

Contact allergy caused by methylisothiazolinone and related isothiazolinones

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Chapter

5

Methylisothiazolinone in
selected consumer products
in Belgium:
adding fuel to the fire?



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Abstract

Background. Methylisothiazolinone (MI) contact allergy is severely affecting consumers with allergic contact dermatitis, owing to its presence in cosmetics, household detergents, and water-based paints, in particular. Data on the true isothiazolinone concentrations in these products are scarce, and labelling may be incorrect.

Objectives. To report on the MI concentrations in such products marketed in Belgium, in order to verify the accuracy of labelling (when applicable) and compliance with EU regulations.

Materials and methods. Thirty cosmetics (18 leave-on and 12 rinse-off), eight detergents and four paints were analysed for MI by the use of high performance liquid chromatography with ultraviolet detection.

Results. The analysed leave-on, and to a lesser extent the rinse-off, cosmetics, contained MI at concentrations far exceeding the permitted 100 ppm use concentration. Household detergents contained high concentrations of MI, and mislabelling occurred for both cosmetics and detergents. The (limited) data on paints are in line with the existing literature.

Conclusion. Cosmetics and detergents may facilitate contact sensitization because of a (too) high MI concentration, and mislabelling may make its avoidance extremely difficult. Safer use concentrations and correct labelling should be ensured by adequate quality control.

5.1. Introduction

The ongoing methylisothiazolinone (MI) contact allergy epidemic is primarily attributable to its use in cosmetics, but also to its use in household detergents and water-based paints (1,2). The aim of the present study was to determine the isothiazolinone concentrations in cosmetics and detergents, and to a lesser extent in water-based paints, available to consumers on the Belgian market. Moreover, compliance with existing EU regulations regarding labelling and content was assessed.

5.2. Materials and methods

A. Products

A total of 30 cosmetics (18 leave-on products and 12 rinse-off products), eight commonly used household detergents and four water-based wall paints were collected from April to November 2014.

The cosmetics, all of which were within the medium price range, were bought in different types of store in the province of Antwerp, comprising smaller specialty (beauty) stores, department stores and supermarkets, but also discount stores and pharmacies. Cosmetic products belonging to one of the four following subtypes were purchased: leave-on products labelled as containing isothiazolinones (n=6), leave-on products labelled as not containing isothiazolinones (n=6), rinse-off products labelled as containing isothiazolinones (n=5), and rinse-off products labelled as not containing isothiazolinones (n=6). Additionally, four cosmetics from MI-sensitized patients, who were patch tested at the Contact Allergy Units of Antwerp or Leuven and who were found to be allergic to MI and/or to methylchloroisothiazolinone/MI, were included, as were three cosmetic leave-on products with a label not declaring MI and MCI/MI, all bought at a pharmacy. The cosmetic samples were very diverse with regard to their galenic form, including both hydrophilic and lipophilic formulations, among which creams, lotions, soaps, shampoos and wet wipes.

The detergents were all bought from supermarkets, also in the Antwerp area. In total six products were collected at random. According to their labels, two contained no isothiazolinones, two contained only MI, one contained only MCI/MI, and one contained benzisothiazolinone (BIT). These were supplemented with two products (containing, according to their labels, a combination of MI and BIT), which were again obtained from patients. The paints were randomly purchased in paint shops in the greater Antwerp area.

The labels of cosmetics and detergents were carefully examined for the presence of isothiazolinones prior to the analysis with high performance liquid chromatography (HPLC) with ultraviolet detection (HPLC-UV), as we wanted to relate the actual isothiazolinone concentration to the information that was present on the label. The buying of the products, and the verification of the information on their labels, was performed by one author (O.A.), and the HPLC-UV investigations were performed by three other authors (H. M., S.J., and S.A.)

