# Isothiazolinone derivatives and allergic contact dermatitis : a review and update

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Article type : Review Article

# Isothiazolinone derivatives and allergic contact dermatitis: a review and update

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**Conflicts of interest:** The authors declare that they have no conflicts of interest.

**Keywords: allergic contact dermatitis**, **cross-reactions, isothiazolinones, *preservatives, biocides***

**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 1980's, and more recently to MI, the Scientific Committee on Consumer Safety of the European Commission banned their use in leave-on products, whilst restricting that in rinse-off cosmetics. Despite a decreasing prevalence of allergic contact dermatitis 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 allergic contact dermatitis, most relevant sensitization sources, and potential cross-reactions between isothiazolinone derivatives. It also provides an update on recent legislative measures.

**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 1980's. More recently, using MI as a stand-alone preservative at increased concentrations (up to 100ppm) in cosmetics has resulted in dramatic sensitization rates in Europe and beyond. Other isothiazolinones, including benzisothiazolinone (BIT; CAS 2634-33- 5; 1,2-benzisothiazol 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 sulfur aromatic ring (1,2-thiazol-3-one), with structural similarities and differences between isothiazolinone derivatives illustrated in **Figure 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 atom (3) – 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.

OIT has moderate sensitizing potential, somewhat comparable to MI, according to the GPMT (6) 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 dichloromethyl-isothiazolinone (DCMIT), have historically contributed to its tendency to cause skin sensitization, considered less common with today's enhanced purity levels (12).

**History**

BIT 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 1980's, 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 MI-containing 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 100ppm, as compared to only 15ppm 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. reported that methyl trimethylene isothiazolinone (MTMIT; CAS 82633-79-2; 2-methyl-4,5-trimethylene-4-isothiazolin-3-one) could be found in seven different products with concentrations ranging from 47.6 to 150ppm (25). In the 1990's, 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 centers revealed a sensitization rate to MI of 6.0% (*e.g.,* 7.3% in Belgium, 5% in Denmark, and 13% in Finland) (29). Surprisingly, isothiazolinones sensitization rates seems 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), 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 is available on the prevalence of contact allergy to BIT and OIT. Geier *et al.* (39) analyzed 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, 41, 42). 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 (43). In children, the perioral skin along with the genital area and buttocks have been commonly affected due to MI in wet wipes in the past (44).

Airborne exposure to isothiazolinone-containing paints or household detergents is commonly described with intense involvement of the face, behind the ears, and the neck (45). Airborne allergic contact dermatitis due to paint exposure has been observed in occupational settings, with the first two cases reported by Lundov *et al.* (46) in 2011. Cases in non-occupational settings were likewise extensively published (47-49), with some patients also reporting respiratory complaints (46, 50, 51). Experimental investigations showed that the emission of MI was measurable up to 42 days after paint application (52), with patients affected in one French clinical study for up to 1 year (53). These observations may account for the occurrence of chronic airborne allergic contact dermatitis in several patients. According to the Bregnbak *et al.* and Kaae *et al.* (49, 54) publications, such airborne exposure might even induce sensitization. Besides MI, also BIT is often present in water-based paints (25, 52, 55).

Several atypical clinical manifestations elicited by isothiazolinones have been described: systemic ACD from BIT after inhalation via airborne exposure (47, 56); nummular eczema in a housepainter (57); lupus erythematosus-like eruptions (58); “lymphomatoid” dermatitis (45, 58, 59);

Kaposi-Juliusberg syndrome-like rash in a boy (37) and, following exposure to paints, (60); lichenoid eruptions; also a flare-up of a longstanding oral lichen planus, after the erroneous use of a dishwashing liquid for a dental prosthesis (61); scalp lesions mimicking folliculitis decalvans due to a MI-containing hair gel (62).

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, 63).

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, 64-66).

**Sensitization sources of isothiazolinone**

*Cosmetic products*

Cosmetics have been the main source of sensitization to MCI/MI and MI (21, 67), 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, 68).

*Household products*

Detergents may cause ACD, both via direct contact or airborne exposure (45). The isothiazolinones potentially present in household products include MCI/MI or MI alone, as well as OIT (10) and BIT (70).

*Industrial products*

*i. Paints, glues*

Although BIT was reported to be among the most common contact allergens in paints associated with occupational contact dermatitis in Danish painters (71), paints also contain MI, and to a lesser extent MCI/MI (25, 52, 55). The occurrence of MI and BIT in paints on the EU market has

been recently reconfirmed (72). In 2015, 93% of 71 different paints contained MI in concentrations varying from 0.7 up to 180.9ppm (55). In 2012, 27% of patch-tested painters were shown to be sensitized to MI (71).

MCI/MI were also found in different kind of glues and in binders (35).

*ii. Metalworking fluids*

MCI/MI, MI, BIT, and OIT are habitually contained in these products (25).

