Methylisothiazolinone, an emerging allergen in cosmetics?

JUAN GARCÍA-GAVÍN, SARA VANSINA, STEFAN KERRE, ALIX NAERT AND AN GOOSSENS

1Faculty of Medicine, Department of Dermatology, University of Santiago de Compostela, University Hospital Complex, Spain, 2Department of Dermatology, University Hospital, K.U. Leuven, B-3000 Leuven, Belgium, and 3Private Dermatologist, B-3200 Aarschot, Belgium

Background: A few cases on primary sensitization by, and occupational contact dermatitis from, methylisothiazolinone in paints and glues have been published. In cosmetics, methylisothiazoline (MI) is permitted in a concentration of 100 p.p.m., while 15 p.p.m. for the mixture of methylchloroisothiazolinone and methylisothiazoline (MCI/MI).

Objectives: To present cases of sensitization to, and allergic contact dermatitis from, cosmetic products containing methylisothiazolinone only.

Patients, Materials, and Methods: Seven patients with suspected contact dermatitis – six of them with (peri-)anal lesions and one with facial dermatitis – were patch tested with the baseline series, the own products exposed to, cosmetic ingredients, as well as with methylisothiazolinone 1000 p.p.m. and MCI/MI 200 p.p.m.

Results: The patients with anal lesions had become sensitized by wipes for intimate hygiene, and one patient with facial dermatitis by a make-up remover, all containing methylisothiazolinone only. Three out of seven cases would have been missed if only MCI/MI 100 p.p.m., as present in the baseline series, had been tested.

Conclusion: The inclusion of methylisothiazolinone as a preservative in cosmetics might not represent the solution to the problem of allergic contact dermatitis from isothiazolinones, since it leads to primary sensitization.

Key words: airborne; allergic contact dermatitis; cosmetics; glues; intimate hygiene; methylchloroisothiazolinone (CAS# 26172-55-4); methylisothiazolinone (CAS# 2682-20-4); occupational; paints; wipes. © John Wiley & Sons A/S, 2010.

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Introduction

Isothiazolinones are heterocyclic organic compounds with bactericidal, algicidal and fungicidal activity (1). In the European Union, two preservatives containing isothiazolinone-derived biocides are approved for use in cosmetic products. The first one, introduced in the 1980s, is a mixture in the ratio of 3:1 of methylchloroisothiazolinone [5-chloro-2-methyl-2H-isothiazolin-3-one (MCI)] and methylisothiazolinone [2-methyl-2H-isothiazolin-3-one (MI)], which has been widely used until several epidemic outbreaks of allergic contact dermatitis were reported (2). Since 1990, the maximum authorized concentration in cosmetics, previously 30 p.p.m, was lowered to 15 p.p.m (3). The second isothiazolinone, approved since 2005, is the non-halogenated derivative methylisothiazolinone alone that is less effective as a biocide than methylchloroisothiazolinone and, hence, requires the high-level usage of concentration. It may be present in the cosmetics up to 100 p.p.m, either in leave-on or rinse-off products (4). This concentration was believed to be safe because methylisothiazolinone is a weak sensitizer.
compared to methylchloroisothiazolinone (5), and has thus been considered to be a good alternative to the MCI/MI mixture in this regard.

In the literature, a few cases on occupational contact dermatitis caused by methylisothiazolinone contained in paints and glues have been reported. In this article, we present the first seven cases of non-occupational sensitization by the use of cosmetic products containing only methylisothiazolinone.

**Case reports**

All the seven patients were patch tested according to the International Contact Dermatitis Research Group (ICDRG) criteria, using van der Bend® patch-test chambers (Van der Bend®; Brielle, the Netherlands) applied on the back with Micropore™ (3M Health Care®; Borken, Germany), and fixed with Mefix® (Mölndycke Health Care®; Göteborg, Sweden) as adhesive tape. The baseline series was obtained from Trolab® (Hermall Chemie®; Reinbek, Germany), and MCI/MI 200 p.p.m. and methylisothiazolinone 1000 p.p.m. came from M. Bruze’s laboratory in Malmö in the frame of an EECDRG study. Readings were performed on days 2 and 4, sometimes also later. Patch-test results are seen in Table 1. The cases 1, 3, 4, 6, and 7 were observed in the Contact Allergy unit in Leuven, cases 2 and 5 by a private dermatologist (S.K.).

