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Contact allergy caused by isothiazolinone derivatives: an overview of non-cosmetic and unusual cosmetic sources

The isothiazolinone derivatives, methylchloroisothiazolinone (MCI), methylisothiazolinone (MI), benzisothiazolinone (BIT), and octylisothiazolinone (OIT), owing to their strong bactericide, fungicide and algicide properties, are widely used in non-cosmetic products, such as chemical (industrial) products, household detergents, and water-based paints, and the former two derivatives are also used in cosmetic products. However, given their inherent sensitization potential (with MCI > MI > BIT > OIT), allergic contact dermatitis is frequently observed, both in consumers as well as workers in various industries. In this review, we provide an update on the use of MCI/MI and MI in cosmetics, highlighting certain aspects of MI; the use of excessive concentrations, the presence in some less familiar cosmetic products, and the association with unusual clinical manifestations. Furthermore, the use of isothiazolinones in dish-washing and washing-machine liquids, cleaning agents for dental care, and their general presence in multi-purpose household detergents, which may elicit (airborne) allergic contact dermatitis, is discussed. Finally, we provide a brief overview of the use of isothiazolinone derivatives in the paint and textile industry, and of OIT in the leather industry in particular.

Key words: allergic contact dermatitis, airborne dermatitis, benzisothiazolinone, cosmetic, detergent, isothiazolinone derivative, leatherwear, methylisothiazolinone, methylchloroisothiazolinone/methylisothiazolinone, non-cosmetic, occupational, octylisothiazolinone, paint, textile, concentration, wipe

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Isothiazolinone derivatives, such as methylisothiazolinone (MI), methylchloroisothiazolinone (MCI), benzisothiazolinone (BIT), and octylisothiazolinone (OIT) (figure 1), are used extensively as preservatives in a wide range of products [1]. However, for both consumers and workers in numerous industries, these chemicals represent potentially important health hazards, as evidenced by the MI pandemic which, anno 2017, still has not completely subsided [2, 3]. At present, up to 9% of all patients referred for patch tests, about equal to ~1% of the general population, are affected by allergic contact dermatitis due to MI, which is highly reminiscent of (and even surpassing) the epidemic caused by MCI/MI in the 80s.

In the literature, cases of allergic contact dermatitis from *unusual* cosmetic sources and *non-cosmetic* applications (primarily household detergents and water-based paints) are increasingly being reported [2]. Most published reports deal with MCI/MI, and recently with MI alone, while cases concerning BIT and OIT are usually described in smaller case reports or series. For example, the database CDREF (a web application developed at the KU Leuven comprising a collection of references since 1967) holds 84 references for

MCI, 79 for MI, 39 for BIT, and 12 for OIT (last accessed 24/05/2016) [4].

The whole MI saga also led to an increased awareness among consumers who actively display, through both classic and social media, their interest in (and concerns about) contact allergy caused by MI (e.g. <https://www.facebook.com/pages/Allergy-to-Isothiazolinone-Methylisothiazolinone-and-Chloroisothiazolinone/307128722674171>).

Interestingly, the first cases of contact allergy due to isothiazolinones occurred in occupational settings with exposure to higher concentrations, for which legislation (unlike that for cosmetics) is still lacking [4].

Methyltrimethylene-isothiazolinone (MTMIT), butyl-benzisothiazolinone (BBIT), dichloro-octylisothiazolinone (DCOIT), and dichloro-methylisothiazolinone (DCMIT) are all less well known (and less used) isothiazolinone derivatives which are beyond the scope of this review.

The relative risk of sensitization associated with those derivatives that are more frequently used, is sometimes represented as MCI > MI > BIT > OIT [5], consistent with their extent of use (tables 1-3).

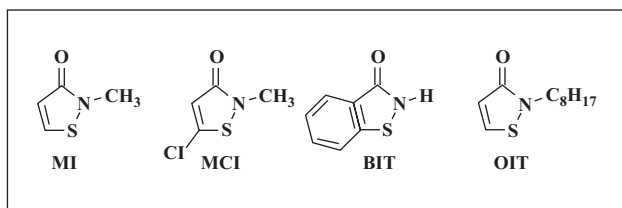


Figure 1. Chemical structure of the most frequently used isothiazolinone derivatives in consumer products.

