REVIEW ARTICLE

Isothiazolinone derivatives and allergic contact dermatitis: a review and update

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Abstract

Allergic contact dermatitis (ACD) from isothiazolinones has frequently been described in the literature. Following an epidemic of sensitization to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in the 1980s, and more recently to MI, the Scientific Committee on Consumer Safety of the European Commission banned their use in leave-on products, while restricting that in rinse-off cosmetics. Despite a decreasing prevalence of ACD from MCI/MI and MI, cases caused by occupational exposure and non-cosmetic isothiazolinone sources are on the rise. Moreover, sensitization to newer and lesser known isothiazolinones has been reported. This paper reviews the epidemiology of contact allergy to different isothiazolinones, clinical presentation of isothiazolinone-induced ACD, most relevant sensitization sources and potential cross-reactions between isothiazolinone derivatives. It also provides an update on recent legislative measures. Received: 8 March 2018; Accepted: 20 August 2018

Conflicts of interest

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Introduction

Isothiazolinone derivatives are widely used as preservatives or biocides in household and industrial products, with several of them contained in cosmetic products. The mixture of methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) (MCI/MI; CAS 55965-84-9), which is composed of MCI (CAS 26172-55-4: 5-chloro-2-methyl-4-isothiazolin-3-one) and MI (CAS no. 2682-20-4: 2-Methyl-4-isothiazolin-3-one) in a 3 : 1 ratio, caused an allergic contact dermatitis (ACD) epidemic in the 1980s. More recently, using MI as a stand-alone preservative at increased concentrations (up to 100 ppm) in cosmetics has resulted in dramatic sensitization rates in Europe and beyond. Other isothiazolinones, including benzisothiazolinone (BIT; CAS 2634-33- 5; 1,2-benzisothiazolin-3-one) and octylisothiazolinone (OIT; CAS 26530-20-1; 2- octyl-1,2 thiazol-3-one), but also less known isothiazolinone derivatives, may also provoke allergic skin reactions in humans.

Chemical structure, properties and skin sensitization potential

Isothiazolinones are heterocyclic compounds characterized by a nitrogen and sulphur aromatic ring (1,2-thiazol-3-one), with

structural similarities and differences between isothiazolinone derivatives as illustrated in Fig. 1. The binding of an activated N–S bond to nucleophilic molecules (e.g. proteins) results in their antimicrobial activity, but also provides a rationale for their sensitizing potential.

Each isothiazolinone is classified as having a weak, moderate or strong sensitizing potential based on risk assessment methods, i.e., animal assays like the guinea pig maximization test $(GPMT)^1$ or local lymph node assay (LLNA).² In 1987, analyses on guinea pigs considered MCI to be a strong sensitizer – because of its chlorine atom³ – and MI to be a weak sensitizer.¹ Roberts *et al.*⁴ and Basketter *et al.*⁵ pointed out that previous LLNA tests had been incorrectly interpreted, with MI rather being a strong sensitizer.

Octylisothiazolinone has moderate sensitizing potential, somewhat comparable to MI, according to the GPMT⁶ and as proposed in recent animal experiments.⁷ BIT in animal models has similar potency to MI,⁸ though rather weaker potency than MI in the LLNA.⁹

According to LLNA data, isothiazolinones are classified in order of sensitization risk: $MCI > MI > OIT > BIT.^7$ This classification seems more accurate than the more frequently cited

one, namely MCI > MI > BIT > OIT,¹⁰ with the difference likely explained by the higher frequency of use and higher exposure to BIT.¹¹ Potential MCI/MI contaminants, such as 4,5 dichloromethylisothiazolinone (DCMIT), have historically contributed to its tendency to cause skin sensitization, considered less common with today's enhanced purity levels.¹²

History

Benzisothiazolinone was introduced in 1960, with the first report of ACD with this derivative published in 1976.¹³ It concerned two employees who manufactured polyacrylate emulsions for paints and waxes preserved with Proxel® CRL (Imperial Chemical Industries, Slough, UK), an industrial biocide, pesticide and preservative containing BIT (10–20%). Patch tests in both workers were positive to BIT 0.1% and 0.01% in ethanol (eth.).