B. Reagents and standards

The solvents used in the chromatographic method, namely methanol and acetonitrile (both HPLC grade), were obtained from Fisher Scientific® (Loughborough, Leicestershire, UK). Formic acid was obtained from Acros Organics® (Geel, Belgium) and water for the HPLC was dispensed with a Milli-Q system from Millipore (Bedford, MA, USA). The reference materials of MCI/MI (14.2%) and MI (98%) were obtained from Santa Cruz Biotechnology® (Dallas, TX, USA), and BIT (99.2%) and octylisothiazolinone (OIT)(99.9%) were obtained from Sigma Aldrich® (St. Louis, MO, USA). With methanol as a solvent, a reference solution containing 10 µg/ml MI was prepared for injection, along with reference solutions of MCI, BIT and OIT, all at a concentration level of 1.5 µg/ml.

C. Chemical analyses

The chemical analyses were performed at the Research group Natural Products and Food – Research and Analysis (NatuRA) of Antwerp University. Briefly, for the majority of samples, the following procedure

was used. An amount of 1 g of sample was dissolved in 6 ml of methanol and placed for 30 min in an ultrasonic bath. This solution was then quantitatively transferred to a 10.0 ml volumetric flask and adjusted to volume with methanol. The solution was then filtered (0.45 μm) and analysed with HPLC-UV. An HPLC Agilent 1200 series (Agilent Technologies®, Eindhoven, The Netherlands) was used and the chromatographic separation was performed on a GraceSmart RP C18-column (5 μm ; 4.6 x 250 mm²) (Grace Alltech®, Deerfield, IL, USA). The mobile phase consisted of formic acid 0.1% (vol/vol) in water as solvent A, and acetonitrile as solvent B; gradient elution was used. A constant flow rate of 1 ml/min and an injection volume of 20 μl were used. The components were detected at 274 nm (MI and MCI), 280 nm (OIT) and 318 nm (BIT) and quantified (mean of 2 independent results) with reference solutions of MI, MCI/MI, BIT and OIT. The method was not validated for each matrix separately, but was verified by checking the response function and by evaluating the accuracy and precision of reconstituted test samples in a general cream base at three concentration levels in triplicate. Spike experiments (adding a known amount of MI, MCI, BIT or OIT to a sample) were additionally performed to confirm the suitability of the applied method, resulting in acceptable recoveries within the predefined range of 80 to 120% for all four isothiazolinones. Small additional adjustments were rarely necessary (e.g. prolongation of the ultrasonic bath time to 45 min in order to obtain proper dissolution, cutting wipes into pieces beforehand, centrifuging some samples before filtration, and, finally, concentrating some other samples by evaporation to avoid missing isothiazolinones below the detection limit). The limits of detection (LODs) were determined to be 1.3, 1.7, 0.9 and 1.5 ppm for MI, MCI, BIT and OIT, respectively.

5.3. Results

The results are outlined in Tables 1-3.

A. Leave-on cosmetics

All leave-on cosmetics were free of BIT and OIT, and those labelled as containing MI (n=7) did contain it. However, in six of them (86 %), surprisingly high concentrations of MI were found (50% - 80% above the permitted concentration of 100 ppm), with the highest concentration being present in a facial serum, containing 188 ppm MI (**Table 5.1**)!

One hand cream contained 159 ppm MI, the presence of which was not labelled. All other leave-on products labelled as not containing MI or MCI (an eye cream, two sun screens, two aftershave creams, three hand creams, one set of wet wipes, an anti-ageing day cream, and a makeup remover) were free of them.

Table 5.1. Leave-on cosmetics labelled as containing MI.