Update on usage in cosmetics

Use of excessive concentrations of MI in some cosmetics

Several studies have shown that *leave-on* cosmetics are the main culprit products causing contact allergy to MI [2, 3]. However, *rinse-off* products may also elicit allergic contact dermatitis [6], and, by repetitive or cumulative use, are even capable of inducing sensitization [7]. Recently, 30 cosmetic products available on the Belgian market were analysed for the presence of MI, MCI, OIT, and BIT at the laboratory NatuRA of Antwerp University (the use of the latter two in cosmetic products is presently against EU law). These analyses showed that MI was often (in 80% of the cases) present at excessive concentrations (*i.e.* >100 ppm) in *leave-on* products, however, the sample size was small, and a selection bias (some of the products were used by MI-allergic patients) cannot be excluded [8]. Moreover, mislabelling of cosmetics and detergents does occur, as recently also reported by others [9, 10]. *Leave-on* cosmetics, not only due to their *leave-on* character but also (excessively) high MI concentrations, are thus the main driving force behind the

Table 1. Concentrations of isothiazolinones used in products available in the EU*.

Cosmetics [°]	MCI/MI <15 ppm* MI <100 ppm** BIT: forbidden*** OIT: forbidden****
Paints [§] , glues [§] , detergents [°]	MCI/MI <15 ppm MI <300 ppm BIT <360 ppm OIT: insufficient data
Industrially used biocides [§]	MCI, MI, BIT: potentially high concentrations (<i>e.g.</i> >5000 ppm) OIT: insufficient data

*based on reference [60]; [°]labelling is legally required; [§]no labelling required; *From April 2016 onwards: forbidden in leave-on cosmetics; **Recommendation to phase out its use in leave-on cosmetics; expected to be officially banned in leave-on cosmetics from 01 January 2017 onwards. ***Exceptionally (illegally) present in cosmetics in the EU market; allowed in cosmetics in the US and Canada; ****Exceptionally (illegally) present in cosmetics in the EU market.

contact-allergy epidemic, and, when incorrectly labelled, may be unavoidable for sensitized patients. The use of high concentrations may also explain why patients sometimes present with very strong patch-test reactions to their own cosmetic products, and to higher test concentrations of MI (500 or 2000 ppm), but much weaker reactions to MCI/MI 100 or 200 ppm (containing only 25 and 50 ppm MI, respectively). The actual reason why some cosmetics contain such high concentrations remains elusive; perhaps the total amount of MI in a given product is raised because this preservative is also present in separate cosmetic ingredients (which the manufacturer might not always be aware of). Similar findings have been reported in the paint industry where, at present, there is no maximum level [8, 11, 12].

Table 2. Overview of the most important non-cosmetic sources of isothiazolinones*.

Water-based paints and varnishes.
Glues (<i>e.g.</i> wallpaper glue, shoe glue) and glue removers; also used during the manufacturing of adhesives and plasters.
Detergents (household and industrial cleaning products, including wet wipes, dish-washing and machine-washing liquids, fabric softeners); maintenance products for clothes (<i>e.g.</i> textile sprays to mask odours, or to make garments wrinkle-free).
Fillers (<i>e.g.</i> for plastering or floor tiling); pottery.
Gloss and polish products (<i>e.g.</i> maintenance products for cars, boats, <i>etc.</i>).
Metal-work fluids (cooling fluids and oils)
Textile, leather (shoes) and fur industry; including aqueous pigment liquids, also used during the manufacturing of carpets and mattresses and (occasionally) gloves.
Printing inks and toners.
Rubber industry (latex emulsions).
Plastics industry (polymer solutions); also used during the manufacturing of plastic materials (<i>e.g.</i> chopping boards, rubbish bags).
Paper and cardboard industry (<i>e.g.</i> as a biocide in paper pulp, in aqueous pigment liquids).
Wood cleaning and maintenance products.
Pesticides
As a bactericide, fungicide and algicide in various industries (<i>e.g.</i> in the production of water softeners, air fresheners, milk and water industry, <i>etc.</i>) and laboratories.