Since the early 1980s, the MCI/MI mixture has been marketed as Kathon® CG (Cosmetic Grade) for use in cosmetic products (Rohm and Haas, Philadelphia, Pennsylvania, USA). The first cases of cosmetic contact dermatitis from Kathon® CG were published in 1984.¹⁴ Three years thereafter, MI was reported to be a contact sensitizer in humans,¹⁵ and it was confirmed in animal experiments.1 While MCI has never been used without MI, MI has been considered less sensitizing than MCI and since 2000, MI has been introduced as single-agent preservative in industrial products (i.e. paints, inks, glues, lacquers, varnishes and cooling fluids), and since 2005, in leave-on and rinse-off cosmetics as well. The first cases of ACD from MI-containing industrial products were reported in 2004, involving one patient occupationally exposed to wallcovering glues.¹⁶ Shortly thereafter, the first cases of consumers suffering from ACD to MIcontaining cosmetics were reported.¹⁷ Since 2010–2012, the prevalence of MCI/MI and MI contact allergies has significantly increased, with a more pronounced increase for MI than MCI/ MI.¹⁸⁻²¹ The main reason for this being that MI is used as an individual preservative in cosmetics at concentrations of up to 100 ppm, as compared to only 15 ppm for the MCI/MI mixture.²² In 2013, MI was eventually elected as 'Allergen of the Year' by the American Contact Dermatitis Society.²³

In 1982, the first two cases of ACD from OIT were published, concerning two employees exposed to paint in a roof factory.²⁴ In 2014, Friis *et al.*²⁵ reported that methyl trimethylene isothia-zolinone (MTMIT; CAS 82633-79-2; 2-methyl-4,5-trimethylene-



Figure 1 Molecular structures of isothiazolinone derivatives.

4-isothiazolin-3-one) could be found in seven different products with concentrations ranging from 47.6 to 150 ppm. In the 1990s, the first contact hypersensitivity case was reported in a laboratory technician who worked with an industrial biocide containing this derivative.²⁶

Epidemiology

In 2006, a Danish study reported that approximately 19.5% of the general population suffered from contact allergy, including 0.2% induced by MI.²⁷ Another more recent European study reported a rate of 0.5% sensitization to MCI/MI in the general population.²⁸ Data published in 2015 from different European centres revealed a sensitization rate to MI of 6.0% (e.g. 7.3% in Belgium, 5% in Denmark, and 13% in Finland).²⁹ Surprisingly, isothiazolinone sensitization rates seem to be drastically increased in Southern Europe compared with the rest of Europe. As examples, in Portugal, the frequency of MI was 10.9% in 2013,³⁰ and in Spain, the rates were 19.6% and 17.6% for MI and MCI/MI, respectively, in 2017.³¹ In Belgium, the 2013 sensitization rates for MCI/MI and MI were 5.3% and 7.2%, respectively.³² The prevalence changes in MI sensitization in Europe are provided in Table 1. Due to the high MI sensitization prevalence, legislation on using MI in cosmetic products was revised in 2013 and 2015. Urwin et al.³³ were the first to demonstrate the regulations' impact on the MI and MCI/MI sensitization prevalence in the UK, documenting a clear decrease from 9.1% in 2014 to 4.8% in 2015.

Recently, attention has shifted to occupational MI exposure. Schwensen *et al.*²⁹ reported that 16.8% of patients with relevant MI contact allergy were exposed to occupational products containing MCI/MI or MI, the risk being highest for those who directly handle isothiazolinones.^{34,35} Painters, machinists, glass makers, cosmetologists, hairdressers, beauticians, mechanics and repairmen have likewise been concerned.^{19,36–38} In Finland, a sixfold increase in occupational contact dermatitis from MI and MCI/MI was noted in 2015.³⁷ In industrial products, MI is at times present at very high concentrations, whereas Friis *et al.*²⁵ reported that the most common isothiazolinone derivative in Danish chemical products is BIT.

