

- CONTRIBUTIONS TO THIS SECTION MAY NOT UNDERGO PEER REVIEW, BUT WILL BE REVIEWED BY THE EDITOR •

Outbreak of methylisothiazolinone allergy targeting those aged ≥ 40 years

John P. McFadden, Jack Mann, Jonathan M. L. White, Piu Banerjee and Ian R. White

St John's Institute of Dermatology, St Thomas' Hospital, London, SE1 7EH, UK

doi:10.1111/cod.12093

Key words: allergic contact dermatitis; cosmetic; methylisothiazolinone; preservative.

Methylisothiazolinone (MI) has been used in a combination of 1:3 with methylchlorisothiazolinone (MCI) since the 1980s. It has been used in toiletries, household products, wall paints, and industry (1). This combination has represented an important cause of preservative contact allergy with regard to its use in consumer products and paints. The MCI/MI combination has been regulated to an upper limit of 15 ppm in household products and cosmetics (i.e. MI concentration of 3.75 ppm) (2). In 2000, MI, which is claimed not to be as potent a sensitizer as MCI, was released onto the market as a single-agent preservative. A published EC3 value of between 0.4 and 2.2, depending upon the vehicle, categorized MI as a 'moderate' sensitizer (3). MI was first used in industrial products and paints, and the first case of allergic contact dermatitis caused by MI through occupational exposure was noted in 2004 (4). In 2005, MI was permitted for use in cosmetics in the United States and Europe at up to 100 ppm, representing a 27-fold increase in the permitted concentration of MI. It is unclear how soon after 2005 MI was incorporated into cosmetics as a single agent, but the first cases of allergic contact dermatitis caused by MI through cosmetic exposure were reported in 2010 (5). In that year we incorporated MI, at a patch test concentration of 0.05% aqua, into our cosmetic/face patch test series.

Case Report

Between July 2010 and September 2012, 1289 (965 female) patients with eczema were patch tested with MI

0.05% aqua (500 ppm) in a cosmetic/face patch test series. Readings were performed at D2/3 and D4/5 according to International Contact Dermatitis Research Group criteria. Statistical comparisons between years and ages were performed with Fisher's exact test.

The results are shown in Table 1 and Figs. 1 and 2.

In the 52 patients with contact allergy to MI, the following areas were involved: face (36; 69%), hands (7; 13%), perineum/genitalia/groin (5; 10%), generalized (6; 12%), axilla (1), and scalp (1) (there was some overlap in the areas involved).

In 28 patients, the onset or exacerbation of dermatitis occurred within 1 year, and in 37 patients (71%), the onset or exacerbation of dermatitis occurred within 2 years.

Thirty-six cases (69%) were thought to be of definite relevance, and 16 (31%) of possible relevance.

There was a wide variety of sources of exposure, including: hair conditioners and shampoos, hand cream, sunscreen, moist tissue wipes, moisturizers, toner, cleansers, shaving gel, mascara, deodorant, anti-chafing cream (for cyclists) and washing-up liquid.

Discussion

This communication reports an outbreak of contact allergy to MI. Although many of the patients would have been previously exposed to MI as part of the MCI/MI combined preservative used in cosmetics (at levels up to 3.75 ppm), it is only since 2005 that MI has been permitted at levels of 100 ppm, and we suspect that it was some years after 2005 that MI was commonly used as a single preservative agent in leave-on and rinse-off products. It is likely (although not certain) that most of the MI allergy observed represented recent sensitization, as most patients had only a recent history of dermatitis.

Correspondence: John McFadden, St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH, UK. Tel: +447881658153.
E-mail: John.mcfadden@kcl.ac.uk

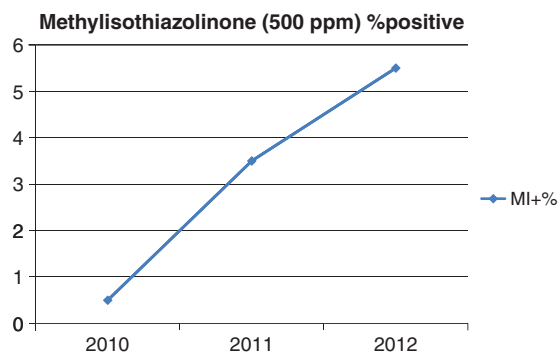
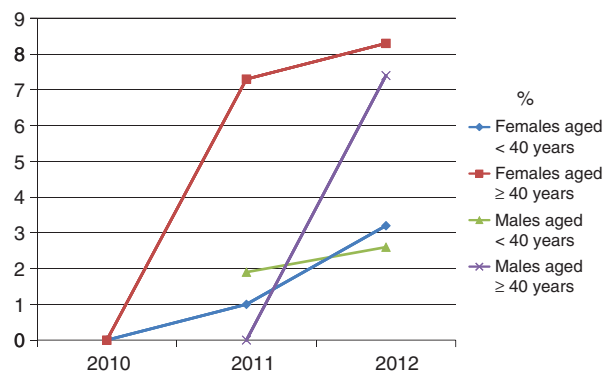
Conflicts of interest: The authors have declared no conflicts.