*iii. Textiles and leather*

MCI/MI has been described as contact sensitizer in textile manufacturing (73).

Besides MCI/MI, BIT and OIT are employed in the production and tanning of leatherwear (74-79), with the latter derivative accounting for ACD (and even primary sensitization) in consumers who have direct skin contact with these articles (66, 76, 80). OIT concentrations ranging from 30 to 281 ppm were detected in leather belts and shoes by high performance liquid chromatography with ultraviolet detection (80). In addition, OIT caused skin eruptions when used in mattress textiles (81) and gel mattress toppers in Japan (82). Recently OIT has also been found in stockings (83).

*iv. Plastics*

BIT has been responsible for occupational hand dermatitis in healthcare workers being present in polyvinyl chloride gloves (84, 85), and in employees producing polyacrylate emulsions for paints (13). The presence of MI, MCI/MI, and OIT was similarly confirmed in polyvinyl alcohol towels (86). 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, 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 600ppm of the active ingredient proved positive in all workers (87). More recently, Umekoji *et al.* (88) 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% (1000ppm) and 0.05% (500ppm). For contact allergy to DCOIT, potential cross-reactions to OIT, but not to either MCI/MI or MI (88, 89), were reported.

2. Butyl-benzisothiazolinone (BBIT, CAS no. 4299-07-4; 2-butyl-1,2-benzisothiazolin-3-one). According to GPMT (90) and murine LLNA data (91), it should be considered an irritant rather than sensitizer. In 2015, however, Dahlin *et al.* (92) 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-benzisothiazolone-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 (93). 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 *versus* 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, 94).

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 (43, 95). In many cases, relevant exposure to MI-containing products could be shown, with cross-reactivity suggested (94). 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 (96).

The possible role of the chlorine atom in the cross-reactivity was also analyzed 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 (97). A more recent study (80) 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.* 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 (80). 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 , have been less frequently observed (95). 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.* (98) 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, 99, 100).

**Patch tests and optimal concentrations**

The patch test concentration may vary from one isothiazolinone to another. In the 1980's, MCI/MI was usually tested at 100ppm (0.01%) in aq. Since the mid 1980's, MCI/MI has been routinely tested, in Sweden, at 200ppm 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 200ppm (0.02%) in aq. (101). In weakly sensitized individuals, it might even be necessary to increase the concentration to 300ppm (0.03%) in aq (101). 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 2000's, several dermatology centers performed patch tests with MI at 200ppm, and later at 500ppm. However, in 2013, the EECDRG recommended including MI in the European baseline series at a concentration of 2000ppm (0.2%) in aq. to maximize the test's sensitivity without increasing the risk of irritation or active sensitization (102).

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 200ppm (21, 103, 104). It is strongly recommended to use a micropipette allowing the application of 15µL for Finn chambers (diameter 8 mm) and 20µL for IQ chambers (102).

The most appropriate patch test concentration and vehicle for BIT is still debated. A concentration of 1000ppm (0.1%) in pet., initially considered as irritant (107), is mostly used (40, 95), whereas other authors prefer a concentration of 500ppm (0.05%). Water has also been used as vehicle (107).

As suggested by Aerts *et al.* (80), OIT at a concentration of 250ppm (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 1000ppm (0.1%) in pet., contrary to Emmet *et al.* (108), who claimed that skin irritation and active sensitization could potentially occur.

For MTMIT, a concentration of 300ppm (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 5J/cm$^2$ ultraviolet A (64). However, lower concentrations or dilution series may be necessary to prove that the dermatitis is photo-aggravated (66). 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 15ppm in the EU (109), and 7.5ppm and 15ppm for leave-on and rinse-off products, respectively, in the USA (110). 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 15ppm.

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 100ppm (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 2015, the SCCS estimated that a concentration of 15ppm 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) (111). Recently, the European Commission banned the use of MI in leave-on cosmetics, effective as of February 2017 (EU 1223/2009) (112) and limited the use of MI to a maximum of 15ppm in rinse-off products, effective as of April 27, 2018 (EU 2017/1224) (113).

BIT 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 (80), for instance.

Lastly, isothiazolinones are likely to be present in imported cosmetic products (*e.g.,* BIT in sunscreen products from the USA 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**.

**Labeling**

While EU legislation restricts the maximum concentration of isothiazolinones in cosmetics, and imposes adequate labeling of cosmetics and domestic products, several publications have reported MI exceeding 100 ppm (114), the maximum permitted concentrations (70, 115), mislabeling (116), or absent information concerning the use of either MCI/MI or MI in several products (37, 117), and in cosmetics regarded as "natural" (68).

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 (118).