Little data are available on the prevalence of contact allergy to BIT and OIT. Geier *et al.*³⁹ analysed positive patch tests obtained with these derivatives between 2009 and 2013, observing a sensitization rate of 1.6% and 1%, respectively, compared to 4.6% for MI.

Clinical aspects

Chemical burns from isothiazolinone derivatives, particularly MCI/MI and MI, were reported to be accounted for by their irritating properties and (very) high concentrations used, often leading to primary skin sensitization.^{16,35,40,41} In adults, ACD from MCI/MI and MI mainly affects the face (especially the eyelids) and hands^{18,19,21,23,24,29} due to the handling of chemical products like paints.⁴² In children, the perioral skin along with the genital area and buttocks has been commonly affected due to MI in wet wipes in the past.⁴³

Airborne exposure to isothiazolinone-containing paints or household detergents is commonly described with intense involvement of the face, behind the ears and the neck.⁴⁴ Airborne ACD due to paint exposure has been observed in occupational settings, with the first two cases reported by Lundov *et al.*⁴⁵ in 2011. Cases in non-occupational settings were likewise extensively published,^{46–48} with some patients also reporting respiratory complaints.^{45,49,50} Experimental investigations showed that the emission of MI was measurable up to 42 days after paint application,⁵¹ with patients affected in one French clinical study for up to 1 year.⁵² These observations may account for the occurrence of chronic airborne ACD in several patients. According to the Bregnbak *et al.* and Kaae *et al.*^{48,53} publications, such airborne exposure might even induce sensitization. Besides MI, also BIT is often present in water-based paints.^{25,51,54}

	France	France Belgium		υκ		Sweden		Denmark		Finland		Germany
	МІ	MCI/MI	МІ	MCI/MI	MI	MCI/MI	МІ	MCI/MI	МІ	MCI/MI	МІ	МІ
2009	ND	ND	ND	ND	ND	3 ¹²⁶	1.9 ¹²⁶	3.3 ³⁶	1.8 ³⁶	ND	ND	1.94 ¹⁹
2010	1.5 ⁶⁶	3.6 ³²	3.1 ³²	ND	0.5 ¹²⁷	4.3 ¹²⁶	2.9 ¹²⁶	2.2 ³⁶	2.0 ²⁰ 1.9 ³⁶	ND	ND	ND
2011	3.3 ⁶⁶	3.7 ³²	3.2 ³²	ND	ND	ND	ND	5.1 ¹²⁸ 3.5 ³⁶	4.8 ¹²⁸ 3.0 ²⁰ 3.5 ³⁶	ND	ND	ND
2012	5.6 ⁶⁶	4.5 ³²	6 ³²	ND	5.7 ¹²⁷	7.6 ¹²⁶	6.5 ¹²⁶	3.7 ³⁶	3.7 ²⁰ 4.2 ³⁶	11.5 ¹²⁹	10.3 ¹²⁹	6.02 ¹⁹
2013	ND	5.3 ³²	7.2 ³²	ND	ND	ND	ND	6.3 ¹²⁸	6.5 ¹²⁸	14.9 ¹²⁹	13.2 ¹²⁹	ND
2014	ND	ND	ND	7.9 ³³	9.1 ³³	ND	ND	ND	ND	ND	ND	ND
2015	ND	ND	7.3 ²⁹	3.9 ³³	4.8 ³³ 5.2 ²⁹	ND	8.8 ²⁹		5.8 ²⁹		13.0 ²⁹	ND

Table 1 MCI/MI and MI sensitization percentage in patients with contact allergy in Europe, according to the countries, from 2009 to 2015

ND, no data.