*including methylisothiazolinone (MI), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), benzisothiazolinone (BIT), and octylisothiazolinone (OIT); non-exhaustive list, based on: contactallergy.uzleuven.be, http://www.cdeskpro.be/files/cdref_n.htm, and derived from articles published in the journal *Contact Dermatitis* during 2014-2015.

Table 3. Examples of less frequently reported, exceptional, or remarkable cosmetic and non-cosmetic sources of MCI/MI (*Kathon CG*[®]) and MI*.

Human cosmetics, such as solid soap cubes, hand barrier creams, liquid makeup products.
Animal cosmetics (<i>e.g.</i> dog shampoo)
Mouth washes, maintenance products for dental prostheses.
Sexual lubricants
Ironing water products
Toilet fresheners
Medical devices to lose weight (<i>e.g.</i> “waist reduction belt”)
Medical devices (wet wipes for skin care, products to decontaminate MRSA, ultrasound gels, <i>etc.</i>)
Antibacterial insoles for shoes
(Gel) mattresses and water beds
Articles, objects and textiles “contaminated” with isothiazolinones, <i>e.g.</i> due to a detergent (sofas, toilet seats, towels, garments, <i>etc.</i>)
Products for gardening, do-it-yourself products.
Antifungal coatings for car tyres and car seats.
Radiographic materials
Fuels (gasoline, diesel)
Medium density fibreboard (MDF)

*MI: methylisothiazolinone; MCI: methylchloroisothiazolinone; non-exhaustive list, based on: http://www.cdeskpro.be/files/cdref_n.htm (web application KU Leuven), and derived from articles published in the journal *Contact Dermatitis* 2014-2015, and on personal observations of the authors.

Unusual cosmetic products

Solid, extra greasy soap cubes may contain MCI/MI (personal communication Dr. A. Pons-Guiraud, REVIDAL [Réseau de Vigilance en Dermato-Allergologie], Paris, 10/01/2014) and MI may also be present in liquid makeup, such as mascara and eye pencils, usually brought in by patients without the packaging that contains the (legally required) content information. Some authors suggested that sun protectors containing MI are low-risk products [13], while others reported the opposite [14]; even potential photo-aggravation by MCI/MI or MI should be kept in mind [2, 15]. Some cosmetic companies have explicitly labelled their products as “methylisothiazolinone-free” (*e.g.* Ombra[®] sunscreen, Emil Kiessling GmbH, Georgensgmünd, Germany). Unfortunately, a manufacturer from the US included MI in a mouth wash (Colgate Total[®] Lasting White[™], Colgate-Palmolive), and at least one female consumer reported throat swelling, resembling food allergy, following its use [16]. Also, cosmetics for pets (*e.g.* dog shampoo) may contain isothiazolinones, which are products that do not have to adhere to the Cosmetics Regulation. A similar observation has been made for methyl-dibromo glutaronitrile (personal communication: M. Isaksson, European Society of Contact Dermatitis [ESCD], Malmö, 13-16 June 2012). Moreover, European legislation, although not always so timely enacted upon, does not apply to cosmetics bought outside the EU, *e.g.* BIT-containing sunscreen products from the US or Canada.

Unusual clinical presentations

It has become clear that contact allergy caused by isothiazolinones, and by MCI/MI and MI in particular, may manifest with unusual clinical and/or histological presentations [2, 17]. Prominent facial swelling and remarkable (sometimes solitary) eyelid oedema, caused by cosmetics, have been observed and may lead the clinician to (erroneously) suspect the occurrence of an immediate (IgE-mediated), instead of a delayed (T cell-mediated), type of allergy. As far as we know, no immediate reactions upon patch testing with MI, nor positive prick tests performed with this preservative or with cosmetics containing it, have been reported. On the contrary, in the abovementioned clinical scenarios, patients always patch tested positively, although sometimes only with the highest test concentration of MI (*i.e.* 2000 ppm aq.).