Similar problems have been described with other products, such as medical devices (119) and industrial (chemical) products with incomplete material safety data sheets, or absent information or labeling concerning MI (52). 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. Labeling 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, labeling, and packaging of substances and mixtures (120). In March 2016, however, the Committee for Risk Assessment (121) 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% (15ppm). Labeling 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 labeled for an MI concentration exceeding 10 000ppm (>1%), while EU H208 labeling is applied when the concentration exceeds 1000ppm (>0.1%) (55).

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% (500ppm), except for exterior paints and wood varnishes, for which the limit is 0.2%(122). All these labels often give consumers a false sense of security, with equally high concentrations potentially present in paints with and without eco-labels (55).

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(123).

**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 labeling 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, polyvinylchloride PVC) resulting in sensitization in patients who wear them (124). Therefore, wearing above-elbow, 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 (125). 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 alkalinisation, to obtain a pH of around 10–11. This still prevents microbial contamination and may guarantee stability for 2 years (126). Another alternative is glutathione, a tripeptide antioxidant, which need to be prepare in a cream at 2.0%, could enable workers sensitized to MCI or MI to continue working with these derivatives (127). As glutathione breaks the chemical ring structure of MCI and MI, it was reported to deactivate MCI/MI up to a concentration of 2400ppm (0.24%) (128).

**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.

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

| | **France** | **Belgium** | | **UK** | | **Sweden** | | **Denmark** | | **Finland** | | **Germany** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MI | MCI/ MI | MI | MCI/ MI | MI | MCI/ MI | MI | MCI/ MI | MI | MCI/ MI | MI | MI |
| **2009** | | | | | | 3 (129) | 1.9 (129) | 3.3 (36) | 1.8 (36) | | | 1.94 (19) |
| **2010** | 1.5 (67) | 3.6 (32) | 3.1 (32) | | 0.5 (130) | 4.3 (129) | 2.9 (129) | 2.2 (36) | 2.0 (20)- 1.9 (36) | | | |
| **2011** | 3.3 (67) | 3.7 (32) | 3.2 (32) | | | | | 5.1 (131)- 3.5 (36) | 4.8 (131)- 3.0 (20)- 3.5 (36) | | | |
| **2012** | 5.6 (67) | 4.5 (32) | 6 (32) | | 5.7 (130) | 7.6 (129) | 6.5 (129) | 3.7 (36) | 3.7 (20)- 4.2 (36) | 11.5 (132) | 10.3 (132) | 6.02 (19) |
| **2013** | | 5.3 (32) | 7.2 (32) | | | | | 6.3 (131) | 6.5 (131) | 14.9 (132) | 13.2 (132) | |
| **2014** | | | | 7.9 (33) | 9.1 (33) | | | | | | | |
| **2015** | | | 7.3 (29) | 3.9 (33) | 4.8 (33)- 5.2 (29) | | 8.8 (29) | | 5.8 (29) | | 13.0 (29) | |

**Table 2**. Optimal concentrations for patch-testing isothiazolinone derivatives

| Derivative | Optimal concentration |
|---|---|
| MCI/MI | 0.02% (aq.) |
| MI | 0.2% (aq.) |
| BIT | 0.1% (pet.) |
| OIT | 0.1% (pet.) |
| BBIT | 0.05% (pet.) |
| DCOIT | 0.1% (pet.) |
| MTMIT | 0.03% (aq.) |

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

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

/: to be avoided according to legislation

References:

1. Bruze M, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG in the guinea pig. Acta Derm Venereol. 1987;67:315-20.

2. Botham PA, Hilton J, Evans CD, Lees D, Hall TJ. Assessment of the relative skin sensitizing potency of 3 biocides using the murine local lymph node assay. Contact Dermatitis. 1991;25:172-7.

3. Alexander BR. An assessment of the comparative sensitization potential of some common isothiazolinones. Contact Dermatitis. 2002;46:191-6.

4. Roberts DW. Methylisothiazolinone is categorised as a strong sensitiser in the Murine Local Lymph Node Assay. Contact Dermatitis. 2013;69:261-2.

5. Basketter D. Skin sensitisation, adverse outcome pathways and alternatives. Altern Lab Anim. 2016;44:431-6.

6. Mathias CG, Andersen KE, Hamann K. Allergic contact dermatitis from 2-n-octyl-4-isothiazolin-3-one, a paint mildewcide. Contact Dermatitis. 1983;9:507-9.

7. Schwensen JF, Menne Bonefeld C, Zachariae C*, et al.* Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay. Br J Dermatol. 2017;176:176-83.

8. Scientific Committee on Consumer Safety. Opinion on Benzisothiazolinone (P96), adopted on 27 June 2012, European Commission. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_099.pdf last accessed 20 December 2017).

9. Basketter DA, Rodford R, Kimber I, Smith I, Wahlberg JE. Skin sensitization risk assessment: a comparative evaluation of 3 isothiazolinone biocides. Contact Dermatitis. 1999;40:150-4.

10. Mose AP, Frost S, Ohlund U, Andersen KE. Allergic contact dermatitis from octylisothiazolinone. Contact Dermatitis. 2013;69:49-52.