Several atypical clinical manifestations elicited by isothiazolinones have been described: systemic ACD from BIT after inhalation via airborne exposure^{46,55}; nummular eczema in a housepainter⁵⁶; lupus erythematosus-like eruptions⁵⁷; 'lymphomatoid' dermatitis^{44,57,58}; Kaposi–Juliusberg syndrome-like rash in a boy³⁷ and following exposure to paints⁵⁹; lichenoid eruptions; also a flare-up of a long-standing oral lichen planus, after the erroneous use of a dishwashing liquid for a dental prosthesis⁶⁰; and scalp lesions mimicking folliculitis decalvans due to a MI-containing hair gel.⁶¹

A combination of urticarial and eczematous skin eruptions has been frequently observed, although Type I hypersensitivity, confirmed by positive prick tests, has never been reported.^{21,62}

Eczematous skin lesions may concern UV-exposed skin areas, representing potential photo-aggravation, sometimes along with transient photosensitivity, due to either MCI/MI or MI alone.^{21,63–65}

Sensitization sources of isothiazolinone

Cosmetic products

Cosmetics have been the main source of sensitization to MCI/ MI and MI,^{21,66} the only isothiazolinones permitted in cosmetic products in Europe, although they should not be used together in any given cosmetic product. Leave-on products have been primarily implicated, including wet wipes (baby wipes, moist tissues and moist toilet paper).^{19,67}

Household products

Detergents may cause ACD, both via direct contact or airborne exposure.⁴⁴ The isothiazolinones potentially present in household products include MCI/MI or MI alone, as well as OIT¹⁰ and BIT.⁶⁸

Industrial products

Paints, glues Although BIT was reported to be among the most common contact allergens in paints associated with occupational contact dermatitis in Danish painters,⁶⁹ paints also contain MI, and to a lesser extent MCI/MI.^{25,51,54} The occurrence of MI and BIT in paints on the EU market has been recently reconfirmed.⁷⁰ In 2015, 93% of 71 different paints contained MI in concentrations varying from 0.7 up to 180.9 ppm.⁵⁴ In 2012, 27% of patchtested painters were shown to be sensitized to MI.⁶⁹

MCI/MI was also found in different kind of glues and in binders. $^{\rm 35}$

Metalworking fluids MCI/MI, MI, BIT and OIT are habitually contained in these products.²⁵

Textiles and leather MCI/MI has been described as contact sensitizer in textile manufacturing.⁷¹

Besides MCI/MI, BIT and OIT are employed in the production and tanning of leatherwear,^{72–77} with the latter derivative

accounting for ACD (and even primary sensitization) in consumers who have direct skin contact with these articles.^{65,74,78} OIT concentrations ranging from 30 to 281 ppm were detected in leather belts and shoes by high-performance liquid chromatography with ultraviolet detection.⁷⁸ In addition, OIT caused skin eruptions when used in mattress textiles⁷⁹ and gel mattress toppers in Japan.⁸⁰ Recently, OIT has also been found in stockings.⁸¹

Plastics Benzisothiazolinone has been responsible for occupational hand dermatitis in healthcare workers being present in polyvinyl chloride gloves,^{82,83} and in employees producing polyacrylate emulsions for paints.¹³ The presence of MI, MCI/MI and OIT was similarly confirmed in polyvinyl alcohol towels.⁸⁴ Repeated washings were shown to decrease the concentration of MI and MCI, yet without decreasing that of OIT due to its hydrophobic properties.

Other potential allergen sources were highlighted, including mouthwashes, toilet fresheners, fuels and animal cosmetics.¹¹

Newer isothiazolinone derivatives

Notwithstanding the recent regulations (i.e. limitations, see below) on further using MCI/MI and MI in cosmetics, non-cosmetic industries have already introduced other isothiazolinone derivatives, such as dichloro-octylisothiazolinone, butyl-benzisothiazolinone (BBIT) and methyl-benzisothiazolinone. To date, only a few cases of ACD induced by these agents have been reported in the literature, with no epidemiological studies available.