Reminiscent of the angioedema-like clinical picture often provoked by paraphenylenediamine (PPD), the observed reactions to MI are another example of a delayed type of hypersensitivity, showing a rapid onset and course; urticaria-like reactions and mixed urticarial-eczematous skin lesions have been reported [2, 18]. It was recently stressed that MI-allergic patients might also show a higher risk of poly-sensitization [19].

Hospital cosmetics and medical devices

Methylisothiazolinone-related occupational hand dermatitis may occur in medical personnel (*e.g.* nurses) [2, 3]. Despite the currently well-known sensitizing potential of MI, some products within the medical sector still contain this preservative. For example, in the University Hospitals of Antwerp and Leuven, as well as in the Cliniques Universitaires St. Luc in Brussels (personal communication: Prof. D. Tennstedt, REVIDAL, Paris, 28/06/2013), wet wipes, bath creams, and MRSA-decontamination bonnets, all used in the daily skin care of patients, have been reported as MI allergen sources, respectively. It may be debated whether such products should still be considered cosmetics, or rather medical devices, given the fact that their main function is antisepsis of the skin. Medical devices, which do not have to comply with the Cosmetics Regulation, may indeed contain MI, and may even be mislabelled. Madsen *et al.* described a female nurse with hand dermatitis caused by the use of an MI-containing ultrasound gel. The material safety data sheets (MSDS), sometimes not always reliable [20], did not mention its presence, although the manufacturer confirmed its use at a concentration of <0.5% [21]. Interestingly, the use of gloves (type not specified) had only provided partial protection. In many professions, MI-containing cosmetics (*e.g.* liquid hand soaps) may account for recalcitrant occupational hand dermatitis [2, 3].

Household detergents: important sources of isothiazolinone derivatives

(Airborne) allergic contact dermatitis caused by detergents

Household detergents may contain several types of isothiazolinones, sometimes at high (legally unrestricted)

concentrations; *e.g.* MI 200 ppm. Due to repetitive skin contact, they may also elicit, or even induce, occupational hand dermatitis in cleaners, cooks, and workers in food catering, cafés or restaurants [2, 7]. However, these products, like water-based paints, may not only cause (hand) dermatitis by direct skin contact, but may also lead to airborne lesions, for instance by using detergent sprays or applying such products onto large in-house surfaces, or at the work place.

Van Steenkiste *et al.* reported a patient with a longstanding and therapy-resistant dermatitis of the face and neck caused by MI in a floor detergent (with floor heating even facilitating its airborne distribution) [22]. Interestingly, photo-aggravation of the dermatitis was also noted in this case, and an atypical clinical presentation (*i.e.* *lymphomatoid* dermatitis) occurred. Moreover, only the patch test with MI 0.2% (2000 ppm) aq. led to a correct diagnosis. A similar case of an airborne, periorbital allergic contact dermatitis was reported in a laboratory technician exposed at work (*by proxy*) to a detergent, and who reacted to OIT 250 ppm (0.025%) pet. [23]. A particular point of interest is the penetration capacity of isothiazolinones, for example through rubber and plastic materials, such as protective gloves, which was shown to occur for MCI/MI, MI and OIT [24–26]. This may well be an important feature when evaluating their induction *c.q.* elicitation capacities. In daily practice, neither natural rubber latex nor polyvinylchloride (PVC) gloves may offer the right protection, and preferably thick (re-usable) nitrile gloves should be advised [25].

With regard to BIT, a recent analysis of patch-test data from the University Hospitals of Antwerp and Leuven revealed that, at least in Belgium, this derivative appears to be only a rare contact allergen; targeted, and partially routine, patch testing during the period of January 1990 to December 2014 showed only 16 positive cases, and the majority of (occupational) hand dermatitis cases was due to its presence in detergents (unpublished data). Although BIT, like MI, is widely used in water-based paints [27], and thus considered an important cause of (also airborne and systemic) allergic contact dermatitis from paints, such patients were not present in our series.

