sofa seat distribution), and 1 case of dermatitis on the shoulder.

Sources of MCI/MI and/or MI

Cosmetics were the most important allergen sources, in 53.7%, 61.3% and 60.6% of cases in 2010, 2011 and 2012, respectively. Although the exact cosmetic was reported only for a subgroup of patients, some specific leave-on products mentioned included wet wipes (which are actually decreasing as an allergen source) and deodorants, but also a considerable number of rinse-off cosmetics (e.g. shampoos). The non-cosmetic sources of exposure were mainly household detergents, the frequency of which doubled from 4.1% in 2010 to 8.7% in 2012, and paints. Exceptional allergen sources included a sexual lubricant, glue and glue remover, a repair product for a boat, an industrial biocide, oil and cooling fluids, water mattress antibacterials contaminating the contact surface of the bed (7), polish, roofing material, a fabric softener, and finally, very likely through contamination with a cleaning product containing MI, a leather sofa, a toilet seat, and towels.

Table 5. Occupational contact dermatitis caused by methylchloroisothiazolinone/methylisothiazolinone (MI) and/or MI*

Occupation	n	Allergen source(s)
Labourers [†]	14	Various sources [†]
Painters	10	Paints
Hairdressers	7	Hair care products
Cleaners	6	Detergents
Nurses	4	Hand soaps
Beauticians	3	Cosmetics
Nursery (of children)	2	Wipes, childrens' cosmetics
Massage therapists	2	Massage creams, detergents
Mechanics	2	Hand soaps
Profession not stated	2	Detergents, skin care products
Stone cutter	1	Detergents

n, number of patients.

*Study period: 2010–2012.

[†]Of which: 1 working in the plastics industry (oil and cooling fluids); 1 working in ship maintenance (oil and cooling fluids); 2 working as forklift drivers (oil and cooling fluids, polish emulsion); 3 with no occupation stated (glues, oil, and cooling fluids); 2 working in the copper wire industry (hand soaps); 1 roofer (roofing material); 3 working in a paint factory (paints); and 1 working in a cosmetic factory (cosmetics)

Occupational versus consumer sensitization

A relatively low number of occupation-related exposures to MCI/MI and/or MI was reported (15.9% of the cases in 2010, 19.4% in 2011, and 13.8% in 2012), as shown in Table 5. Although industrial products were the most common sources, cosmetics, such as hand soaps, constituted a reasonable number: of the 55 mentioned responsible work-related allergen sources, 24 (44.4%) were cosmetics and 31 (56.4%) were industrial products.

Airborne dermatitis, respiratory complaints, and other symptoms

In 29 of 335 (8.7%) patients who reacted to MCI/MI and/or MI in the period 2010–2012, an airborne distribution was present, in all cases but 1 (roofing material) caused by water-based paints in which MI (sometimes in association with other isothiazolinones) was used as a preservative. No respiratory symptoms were mentioned, and only 1 patient had a conjunctivitis complicating eyelid dermatitis, presumably caused by an eye-care cream and/or hair spray containing MI.

Simultaneous reactions to BIT and OIT

As BIT and OIT were not systematically tested, we report only MCI/MI-allergic and/or MI-allergic patients and their profiles of reactions to BIT and OIT: among the 335

patients testing positively during the period 2010–2012, only 194 were tested with BIT and 199 with OIT, of whom 4 reacted only to BIT, 23 only to OIT (among which were 3 patients who were not tested with BIT), and 8 to both BIT and OIT. Relevant allergen sources for BIT and OIT could be traced in only 19 of 35 cases (54.3%), and, among these, 11 were considered to be occupational and 8 non-occupational: paints (10 cases), detergents (5 cases), oils and cooling fluids (2 cases), glue or glue remover (1 case), and a fabric softener (1 case). The remaining 16 patients (45.7%) all showed non-occupational sensitization to MCI/MI and/or MI through exposure to cosmetics; no relevance was found for BIT (in 5 patients of which 1 patient reacting only to BIT and 4 patients reacting to both BIT and OIT) nor for OIT (in 15 patients of which 11 reacting only to OIT and 4 reacting to both BIT and OIT). In 15 of 31 patients reacting to OIT without any relevant source, cross-reaction with MI was considered to be likely and in 6 of them (40%) MI was pointed out as the primary sensitizer, based on the gradation of the patch test reaction (MI > MCI/MI).