**Case 1**

A 55-year-old non-atopic, male, bank clerk was tested in November 2009 because of a history of an eczematous eruption affecting his face, neck, retroauricular area, and forearms, which had appeared 2 months previously after an exposure to fresh paint during refurbishment in his workplace. The condition had cleared completely during a two-week holiday only to worsen again at work, where now the carpet was being replaced and glued on to the floor. During this process, he also had, occasionally, minor respiratory symptoms. During the refurbishment, there were 10 people working in the bank; one woman had developed a skin complaint but she did not consult any physician.

Since early 2009, he had suffered from pruritus ani and occasional eczema in the perineal area, but had continued to use wipes on the area (similar to those which he had already been using...
for almost 10 years without any problem), namely Page Fresh® humid toilet paper (Kimberly-Clark®; Dallas, Texas). Additionally, in March 2009, he had experienced facial dermatitis following his first use of a perfume after shaving (Eau de parfum Classic collection®, FM Group; Benelux), and previously also to a particular deodorant.

Since patch tests with the baseline and a cosmetics series had been undertaken by a private dermatologist and were negative, we first only tested him to the wipes and the perfume ‘as is’ together with their ingredients (as labelled on the packaging), including methylisothiazolinone 1000 p.p.m. (present in the wipes), as well as Fragrance Mix (FM) II and its components. On day 2, positive reactions were observed to the wipes, perfume, methylisothiazolinone, and FM II; farnesol was present in his perfume (and possibly also in the deodorant that he had not tolerated). We then repeated the process of testing first with the baseline series and then with aqueous dilutions of both methylisothiazolinone and MCI/MI (Fig. 1). The patch test results are seen in Table 1.

Since 2008, methylisothiazolinone had been the only isothiazolinone present in Page® humid toilet paper. According to the information obtained from the respective manufacturers of the products used at work, methylisothiazolinone was (100 p.p.m. concentration) present, both in the carpet glue and the water-based paint, the latter containing also MCI/MI in a concentration below 0.01% (100 p.p.m.). When he stopped using the wipes, the perianal lesions settled, but notwithstanding the advice on the use of cosmetic products that do not contain his allergens, he later presented with dermatitis on his fingers. This was found to be because of the soap used at work (System 1000®; Kimberly-Clark®) and which did contain MCI/MI. Avoidance of all the allergens completely resolved all his skin problems.

Case 2

A 62-year-old non-atopic woman presented with an eczematous eruption affecting her face, trunk, arms, and legs. The lesions had started one month earlier as an acute eczema in the perineal area that she treated it with Lactacyd Femina® emulsion (GlaxoSmithKline®; Genval, Belgium) and Gyno-Daktarin® cream (Janssen-Cilag®; Berchem, Belgium). The patient revealed that 2 months before the initial lesions appeared, she had started to use Scottex Fresh® humid toilet paper (Kimberly-Clark®) for intimate hygiene.

Patch testing was performed with the European baseline, cosmetic series, and both Scottex Fresh® and Lactacyd Femina® tested ‘as is’ (open and semi-open test, respectively). This resulted in multiple positive reactions that evidenced an allergic contact dermatitis from the wipes (Table 1). According to the respective companies, Scottex Fresh® wipes contain methylisothiazolinone in a concentration of 90 p.p.m. and Lactacyd Femina® contains MCI/MI. These results were relevant for the anogenital lesions. Other allergens that had produced positive reactions did not seem to be in relevant to the actual problem. The lesions cleared upon avoidance of the allergen-containing products.

Four months later, the patient presented with a one-week history of swollen eyelids and face with severe itching and burning, in relation to the use of water-based wall paint in her house. On day 2, an open test with the paint ‘as is’ produced a +++ positive reaction. The company confirmed that the paint indeed contained both methylisothiazolinone at a concentration of 0.01% and the mixture MCI/MI at a concentration lower than 0.01%, which may explain the patient’s possible airborne contact dermatitis.

Fig. 1. Dilution series with methylchloroisothiazolinone and methylisothiazolinone (MCI/MI), and methylisothiazolinone (MI) in case 1.
Case 3

A 50-year-old non-atopic woman presented in October 2009 with a 1-year history of perianal dermatitis for which several corticosteroid-containing topical products had been prescribed. She admitted using moist toilet paper (Scottex Fresh®; Kimberly-Clark®) to control anal pruritus, the same brand as in the previous case. Patch testing was performed with the European baseline, methylisothiazolinone 1000 p.p.m., and MCI/MI 200 p.p.m. showing an allergic response to methylisothiazolinone (Table 1).