Unusual applications of isothiazolinone-containing detergents

Unusual applications of detergents may also harbour risks; for example, a female patient was reported to experience a dramatic flare-up of a longstanding (>15 years), but quiescent, oral lichen planus following the (erroneous) use of an MI-containing household detergent (as advised by her dentist) to clean her dental prosthesis [28]. The patient suffered from intra-oral vesicles, aphtous lesions, a dry mouth, and taste disturbances, related to the wearing of the prosthesis which she used to soak, several times a week, in a small amount of water to which she added variable amounts of the detergent. Patch tests showed a clear sensitization to MCI/MI and MI and high-performance liquid chromatography with UV-detection (HPLC-UV) showed the presence of MI in the detergent at a rather high concentration (~135 ppm). The film-forming capacities of the detergent, inadequate rinsing, and the porosity of the (acrylate) prosthesis may all have led to accumulation of MI, causing sensitization and subsequent koebnerisation,

accounting for the flare-up of the lichen planus. This case teaches us that MI, apart from being a skin sensitizer, also acts as a mucosal sensitizer, and that its presence in products designated to be used on mucosal surfaces, such as, for example, sexual or medical lubricants [2], may also constitute a health risk.

What about liquids used for textile washing?

Although often suspected by patients as contributing to their skin problems, the relative significance of isothiazolinone derivatives in washing-machine liquids and fabric softeners is at present unclear, and studies are lacking. It does not seem illogical to suspect that residual amounts of MCI and MI in wet clothing, upon drying, may still provoke (discrete) skin lesions, or an intractable itch, especially in highly-sensitized individuals. From a practical point of view, the following recommendations may be helpful: (1) do not use excessive amounts of washing-machine liquid (or the equivalent powder form), (2) use extra rinsing cycles, and (3) do not use fabric softeners containing isothiazolinones (used during the final stage of washing, which potentially reside in the fabrics). Alternatively, one might use isothiazolinone-free detergents, for example, those with the label “AC (Allergènes Contrôlés) premium”, issued by the French ARCAA (l’Association de Recherche Clinique en Allergologie et en Asthmologie), a panel of experts in allergology, as mentioned by M. Vigan (“Lessives sans isothiazolinones”, REVIDAL meeting, Paris, 10/01/2014). The eco-brand “Arbre Vert” (www.arbrevert.fr, and soon also www.arbrevert.be), among others, distributes a large number of such products. Of note, the *induction* of sensitization, due to residual amounts in washed clothing, is considered highly unlikely.

The textile industry

Antimicrobials, including isothiazolinones [29], are highly appreciated in the textile industry, because they serve: (1) to protect the textiles (during production and transport, *e.g.* to prevent discolouration), and (2) to protect the consumer from being affected by micro-organisms (*e.g.* malodor, infection). Valsecchi *et al.* reported three patients, employed in the spinning department of a nylon-producing company, who developed hand eczema caused by MCI/MI present in a preservation oil administered onto the yarn [30]. Aalto-Korte *et al.* reported on several patients occupationally sensitized to OIT, including a woman with vesicular hand dermatitis who had been working with mattresses containing (relatively low amounts of) OIT [31]. Later on, the same author showed BIT to be a contact allergen in non-powdered polyvinylchloride (PVC) gloves, responsible for hand dermatitis in (para)medical professionals [32]. Fukunaga *et al.* published a report on a consumer suffering from allergic contact dermatitis caused by OIT present in a mattress used at home; this preservative was present in an inner gel and penetrated through a middle polyethylene layer to the textile surface that came into contact with the patient’s skin [26]. A similar case was reported of a male patient who presented with a widespread, therapy-resistant nummular dermatitis, caused by MCI/MI present in a preservative fluid added to the water reservoir of a waterbed mattress [33]; accidental leakage, contaminating the surface of the bed (with an

estimated MCI/MI concentration ranging between 19 and 92 ppm), induced contact allergy. Mose *et al.* also highlighted one textile worker, presenting with hand dermatitis, who was found to have a relevant contact allergy to OIT used during the processing of textiles [5]. Despite the fact that only few reports have been published, it appears that the use of isothiazolinone derivatives by the textile industry, during processing and applied to the final products, might be more widespread than has been acknowledged hitherto, indicating that vigilance is warranted when considering the potential implications, both in an occupational and non-occupational context. During a recent REVIDAL meeting in Paris (09/01/2015), the French “*Institut Français du Textile et de l’Habillement*” acknowledged that these derivatives are indeed used by the industry, but that their true extent of use within the sector remains elusive. In fact, an entire (online) market exists of so-called “*treated textiles*”, *i.e.* materials (*e.g.* mattresses) and garments (*e.g.* sports clothing), to which isothiazolinones such as BIT, butyl-BIT, and OIT are added to avoid bacterial and fungal contamination (*e.g.* Sanitized®; www.sanitized.com).