Unusual clinical manifestations

The following unusual clinical manifestations were mentioned: (i) widespread papular eruption mimicking a drug eruption (3 patients); (ii) worsening of atopic dermatitis (1 patient); (iii) systemic allergy mimicking atopic eczema (3 patients); (iv) mixed eczematous–urticarial skin eruption (2 patients); (v) asteatotic eczema (1 patient); (vi) possible photoaggravation (1 patient); (vii) dermatitis according to a toilet seat (1 patient) and to a leather sofa seat (1 patient) distribution; and (viii) genital dermatitis causing relapsing episodes of bacterial cellulitis (1 patient).

Discussion

Since 2005, MI, the less potent allergen in MCI/MI and considered to be a moderate to strong sensitizer (8, 9), has been permitted in concentrations up to 100 ppm in both leave-on and rinse-off cosmetics, whereas in industrial products (e.g. paints) no maximum concentration has been set. Unfortunately, we are now again confronted with an epidemic progressing at a much higher rate than previous ones (10).

The rate of MCI/MI sensitization in Belgium showed a clear increase up to 4.5% in 2012, and a further increase to 5.3% in 2013, whereas the rate of MI sensitization almost doubled, from 3.1% in 2010 to 6.0% in 2012, and increasing even further up to 7.2% in 2013 (with data in 2013 retrieved from six of nine centres), in agreement with other reported sensitization

rates (2, 11); meanwhile, even higher rates have been published (5). It has already been shown that MI is responsible for the sudden increase in MCI/MI contact allergy (3). Furthermore, our study confirms that a test concentration of 100 ppm MCI/MI in the baseline series is definitely inadequate to detect MI allergy, as up to 36.2% of patients with an MI contact allergy in 2013 would have been missed if only the mixture had been tested. Moreover, in some cases, contact allergy to MCI could only be shown by testing with MCI/MI 200 ppm.

The higher rate of consumer exposure to MI, through both leave-on and rinse-off cosmetics, offers the most reasonable explanation for the present epidemic, taking into account that most patients were usually referred for patch testing for the first time without known prior contact dermatitis. Although we did not conduct a formal survey to confirm this, both types of cosmetic on the Belgian market increasingly contained MI. We cannot completely exclude the possibility that the increase in the number of reactions to MI from 2010 to 2013 was, in part, caused by the fact that more dermatologists started to test MI in addition to MCI/MI, usually at 500 ppm, and sometimes at 2000 ppm, thereby causing a higher number of reactions in 2013 than in earlier years. However, the proportion of MI-positive patients detected in 2013 reached 7.2%, which is a tremendously high sensitization rate for any given allergen.

MI-positive patients are mostly females, with a median age of 49 years; this is comparable with data from a UK study (12), the authors of which attribute this to the lack of a sufficient downregulatory response in older individuals, although more intensive use of anti-ageing products (e.g. face and eye contour creams) is another explanation. The female preponderance is probably attributable to more females attending patch test clinics (for example, in the KU Leuven Contact Allergy Unit: 65% females versus 35% males), especially regarding allergy to cosmetics. The age range is very broad, and MI contact allergy has recently been observed even in very young children (13, 14).

The face and hands were most frequently affected, whereas, in contrast to other reports (11), the number of patients with anogenital dermatitis had significantly decreased, probably along with the decrease in the use of isothiazolinone-containing wipes in Belgium (15). Eyelid dermatitis could sometimes be traced to specific leave-on products for use on periocular skin. Axillary dermatitis was always caused by MI in deodorants, in agreement with previous reports (11, 16), with the occluded area of the axillary fold (like the anogenital region) facilitating skin penetration and sensitization. The gradual reporting of more than one affected body location, together with more generalized and severe reactions, the latter also

being recently reported (17), both support the idea that the rates of MI exposure and contact allergy are increasing, and that a cumulative effect, attributable to the use of several MI-containing products, might be present in a given patient.

Regarding cosmetics as allergen sources, particularly leave-on products, but also rinse-off products, were involved, the latter presumably in patients previously sensitized. It should be noted, however, that, in an occupational setting (e.g. in hairdressers), a given rinse-off product (e.g. a shampoo), through repeated and cumulative exposure, might act as a 'leave-on' product and induce sensitization (11). Sometimes, the EU Cosmetic Regulation is even violated; for example, industrially used soaps may contain non-allowed isothiazolinones such as BIT (data on file), and OIT has recently been identified in a baby liquid soap (18) and MI in concentrations exceeding the maximum allowed limit, that is, >100 ppm, in another liquid soap (18). Validation of the most appropriate chemical analytical tools for determining the qualitative and quantitative isothiazolinone content of a given product, thus ensuring adequate quality control in cosmetics and non-cosmetics, seems desirable (18).