- 1 Dichloro-octylisothiazolinone (DCOIT; CAS 64359-81-5; 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one) is used as a biocide in paints, construction products, silicone materials, plastics and wood processing. The first cases of ACD were reported in 1993 in workers of a Japanese textile finishing factory, when open tests with 0.2% of the biocidal product containing 600 ppm of the active ingredient proved positive in all workers.⁸⁵ More recently, Umekoji *et al.*⁸⁶ reported the case of a female consumer who developed ACD after wearing new black trousers. Patch tests in pet were positive to DCOIT 0.1% (1000 ppm) and 0.05% (500 ppm). For contact allergy to DCOIT, potential cross-reactions to OIT, but not to either MCI/MI or MI,^{86,87} were reported.
- 2 Butyl-benzisothiazolinone (BBIT, CAS no. 4299-07-4; 2butyl-1,2-benzisothiazolin-3-one). According to GPMT⁸⁸ and murine LLNA data,⁸⁹ it should be considered an irritant rather than sensitizer. In 2015, however, Dahlin *et al.*⁹⁰ described a case of occupational hand dermatitis attributed to a BBIT-containing cooling fluid. Patch tests were positive to BBIT (0.05% in eth. and pet.), yet remaining negative to MCI/MI, MI, OIT or BIT.
- 3 Methyl-benzisothiazolinone (MBIT; CAS 2527-66-4; methyl-1,2-benzisothiazol-3-one) and its derivatives [methyl-

benzisothiazole-thione (CAS 15871-24-6; 2-methyl-1,2-benzothiazole-3-thione) and methyl-benzisothiazolinone-dioxide (CAS 15448-99-4; 1,2-benzisothiazolin-3-one, 2-methyl-,1,1 dioxide, or N-methyl saccharin)] were found, by means of gas chromatography–mass spectrometry, in carpets.⁹¹ The case involved 32 office employees who presented symptoms of eczema, rhinitis or urticarial skin eruptions, which only improved when the isothiazolinone-containing carpets were removed.

Cross-reactivity vs. concomitant sensitization

Considering the structural similarity between isothiazolinone derivatives, particularly the isothiazolinone ring common to all of them, potential cross-reactivity has been suggested.³ In view of concomitant exposure to many of these derivatives in real life, concomitant sensitization rather than cross-reactivity has been considered more likely by several authors.^{10,92}

Animal data and more recent epidemiological studies have posited cross-reactivity between MI and MCI. Indeed, up to 72% of MI-sensitized patients show patch test reactions to MCI/ MI.^{42,93} In many cases, relevant exposure to MI-containing products could be shown, with cross-reactivity suggested.⁹² On the other hand, analyses using reconstructed human epidermis model revealed that the probability of cross-reactivity between MI and MCI proves rather low, due to the chlorine atom present in MCI.⁹⁴

The possible role of the chlorine atom in the cross-reactivity was also analysed in an animal model.¹ In this model, role of another chlorinated molecule – dichloromethylisothiazolinone – has been found. According to Bruze *et al.*,¹⁵ the chlorinated derivative is to be considered the stronger sensitizer.

Basketter *et al.*⁹ previously confirmed the low probability of cross-reactions between MI and MCI using human repeat insult patch tests. Nevertheless, potential cross-reactivity between MCI and MI is still a matter of debate.

Concerning OIT, Geier et al.39 found that <10% of MI-sensitized patients co-reacted to this derivative, and they thus considered cross-reactivity between MI and OIT unlikely. In addition, patients sensitized to MCI did not react to OIT or DCOIT.95 A more recent study⁷⁸ revealed, however, that patients primarily sensitized to OIT from leather goods exhibited cross-reactivity to MI, but only when MI and OIT were patch-tested at sufficiently high concentrations. On the other hand, in a previous retrospective epidemiological study, the same authors reported that the opposite may likewise occur.²¹ No relevant exposure could be found for approximately 40% of patients with a positive patch test to OIT, and cross-reactivity to the primary sensitizer (MI in cosmetics) was thus considered very likely. Aerts et al.⁷⁸ hypothesized that authors rejecting cross-reactivity between OIT and MI had probably tested OIT or MI at inadequate concentrations, potentially resulting in false negative reactions. These clinical observations were supported by a Danish study that suggested that cross-reactivity to BIT and OIT may occur in MI-sensitized animals.⁷