In Antwerp, a female patient, working in a clothing boutique, recently presented with new-onset hand dermatitis strongly related to textiles. Patch tests read at Day 4, *i.e.* 96 hours following their application, showed, except for weak reactions to several disperse dyes, a remarkable sensitization (++) to MCI/MI for which initially no clear relevance could be found. However, chemical analysis of several garments confirmed the presence of low amounts of MCI, the most sensitizing isothiazolinone derivative, which may thus have contributed to her hand dermatitis (unpublished data). Other examples of antimicrobials used by the textile industry include: (1) triclosan, (2) quaternary ammonium salts, (3) zinc pyrithione, (4) (nano) silver particles, (5) chitosan, and (6) biguanides [34]. Several reports have been recently published concerning the latter group of preservatives, which can induce both immediate and delayed types of hypersensitivities, when present in cosmetics (*e.g.* make-up removers, wet wipes), lens solutions, and medical devices (*e.g.* wound cleansers) [35-37].

The leather industry

In 1984, Foussereau *et al.* published the case of a female worker with occupational hand dermatitis, employed in a leather shoe factory, who was found to be sensitized to OIT and MCI/MI, both present as biocides in a preservative fluid that had been used to treat the leather [38]. Isothiazolinones are used mainly for their strong fungicide properties, during several stages of leather processing (before, during, and after tanning) [39]. In 1992, Oleaga *et al.* confirmed that OIT is a contact allergen in leather shoes, which can provoke foot dermatitis in consumers [40]. For several years, OIT has been included in commercialised shoe series for patch testing, often only at a concentration of 250 ppm (0.025%) pet. (Trolab®, SmartPractice Europe GmbH, Barsbüttel, Duitsland and AllergEaze®, SmartPractice Canada, Calgary, Canada), and more rarely at a higher concentration of 1000 ppm (0.1%) pet. (Chemotechnique®, Chemotechnique Diagnostics, Vellinge, Sweden). In 2003, Rani *et al.* reported four consumers from Pakistan with foot dermatitis caused by OIT in leather shoes [41], and more recently Febriana *et al.* published a case series of patients

from Indonesia suffering from shoe dermatitis owing to the use of these biocides during leather processing [42]. This report concerned four patients who were contact-allergic to MCI/MI, two to OIT, and another two to thiocyanomethylthiobenzothiazole (TCMBT; patch tested at 0.2% pet.), an allergen which the authors concluded might serve as a screening allergen in a shoe series. Some of their patients also showed positive skin reactions to pieces of their own shoes, or to extracts made from them, but chemical analyses were not performed. The same authors had previously reported on two labourers, involved in the processing of leather in two tanning factories in Indonesia, of whom one was sensitized to MCI/MI and the other to OIT, which were both used on animal hides, before the actual tanning process [43]. The leather industry communicated in 2008 that OIT, and to a lesser extent BIT, but mainly TCMBT (largest market share), are used [39]. In the above-mentioned review by Mose *et al.* [5], four patients with non-occupational foot dermatitis were also reported, with a possible link to OIT in (leather) shoes for two of them. At the KU Leuven and Antwerp department, six similar patients (four and two patients, respectively) with relevant OIT sensitization from leather goods (mainly shoes, but also a belt, a sofa, and leather watch straps) were observed. These clinical cases, and their extensive work-up including a HPLC-UV method to analyse the presence of several isothiazolinone derivatives in leatherwear, have been described in detail elsewhere [44, 45]. Furthermore, it is interesting to highlight that maintenance products for leather may also contain these biocides, which, through contamination (and/or potential penetration), may reside on (or in) the leatherwear and, as such, cause (sometimes long-lasting) contact dermatitis. A recent publication described the case of a male patient suffering from chronic, recalcitrant dermatitis in whom patch tests showed a strong positive reaction (++++) to MI, found to be present in two leather care products (a detergent and a balm), used for the cleaning and maintenance of a leather sofa [46]. The patient also reacted to OIT (++), which was believed to be a possible cross-reaction to MI, although in the light of the above discussion, its presence in the leather might also have been an alternative explanation. Interestingly, patients sensitized to OIT from leather may not always exhibit clear-cut strong dermatitis lesions, but may also present with rather subtle, discrete eczema and a chief complaint of intractable itch [44]. BIT has been held responsible for the occurrence of occupational hand dermatitis (pulpitis) in a patient working with shoe glue containing this preservative [47].