11. Aerts O, Goossens A, Lambert J, Lepoittevin JP. Contact allergy caused by isothiazolinone derivatives: an overview of non-cosmetic and unusual cosmetic sources. Eur J Dermatol. 2017;27:115-22.

12. Bruze M, Gruvberger B, Persson K. Contact allergy to a contaminant in Kathon CG in the guinea pig. Derm Beruf Umwelt. 1987;35:165-8.

13. Pedersen NB. Occupational allergy from 1,2-benzisothiazolin-3-one and other preservatives in plastic emulsions. Contact Dermatitis. 1976;2:340-2.

14. Foussereau J BI, Boujnah-Khouadja A. Allergisches Kontaktekzem durch isothiazolin-3-on Derivate. Dermatosen. 1984;32:208-11.

15. Bruze M, Dahlquist I, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG. Contact Dermatitis. 1987;16:183-8.

16. Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. Dermatitis. 2004;15:201-5.

17. Garcia-Gavin J, Vansina S, Kerre S, Naert A, Goossens A. Methylisothiazolinone, an emerging allergen in cosmetics? Contact Dermatitis. 2010;63:96-101.

18. Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new 'epidemic'. Contact Dermatitis. 2013;68:253-5.

19. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. Contact Dermatitis. 2013;69:231-8.

20. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy-growing epidemic. Contact Dermatitis. 2013;69:271-5.

21. Aerts O, Baeck M, Constandt L*, et al.* The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicentre study. Contact Dermatitis. 2014;71:41-8.

22. Lundov MD, Krongaard T, Menne TL, Johansen JD. Methylisothiazolinone contact allergy: a review. Br J Dermatol. 2011;165:1178-82.

23. Castanedo-Tardana MP, Zug KA. Methylisothiazolinone. Dermatitis. 2013;24:2-6.

24. Thormann J. Contact dermatitis to a new fungicide, 2-n-octyl-4-isothiazolin-3-one. Contact Dermatitis. 1982;8:204.

25. Friis UF, Menne T, Flyvholm MA*, et al.* Isothiazolinones in commercial products at Danish workplaces. Contact Dermatitis. 2014;71:65-74.

26. Burden AD, O'Driscoll JB, Page FC, Beck MH. Contact hypersensitivity to a new isothiazolinone. Contact Dermatitis. 1994;30:179-80.

27. Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. Br J Dermatol. 2009;161:1124-9.

28. Diepgen TL, Ofenloch RF, Bruze M*, et al.* Prevalence of contact allergy in the general population in different European regions. Br J Dermatol. 2016;174:319-29.

29. Schwensen JF, Uter W, Bruze M*, et al.* The epidemic of methylisothiazolinone: a European prospective study. Contact Dermatitis. 2016;76:272-9.

30. Gameiro A, Coutinho I, Ramos L, Goncalo M. Methylisothiazolinone: second 'epidemic' of isothiazolinone sensitization. Contact Dermatitis. 2014;70:242-3.

31. Uter W, Amario-Hita JC, Balato A*, et al.* European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. J Eur Acad Dermatol Venereol. 2017;31:1516-25.

32. Aerts O, Goossens A, Giordano-Labadie F. Contact allergy caused by methylisothiazolinone: the Belgian-French experience. Eur J Dermatol. 2015;25:228-33.

33. Urwin R, Craig S, Latheef F, Wilkinson M. Methylisothiazolinone: the epidemic is declining - but not gone. Contact Dermatitis. 2017;76:301-2.

34. Pesonen M, Jolanki R, Larese Filon F*, et al.* Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe - analyses of the European Surveillance System on Contact Allergy network, 2002-2010. Contact Dermatitis. 2015;72:154-63.

35. Gruvberger B, Bruze M, Almgren G. Occupational dermatoses in a plant producing binders for paints and glues. Contact Dermatitis. 1998;38:71-7.

36. Schwensen JF, Menne T, Andersen KE, Sommerlund M, Johansen JD. Occupations at risk of developing contact allergy to isothiazolinones in Danish contact dermatitis patients: results from a Danish multicentre study (2009-2012). Contact Dermatitis. 2014;71:295-302.

37. Vauhkala AR, Pesonen M, Suomela S*, et al.* Occupational contact allergy to methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone. Contact Dermatitis. 2015;73:150-6.

38. Aerts O, Goossens A. Allergies professionnelles aux isothiazolinones. In: Progrès en Dermato-Allergologie, 37ème cours d'actualisation, John Libbey Eurotext, Montrouge, Nancy, France. 2016:137-58.

39. Geier J, Lessmann H, Schnuch A, Uter W. Concomitant reactivity to methylisothiazolinone, benzisothiazolinone, and octylisothiazolinone. International Network of Departments of Dermatology data, 2009-2013. Contact Dermatitis. 2015;72:337-9.