	MCI (ppm)	MI (ppm)	BIT (ppm)	OIT (ppm)
Make-up remover (face/eyelids)	<LOD	171	<LOD	<LOD
Make-up remover (face/eyelids)	<LOD	39	<LOD	<LOD
Day cream	<LOD	171	<LOD	<LOD
Facial toner	<LOD	150	<LOD	<LOD
Make-up remover (eyelids)	<LOD	170	<LOD	<LOD
Facial serum	NT	188	NT	NT
After-shave cream (sensitive skin, old version)	<LOD	156	<LOD	<LOD

NT : not tested

<LOD : below the limit of detection

MI: methylisothiazolinone

MCI: methylchloroisothiazolinone

BIT: benzisothiazolinone

OIT: octylisothiazolinone

B. Rinse-off cosmetics

All rinse-off cosmetics without MCI/MI or MI labelling (a facial cleanser, two shower gels, a shampoo, a hair conditioner and an intimate hygiene wash emulsion) did not contain any of these derivatives. However, of six rinse-off cosmetics that were labelled with MCI/MI or MI, 2 (33%), a shower gel and a baby shampoo, contained concentrations of MI exceeding the permitted limit (128 and 163 ppm, respectively). Moreover, the baby shampoo was mislabelled, because, besides MI (on the label), MCI was found. Moreover, of two other cosmetics labelled as containing both MCI and MI, a shampoo contained only MCI (in a very low concentration of only 3 ppm, with MI possibly being below the LOD, given the expected 3:1 ratio of MCI/MI), and a hand soap contained only MI (**Table 5.2**).

Table 5.2. Rinse-off cosmetics labelled as containing MCI/MI or MI*.

	MCI (ppm)	MI (ppm)	BIT (ppm)	OIT (ppm)
Intimate hygiene soap (MCI/MI)	5	2	<LOD	<LOD
Hand soap n° 1 (MCI/MI)	8	4	<LOD	<LOD
Shower gel (MI)	<LOD	128	<LOD	<LOD
Shampoo (MCI/MI)	3	<LOD	<LOD	<LOD
Baby shampoo (MI)	3	163	<LOD	<LOD
Hand soap n° 2 (MCI/MI)	<LOD	8	<LOD	<LOD

*Between brackets: the type of isothiazolinone, MI or MCI/MI, that was present on the label.

<LOD : below the limit of detection.

MI: methylisothiazolinone

MCI: methylchloroisothiazolinone

BIT: benzisothiazolinone

OIT: octylisothiazolinone

C. Detergents

Of the eight detergents analysed, 2 (25%) were mislabelled: (i) in one case, only MI was found, although the label stated it contained MCI/MI; (ii) in a similar case, MI and BIT were mentioned on the label, but the analysis did not show either of these isothiazolinones. Household detergents sometimes contained remarkably high concentrations of MI (e.g. 135 and 181 ppm)(Table 5.3).

Table 5.3. Detergents* containing or not containing MCI/MI, MI, BIT and/or OIT.

	MCI (ppm)	MI (ppm)	BIT (ppm)	OIT (ppm)
Dish washing liquid (MI)	<LOD	135	<LOD	<LOD
Multipurpose cleaning spray (MI)	<LOD	71	<LOD	<LOD
Window cleaning spray (MCI/MI)	<LOD	2	<LOD	<LOD
Household wet wipes (NONE)	<LOD	<LOD	<LOD	<LOD
Dish washing liquid (NONE)	<LOD	<LOD	<LOD	<LOD
Floor cleaning detergent (BIT)	<LOD	<LOD	26	<LOD
Floor cleaning agent (MI and BIT)	<LOD	181	5	NT
Laundry detergent (MI and BIT)	NT	<LOD	<LOD	NT

*Between brackets: the type of isothiazolinone on the label (MI, MCI/MI, BIT or OIT) or no isothiazolinone (NONE).

NT: not tested.

<LOD : below the limit of detection.

MI: methylisothiazolinone

MCI: methylchloroisothiazolinone

BIT: benzisothiazolinone

OIT: octylisothiazolinone

D. Paints

In the four paints that we analysed, MI was always found (respectively 8, 225, 65 and 66 ppm), in three of four paints together with BIT [respectively, 23, 35, 0 (below the LOD) and 41 ppm]. Neither MCI nor OIT was present in our small number of samples. The label of one paint specifically stated “contains BIT, which may cause allergic reactions”, although a small amount of MI was also found (8 ppm); the label of another paint specifically stated “contains MI, which may cause allergic reactions”, although it also contained BIT (35 ppm).