The paint industry

Water-based paints, often containing MI and BIT [12], represent a specific occupational health hazard, but also for consumers at home or at work, or even in public places, where painting is being undertaken.

Airborne sensitization and elicitation of allergic contact dermatitis, caused by the continuous evaporation of isothiazolinones at low concentrations over several weeks to months, constitutes an important health risk [11]. This risk of airborne sensitization has been confirmed by researchers studying their emission from 19 different water-based paints, all potentially containing MI, MCI, and/or

BIT [11]. First, chemical analysis, by means of liquid chromatography in association with mass spectrometry (LC-MS), was used to verify their presence and concentrations; MI was found in all 19 paints (concentration range: 10-300 ppm), BIT in 16 paints (concentration range: 1.5-360 ppm), and MCI was only present in four paints at low concentrations (range: 2-14 ppm). Subsequently, emission studies in a laboratory chamber were performed using painted plaster walls (two layers). This confirmed the continuous emission of MI from the paints during a long period (up to 42 days), while, for BIT, only emission of weak concentrations (close to the detection limit) were noted. Finally, to further confirm the risk of airborne sensitization to MI from paints, emission studies were performed in a two-storey, painted, 111-m² apartment, with paint containing MI (44 ppm) and BIT (1.5 ppm); after seven days the airborne concentrations were measured. During the first few days, MI emission was measured with a magnitude of 20 µg.m⁻³, and subsequently 3 µg.m⁻³ over several weeks. Recently, we were also able to confirm that paints on the Belgian market mainly contain MI and BIT, the latter clearly at lower concentrations (range: 23-41 ppm) when compared to those present on the Scandinavian market [8]. Some paint manufacturers use MCI/MI together with MI (and/or BIT), a practice that is forbidden in the cosmetic industry. Moreover, a paint product may consist of a basic paint to which other substances (e.g. colour pastes, sometimes also containing MI) may be added, hence augmenting the total MI content. Although Thormann in 1982 [48], and more recently Mose *et al.* [5], reported OIT to be a potentially important contact allergen in paints, its use in paint may be rather limited.

Allergic contact dermatitis caused by water-based paints often has a chronic character and may display atypical clinical features (e.g. *dermatomyositis-like*; unpublished data). Moreover, mucosal complaints, including rhinitis, conjunctivitis, and respiratory (asthmatic) complaints, and even (through inhalation) systemic contact dermatitis, may occur [49, 50]. Devos *et al.* showed that in skin-sensitized mice, when looking at airway reactivity and the type of pulmonary inflammation involved, MI following intranasal application mainly acts as an irritant to the mucosal surfaces, and not as an allergen (asthmogen) [51]. Whether this is also the case in humans by airborne sensitization, remains to be elucidated.

Another important element is the addition of so-called nanoparticles to paint (e.g. to provide self-cleaning properties). Researchers from the KU Leuven reported that, in an experimental mouse model, nano-titaniumdioxide (nano-TiO₂) strongly enhanced the induction of contact allergy by the well-known sensitizer, dinitrochlorobenzene (DNCB) [52]. This observation raises questions as to whether the simultaneous presence of such nanoparticles and isothiazolinone derivatives in water-based paints, but also in cosmetics (e.g. sunscreens), might influence their sensitization induction and elicitation capacities. To illustrate a doom scenario, the presence of MI in sunscreens, sometimes applied onto damaged (*i.e.* sunburned and more easily penetrable) skin, together with the (theoretical) contact-allergy facilitating effects of nano-TiO₂, and the knowledge that contact dermatitis by MI might become photo-aggravated, may give rise to a potentially dangerous cocktail.