40. Madsen JT, Andersen KE. Contact allergy to 1,2-benzisothiazolin-3-one. Contact Dermatitis. 2016;75:324-6.

41. Primka EJ, 3rd, Taylor JS. Three cases of contact allergy after chemical burns from methylchloroisothiazolinone/methylisothiazolinone: one with concomitant allergy to methyldibromoglutaronitrile/phenoxyethanol. Am J Contact Dermat. 1997;8:43-6.

42. Willi R, Pfab F, Zilker T*, et al.* Danger from the workplace: allergic contact dermatitis from the first exposure to isothiazolinones. Contact Dermatitis. 2011;64:361-2.

43. Isaksson M, Ale I, Andersen KE*, et al.* Multicenter Patch Testing With Methylisothiazolinone and Methylchloroisothiazolinone/Methylisothiazolinone Within the International Contact Dermatitis Research Group. Dermatitis. 2017;28:210-4.

44. Goldenberg A, Lipp M, Jacob SE. Appropriate Testing of Isothiazolinones in Children. Pediatr Dermatol. 2017;34:138-43.

45. Van Steenkiste E, Goossens A, Meert H, Apers S, Aerts O. Airborne-induced lymphomatoid contact dermatitis caused by methylisothiazolinone. Contact Dermatitis. 2015;72:237-40.

46. Lundov MD, Mosbech H, Thyssen JP, Menne T, Zachariae C. Two cases of airborne allergic

contact dermatitis caused by methylisothiazolinone in paint. Contact Dermatitis. 2011;65:176-9.

47. 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;68:250-1.

48. Madsen JT, Andersen KE. Airborne allergic contact dermatitis caused by methylisothiazolinone in a child sensitized from wet wipes. Contact Dermatitis. 2014;70:183-4.

49. Bregnbak D, Johansen JD. Airborne sensitization to isothiazolinones observed in a 3-month-old boy. Contact Dermatitis. 2013;69:55-6.

50. Herry J, Esquirol Y, Giordano-Labadie F. An intriguing occupational atypical dermatitis with respiratory symptoms. Contact Dermatitis. 2016;75:322-3.

51. Bohn S, Niederer M, Brehm K, Bircher AJ. Airborne contact dermatitis from methylchloroisothiazolinone in wall paint. Abolition of symptoms by chemical allergen inactivation. Contact Dermatitis. 2000;42:196-201.

52. Lundov MD, Kolarik B, Bossi R, Gunnarsen L, Johansen JD. Emission of isothiazolinones from water-based paints. Environ Sci Technol. 2014;48:6989-94.

53. Amsler E, Aerts O, Raison-Peyron N*, et al.* Airborne allergic contact dermatitis caused by isothiazolinones in water-based paints: a retrospective study of 44 cases. Contact Dermatitis. 2017;77:163-70.

54. Kaae J, Menne T, Thyssen JP. Presumed primary contact sensitization to methylisothiazolinone from paint: a chemical that became airborne. Contact Dermatitis. 2012;66:341-2.

55. Schwensen JF, Lundov MD, Bossi R*, et al.* Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. Contact Dermatitis. 2015;72:127-38.

56. Kaur-Knudsen D, Menne T, Christina Carlsen B. Systemic allergic dermatitis following airborne exposure to 1,2-benzisothiazolin-3-one. Contact Dermatitis. 2012;67:310-2.

57. Ezzelarab M HQ, Wallengren J. Occapational allergy caused by 1,2- benzisothiazolin-3-one in water-based paints and glues. Am J Contact Dermat.165–7.

58. Morren MA, Dooms-Goossens A, Delabie J*, et al.* Contact allergy to isothiazolinone derivatives: unusual clinical presentations. Dermatology. 1992;184:260-4.

59. Smets K BA, Hauben E, Goossens A. B-cell lymphomatoid contact dermatitis caused by methyl- and methylchloroisothiazolinone. Eur J Dermatol. 2018;28:91-3.

60. Du-Thanh A, Lalande M, Raison-Peyron N, Dereure O. Atypical and severe airborne isothiazolinone contact dermatitis mimicking Kaposi-Juliusberg syndrome. Contact Dermatitis. 2017;76:297-8.

61. Aerts O, Meert H, Janssens S*, et al.* A sudden flare-up of a quiescent oral lichen planus: methylisothiazolinone as the prime suspect? Contact Dermatitis. 2015;72:186-9.

62. Aerts O, Van Dyck F, Dandelooy J, Mellaerts T, Lambert J. Contact dermatitis masquerading as folliculitis decalvans: methylisothiazolinone strikes again! Dermatitis. 2014;25:276.

63. Gebhardt M, Looks A, Hipler UC. Urticaria caused by type IV sensitization to isothiazolinones. Contact Dermatitis. 1997;36:314.

