

Methylisothiazolinone contact allergy – a growing epidemic

Michael D. Lundov, Morten S. Opstrup and Jeanne D. Johansen

National Allergy Research Centre, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Gentofte, DK-2820, Denmark

doi:10.1111/cod.12149

Summary

Background. The prevalence of contact allergy to the isothiazolinone preservative methylchloroisothiazolinone (MCI) in combination with methylisothiazolinone (MI) and MI alone has increased in the last couple of years.

Objectives. To investigate the prevalence of contact allergy to MI, MCI/MI and benzisothiazolinone (BIT) among patch tested patients at Gentofte Hospital, as well as the use of MI in cosmetic products.

Methods. Patients patch tested with either MI, MCI/MI or BIT from 2010 to 2012 were included in the study. The MOAHLFA index was registered in all patch tested patients, and relevant exposures were determined in patients with an isothiazolinone allergy. In a market survey, the ingredient labels of cosmetic products were investigated for MI content.

Results. The prevalence of MI and MCI/MI contact allergy increased significantly from 2010 to 2012: from 2.0% to 3.7% for MI ($n = 2766$), and from 1.0% to 2.4% for MCI/MI ($n = 2802$). MI-allergic patients had occupational, hand and face dermatitis significantly more often, and were aged > 40 years. Cosmetics were the most common substances causing relevant exposure found in both MCI/MI-allergic and MI-allergic patients. MI was found in 3.3% of cosmetics on the Danish retail market.

Conclusions. The increase in MI contact allergy is alarming, and urgent action is needed.

Key words: contact allergy; cosmetics; epidemic; methylisothiazolinone.

The isothiazolinone preservatives methylisothiazolinone (MI; CAS no. 2682-20-4), benzisothiazolinone (BIT; CAS no. 2634-33-5) and methylchloroisothiazolinone (MCI; CAS no. 2617-55-4) in a 3:1 combination with MI (MCI/MI) are known causes of allergic contact dermatitis. In the last couple of years, MI has received increased attention, owing to an alarming increase in the prevalence of MI contact allergy in different European countries (1–3). Combined with an increase in the number of

case reports with severe reactions caused by exposure to MCI/MI, MI and/or BIT from various sources, for example paint or workplaces (4–7), this has led to an increased awareness of the use of isothiazolinones and, in particular, MI in consumer products and occupational settings. In cosmetic products, MI is limited to 100 ppm and MCI/MI is limited to 15 ppm (8), whereas the use of BIT in cosmetics was rejected by the Scientific Committee for Consumer Safety in 2012 (9). Previous studies showed that only 1.5% of cosmetic products in Denmark, 0.7% of leave-on cosmetics in Germany and one of 204 (0.5%) Swedish cosmetic products were preserved with MI (10–12). Despite the relatively rare use of MI in cosmetics at the times of the surveys, these products constitute the most relevant exposure in MI-allergic patients (1, 13, 14). The prevalence of MCI/MI contact allergy has been relatively stable for several years, but new studies have

Correspondence: Michael D. Lundov, National Allergy Research Centre, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Gentofte DK-2820, Denmark. Tel: +45 39 77 73 09; Fax: +45 39 77 71 18. E-mail: Michael.dyrgaard.lundov@regionh.dk

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

Accepted for publication 11 August 2013

shown that the recent increase in MI contact allergy has been accompanied by a similar increase in MCI/MI contact allergy prevalence (1–3). No studies on the prevalence of BIT contact allergy have been published, as all publications on BIT contact allergy are case reports. At Gentofte Hospital, the prevalence of MI contact allergy fluctuated between 1.1% and 1.7% from 2006 to 2009 (13). In this study, we present the patch test data from 2010 to 2012 on MCI/MI, MI, and BIT, as well the frequency of use of MI in cosmetic products based on a new market survey.

Materials and Methods

Clinical study

Patients patch tested with 2000 ppm MI in aqua ($n = 2766$), 100 ppm MCI/MI in aqua ($n = 2802$) and 1000 ppm BIT in aqua ($n = 2413$) in 2010, 2011 and 2012 at the Department of Dermato-Allergology at Gentofte Hospital were included in the study. Patch tests were applied on the upper back and occluded for 2 days. Readings were performed at D2, D3 or D4, and D7, according to international guidelines (15). A +, ++ or +++ reaction was considered to be a positive reaction; all other reactions (irritant, doubtful, and negative) were registered as negative. The MOAHLFA index (Male, Occupation, Atopic Dermatitis, Hand, Legs, Face, Age above 40 years) were routinely registered for all patients. Patients' exposures to products containing MI, MI/MCI or BIT were assessed systematically. This means that patients with a positive reaction to either of these allergens brought in all their cosmetic products for inspection of the ingredient label. Potential exposures at work were assessed, safety material data sheets were systematically analysed, and producers were contacted, if relevant, according to previously published methods (16). If exposure to MI that could partly or fully explain the patient's dermatitis was identified, the allergy was recorded as being of 'current relevance' (17). The information was recorded in the patients' files and the database of the department.