5.4. Discussion

Isothiazolinone derivatives, which are at the centre of attention because of the unprecedented contact allergy epidemic caused by MI, are highly efficient preservatives at low concentrations, with little danger of resistance, and are compatible with most industrial formulations (3,4). Their bactericidal, fungicidal and algicidal properties are fairly similar, with the exception of MI, for which, according to the industry (5), higher concentrations are necessary. Therefore, following the EU Cosmetics Regulation (6), MI and its mixture with MCI may still be used in leave-on and rinse-off cosmetics, but with maximum allowed concentrations of 100 ppm and 15 ppm, respectively; recently, it was decided that the use of MCI/MI in leave-on cosmetics will be prohibited from 16 April 2016 onwards (7) ; both BIT and OIT are not permitted for cosmetic use, but they are routinely, and without restrictions, used in detergents and paints, where they can often be found together with MCI/MI and/or MI. Furthermore, labelling of all of these preservatives is mandatory in the EU for both cosmetics and household products (6,8), whereas it is not requested for chemical products such as paints. Indeed, at present, no legally binding (harmonized) classification of MI as a contact allergen exists in the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)/Classification, Labelling and Packaging-regulation (CLP) (9). According to the rules of self-classification, set out by the industry itself, paints containing MI above a certain,

self-defined concentration (usually still a very high threshold, e.g. MI 0.1% or 1000 ppm) are labelled as “may cause allergic sensitisation” (10). Moreover, so-called “environmental labels (eco labels)” are also in use for products containing isothiazolinones in self-defined (but often again still high) concentration ranges (e.g. MCI/MI maximum 15 ppm, MI maximum 200 ppm, BIT maximum 500 ppm) (9,10). A summary of the existing legal requirements is shown in **Table 5.4**.

Table 5.4. EU Regulation of isothiazolinones in cosmetics, detergents and paints.

Product type	Labelling	MCI/MI	MI	OIT	BIT
Cosmetics (leave-on and rinse-off) (6-7)	Obligatory	Maximum 15 ppm#*	Maximum 100 ppm*	Not allowed	Not allowed
Household detergents (8)	Obligatory	No Maximum	No Maximum	No Maximum	No Maximum
Water-based paints (9-12)	Only rules of self-classification by the industry are in use§	No Maximum°	No Maximum°	No Maximum	No Maximum

MI: methylisothiazolinone

MCI: methylchloroisothiazolinone

BIT: benzisothiazolinone

OIT: octylisothiazolinone

No maximum: no maximum concentration defined.

*: MCI/MI and MI should not be used together in cosmetic products (6).

#: its presence in leave-on cosmetics will be prohibited from 16/04/2016 onwards (7); for rinse-off cosmetics the 15 ppm rule will still apply.

°: MCI/MI and MI are being used together in some water-based paints (9-10)

§ Paints containing MI above a certain concentration, self-defined by the industry (e.g. > 0.1% or 1000 ppm) are labelled as “may cause allergic sensitisation” (11,12).

Although a recommendation has been proposed to ban the use of MI in leave-on cosmetics (13,14), the rate of reduction of MI in those products is difficult to evaluate at present, and various EU countries continue to report disturbing increases in their rates of MI-allergic patients, among both adults and children (15). In our patch test units in Antwerp and Leuven 9% of patients tested between January 2014 and June 2014 had been sensitized to MI, with a relevance rate of ~ 80%, and with MI-containing cosmetics as the major culprit sources (16). At present (March 2015), these figures remain unchanged. Apart from leave-

on cosmetics, which are held to be primarily responsible for inducing MI-allergy, rinse-off cosmetics, detergents and paints have gained attention as important MI-containing sources, mainly in eliciting *Contact Dermatitis* (2,17). However, detergents, and even rinse-off cosmetics, might act as “leave-on” products, when used repetitively (e.g. cleaning agents used by a cleaner or shampoo used by a hairdresser) or in a cumulative way, hence possibly inducing contact allergy (18,19). Furthermore, airborne sensitization from paints is well-known (20). Therefore, the MI concentration in detergents and paints should be lowered, and perhaps even restricted to 15 ppm, as was already advised for rinse-off cosmetics in the aforementioned SCCS Opinion (13).