64. Pirmez R, Fernandes AL, Melo MG. Photoaggravated contact dermatitis to Kathon CG (methylchloroisothiazolinone/methylisothiazolinone): a novel pattern of involvement in a growing epidemic? Br J Dermatol. 2015;173:1343-4.

65. Trokoudes D, Banerjee P, Fityan A*, et al.* Photoaggravated contact dermatitis caused by methylisothiazolinone. Contact Dermatitis. 2017;76:303-4.

66. Aerts O, Goossens A MM, Castelain M, Boursault L, Giordano-Labadie F et al. Photo-aggravated allergic contact dermatitis and transient photosensitivity caused by methylisothiazolinone. Contact Dermatitis. 2018;78:241-5.

67. Hosteing S, Meyer N, Waton J*, et al.* Outbreak of contact sensitization to methylisothiazolinone: an analysis of French data from the REVIDAL-GERDA network. Contact Dermatitis. 2014;70:262-9.

68. Vanneste L, Persson L, Zimerson E*, et al.* Allergic contact dermatitis caused by methylisothiazolinone from different sources, including 'mislabelled' household wet wipes. Contact Dermatitis. 2013;69:311-2.

69. Yazar K, Lundov MD, Faurschou A*, et al.* Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study. Br J Dermatol. 2015;173:115-22.

70. Alvarez-Rivera G, Dagnac T, Lores M*, et al.* Determination of isothiazolinone preservatives in cosmetics and household products by matrix solid-phase dispersion followed by high-performance liquid chromatography-tandem mass spectrometry. J Chromatogr A. 2012;1270:41-50.

71. Mose AP, Lundov MD, Zachariae C*, et al.* Occupational contact dermatitis in painters: an analysis of patch test data from the Danish Contact Dermatitis Group. Contact Dermatitis. 2012;67:293-7.

72. Thomsen AV, Schwensen JF, Bossi R*, et al.* Isothiazolinones are still widely used in paints purchased in five European countries: a follow-up study. Contact Dermatitis. 2018;78:246-53.

73. Valsecchi R, Leghissa P, Piazzolla S, Cainelli T, Seghizzi P. Occupational dermatitis from isothiazolinones in the nylon production. Dermatology. 1993;187:109-11.

74. Ayadi M, Martin P. Pulpitis of the fingers from a shoe glue containing 1,2-benzisothiazolin-3-one (BIT). Contact Dermatitis. 1999;40:115-6.

75. Febriana SA, Zimerson E, Svedman C*, et al.* Thin-layer chromatography and gas chromatography-mass spectrometry examination of shoe materials from patients with shoe

dermatitis. Contact Dermatitis. 2015;72:248-52.

76. Febriana SA, Soebono H, Coenraads PJ, Schuttelaar ML. Contact allergy in Indonesian patients with foot eczema attributed to shoes. J Eur Acad Dermatol Venereol. 2015;29:1582-9.

77. Rani Z, Hussain I, Haroon TS. Common allergens in shoe dermatitis: our experience in Lahore, Pakistan. Int J Dermatol. 2003;42:605-7.

78. Concha-Garzon MJ, Solano-Lopez G, Montes A, Fraga J, Sanchez J. Follicular allergic contact dermatitis due to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in a rinse-off soap product. Clin Exp Dermatol. 2015;40:690-1.

79. Oleaga JM, Aguirre A, Landa N, Gonzalez M, Diaz-Perez JL. Allergic contact dermatitis from Kathon 893. Contact Dermatitis. 1992;27:345-6.

80. Aerts O, Meert H, Romaen E*, et al.* Octylisothiazolinone, an additional cause of allergic contact dermatitis caused by leather: case series and potential implications for the study of cross-reactivity with methylisothiazolinone. Contact Dermatitis. 2016;75:276-84.

81. Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Kuuliala O, Jolanki R. Occupational allergic contact dermatitis from 2-N-octyl-4-isothiazolin-3-one. Contact Dermatitis. 2007;56:160-3.

82. Fukunaga A, Nishiyama S, Shimizu H*, et al.* Non-occupational allergic contact dermatitis from 2-N-octyl-4-isothiazolin-3-one in a Japanese mattress gel-sheet used for cooling. Contact Dermatitis. 2010;62:317-8.

83. Hamnerius N, Ponten A, Mowitz M. Textile contact dermatitis caused by octylisothiazolinone in compression stockings. Contact Dermatitis. 2018;78:419-21.

84. Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Jolanki R. Antimicrobial allergy from polyvinyl chloride gloves. Arch Dermatol. 2006;142:1326-30.

85. Aalto-Korte K, Ackermann L, Henriks-Eckerman ML*, et al.* 1,2-benzisothiazolin-3-one in disposable polyvinyl chloride gloves for medical use. Contact Dermatitis. 2007;57:365-70.