Case 4

A 43-year-old non-atopic woman presented with a 3-month history of eczematous lesions on the genital and perianal area. When local corticosteroids were applied, the symptoms disappeared and recur upon stopping them. She was also using Scottex Fresh® wipes for intimate hygiene. Patch testing with the European baseline, methylisothiazolinone 1000 p.p.m., and the humid toilet paper ‘as is’ confirmed an allergic contact dermatitis from the wipes (Table 1), which indeed contained both methylisothiazolinone and limonene. When she discontinued their use, she became symptom free.

Case 5

A 20-year-old non-atopic man consulted because of perianal itch and genital lesions of 4 years duration. For this problem, he had already consulted a proctologist 1 year earlier, who advised him to use humid toilet paper (Scottex Fresh®) for intimate hygiene. After initial improvement, the condition worsened and he developed an oozing dermatitis. The European baseline and the wipes ‘as is’ were patch tested and he showed positive reactions to several allergens including the wipes (Table 1). When he ceased using them, the eczematous lesions completely cleared.

Case 6

A 57-year-old atopic woman consulted, in January 2009, because of eczematous lesions on the eyelids of 6 months duration, mainly localized at the corners of the eyes (Fig. 2). She had been treated with several eyedrops and only those containing corticosteroid had brought relief for her symptoms. She was using several facial cosmetic products which she had continued to use since the beginning of the condition. Patch tests were performed with the European baseline, cosmetic series, as well as with a 1000 p.p.m. concentration of methylisothiazolinone, that was found on the label of Biocura eye cleansing lotion® (Biocura cosmetic®; Manisa, Turkey). This resulted in positive reactions to nickel and benzoic acid (present in two make-up removers, i.e. a purifying lotion and cleansing tissues she had previously used as well), and also to methylisothiazolinone, with no reaction to MCI/MI 100 p.p.m. in the baseline series (Table 1). The lesions cleared when she discontinued the use of all products containing the allergens.

Case 7

A 44-year-old atopic woman presented, in January 2010, because of pruritus and perianal eczema of 1-year duration. Two years ago she had started to use humid toilet paper Scottex® for intimate hygiene (alternating between Scottex Fresh®; Scottex Aloë vera and Camomila®; and Scottex Sensitive®; Kimberly-Clark®). The history revealed that she also did not tolerate perfumed bath salt with lavender, a recent Christmas gift from her son, and that she occasionally had experienced severe itch on the scalp.

Patch tests were performed with the European baseline and cosmetic series, methylisothiazolinone 1000 p.p.m., MCI/MI 10 p.p.m., methylisothiazolinone 10 p.p.m., FM II ingredients, Scottex® moist toilet paper ‘as is’, and lavender oil 5% ethanol (Table 1). The presence

Fig. 2. Eyelid dermatitis (case 6) owing to a make-up remover containing MI.
of methylisothiazolinone in Scottex® toilet tissues renders this allergen relevant for the perianal eczema. Moreover, her shampoo (herbal essences Colour Queen®, Procter and Gamble®) containing the mixture MCI/MI could explain the itch on her scalp, while the positive test to lavender oil could account for her intolerance to the bath salt.

**Discussion**

In 2004, Isaksson et al. first published two occupational cases of allergic contact dermatitis owing to wallpaper glue containing methylisothiazolinone only (6), and 2 years later, Thyssen et al. described an occupational outbreak in a paint factory affecting four patients (7). All the cases were considered to be of primary sensitization to methylisothiazolinone, demonstrating the potential of this substance to elicit and induce contact allergy in humans. Since its introduction as a cosmetic preservative in 2005, in a use concentration up to 100 p.p.m. as far as we know, primary sensitization from it in cosmetics has not been reported before. In this article, we discussed seven cases: six patients reacted to wipes for intimate hygiene and one to a make-up remover.