Recently, some studies have reported on the presence of isothiazolinones in paints (9,10), but only a few have investigated their true concentrations in cosmetics and household detergents. Some publications have highlighted the sporadic occurrence of (i) too high concentrations of MI or MCI/MI in certain cosmetic products, (ii) mislabelling, or even (iii) the use of forbidden isothiazolinones (BIT and OIT) in cosmetics (2, 5, 21). Occasionally, we were able to make similar observations, for example BIT being present in an occupational hand soap (2), and as such explaining a work-related hand dermatitis, or MI being present in household wet wipes, although the label did not mention it and was confirmed to be “isothiazolinone-free”, even after repeated contact with the manufacturer (22). Similar findings have been reported for formaldehyde, which was present in extremely high concentrations in certain cosmetic products (23,24), and was present in products that were found to be incorrectly labelled, that is, stating no formaldehyde(releasers) were present (25).

Cosmetics

With regard to the observed MCI/MI levels and the origin of the higher MI concentrations in some cosmetics, the most important sensitization source, three hypotheses seem likely:

- (i) The cosmetic industry might be using MCI and MI together in a 2:1 ratio rather than a 3:1 ratio (e.g. hand soap number 1 in **Table**

5.2, containing MCI 8 ppm and MI 4 ppm). However, this seems highly unlikely, as MCI/MI in a 3:1 ratio is commercially available as Kathon CG[®] (Rohm and Haas, Croydon, UK) and we are not aware of any products currently on the market containing MCI/MI in a 2:1 ratio; moreover, this still would not explain the absolute MI level being (much) higher than 100 ppm in some products.

- (ii) The cosmetic industry still uses MCI/MI in a 3:1 ratio, but *deliberately adds* MI, considered as another individual ingredient, separately (thereby sometimes exceeding the 100 ppm level for MI), as is being done, for example, in the paint industry; this has been previously reported (9,10), and was also confidentially confirmed to us by at least one Belgian paint manufacturer. When considering only the label of a cosmetic product, stating the presence of MCI and MI, one cannot tell whether or not MI was separately added to MCI/MI (26). Alternatively, in some products containing only MI, this isothiazolinone might deliberately be used in a concentration over 100 ppm.
- (iii) Given the fact that no information is available on MI concentrations in individual cosmetic ingredients, another explanation might be the hidden presence of MI in ingredients that are included within the same formula, as such augmenting the total MI concentration of a given MI-containing or MCI/MI-containing product, possibly without the cosmetic manufacturer being aware of this.

With regard to this, some patients examined at our patch test units showed extreme reactions (3+) to their own leave-on cosmetics containing MI (**Figure 5.1**), with little reaction or no reactions to MCI/MI 100 ppm or 200 ppm aq. (containing only 25 or 50 ppm MI, respectively), although they did react to MI tested at 500 ppm aq. or, more recently, 2000 ppm aq. Besides their leave-on character, or, with regard to rinse-off cosmetics, their repetitive or cumulative use, these very high concentrations of MI are liable to facilitate contact sensitization even more.

