

METHYLISOTHIAZOLINONE AND METHYLCHLOROISOTHIAZOLINONE: NEW INSIGHTS

*Ana Rita Rodrigues-Barata, Luis Conde-Salazar

Contact Dermatitis Unit, Department of Dermatology, Grupo Dermatología Pedro Jaén, Madrid, Spain
*Correspondence to rita.rodrigues.md@gmail.com

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ABSTRACT

Methylisothiazolinone (MI), along with Kathon™ CG (methylchloroisothiazolinone/MI), are widely used preservatives to prevent bacterial overgrowth in aqueous solutions of various types of cosmetic, household, and industrial products. Because of its high sensitising power and widespread use, MI is currently one of the most common causes of allergic contact dermatitis, both in our private lives and in the occupational field. As it was thought that MI had less sensitivity capacity, it started to be commercialised separately, and a new epidemic of sensitisation to these preservatives has been observed in recent years. MI should be included separately in the standard patch testing series. Also, the use of isothiazolinones should be revised, and legislative measures from the competent authorities should be implemented in order to resolve this problem.

Keywords: Contact dermatitis, contact allergy, preservative, cosmetics, methylisothiazolinone, methylchloroisothiazolinone.

INTRODUCTION

Preservatives (or biocides) are essential additives in the manufacturing of water-based products, because they avoid the overgrowth of microorganisms.^{1,2} Methylisothiazolinone (MI) along with methylchloroisothiazolinone (MCI) are actually among the most used preservatives in the process of manufacturing cosmetics, household cleaning products, and also products of industrial use because of their low price and high efficacy at low concentrations.³ Recently, MCI was found to be the second most common cause of allergic contact dermatitis (CD) in a limited preservative series by Schnuch et al.,⁴ after the formaldehyde releasers. In the 1980s the use of MCI/MI was responsible for an epidemic of CD and, in order to control the problem, its maximum concentration was regulated.⁵ However, in 2005 MI was commercialised separately and we are now observing a new epidemic of sensitisation to MI and MCI/MI.^{6,7} The increased frequency of contact sensitisation in the population to MI shows that there has been a failure in assessing the risk of using

this preservative separately, and that its use should be revised.

Background

MCI (5-chloro-2-methyl-4-isothiazolin-3-one) in combination with MI (2-methyl-4-isothiazolin-3-one), known commercially as Kathon™ CG (Cosmetic Grade), has been synthesised since the early 1960s (Rohm and Haas, Philadelphia, Pennsylvania, USA). They are found at a concentration of 1.125% of MI and 0.375% of MCI (ratio of 1:3, respectively).^{2,8} Also, besides MCI and MI, there are other isothiazolinones available for the production of industrial products, in particular benzisothiazolinone (BIT), which is frequently used in emulsion paints, varnishes, and adhesives, among other products, and can be responsible for concomitant contact sensitisation and/or cross-reactions with MCI/MI.⁹ Allergic CD to BIT in the occupational setting was described, for example, in carpet making, printing, paint, and in air freshener manufacturing. On the other hand, BIT is present in consumer products such as laundry detergents, dish soaps, or sunscreens, but recently

it has been estimated that BIT concentrations used in these later products are insufficient in inducing skin sensitisations in most individuals.¹⁰

MI Sensitisation and Elicitation

Several clinical studies showed, despite the fact that both can cause contact sensitisation, MCI was a 30-times more potent sensitiser than MI,¹¹ and if utilised separately, MI needs to be used at higher concentrations to maintain adequate preservative properties. Later, Basketter et al.¹² inaccurately classified MI as a moderate sensitiser, based on murine local lymph node assays, but other authors like Roberts,¹³ performing similar studies, have reached the conclusion that it is a strong allergen. Both animal and human studies on MI sensitisation capacity were performed, concluding that, until concentrations of 600 ppm are reached, MI does not act as a contact sensitiser.¹⁴ In relation to MI elicitation, which corresponds to the concentration that triggers CD in a sensitised patient, Lundov et al.¹⁵ carried out a study by performing a repeat open application test on MI sensitised patients, and concluded that MI elicitation concentration could be as low as 5 ppm.