86. Kawakami T, Isama K, Ikarashi Y. Analysis of isothiazolinone preservatives in polyvinyl alcohol cooling towels used in Japan. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2014;49:1209-17.

87. Kawai K, Nakagawa M, Sasaki Y, Kawai K. Occupational contact dermatitis from Kathon 930. Contact Dermatitis. 1993;28:117-8.

88. Umekoji A, Fukai K, Sowa-Osako J*, et al.* Allergic contact dermatitis caused by the preservative 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one in black trousers. Contact Dermatitis. 2016;75:326-8.

89. Isaksson M, Gruvberger B, Bruze M. Patch testing with serial dilutions of various isothiazolinones in patients hypersensitive to methylchloroisothiazolinone/methylisothiazolinone. Contact Dermatitis. 2014;70:270-5.

90. Zissu D. The sensitizing potential of various biocides in the guinea pig maximization test.

Contact Dermatitis. 2002;46:224-7.

91. Yamano T, Shimizu M, Noda T. Quantitative comparison of the results obtained by the multiple-dose guinea pig maximization test and the non-radioactive murine local lymph-node assay for various biocides. Toxicology. 2005;211:165-75.

92. Dahlin J, Isaksson M. Occupational contact dermatitis caused by N-butyl-1,2-benzisothiazolin-3-one in a cutting fluid. Contact Dermatitis. 2015;73:60-2.

93. Ebbehoj NE, Agner T, Zimerson E, Bruze M. Outbreak of eczema and rhinitis in a group of office workers in Greenland. Int J Circumpolar Health. 2015;74:27919.

94. Geier J, Schnuch A. No cross-sensitization between MCI/MI, benzisothiazolinone and octylisothiazolinone. Contact Dermatitis. 1996;34:148-9.

95. Craig S, Urwin R, Latheef F, Wilkinson M. Patch test clinic experience of potential cross-reactivity of isothiazolinones. Contact Dermatitis. 2017;76:299-300.

96. Debeuckelaere C, Moussallieh F-M, Elbayed K*, et al.* In situ chemical behaviour of methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) in reconstructed human epidermis: a new approach to the cross-reactivity issue. Contact Dermatitis. 2016;74:159-67.

97. Isaksson M, Bruze M, Gruvberger B. Cross-reactivity between methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, and other isothiazolinones in workers at a plant producing binders for paints and glues. Contact Dermatitis. 2008;58:60-2.

98. Aerts O, Lambert J, Goossens A. Structures chimiques et allergies croisées entre isothiazolinones. Revue Française d'Allergologie. 2017;57:178-80.

99. Martin-Gorgojo A, Curto-Barredo L, Rovira-Lopez R, Pujol RM, Gimenez-Arnau A. Is methylisothiazolinone contact allergy a risk factor for polysensitization? Contact Dermatitis. 2015;72:400-2.

100. Ponten A, Bruze M, Engfeldt M, Hauksson I, Isaksson M. Concomitant contact allergies to formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, and fragrance mixes I and II. Contact Dermatitis. 2016;75:285-9.

101. Bruze M, Goossens A, Isaksson M. Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series - on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. Contact Dermatitis. 2014;71:35-40.

102. Bruze M, Engfeldt M, Goncalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series--on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. Contact Dermatitis. 2013;69:263-70.

103. Milanesi N, Gola M, Francalanci S. The Utility of Patch Testing Methylisothiazolinone 2000

ppm aqua. Dermatitis. 2015;26:242.

104. Ackermann L, Aalto-Korte K, Alanko K*, et al.* Contact sensitization to methylisothiazolinone in Finland--a multicentre study. Contact Dermatitis. 2011;64:49-53.

105. Isaksson M, Gruvberger B, Bruze M. Can methylisothiazolinone be patch tested in petrolatum? Contact Dermatitis. 2014;70:240-2.

106. Spiewak R. SZ, Pasnicki M., Czarnobilska E., Grubska-Suchanek E., Bukiel M., Jedrzejewska-Jurga K., Czarnecka-Operacz M., Cisowska, B. Niklasson A. Methylisothiazolinone/methylchloroisothiazolinoneand formaldehyde: petrolatum-based patchtests detect more sensitizations Contact Dermatitis. 2014;70:5-8.

107. Chew AL, Maibach HI. 1,2-Benzisothiazolin-3-one (Proxel): irritant or allergen? A clinical study and literature review. Contact Dermatitis. 1997;36:131-6.

108. Emmett EA, Ng SK, Levy MA, Moss JN, Morici IJ. The irritancy and allergenicity of 2-n-octyl-4-isothiazolin-3-one (Skane M-8), with recommendations for patch test concentration. Contact Dermatitis. 1989;20:21-6.

109. Council of the European Communities, COUNCIL DIRECTIVE of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC). European Commission. 1976. 2014 Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20100301:en:PDF (last accessed 05/12/2017).