Statistics

Patients with a positive patch test reaction to either MI, MCI/MI or BIT were compared with patients with a negative patch test result with the same isothiazolinone. Statistical calculations were performed with the χ^2 -test. A χ^2 trend test (linear by linear association) was used to test for possible significant trends of contact allergy across patch test years. For prevalence of MI allergy, we

also included data from the period 2006–2009, which have been published previously (13). Data analyses were performed with IBM SPSS™ STATISTICS 19 (IBM, Armonk New York, USA).

Market analysis

In March 2013, a market survey was performed concerning the use of MI in cosmetic products by visiting 14 different supermarkets in the greater Copenhagen area. Two of the stores were in the same chain, but otherwise they were different stores. The ingredient lists of all cosmetic products were checked, and all products preserved with MI were photographed in order to ensure that the same product was not registered twice in different stores. Furthermore, which kind of brands and product types sold by each store were registered, in order to reduce the risk of double checking/registering products.

Results

The prevalence of MI contact allergy showed a statistically significant steep increase from 2.0% in 2010 to 3.0% in 2011 and 3.7% in 2012 ($p = 0.03$), and, when data from 2006–2009 were included, the increase was even more apparent (Fig. 1). The prevalence of MCI/MI fluctuated between 2.4% and 1% in the period, but increased significantly from 2010 to 2012 ($p = 0.03$) (Fig. 1). Only 5 of the 2411 (0.2%) patients patch tested with BIT had a positive reaction. Occupation and hand eczema were strongly associated with MI contact allergy ($p < 0.001$) (Table 1). A classical example is shown in Fig. 2, where a patient developed hand eczema after he submerged his left hand in water with a dishwashing detergent preserved with MI numerous times every day, owing to work with grout. After he changed to another dishwashing detergent (without MI) and had been treated with topical steroids, his symptoms disappeared (Fig. 2). The MI-allergic patients were also significantly more often aged > 40 years and more often had facial dermatitis than those not allergic to MI (Table 1). Patients with a positive patch test reaction to MCI/MI had similar characteristics, except for age (Table 1). Seventy per cent of the MI-allergic patients were women.

Half (51%) of the MI-positive patients also had a positive reaction to MCI/MI, and 76% of the MCI/MI-positive patients also reacted to MI.

In total 82, patients reacted to the MI patch test from 2010 to 2012. In 52 (63%) of the patients, relevant exposures to MI were found. Relevant exposures were found in 37 (67%) of the 55 patients with a positive patch test reaction to MCI/MI (Table 2). Cosmetics were the most



Fig. 1. Prevalence of methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI)/MI patch test-positive patients at Gentofte Hospital from 2006 to 2012. MI patch test data from 2006 to 2010 have been published previously (13).

Table 1. The MOALHFA index in methylisothiazolinone (MI) patch test-positive and MI patch test-negative patients, and methylchloroisothiazolinone (MCI)/MI patch test-positive and MCI/MI patch-test negative patients

	MI-positive, n = 82, % (no.)	MI-negative, n = 2684, % (no.)	p-value	MCI/MI-positive, n = 55, % (no.)	MCI/MI-negative, n = 2753, % (no.)	p-value
Male	30 (25)	30 (813)	0.53	31 (17)	30 (837)	0.52
Occupational	39 (32)	21 (571)	0.0003	38 (21)	21 (587)	0.04
Atopic dermatitis	12 (10)	19 (520)	0.06	15 (8)	20 (539)	0.23
Leg	1 (1)	2 (55)	NT	0	2 (56)	NT
Hands	57 (47)	38 (1025)	0.0004	56 (31)	38 (1052)	0.05
Face	38 (31)	28 (756)	0.04	40 (22)	28 (780)	0.04
Age > 40 years	79 (65)	65 (1750)	0.005	73 (40)	65 (1776)	0.13

NT, not tested.

commonly relevant substances causing exposure in both the MI-allergic and MCI/MI-allergic patients, constituting 62% and 58% of the relevant exposures, respectively. In some cases, patients were exposed to more than one cosmetic product with either MI or MCI/MI in it. A total of 60 cosmetic products with MI were registered as a relevant exposure; 27 (45%) were leave-on and 33 (55%) were rinse-off. Finally, paints were identified as a relevant exposure in one-quarter of the MI-allergic patients with a known relevant exposure (Table 2). Three of the five BIT-allergic patients had a relevant exposure to BIT from paint.