LEGISLATION AND PREVALENCE OF PROBLEM

When MCI/MI was initially introduced in the 1980s, its frequency of contact sensitisation rose to 8%, which was related to its high concentration in leave-on products.^{5,16} This triggered the implementation of restrictive recommendations for their use in terms of regulating the concentration, both in the USA and in Europe. However, these measures did not present a significant impact on the prevalence of sensitisation in the general population, and the frequencies of contact sensitisation remained between 1.8-4.4%.¹⁷⁻²¹

Under the current legislation the maximum concentration of MCI/MI is 15 ppm for all cosmetics in the European Community, while the USA has set a maximum concentration of 15 ppm for all rinse-off products, and 7.5 ppm for leave-on products,^{22,23} these being the manufacturer's recommendations.²⁴ In some countries, such as Japan, the use of MCI/MI is prohibited in rinse-off products. In the industrial context, in Europe MCI/MI is allowed at concentrations between 15-55 ppm, while also requiring labelling if used at concentrations >15 ppm.

In 2005, thoughts that MI was a weaker sensitiser when compared to MCI led to the approval of commercialising it separately as a preservative in cosmetics and household-cleaning products (allowed at a concentration up to 100 ppm with mandatory labelling).²⁵ This represents a higher concentration of MI compared to when it is used along with MCI. Regarding industrial products, no limits were set on the MI concentrations, nor even the obligation to specify its presence in the former.

The Recent MI Epidemic

Parallel to the increase in the last few years of MI presence in cosmetics, toiletries, and sunscreens, epidemics of contact sensitisation to this preservative were published in the literature by several authors.^{6,20,26} Similarly, there has been an increase in the frequency of sensitisation to MCI/MI.^{6,19} It is attributed especially to the presence of MI and/or MCI/MI in leave-on products, such as creams and lotions.²⁷ On the other hand, there is also evidence of several cases of allergy to MI/MCI, in which the source of exposure was clearly related to products containing MI.²⁷

Isaksson et al.²⁸ and Thyssen et al.²⁹ published the first cases of occupational sensitisation to MI, to wallpaper glue in 2004, and to paints in 2006, respectively. The first series of non-occupational cases of allergic CD to MI was described in 2010 by Garcia-Gavin et al.,²⁶ due to moist toilet paper and makeup remover containing this preservative separately. After that, similar case reports were described in the literature,^{30,31} as was airborne CD attained from paints or glues containing MI.^{32,33}

In the USA, MI is not routinely patch tested, while it has been recently included in the European standard patch testing series.³⁴ There are some available studies of prevalence and, although they used different concentrations when patch testing, a prevalence of MI contact sensitisation between 1.4-1.54% was observed.^{4,19,20} Other series have found a frequency of up to 10% of patients sensitised to MI.³⁵ These studies show that, despite its recent commercialisation, the frequency of contact sensitisation to this allergen is already at the same level as other preservatives that have been on the market for many years.³¹

It is well assumed that the current concentration of MCI/MI and MI used in the products is the critical factor for the risk of being sensitised against it, or to elicit the allergic CD. But, accepting that the

mandatory regulations are carried out, the high prevalence of sensitisation to these allergens could be also partly explained by several scenarios that can predispose to this risk. We believe that the current high consumption of cosmetics originates summation of MCI/MI or MI concentrations by applying more than one product on the same skin surface, mostly leave-on products; on the other hand, patients with pre-existing dermatitis are one of the major consumers, and having an impaired skin barrier increases the penetration of the allergen and risk of sensitisation.³⁶

This was reflected in the review by Conti et al.³⁷ in a paediatric dermatology consultation where MCI/MI was the most common allergen responsible for allergic CD in this age group. Moreover, the frequency of sensitisation to MI has increased, especially in the last couple of years. This phenomenon could also be explained by the fact that MI has started to be patch tested separately, so more cases of sensitisation to this preservative can be detected.

SOURCES OF EXPOSURE

The sources of exposure are varied and multiple. Isothiazolinones can be found both in cosmetics and household cleaning products, as well as in occupational sources.

Cosmetics

MI and MCI can be found in childcare products such as powders, oils, lotions, and creams; bathing and hair care products such as gels, soaps, shampoos, conditioners, colouring, and styling products. They can also be found in makeup and makeup removers, cosmetic nail products, toiletries such as deodorants, shaving gels, skincare items, sunscreens, and many other products. Regarding MI, it has been estimated that its presence is mainly in rinse-off products.³⁸ Wet wipes for personal hygiene, a type of leave-on skin product, are also actually a major and well-identified source of sensitisation to MI.³⁰ Lundov et al.,³¹ during a retrospective study in 2,536 patients in whom MI was patch tested separately from MCI/MI, discovered that 32% of the cases were sensitisations throughout cosmetics, and the most frequent source was haircare products.