110. Elder R. Final report on the safety assessmentofmethylchloroisothiazolinone and methylisothiazolinone. J Am Coll Toxicol. 1992;11:75–128.

111. Scientific Committee on Consumer Safety. Opinion on Methylisothiazolinone (P94) Submission III, SCCS/1557/15, Adopted on 25 June 2015. European Commission 2015. available at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_178.pdf (last accessed: 5 April 2017).

112. Council on cosmetic products. Opinion on methylisothazolonone (EC No 1223/2009), adopted 22 July 2016. European Commission. 2016. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R1198&from=FR (last accessed in November 2017).

113. Council on cosmetic products. Opinion on methylisothiazolinone (EC. No 1223/2009), adopted on 6 July 2017. European Commission. 2017. Avialable at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1224&from=EN (last accessed in Novembre 2017).

114. Horev L, Isaksson M, Engfeldt M*, et al.* Preservatives in cosmetics in the Israeli market conform well to the EU legislation. J Eur Acad Dermatol Venereol. 2015;29:761-6.

115. Aerts O, Meert H, Goossens A*, et al.* Methylisothiazolinone in selected consumer products in Belgium: Adding fuel to the fire? Contact Dermatitis. 2015;73:142-9.

116. Isaksson M, Persson L. 'Mislabelled' make-up remover wet wipes as a cause of severe,

recalcitrant facial eczema. Contact Dermatitis. 2015;73:56-9.

117. Gruvberger B, Bruze M, Tammela M. Preservatives in moisturizers on the Swedish market. Acta Derm Venereol. 1998;78:52-6.

118. Kerre S, Naessens T, Theunis M*, et al.* Facial dermatitis caused by undeclared methylisothiazolinone in a gel mask: is the preservation of raw materials in cosmetics a cause of concern? Contact Dermatitis. 2018;78:421-4.

119. Madsen JT, Broesby-Olsen S, Andersen KE. Undisclosed methylisothiazolinone in an ultrasound gel causing occupational allergic contact dermatitis. Contact Dermatitis. 2014;71:312-3.

120. Friis UF, Menne T, Flyvholm MA, Bonde JP, Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. Contact Dermatitis. 2013;69:153-63.

121. European Chemicals Agency. Committee for risk assessment. Opinion, proposing harmonised classification and labelling at EU level of 2-methylisothiazol-3(2H)-one, adopted 10 March 2016. Available at: https://echa.europa.eu/documents/10162/b32e77aa-b720-4f66-ad16-a413dadf1631 (last accessed 12 April 2017).

122. Chemicals Agency. Opinion on the ecological criteria for the award of the EU Ecolabel for indoor and outdoor paints and varnishes, adopted 28 May 2014, C(2014) 3429. No. 2014/312/EU. European Commission. 2014. Available at: http://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32014D0312&from=EN (last accessed 11 April 2017).

123. Santiago L, Goncalo M. Occupational allergic contact dermatitis caused by Acticide MV, a brand name for the mixture methylchloroisothiazolinone/methylisothiazolinone. Contact Dermatitis. 2018;doi: 10.1111/cod.12984.

124. Maor D, Nixon R. Allergic contact dermatitis to methylchloroisothiazolinone/methylisothiazolinone in cooling tower technicians. Dermatitis. 2015;26:62-4.

125. Gruvberger B, Bruze M. Can chemical burns and allergic contact dermatitis from higher concentrations of methylchloroisothiazolinone/methylisothiazolinone be prevented? Am J Contact Dermat. 1998;9:11-4.

126. Braun-Falco M, Knott E, Huss-Marp J, Ring J, Hofmann H. Alkalization of wall paint prevents airborne contact dermatitis in patients with sensitization to isothiazolinones. Contact Dermatitis. 2008;59:129-31.

127. Isaksson M. Successful inhibition of allergic contact dermatitis caused by methylchloroisothiazolinone/methylisothiazolinone with topical glutathione. Contact Dermatitis. 2015;73:126-8.

128. Gruvberger B, Bruze M. Can glutathione-containing emollients inactivate methylchloroisothiazolinone/methylisothiazolinone? Contact Dermatitis. 1998;38:261-5.

129. Isaksson M, Hauksson I, Hindsen M*, et al.* Methylisothiazolinone contact allergy is rising to alarming heights also in southern Sweden. Acta Derm Venereol. 2015;95:31-4.

130. McFadden JP, Mann J, White JM, Banerjee P, White IR. Outbreak of methylisothiazolinone allergy targeting those aged >/=40 years. Contact Dermatitis. 2013;69:53-5.

131. Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. Contact Dermatitis. 2014;70:246-7.

132. Lammintausta K, Aalto-Korte K, Ackerman L*, et al.* An epidemic of contact allergy to methylisothiazolinone in Finland. Contact Dermatitis. 2014;70:184-5.

**Fig. 1**. Molecular structures of isothiazolinone derivatives