Market survey

The ingredient labels of 1795 different cosmetic products were checked, and 60 (3.3%) of them stated that the products were preserved with MI alone. Of the 60 products 25 (42%) were leave-on, 22 (37%) were rinse-off, six (10%) were hair waxes, four (7%) were wet wipes, and three (5%) were paint for nails.

Discussion

The results presented in this article illustrate yet again the need for an urgent intervention to reduce the increasing number of patients in Europe who daily become sensitized to MI. The prevalence of MI contact allergy increased significantly from 2006 to 2012 ($p = 0.00002$). The same concerning increase has been seen in other European countries in the last couple of years (1–3). MCI/MI contact allergy also increased significantly, from 1.0% in 2010 to 2.4% in 2011–2012. The increase in MCI/MI contact allergy is likely to be linked to the increase in MI contact allergy in recent years, as illustrated by the two prevalence curves (Fig. 1). The curves follow the same pattern until 2010, when MI allergy increases dramatically and becomes more prevalent than MCI/MI allergy. The concomitant reactions to MI in MCI/MI-allergic patients doubled from 37% in our previous study in 2006–2009 to 76% in 2010–2012, and indicates an increased role of MI as



Fig. 2. Typical occupational methyisothiazolinone hand eczema in patient exposed to a dishwashing soap daily while working with grout.

Table 2. Categories of sources of exposure to methyisothiazolinone (MI) or methylchlorisothiazolinone (MCI)/MI found to be of clinical relevance in MI-allergic and MCI/MI-allergic patients from 2010 to 2012

	Cosmetics, n (%)	Cleaning agents, n (%)	Cleaning and cosmetics, n (%)	Paint, n (%)	Glue factory, n (%)	Total n
MI	32 (61.5)	4 (7.7)	3 (5.8)	13 (25)	0	52
MCI/MI	22 (57.9)	4 (10.5)	5 (13.2)	6 (15.8)	1 (2.6)	38

Relevant exposures were found in 52 of 82 MI-allergic patients and in 38 of 55 MCI/MI-allergic patients.

the primary sensitizer. A similar but smaller increase was also found in the Information Network of Departments of Dermatology network, where the proportion of MCI/MI-allergic patients with a concomitant reaction to MI increased from 43% to 59% between 2009 and 2011 (1). Other dermatology departments in Europe have reported similar changes (3). Half of the MI-allergic patients did not react to MCI/MI, providing further evidence that MI is an independent primary sensitizer.

In the MOAHLFA index, MI-allergic patients were more often exposed through their occupation, had hand eczema and were aged > 40 years than patients without MI allergy; this is identical to the previous findings in MI-allergic patients from Gentofte Hospital (13). Furthermore, the MI-allergic patients also significantly more often had facial dermatitis, which could indicate exposure to cosmetics as well as exposure to MI emitted from paint, which has been described several times recently (5–7, 18). Previously, we found that 17 of 17 different paints all contained MI (7). BIT is also frequently

used in paint, and the 3 patients with BIT allergy where a relevant exposure were identified were all exposed to BIT from paint.

The MCI/MI-allergic patients were younger than the MI-allergic patients, but still had significantly more occupational hand and face dermatitis, just like the MI-allergic patients. Notably, the *p*-values for occupational and hand dermatitis in the MI-allergic patients were markedly lower than those of the MCI/MI-allergic patients (Table 2). The majority (70%) of the MI-allergic patients were women. As compared with the patch test data from our previous study, this is a 15% increase, which could also indicate that cosmetic products are of especial importance (13).

This is also seen in the relevant exposures identified in the patients, where 62% of the MI-allergic patients with a relevant exposure were exposed to a cosmetic product. In the MCI/MI-allergic patients, we found 58% of relevant exposures to be caused by cosmetics. The relevant products containing MI were almost evenly distributed between leave-on (*n* = 27) and rinse-off (*n* = 33) products. In our market survey, 3.3% (*n* = 60) of the investigated cosmetics had labels stating that they contained MI alone. As compared with other surveys on MI in cosmetics, these results indicate that the use of MI in cosmetic products is increasing. We found only 1.5% in an almost identical investigation 3 years ago (11), and Yazar et al. found that only one of 204 (0.5%) cosmetic products had a label stating that it contained MI (12). Furthermore, the majority (63%) of the 19 products identified previously were rinse-off, and only three of 19 were leave-on (11). In this study, we found that 42% were leave-on products and 37% were rinse-off products. Besides an increase in the use of MI in cosmetic products, we have also seen a shift in the use of MI towards more leave-on products, where the exposure is longer than for rinse-off products. MI was recently named allergen of the year by the American Contact Dermatitis Society, and it reported that the use of MI in cosmetic products more than doubled from 2007 to 2010, and that the majority of products in 2007 were rinse-off (19). Currently, there are no prevalence data available from the United States for comparison with regard to the increased use of MI. The concentrations of MI in the products found in this market surveys are unknown, but previously we have seen that the majority of products are preserved with > 50 ppm MI (11). In a clinical study, it was shown that 64% of MI-allergic patients reacted to 50 ppm MI in a repeated open application test (20). The trend in MI contact allergy, concerning prevalence, increase in use, and increase in current relevance in rinse-off products, is similar to the trend seen previously with the preservative