Concerning BIT, considered to be the least sensitizing derivative, co-sensitization or cross-reactivity to other isothiazolinones, and particularly to MI, has been less frequently observed.⁹³ Indeed, patch tests have proved positive irrespective of reactivity to other isothiazolinones. Its chemical structure clearly differs from MI, whereas OIT may be considered a chemical homologue of MI, which may account for the more frequently observed concomitant reactions to MI and OIT. Schwensen *et al.*⁷ and Aerts *et al.*⁹⁶ concluded that using BIT or OIT as an alternative to MI in (cosmetic) products is not advisable. Accordingly, MI-sensitized patients should thus also try to avoid BIT- or OIT-containing products.

To date, no cross-reaction studies regarding MI and BBIT or MBIT have been conducted.

More recently, several epidemiological studies reported polysensitization in isothiazolinone-sensitized subjects, notably to fragrances, including *Myroxylon pereirae*, and formaldehyde and releasers (e.g. bronopol), as well as to methyldibromo glutaronitrile.^{29,97,98}

Patch tests and optimal concentrations

The patch test concentration may vary from one isothiazolinone to another. In the 1980s, MCI/MI was usually tested at 100 ppm (0.01%) in aq. Since the mid-1980s, MCI/MI has been routinely tested, in Sweden, at 200 ppm in small Finn Chamber. In 2014, to avoid missing sensitization to the chlorinated derivative, the European Environmental and Contact Dermatitis Research Group (EECDRG) recommended increasing the patch test concentration to 200 ppm (0.02%) in aq.⁹⁹ In weakly sensitized individuals, it might even be necessary to increase the concentration to 300 ppm (0.03%) in aq.⁹⁹ However, this should be done with caution, only if MCI/MI at 200 ppm is doubtful, because of risk of patch test active sensitization.

During the 2000s, several dermatology centres performed patch tests with MI at 200 ppm, and later at 500 ppm. However, in 2013, the EECDRG recommended including MI in the European baseline series at a concentration of 2000 ppm (0.2%) in aq. to maximize the test's sensitivity without increasing the risk of irritation or active sensitization.¹⁰⁰

Other studies confirmed the relevance of patch-testing MI at such a high concentration and estimated the risk of missing MI sensitization range between 33% and 66% when MCI/MI is tested at 200 ppm.^{21,101,102} It is strongly recommended to use a micropipette allowing the application of 15 μ L for Finn chambers (diameter 8 mm) and 20 μ L for IQ chambers.¹⁰⁰

The most appropriate patch test concentration and vehicle for BIT is still debated. A concentration of 1000 ppm (0.1%) in pet., initially considered as irritant,¹⁰³ is mostly used,^{93,104} whereas other authors prefer a concentration of 500 ppm (0.05%). Water has also been used as vehicle.¹⁰³

As suggested by Aerts *et al.*,⁷⁸ OIT at a concentration of 250 ppm (0.025%) in pet. may be too low and thus fail to detect weakly sensitized subjects. Therefore, these authors advised performing patch tests with a concentration of 1000 ppm (0.1%) in pet., contrary to Emmet *et al.*,¹⁰⁵ who claimed that skin irritation and active sensitization could potentially occur.

For MTMIT, a concentration of 300 ppm (0.03%) in aq. seems to be the threshold for skin sensitization.⁹ Hence, patch tests should be performed with lower concentrations.²⁶

Table 2 summarizes the different patch test concentrations and vehicles for isothiazolinone derivatives.

In cases of photo-aggravation, it is recommended to perform photo-patch tests with isothiazolinones at the usual concentration irradiated with 5 J/cm² ultraviolet A.⁶³ However, lower concentrations or dilution series may be necessary to prove that the dermatitis is photo-aggravated.⁶⁵ Additionally, photo-tests using ultraviolet A and B may prove necessary to detect the transient photosensitivity sometimes associated.

Legislation

Due to the increased prevalence of ACD from isothiazolinones, EU legislation on their use in cosmetics in particular has changed over the past years.