Table 1. Positive patch tests reactions to methylisothiazolinone (0.05% aqua) 2010–2012

	All tested positive	Females aged < 40 years	Females aged ≥ 40 years	Males aged < 40 years	Males aged ≥ 40 years
2010 July to December	1/185 (0.5%)	0/73	0/78	0/17	1/17
2011 January to December	18/521 (3.5%)	2/199 (1.0%)	15/204 (7.4%)	1/52 (1.9%)	0/66
2012 January to September	33/584 (5.7%)	7/218 (3.2%)	17/193 (8.8%)	2/78 (2.6%)	7/95 (7.4%)

All tested 2010 versus 2011 $p < 0.05$, 2010 versus 2012 $p = 0.0015$.

All tested < 40 years versus ≥ 40 years $p < 0.01$.

**Fig. 1.** Frequency of methylisothiazolinone (MI) allergy.**Fig. 2.** Methylisothiazolinone allergy by age and sex.

Most cases that we saw were patients aged ≥ 40 years with facial involvement, as described in another report (6). The commonest sources of exposure were personal toiletries, moist tissue wipes, hair products, and sunscreens. Unlike in a recent Danish report, none of our cases was attributable to wall paints (1).

In the second half of 2010, there was a single case of MI allergy resulting from a sunscreen. In 2011, the first year of the significant outbreak of MI allergy, most patients were females aged ≥ 40 years. In 2012, the second year of the outbreak, there was a marked increase in MI contact allergy among males aged ≥ 40 years, with less MI allergy

being observed in males and females aged < 40 years. MI allergy in females aged ≥ 40 years remained high in 2012.

During the first year of the outbreak of MI allergy (2011), most cases were females, and this could be explained in terms of exposure patterns. However, in the second year (2012), MI contact allergy was higher as a ratio of those tested in both males and females in the ≥ 40-year groups, and this is most unlikely to be explained in terms of exposure patterns. The more probable explanation is that older subjects are generally more prone to develop allergic contact dermatitis caused by cosmetic allergens. Many studies have reported that contact allergy to cosmetic allergens increases with age (7–9). The conventional wisdom that adult cosmetic allergy increases with age because of more cumulative years of exposure, leading to a ‘tipping point’ with subsequent contact sensitization, needs to be re-examined.

At first sight, it may appear surprising that older subjects may be more susceptible to cosmetic allergic contact dermatitis. There appears to be a general decline in immune function in the elderly (10–12) and an age-dependent decreased ability to be sensitized to a new allergen (13, 10).

It is of concern that, despite both human and animal data being available for toxicological assessment [summarized in Burnett 2010 (14)], in retrospect, the hazard of potential allergenicity of MI in cosmetics at levels of 100 ppm was not identified. Indeed, there is a long history of new preservatives being introduced into cosmetics at levels thought to be safe with regard to inducing allergic contact dermatitis that subsequently progress to cause outbreaks of allergic contact dermatitis (15).

Exposure to cosmetic chemicals is characterized by repeated application on the skin, and, as most concentrations of potential allergens are limited by regulatory authorities, relatively low-level exposure. This means of exposure may give rise to a dual response by the immune system, consisting of not only a stimulatory response but also a regulatory response (16). A relative lack of regulatory response in the older adult age group could be one reason why cosmetic allergy is commoner in this group.

References

- 1 Lundov MD, Zachariae C, Menné T, Johansen J D. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. *Br Med J* 2012; **345**: e8221.
- 2 Lundov MD, Krongaard T, Menné T L, Johansen J D. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011; **165**: 1178–1182.
- 3 Basketter D A, Gilmour N J, Wright Z *et al.* Biocides: characterization of the allergic hazard of methylisothiazolinone. *Cutan Ocul Toxicol* 2003; **22**: 187–199.
- 4 Isakson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wall-covering glue and after a chemical burn from a biocide. *Dermatitis* 2004; **15**: 201–205.
- 5 Garcia-Gavin J, Vansina S, Kerre S *et al.* Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis* 2010; **63**: 96–101.
- 6 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.
- 7 Warshaw EM, Rajau S I, Fowler J F Jr *et al.* Positive patch test reactions in older individuals: retrospective analysis from the North American Contact Dermatitis Group, 1994–2008. *J Am Acad Dermatol* 2012; **66**: 229–240.
- 8 White J M, Gilmour N J, Jeffries D *et al.* A general population from Thailand: incidence of common allergens with emphasis on para-phenylenediamine. *Clin Exp Allergy* 2007; **37**: 1848–1853.
- 9 Buckley D A, Rycroft R J, White I R, McFadden J P. The frequency of fragrance allergy in patch-tested patients increases with their age. *Br J Dermatol* 2003; **149**: 986–989.
- 10 Kwangstokstith C, Maibach H I. Effect of age and sex on the induction and elicitation of allergic contact dermatitis. *Contact Dermatitis* 1995; **33**: 289–298.
- 11 Zhai H, Meier-Davis S R, Cayme B *et al.* Allergic contact dermatitis: effect of age. *Cutan Ocul Toxicol* 2012; **31**: 20–25.
- 12 Weksler M E. The senescence of the immune system. *Hosp Pract* 1981; **16**: 75–84.
- 13 Waldorf D, Willkens R, Decker J. Impaired delayed hypersensitivity in an aging population. *JAMA* 1968; **203**: 111–114.
- 14 Burnett C L, Bergfield W F, Belsito D V *et al.* Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol* 2010; **29**: 187S–213S.
- 15 Dillarstone A. Cosmetic preservatives. *Contact Dermatitis* 1997; **37**: 190(Letter).
- 16 Kimber I, Travis M A, Martin S, Dearman R J. Immunoregulation of skin sensitization and regulatory T cells. *Contact Dermatitis* 2012; **67**: 179–183.