With regard to household cleaning products, previous surveys had already indicated that up to 16.5% of them contained MI (19, 20), but this might be an underestimate, given that products are not always correctly labelled (21).

Water-based paints, as in other studies, appear to cause specific problems (22–24): they are not only occupational allergen sources, but, owing to their widespread use in homes, at work, and in public spaces, are also able to cause airborne and/or systemic allergic dermatitis, the latter by inhalation, usually in individuals previously sensitized to cosmetics; however, primary sensitization can often not be excluded (25), as concentrations ranging from 100 to 270 ppm (26) may be found. Although 1 case report (13) suggested the possibility of MI evaporation from wall paint during a period of ~4 weeks, and another study reported 5 cases with persistent dermatitis for several weeks up to 4 months following exposure (24), the question of how long MI evaporates from paints remains unresolved.

Within the group of exceptional allergen sources, it is noteworthy that dermatitis could be elicited even through the use of contaminated personal objects (e.g. a leather sofa contaminated with MI present in a cleaning product), an elicitation route that has been previously reported for other strong allergens (27). Interestingly, a patient was recently reported in whom penetration of MI through natural rubber gloves might have been the cause of persistent hand dermatitis (28). Other surprising sources of MCI and MI have recently been published in the literature (29, 30).

Occupational dermatitis was observed in only a minority of cases, with work-related cosmetics often being the culprits. The occupations at risk were mainly (in declining order of importance): (i) labourers in various industries; (ii) painters; (iii) hairdressers; (iv) cleaners; and (v) nurses.

No respiratory symptoms were mentioned, although such cases have been previously reported (e.g. 22, 24, 31), and nor were lupus-like or urticarial reactions, as has been reported previously (32, 33). The way in which our study was conducted made it difficult to evaluate these manifestations thoroughly.

With regard to other isothiazolinone derivatives, for which contact allergy is probably underestimated, our patients testing positively to them more frequently showed reactions to OIT than to BIT, with MI being considered the likely primary sensitizer in 6 of 15 (40%) OIT-positive subjects. Despite their chemical similarity, only a few studies have investigated possible cross-reactions between these derivatives (34–36). Paints, but also household detergents and industrial products, often contain different isothiazolinones; hence, co-sensitization may also account for the simultaneous reactions (34, 37). However, in nearly half of the cases in our study, which mainly consisted of patients primarily sensitized to MI by exposure to cosmetics, the reactions could not be explained by a simultaneous or occupational exposure to a BIT-containing or OIT-containing source. As not all patients sensitized to MI showed a reaction to OIT, partial cross-reactivity seems the most likely explanation. It is of note that research regarding optimal patch test vehicles and/or concentrations for OIT, as has been performed for MI in recent years, is lacking (38).

A limitation of our study is that only MCI/MI-positive and/or MI-positive patients were evaluated; moreover, the retrospective design of this study did not allow accurate tracing of all possible allergen sources.

Conclusions

Despite its limitations, owing to its multicentre and retrospective design, our study confirms the increasing rate of MI allergy in Belgium, with a dramatic 7.2% sensitization rate in 2013. Our data might even underestimate the MI epidemic in Belgium, as patch tests were mainly performed with MI 500 ppm, and in a minority of cases even with 200 ppm. Indeed, testing with 2000 ppm MI, as recently recommended (39), might have detected even more cases, as already found by some BCEDG members who started using the latter concentration routinely in 2013.

We have confirmed that contact dermatitis caused by MI is mainly attributable to leave-on cosmetics, including wet wipes and deodorants, but rinse-off products (e.g.

hair care products), household detergents and water-based paints are highly represented as well. Although regulatory action to limit the further spread of the MI epidemic was not initially considered to be a priority (40), the European Commission's Scientific Committee on Consumer Safety (SCCS) recently adopted an Opinion (41) on the use of MI in cosmetics, and at the same time Cosmetics Europe, representing the industry, discouraged the further use of MI in leave-on cosmetics (42); in Belgium, the effect of this is probably already apparent, with the decreasing use of MI in wet wipes. However, at this point, the question remains of how quickly this recommendation will be implemented for all leave-on cosmetics in Belgium, and in the rest of Europe, and how this will affect MI sensitization. Given the enormous reported rates thus far, follow-up studies are vital to monitor MI sensitization closely in the coming years. Moreover, a

safer use concentration of 15 ppm, or even lower, for MI in rinse-off cosmetics, the former being expressed in the SCCS Opinion, is warranted, and one might even consider lowering the permitted use concentration for MCI/MI (5). Moreover, regulation of MI in industrial products, especially paints and detergents, is strongly advocated.