methyldibromo glutaronitrile, which is now banned for use in cosmetic products in the EU (21).

The increase in MI and MCI/MI contact allergy is alarming, and requires urgent action from regulators. Even though only a small proportion of cosmetics are preserved with MI as a single isothiazolinone, it is the most prevalent relevant exposure seen in MI-allergic patients. The increase in the number of cosmetic products containing MI and a shift towards using it more in leave-on cosmetics makes the need for action even greater. In this study, we also found that one-quarter of the

MI-allergic patients had a relevant exposure to MI from paint. Currently, there is no relevant legislation on the use of MI in paint, and MI is the preferred preservative in paint, causing severe reactions through airborne exposure. MI is a special case, where exposures are not only cutaneous, but also airborne, meaning that patients may unexpectedly be exposed in public spaces and shops. It has been known for many years that isothiazolinones can cause allergic symptoms, but the number of cases and the severity of symptoms are without precedence and are a cause of great concern.

References

- Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; **67**: 334–341.
- Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new 'epidemic'. *Contact Dermatitis* 2013; **68**: 253–255.
- Gonçalo M, Goossens A. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis* 2013; **68**: 257–258.
- Friis U F, Menné T, Thyssen J P, Johansen J D. A patient's drawing helped the physician to make the correct diagnosis: occupational contact allergy to isothiazolinone. *Contact Dermatitis* 2012; **67**: 174–176.
- Lundov M D, Mosbech H, Thyssen J P, Menné T, Zachariae C. Two cases of airborne contact dermatitis caused by methylisothiazolinone in wall paint. *Contact Dermatitis* 2011; **65**: 176–179.
- Aerts O, Cattaert N, Lambert J, Goossens A. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. *Contact Dermatitis* 2013; **68**: 250–251.
- Lundov M D, Bossi R, Kolarik B, Gunnarsen L, Johansen J D. Methylisothiazolinone – direct and airborne exposure from paint. *Contact Dermatitis* 2012; **66** (Suppl. 2): 30–31.
- European Commission (2007) Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products, Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.
- SCCS. Opinion on benzisothiazolinone, 2012 July 26.
- Schnuch A, Mildau G, Kratz E M, Uter W. Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. *Contact Dermatitis* 2011; **65**: 167–174.
- Lundov M D, Krongaard T, Menné T, Johansen J D. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011; **165**: 1178–1182.
- Yazar K, Johnsson S, Lind M L, Boman A, Lidén C. Preservatives and fragrances in selected consumer-available cosmetics and detergents. *Contact Dermatitis* 2010; **64**: 265–272.
- Lundov M D, Thyssen J P, Zachariae C, Johansen J D. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010; **63**: 164–167.
- Garcia-Gavin J, Vansina S, Kerre S, Naert A, Goossens A. Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis* 2010; **63**: 96–101.
- Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; **50**: 287–292.
- Friis U F, Menné T, Flyvholm M A, Bonde J P E, Johansen J D. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. *Contact Dermatitis* 2013; **69**: 153–163.
- Menné T, Johansen J D, Sommerlund M, Veien N K. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011; **65**: 3–12.
- Kaae J, Menné T, Thyssen J P. Presumed primary contact sensitization to methylisothiazolinone from paint: a chemical that became airborne. *Contact Dermatitis* 2012; **66**: 341–342.
- Castanedo-Tardana M P, Zug K A. Methylisothiazolinone. *Dermatitis* 2013; **24**: 2–6.
- Lundov M D, Zachariae C, Johansen J D. Methylisothiazolinone contact allergy and dose–response relationship. *Contact Dermatitis* 2011; **64**: 330–336.
- Johansen J D, Veien N K, Laurberg G, Kaaber K, Thormann J, Lauritzen M, Avnstorp C. Contact allergy to methyldibromo glutaronitrile – data from a 'front line' network. *Contact Dermatitis* 2005; **52**: 138–141.