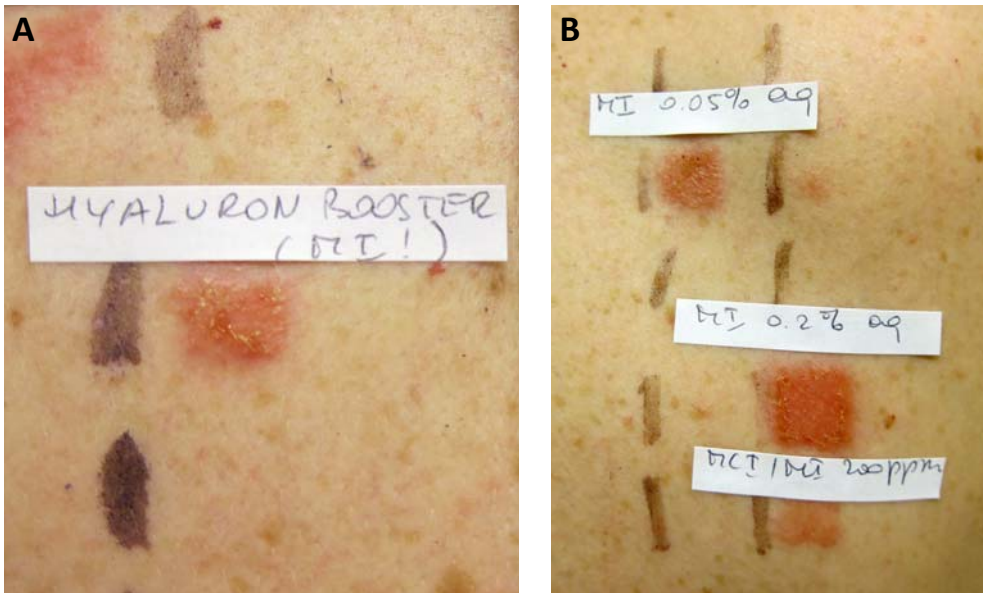


Figure 5.1. (A) A patient reacting to a cosmetic serum (+++) containing methylisothiazolinone (MI) 188 ppm. (B) Patch test reactions to methylchloroisothiazolinone/MI 200 ppm (+), MI 500 ppm (++) and MI 2000 ppm (+++). (Courtesy of Professor An Goossens).

It is useful to compare our results with those of a previous study, conducted by Lundov *et al.* in 2010 and published in 2011, in which 19 cosmetics from the Danish market were found to contain high MI concentrations (three of four of products, > 50 ppm; and one of four products, > 95 ppm), but still below the maximum limit of 100 ppm (27). However, the majority of the examined products in that study, and at that time, were rinse-off cosmetics, whereas mainly leave-on cosmetics were analysed in the present study. As already suggested (26), the use of MI as a preservative in cosmetics, including leave-on products, may well have increased substantially since 2010 and the present study –taking into account some limitations (see below)- shows that certain leave-on cosmetics, at least on the Belgian market, do contain MI at levels that are too high.

Detergents

Detergents, including wet household wipes, often contain isothiazolinones (2), usually MI, MCI/MI and/or BIT, as shown in the present study, and constitute the second most important allergen source of MI, which is sometimes present in high use concentrations. These results support the earlier observations made by Uter *et al.* that repeated skin contact with such products may elicit and even induce contact allergy to MI (18). Furthermore, as MI is a volatile allergen, as with paints (9, 10, 28-30), household detergents applied to large surfaces inside a house may also give rise to airborne *Contact Dermatitis*, sometimes even with unusual clinical manifestations, as recently reported (31). Furthermore, a cleansing agent containing a high amount of MI, used to clean a dental prosthesis, was held to be responsible for inducing a flare-up of a quiescent oral lichen planus (32). Finally, also in this group of products, mislabelling may occur (22), as has even been reported for a medical device (33). In this regard, it is interesting to note that not all types of gloves seem to be able to protect against (occupational) hand dermatitis (34), and the use of thick (reusable) nitrile gloves, instead of natural rubber latex or polyvinylchloride, has thus been proposed (35).