Addition of MI 500 ppm (43), and even 2000 ppm, with a micropipette for application (39), and also MCI/MI 200 ppm to the European baseline series is urgently needed for the correct diagnosis of contact allergy to MI and MCI.

Finally, future studies might focus on cross-reactions between different isothiazolinone derivatives, more appropriate test conditions (vehicles and/or concentrations) for those other than MCI/MI and MI, and on clinical manifestations other than skin involvement (e.g. respiratory complaints).

References

- Burnett C L, Bergfeld W F, Belsito D V et al. Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol* 2010; **29**: 187S–213S.
- Urwil R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new epidemic. *Contact Dermatitis* 2013; **68**: 250–256.
- Geier J, Lessmann H, Schnuch A et al. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; **67**: 334–341.
- Lundov M D, Opstrup M S, Johansen J D. Methylisothiazolinone contact allergy – a growing epidemic. *Contact Dermatitis* 2013; **69**: 271–275.
- Lammintausta K, Aalto-Korte K, Ackerman L et al. An epidemic of contact allergy to methylisothiazolinone in Finland. *Contact Dermatitis* 2014; **70**: 183–192.
- Castaneda-Tardana M P, Zug K A. Methylisothiazolinone. *Dermatitis* 2013; **24**: 2–6.
- Vandevenne A, Goossens A, Verreycken E et al. Dermite de contacto alérgica ao metilcloro- e metilisotiazolinona numa cama de água? *J Port Soc Dermatol Venereol* 2012; **70**: 223–225.
- Basketter D A, Gilmour N J, Wright Z et al. Biocides: characterization of the allergenic hazard of methylisothiazolinone. *Cutan Ocul Toxicol* 2003; **22**: 187–199.
- Roberts D W. Methylisothiazolinone is categorised as a strong sensitizer in the murine local lymph node assay. *Contact Dermatitis* 2013; **69**: 261–262.
- Wilkinson J D, Shaw S, Anderen K E et al. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; **46**: 207–210.
- Uter W, Geier J, Bauer A et al. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013; **69**: 231–238.
- McFadden J P, Mann J, White J M L et al. Outbreak of methylisothiazolinone allergy targeting those aged > 40 years. *Contact Dermatitis* 2013; **69**: 53–63.
- Aerts O, Cattaert N, Lambert J et al. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. *Contact Dermatitis* 2013; **68**: 250–256.
- Bregnbak D, Johansen J D. Airborne sensitization to isothiazolinones observed in a 3-month-old boy. *Contact Dermatitis* 2013; **69**: 55–56.
- Timmermans A, De Hertog S, Gladys K et al. 'Dermatologically tested' baby toilet tissues: a cause of allergic contact dermatitis in adults. *Contact Dermatitis* 2007; **57**: 97–99.
- Amaro C, Santos R, Cardoso J. Contact allergy to methylisothiazolinone in a deodorant. *Contact Dermatitis* 2011; **64**: 289–302.
- Bregnbak D, Lundov M D, Zachariae C et al. Five cases of severe chronic dermatitis caused by isothiazolinones. *Contact Dermatitis* 2013; **69**: 57–59.
- Alvarez-Rivera G, Dagnac T, Lores M et al. Determination of isothiazolinone preservatives in cosmetics and household products by matrix solid-phase dispersion followed by high-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr A* 2012; **1270**: 41–50.
- Yazar K, Johnsson S, Lind M L et al. Preservatives and fragrances in selected consumer-available cosmetics and detergents. *Contact Dermatitis* 2010; **64**: 265–272.
- Magnano M, Silvani S, Vincenzi C et al. Contact allergens and irritants in household washing and cleaning products. *Contact Dermatitis* 2009; **61**: 337–341.
- Vanneste L, Persson L, Zimerson E et al. Allergic contact dermatitis caused by methylisothiazolinone from different sources, including 'mislabelled' household wet wipes. *Contact Dermatitis* 2013; **69**: 311–312.
- Lundov M D, Mosbech H, Thyssen J P et al. Two cases of airborne allergic contact dermatitis caused by methylisothiazolinone in paint. *Contact Dermatitis* 2011; **65**: 176–179.
- Lundov M D, Zachariae C, Menné T L et al. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. *BMJ* 2012; **345**: e8221; doi:10.1136/bmj.e8221.
- Bohn S, Niederer M, Brehm K et al. Airborne contact dermatitis from methylchloroisothiazolinone in wall paint. Abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; **42**: 196–201.