Concerning MCI/MI, a 1990 recommendation allowed its use in cosmetic products at a concentration not exceeding 15 ppm in the EU,¹⁰⁶ and 7.5 and 15 ppm for leave-on and rinse-off products, respectively, in the United States.¹⁰⁷ This European regulation (EC no. 1223/2009) was updated in 2014, and MCI/ MI was forbidden in Europe in leave-on cosmetics products but still remained permitted in rinse-off cosmetics products at a maximal concentration of 15 ppm.

In 2004, MI was introduced as a preservative in cosmetic products. The Scientific Committee on Consumer Safety (SCCS; European Commission Directorate-General For Health and Consumers) considered at the time that there was no sensitization risk when MI was used at a maximum concentration of 100 ppm (0.01%) in both leave-on and rinse-off cosmetics (EU 1223/2009). However, after many cases of contact allergy to MI had resulted in a worldwide epidemic, in 2013, the European Commission ordered several safety assessments. In December

 Table 2
 Optimal concentrations for patch-testing isothiazolinone derivatives

Optimal concentration, %
0.02 (aq.)
0.2 (aq.)
0.1 (pet.)
0.1 (pet.)
0.05 (pet.)
0.1 (pet.)
0.03 (aq.)

2015, the SCCS estimated that a concentration of 15 ppm MI could be considered safe in rinse-off cosmetics. However, no conclusion was formulated then concerning MI concentration in leave-on cosmetics, including wet wipes (SCCS/1557/15).¹⁰⁸ Recently, the European Commission banned the use of MI in leave-on cosmetics, effective as of February 2017 (EU 1223/2009)¹⁰⁹ and limited the use of MI to a maximum of 15 ppm in rinse-off products, effective as of 27 April 2018 (EU 2017/1224).¹¹⁰

Benzisothiazolinone is not allowed in cosmetic products in Europe, and the SCCS confirmed in 2012 that its use was not safe due to its sensitizing properties.⁸ OIT is likewise prohibited in cosmetics, while little is known about the concentrations allowed in industrial products. However, as for MI in paints, 'self-regulation' governs the use of OIT in the leather industry,⁷⁸ for instance.

Lastly, isothiazolinones are likely to be present in imported cosmetic products (e.g. BIT in sunscreen products from the United States or Canada).¹¹ Indeed, the legislation may vary across geographical regions. The difference between European and international legislation regarding the use of MCI/MI and MI is summarized in Table 3.

Labelling

While EU legislation restricts the maximum concentration of isothiazolinones in cosmetics, and imposes adequate labelling of cosmetics and domestic products, several publications have reported MI exceeding 100 ppm,¹¹¹ the maximum permitted concentrations,^{68,112} mislabelling¹¹³ or absent information concerning the use of either MCI/MI or MI in several products,^{37,114} and in cosmetics regarded as 'natural'.⁶⁷

Additionally, also the preservative systems of individual, raw materials, used for the fabrication of cosmetics, have been shown to contain (high concentrations) of MI, potentially explaining the occurrence of too high use concentrations of MI in some cosmetic products on the EU market. In this particular paper, the authors also detailed on an experimental 'spot test' used for the rapid detection of MI in cosmetic products.¹¹⁵

Similar problems have been described with other products, such as medical devices¹¹⁶ and industrial (chemical) products with incomplete material safety data sheets, or absent information or labelling concerning MI.⁵¹ While EU regulation appears rather clear for cosmetic products, this is not the case for industrials products, given that MI was previously not recognized as skin sensitizer. Labelling of a substance is not mandatory as long as the chemical is not classified as skin sensitizer (H317, formerly R43), according to the CLP regulation (EC No. 1272/2008) on classification, labelling, and packaging of substances and mixtures.¹¹⁷ In March 2016, however, the Committee for Risk Assessment¹¹⁸ concluded that MI should be recognized as skin sensitizer in the 1A, H317 Category ('may cause an allergic skin reaction') with a specific concentration limit of 0.0015%