Paints

Water-based paints, often containing different isothiazolinones, usually MI together with BIT (9,10), represent a specific health hazard. Indeed, airborne elicitation and sensitization may result in long-lasting skin and mucosal complaints, given the ongoing emissions of isothiazolinones in low concentrations for several months. In the present study, which was mainly focused on cosmetics and detergents, only four water-based paints were examined, and our findings with regard to MI are in line with previous studies (9,10). The BIT concentration in our paints seems to be considerably lower (range: 23-41 ppm) than that in paints from Denmark and Sweden in particular, which may contain up to 462.5 ppm (9). We earlier reported on the occurrence of an airborne and systemic dermatitis following inhalation from a paint containing even as

low as 53 ppm MI (28), which is now clearly labelled by the manufacturer as “containing methylisothiazolinone which can cause allergic reactions”. Although some paint producers may use only MI, or more often MI together with BIT, one manufacturer (confidentially) confirmed to us that MCI/MI may also be combined with MI and BIT [as already mentioned by others (9,10)]. Furthermore, the total content may be increased by the addition of other isothiazolinone-containing additives (e.g. colour pastes added to a basic, colourless paint). Apart from the need to regulate isothiazolinone concentrations and institute proper labelling, another potential health hazard that should be urgently evaluated is the addition to paints of so-called nanoparticles (measuring between 1 nm and 100 nm), such as titanium dioxide (TiO₂), which is also used in cosmetics (e.g. sunscreens). Recently, it has been shown that TiO₂ increases the sensitization capacity of dinitrochlorobenzene in an experimental mouse model (36); hence, the exact influence of nanoparticles on human skin sensitization is currently not at all certain. Interestingly, although proper labelling of paints is not yet mandatory, some companies have made efforts to point out (some) allergy risks on their label (e.g. Gamma[®], Antwerp, Belgium) and others have restricted their biocide use to MCI/MI at a maximum of 15 ppm [e.g. Boss paints, (www.boss.be), Waregem and Antwerp, Belgium, and Nutshell (<http://nutshellpaints.co.uk/>), Exeter, UK – see (37)]. Both initiatives should be encouraged, and regulated, by EU authorities. However, one should keep in mind that certain environmental labels (eco labels), as mentioned above and exemplified in (9), may be misleading, especially with regard to the permitted MI and BIT concentrations, as most analysed (and problematic) regular paints so far seem to contain much lower concentrations of MI and BIT. The recent multicentre study of paints by Schwensen *et al.* (9) confirmed that there is no clear difference in MI concentrations between regular paints and so-called eco-labelled paints.

5.5. Limitations of this study

The present study, although pointing towards too high use concentrations of MI in leave-on cosmetics, has some limitations that should be taken into account. Apart from the small sample size, the selection of the samples might have been biased by two main factors: (i) some of the analysed MI-containing cosmetics were retrieved from MI-sensitized patients; and (ii) the collection of the other samples by the main author –who also performs the patch tests in Antwerp and specifically follows up MI-sensitized patients – might have led to the inclusion and overrepresentation of MI-containing products of those brands that were also often involved in those patients. Notwithstanding the actual existence of too high use concentrations, and mislabelling, caution should be exercised in extrapolating these results too easily to all cosmetic products available on the market today.

5.6. Conclusions

Approximately 1 year after the recommendation to discontinue the use of MI in leave-on cosmetics, and to reduce its content in rinse-off cosmetics, the present study shows that MI may be found in cosmetics in concentrations far exceeding the permitted maximum EU level of 100 ppm. Detergents often also contain high amounts of this preservative, and are frequent causes of hand dermatitis, and potential causes of airborne reactions. These phenomena might be contributing to the escalating MI-epidemic.

With regard to paints, it seems that OIT, although considered to be an important occupational allergen for painters (38), is less used (or less studied?). In the future, attention should be given to the relevance of the addition of nanoparticles to paints, a feature that might also be important for cosmetics.

Mislabelling of cosmetic products, but also of detergents, and the effectively non-existent labelling of paints –with very few modest exceptions – add to the difficulty for sensitized patients in strictly avoiding

this important and highly relevant allergen, both in consumer-related products and in the occupational environment. Therefore, apart from reconsidering the safe use concentrations for MCI and MI in cosmetics, they should also be re-evaluated for detergents and paints, and full ingredient labelling should be required for all of these product types. This implies that authorities recognize MI as an important allergen, and by extension, as an important occupational allergen, and should implement adequate control mechanisms at a European level.

5.7. References

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