- 25 Kaae J, Menné T L, Thyssen J P. Presumed primary contact sensitization to methylisothiazolinone from paint: a chemical that became airborne. *Contact Dermatitis* 2012; **66**: 340–355.
- 26 Lundov M D, Krongaard T, Menné T L et al. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011; **165**: 1178–1182.
- 27 Hindsén M, Isaksson M, Persson L et al. Photoallergic contact dermatitis from ketoprofen induced by drug-contaminated personal objects. *J Am Acad Dermatol* 2004; **50**: 215–219.
- 28 Espasandín Arias M, Goossens A. Natural rubber gloves might not protect against skin penetration of methylisothiazolinone. *Contact Dermatitis* 2014; **70**: 249–251.
- 29 Lundov M D, Menné T. Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner. *Contact Dermatitis* 2013; **68**: 250–256.
- 30 Uter W, Uter M, Steen-Schubert B et al. Allergic contact dermatitis caused by methylisothiazolinone from a 'waste reduction belt'. *Contact Dermatitis* 2012; **66**: 340–355.
- 31 Lundov M D, Friis U F, Menné T et al. Methylisothiazolinone in paint forces a patient out of her apartment. *Contact Dermatitis* 2013; **69**: 251–259.
- 32 Morren M A, Doms-Goossens A, Delabie J et al. Contact allergy to isothiazolinone derivatives: unusual clinical presentations. *Dermatology* 1992; **184**: 260–264.
- 33 Gebhardt M, Looks A, Hipler U C. Urticaria caused by type IV sensitization to isothiazolinones. *Contact Dermatitis* 1997; **36**: 314.
- 34 Mose A P, Frost S, Öhlund U et al. Allergic contact dermatitis from octylisothiazolinone. *Contact Dermatitis* 2013; **69**: 49–52.
- 35 Geier J, Schnuch A. No cross-sensitization between MCI/MI, benzisothiazolinone and octylisothiazolinone. *Contact Dermatitis* 1996; **34**: 148–149.
- 36 Reyes Balaguer J, Martín Herrera A, De la Cuadra Oyanguren J et al. Occupational allergic contact dermatitis to 2-N-octyl-4-isothiazolin-3-one. *J Investig Allergol Clin Immunol* 2008; **18**: 76–77.
- 37 Mose A P, Lundov M D, Zachariae C et al. Occupational contact dermatitis in painters – an analysis of patch test data from the Danish Contact Dermatitis Group. *Contact Dermatitis* 2012; **67**: 293–297.
- 38 Fousereau J, Brandle I, Boujnah-Khouadja A et al. Allergic contact eczema caused by isothiazolin-3-one derivatives. *Derm Beruf Umwelt* 1984; **32**: 208–211.
- 39 Bruze M, Engfeldt M, Gonçalves M et al. Recommendation to include methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2013; **69**: 263–270.
- 40 Gonçalves M, Goossens A. While Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis* 2013; **68**: 257–258.
- 41 Scientific Committee on Consumer Safety. Opinion on methylisothiazolinone (P94) submission II (sensitisation only), adopted on 12 December 2013. DG Sanco European Commission, 2006. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_145.pdf (last accessed 24 February 2014).
- 42 Cosmetics Europe. Cosmetics Europe issues recommendation to discontinue use of MIT in leave-on cosmetic products, 13 December 2013, 2013. Available at: <https://www.cosmeticseurope.eu/news-a-events/news/647-cosmetics-europe-recommendation-on-mit.html> (last accessed 24 February 2014).
- 43 Waton J, Poreaux C, Schmutz J L et al. Is 500 ppm a better concentration than 200 ppm for diagnosing contact allergy to methylisothiazolinone? *Contact Dermatitis* 2013; **69**: 251–259.