Table 4. Examples of paint manufacturers producing paints without (or with low amounts of) isothiazolinones*.

www.afmsafecoat.com
www.aurosa.com
www.ecowise.com
www.murphywallproducts.com
www.milkpaint.com (powder paint)
www.realmilkpaint.com (powder paint)
www.lime.org.uk (powder paint)
www.uneartedpaints.com
http://www.organicnaturalpaint.co.uk
www.nutshell.co.uk (contains MCI/MI, max. 15 ppm)
www.boss.be (contains MCI/MI, max. 15 ppm)
www.springcolor.it (without any isothiazolinones)**

Based on: <http://www.scribd.com/doc/235153767/Paint-Products-Without-Methylisothiazolinone> by Christine Marie Schroeder, March 2015; as a precaution the exact product details should be verified with the manufacturer.**Based on: Dr. Michèle Debons, Nantes, France; REVIDAL-GERDA mailing list, e-mail communication 15/03/2016.

Some paint manufacturers have spontaneously started to label their products with “contains methylisothiazolinone, may cause an allergic reaction”, while others have restricted the use of MCI/MI to a maximum of 15 ppm. However, in daily practice, we are now confronted with a number of patients *already* sensitized to MI, and this is very problematic because MI, even at low concentrations (e.g. 53 ppm), may elicit skin lesions and other symptoms [49], and the individual level for elicitation, as in the case of cosmetics [53], may even be much lower (<10 ppm). This is also evidenced by case reports in which MI-based paints used in public places were shown to elicit skin symptoms [54]. Possible solutions, besides good ventilation and temporary (or even definitive) relocation [55], include: (1) the addition of sulphites to water-based paints [56] (although they may act as allergens themselves, inducing both skin lesions and/or bronchospasms); (2) alkalization of such paints (which may also pose health risks, e.g. skin burns [57]); and (3) the use of isothiazolinone-free water-based paints (table 4). The latter are sometimes hard to find, may be less practical, more expensive, and offer less creative options (e.g. fewer colour shades). Recently, Isaksson *et al.* reported the use of a compounded cream containing the antioxidant glutathion 2%, a peptide capable of breaking the N-S bond of the ring structure of MI, thereby destroying the allergenic (and also antimicrobial) character. This creative solution helped a patient with relapsing airborne allergic contact dermatitis due to work-related MI vapours [58]. Safer use concentrations and adequate labelling of isothiazolinones in paints are urgently needed. In this regard, it should be mentioned that so-called “eco-labels” may be misleading, as the concentrations can be as high as those found in regular paints [12].

Conclusion

The widespread use of isothiazolinone derivatives is striking, with household detergents and water-based paints

constituting the most important non-cosmetic allergen sources, however, other applications and various industries are also widely represented. Our ever-growing knowledge on the risk of sensitization to these chemicals, together with some of their remarkable properties (e.g. the penetration of seemingly solid materials), lead us to realise that adequate legislation and control of their adherence are more than ever necessary.

The European authorities recently decided to no longer allow the use of MCI/MI in *leave-on* cosmetics (from April 2016 onwards); hopefully in the future, the use of MI alone in such products will also be prohibited. With regards to non-cosmetics, such as paints and related chemical (industrial) products, we urge for more thorough regulations, correct labelling, and reliable and complete information on the Material Safety Data sheets (MSDS), ideally mentioning the presence of all isothiazolinones, regardless of their concentration. The very high concentrations in industrial biocides, with the risk of contracting chemical burns and active sensitization [59], necessitate adequate protective measurements (e.g. closed systems and sufficient ventilation), but also correct education of employees (e.g. risk management in case of spillage, leakage, etc.). ■

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