Household Products and Occupational Exposure

In household cleaning products, isothiazolinones are also prevalent and can be found in dishwashing

and laundry detergents, stain removers, degreasers, softeners, window-cleaning liquids, air refreshers, and other types of cleansers. Sources of occupational exposure include mainly soaps for hand washing in the workplace, paints, inks, adhesives, lacquers and varnishes, toners and printing inks, cutting oils, and coolants, among others. Lundov et al.³¹ found that painters were the occupation at higher risk of developing contact sensitisation to MI. These results can be due to the replacement, in recent years, of solvent-based paints to the preferred use of water-based paints, which contain a higher proportion of preservatives, with MCI/MI and MI the most frequently used.³⁹

Such products will not only originate cases of occupational sensitisation, but they also have the possibility to trigger cases of allergic CD by airborne exposure in users. Due to the fact, as mentioned before, that there is no regulation regarding the maximum allowed concentration of MI in industrial products, as well as no labelling requirements in terms of the product composition, sensitised patients have difficulty avoiding contact with this allergen.

PATCH TESTING

Allergic CD to MI or MCI/MI should be suspected in patients with subacute or chronic eczema on the hands, mostly in occupational context, or in patients with facial eczema, in relation to the application of cosmetics or sunscreens.^{6,7,35} In other occasions it can present with a generalised distribution, simulating an atopic dermatitis, or it can be responsible for a poorly controlled pre-existing one. Also, it can originate perianal eczema, due to the use of hygienic wet wipes,³⁰ and airborne dermatitis, especially in patients who are in contact with paints, therefore, in the occupational setting as well as in the context of personal use.

Performing patch testing will allow confirmation of the suspected diagnosis of allergic CD to isothiazolinones. Currently MCI/MI is patch tested at concentrations of 100 ppm, which corresponds to 25 ppm of MI, leading to possible false negative test reactions. Leiva-Salinas et al.⁴⁰ observed that patch testing MCI/MI at 100 ppm could not diagnose 24.5% of MCI/MI allergies. They further noted that the same concentration detected only 68.2% of MI allergies, whereas MCI/MI at 200 ppm could detect all such MI contact sensitisations. Lundov et al.³¹ estimated that performing patch

testing with MCI/MI but not MI separately could obtain a percentage of 33-60% of false negative results to MI.

There are few data on cross-reactions between MI and MCI/MI. Research by Bruze et al.¹¹ and Isaksson et al.⁴¹ concluded that MI can lead to primary sensitisation, but also subjects sensitised by MCI/MI could react to MI. Recent research from the European Surveillance System Network⁴² ended with the inclusion of MI in the standard basal European series, but there is still no consensus on which is the optimal concentration for patch testing with MI alone. Previous studies patch tested MI at different concentrations, and all obtained a similar frequency of positive reactions. A Danish group proposes a concentration of 2,000 ppm (0.2% aqueous) as the ideal for patch testing, as it detects a high percentage of positive reactions, and does not induce active sensitisation nor irritant reactions.²⁵

NEW DIRECTIONS

In December 2013, the European Commission recommended that manufacturers should not use MI in leave-on cosmetic products, and also that there should be a restriction of 15 ppm of MI in rinse-off products.⁴³ The recent epidemiological studies and case reports in the literature corroborate that a new epidemic of contact sensitisation to MI is

up-and-coming. A wake up call is needed to address the urgency of the maximum allowed concentration of MI in Europe, which should be revised seriously, encouraging the competent authorities to establish proper legislative measures to limit the use of MI.

CONCLUSIONS

The use of MI independently from MCI/MI as a preservative in a wide range of cosmetic, cleaning, and industrial products is responsible for a new epidemic of contact sensitisation to isothiazolinones, which is added to the still-high frequency of sensitisation to MCI/MI. Contact sensitisation to MI should always be suspected in all patients with facial dermatitis, related to the application of cosmetics or sunscreens, or in patients with hand eczema of occupational origin.

Patch testing concentration of MCI/MI should rise from 100 to 200 ppm. Similarly, patch testing patients only with MCI/MI could miss an important proportion of positive reactions to MI, and consequently underdiagnose the real frequency of this problem. It is mandatory, therefore, that MI should have a separate inclusion into the standard series in several countries to be generalised, in order to obtain more reliable data on the actual situation of sensitisation to this allergen, and promote the industry to establish measures to tackle this problem.

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