	Cosmetics	Europe	Canada	USA	Asia			
					Japan	Korea	Singapore	
MCI/MI	Rinse-off	15 ppm	15 ppm	15 ppm	1000 ppm	15 ppm	15 ppm	
	Leave-on	/	/	7.5 ppm	/	/	/	
MI	Rinse-off	15 ppm	100 ppm	100 ppm	100 ppm	100 ppm	100 ppm	
	Leave-on	/	100 ppm	100 ppm	100 ppm	/	/	

 Table 3
 European and international legislation on MCI/MI and MI in cosmetics (max. concentration allowed according to legislation in ppm)

/, to be avoided according to legislation.

(15 ppm). Labelling with EU H208 ('contains 2-methylisothiazol-3(2H)-one, may produce an allergic reaction') must be applied to other industrial products containing less than a tenfold concentration. In the paint industry rules of 'self-classification' currently apply, and H317 is only labelled for an MI concentration exceeding 10 000 ppm (>1%), while EU H208 labelling is applied when the concentration exceeds 1000 ppm (>0.1%).⁵⁴

The development of so-called ecolabels (e.g. the Nordic Swan label, Der Blaue Engel and others) limits the concentration of isothiazolinones in paints. The maximum concentration of all derivatives should not exceed 0.050% (500 ppm), except for exterior paints and wood varnishes, for which the limit is 0.2%.¹¹⁹ All these labels often give consumers a false sense of security, with equally high concentrations potentially present in paints with and without ecolabels.⁵⁴

As mentioned by Friis *et al.*,²⁵ the presence of all isothiazolinones, regardless of their concentrations, should ideally be stated in the material safety data sheets of industrial products, and perhaps even on the packaging. However, professional products use labels to note the presence of Kathon CG, or other commercial designations/brand names, instead of clearly specifying the use of chemical designation MI or MCI/MI as recently reported from a ACD with professional soap where MCI/MI was labelled as Acticide MV.¹²⁰

Prevention

Preventive measures to avoid sensitization to isothiazolinone derivatives are paramount. A recent EU legislation update has restricted MCI/MI and MI concentrations in cosmetics, with adequate MI labelling for industrial (chemical) products put forward. However, primary prevention in the workplace and personal preventive measures prove equally essential (e.g. protective gloves). Isothiazolinones may easily penetrate several types of gloves (e.g. latex, polyvinyl chloride PVC) resulting in sensitization in patients who wear them.¹²¹ Therefore, wearing aboveelbow, reusable nitrile rubber gloves, especially for industrial workers, has been recommended.

In the event of accidental chemical burns with industrial products containing high MCI/MI or MI concentrations, it has been advised to rinse thoroughly with water (dilution effect) or use sodium bisulphite that deactivates MCI/MI.¹²² Concerning paints, isothiazolinone-free water-based paints are available, though hard to find in daily practice.¹¹ Chemical deactivation procedures have also been reported, such as paint alkalinization, to obtain a pH of around 10–11. This still prevents microbial contamination and may guarantee stability for 2 years.¹²³ Another alternative is glutathione, a tripeptide antioxidant, which need to be prepared in a cream at 2.0%, could enable workers sensitized to MCI or MI to continue working with these derivatives.¹²⁴ As glutathione breaks the chemical ring structure of MCI and MI, it was reported to deactivate MCI/MI up to a concentration of 2400 ppm (0.24%).¹²⁵

Conclusion

Isothiazolinone derivatives in general, and MCI/MI and MI in particular, have caused a tremendous amount of contact allergic reactions, whereas recent changes in EU cosmetic legislation have apparently stabilized their occurrence. Some isothiazolinone derivatives, such as OIT and especially BIT, are, however, increasingly used by the chemical industry, resulting not only in cases of occupational sensitization, but also in a potential hazard to consumers of non-cosmetic products containing these particular derivatives (e.g. paints, glues and detergents). Moreover, cases of contact dermatitis caused by newer and currently lesser known isothiazolinone derivatives (MTMIT, BBIT, DCOIT and MBIT) may still be expected in the near future.

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