Allergic contact dermatitis from wipes had previously been reported (8) and such products, introduced primarily for babies, are now widely used by adults for their intimate hygiene. The most common allergens are fragrances and preservatives, particularly MCI/MI (8, 9). Allergic contact dermatitis should be suspected not only in patients with perianal lesions but also in those with hand eczema, especially when they take care of babies (10), who by themselves may present a recalcitrant ‘diaper dermatitis’ (11, 12). The use of such products in non-keratinized areas and under occlusion certainly contributes to the sensitizing potential.

Airborne allergic contact dermatitis owing to isothiazolinones contained in wall paints and glues had been previously reported (6, 7, 13), and even a limited and indirect exposure is sufficient to elicit a severe allergic reaction (14). Two of the patients described in the above case studies became sensitized by cosmetics (wipes) and subsequently presented with a possible airborne dermatitis after being exposed to paint and/or glue containing MCI/MI or methylisothiazolinone alone.

With the aim to estimate the elicitation threshold, dilution series of methylisothiazolinone and MCI/MI were tested in cases 1 and 7: a + reaction (day 5, Fig.1) down to a concentration of 10 p.p.m. methylisothiazolinone and 50 p.p.m. MCI/MI, the latter also containing 10 p.p.m. methylisothiazolinone as it is a 3:1 mixture, was observed. This suggests that methylisothiazolinone also has a very low elicitation threshold, similar to MCI/MI (<2 p.p.m.) (15). Bearing in mind that the use of preservatives containing methylisothiazolinone alone is increasing in household and industrial products as well (16), contact allergy to this substance should be suspected in patients with airborne dermatitis following glue or paint exposure. If an allergic contact dermatitis from isothiazolinones is suspected, both the mixture MCI/MI and methylisothiazolinone should be patch tested. MCI/MI 100 p.p.m., which only contains 25 p.p.m. of methylisothiazolinone, may lead to false-negative patch-test results (as in cases 3, 4 and 6 here), hence, a concentration of 200 p.p.m. has been recommended (17). This is especially important if it is not possible to obtain methylisothiazolinone alone. If only methylisothiazolinone is positive, or if both methylisothiazolinone and MCI/MI are positive and the patch-test reaction is clearly stronger to the former, primary sensitization to methylisothiazolinone should be diagnosed (6, 7). Otherwise, if both methylisothiazolinone and MCI/MI react positively with the same intensity, primary sensitization to MCI with cross-reaction to methylisothiazolinone should be suspected (18). For example, our contact-allergy unit in Leuven patch tested 605 patients to both MCI/MI and methylisothiazolinone: out of the 36 patients reacting positive to the mixture 16 also presented with a weak positive test result to methylisothiazolinone. Hence, patients who have been sensitized to the mixture MCI/MI have a high risk of reacting to methylisothiazolinone as well.

Finally, in all the seven cases, several positive reactions were also found to other allergens: four to nickel (of which one also to cobalt) and to fragrance components, three to methylidibromo glutaronitrile and 2-bromo-2-nitropropane-1,3-diol, and one to octylisothiazolinone, colophonium, lanolin, and benzoic acid, respectively. It is also noteworthy that five patients had multiple contact allergies [i.e. contact allergy to three or more allergens (19)]. As has recently been reported in a large study from the United Kingdom (20), concomitant reactions particularly to other cosmetic preservatives are indeed frequently observed.

**Conclusion**

We estimate that the inclusion of methylisothiazolinone as a preservative in cosmetics might not represent the solution to the problem of allergic contact dermatitis from isothiazolinones, since it leads to primary sensitization. It is well known that the potential for induction of sensitization and/or elicitation of allergic contact dermatitis increases with the dosage (21). In cosmetics, methylisothiazolinone is permitted in a concentration of 100
p.p.m., while limited to 15 p.p.m. for the mixture MCI/MI. Moreover, methylisothiazolinone can also cross-react with methylchloroisothiazolinone (18). This means that not only patients who are previously sensitized to the mixture MCI/MI may react to the new preservative containing methylisothiazolinone alone but also that patients primary sensitized to methylisothiazolinone may react to products containing MCI/MI.

The use of preservatives containing methylisothiazolinone, especially in leave-on products and wipes, may need to be more thoroughly regulated.

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Address:
Prof. An Goossens
Department of Dermatology, University Hospital, Kapucijnenvoer 33, Katholieke Universiteit Leuven, 3000 Leuven, Belgium
Tel: +32 16 33 78 60
Fax: +32 16 33 70 12
e-mail: an.goossens@uz.kuleuven.ac.be