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

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Running head: Methylisothiazolinone in consumer products in Belgium.

Abstract

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

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

Materials and methods
A total of 30 cosmetics (18 leave-on and 12 rinse-off), 8 detergents and 4 paints were analysed for MI using High Performance Liquid Chromatography with UV-detection.

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

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

Keywords: benzisothiazolinone, cosmetics, chemical analysis, detergents, labelling, octylisothiazolinone, methylisothiazolinone, methylchloroisothiazolinone, paints, use concentrations.

Introduction

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

Materials and methods

A. Products

A total of 30 cosmetics, 18 leave-on and 12 rinse-off products, as well as 8 commonly used household detergents and 4 water-based wall paints were collected from April to November 2014.
The cosmetics, all situated in the medium price range, were bought in different types of stores 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 4 following subtypes were purchased: leave-on products with a label containing isothiazolinones (n=6), leave-on products with a label not containing isothiazolinones (n=6), rinse-off products with a label containing isothiazolinones (n=5), rinse-off products with a label not containing isothiazolinones (n=6). Additionally 4 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 (MCI/MI), were included, as well as 3 cosmetic leave-on products, with a label free from MI and MCI, 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 6 products were collected at random with, according to their label, 2 containing no isothiazolinones, 2 only MI, 1 only MCI/MI and 1 BIT. These were supplemented with 2 products (containing, according to their label, a combination of MI and BIT) which were again retrieved 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 with UV-detection (HPLC-UV) as we wanted to relate the actual isothiazolinone-content to the information that was present on the label. The buying of the products, and the verification of the information on their labels, was done by 1 author (O.A.), while the HPLC-UV investigations were done by 3 other authors (H. M., S.J., and S.A.)

B. Reagents and standards

The solvents used in the chromatographic method, methanol and acetonitrile (both HPLC grade), were purchased from Fisher Scientific® (Leicestershire, UK). Formic acid was obtained from Acros Organics® (Geel, Belgium) and water for the HPLC was dispensed by 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, Texas, USA), while benzisothiazolinone (BIT, 99.2%) and octylisothiazolinone (OIT, 99.9%) were purchased from Sigma Aldrich® (St. Louis, MO, USA). Using 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 the Antwerp University. Briefly, for the majority of samples, the following procedure was used: an amount of 1 g sample was dissolved in 6 ml methanol and placed for 30 min in an ultrasonic bath. This solution was then quantitatively transferred to a volumetric flask of 10.0 ml and adjusted to volume with methanol. Afterwards, the solution was filtered (0.45 µm) and analysed using HPLC-UV. An HPLC Agilent 1200 series (Agilent Technologies®, Eindhoven, The Netherlands) was used and the chromatographic separation was performed on a GraceSmart RP C_{18}-column (5 µm; 4.6 x 250 mm) (Grace Alltech ®, Deerfield, Illinois, USA). The mobile phase consisted of formic acid 0.1% (v/v) in water as solvent A and acetonitrile as solvent B, using gradient elution. A constant flow rate of 1 ml/min and an injection volume of 20 µl were applied. The components were detected at 274 nm (MI and MCI), 280 nm (OIT) and 318 nm (BIT) and quantitated (mean of 2 independent results) using 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 on 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 4 isothiazolinones. Small additional adjustments were rarely necessary (e.g. prolongation of the ultrasonic bath time to 45 min in order to obtain proper dissolution, wipes had to be cut into pieces beforehand, some samples had to be centrifuged before filtration and, finally, some other samples were concentrated by evaporation to avoid missing isothiazolinones below the detection limit). The limits of detection were determined at 1.3 ; 1.7 ; 0.9 and 1.5 ppm for MI, MCI, BIT and OIT, respectively.

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 indeed contain it. However, in 6 of them (86 %) surprisingly high amounts of MI were found (50% to 88% above the permitted level of 100 ppm), with the highest level being present in a facial serum, containing 188 ppm MI!

One hand cream did contain 159 ppm of MI, the presence of which was not labelled. All other leave-on products labelled as not containing MI or MCI (an eye cream, 2 sun screens, 2 after-shave creams, 3 hand creams, 1 set of wet wipes, an anti-aging day cream and a makeup-remover) were indeed free of them.

B. Rinse-off cosmetics

All rinse-off cosmetics without MCI/MI- or MI-labelling (a facial cleanser, 2 shower gels, a shampoo, a hair conditioner and an intimate hygiene wash emulsion) did not contain any of these derivatives. However, of 6 rinse-off cosmetics that were labelled with MCI/MI or MI, 2 of them (33%), a shower gel and a baby shampoo, contained an amount of MI again exceeding its limit (128 and 163 ppm, respectively). Moreover, the baby shampoo was

mislabelled since, besides MI (on the label), also MCI was found. Moreover, in 2 other cosmetics, said to contain both MCI and MI, a shampoo only contained MCI (in a very low concentration of only 3 ppm, with possibly MI being below the limit of detection [LOD], given the expected 3/1 ratio of MCI/MI), while in a hand soap only MI was detected.

C. Detergents

Of the 8 detergents analysed, 2 (25%) were mislabelled: (i) in 1 case only MI was found, although the label stated MCI/MI; (ii) in a similar case, MI and BIT were mentioned on the label, but the analysis did not show any of these isothiazolinones. Household detergents sometimes contained remarkably high amounts of MI (e.g. 135 and 181 ppm).

D. Paints

In the 4 paints that we analysed, MI was always found (respectively 8 ppm, 225 ppm, 65 ppm and 66 ppm), in 3 out of 4 paints together with BIT (respectively 23 ppm, 35 ppm, 0 ppm [<LOD], 41 ppm). Neither MCI nor OIT were present in our small sample size. One paint was labelled specifically with "contains BIT, which may cause allergic reactions", although a small amount of MI was also found (8 ppm), while another paint explicitly mentioned "contains MI, which may cause allergic reactions", although it did also contain BIT (35 ppm).

Discussion

Isothiazolinone-derivatives, in the centre of attention due to the massive contact-allergy crisis caused by MI, are highly efficient preservatives at low concentrations, with little danger for resistance, and compatible with most industrial formulations (3,4). Their bactericide, fungicide and algaecide properties are fairly comparable, with the exception of MI for which, according to the industry (5), higher concentrations are deemed necessary. As such, 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 a maximum allowed concentration of 100 ppm and 15 ppm, respectively; recently, it was decided that MCI/MI will be prohibited in leave-on cosmetics from 16/04/2016 onwards (7) ; both BIT and OIT are not allowed 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 these preservatives is mandatory in the EU for both cosmetics and household products (6,8), while not requested for chemical products such as paints. Indeed, at present no legally binding (harmonised) classification of MI as a contact allergen exists in the "Registration, Evaluation, Authorisation and Restriction of Chemicals" –regulation (REACH)/Classification, Labelling and Packaging-regulation (CLP) (9). According to 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 containing isothiazolinones in self-defined (but often again still high) concentration ranges (e.g. MCI/MI max. 15 ppm, MI max. 200 ppm, BIT max. 500 ppm) (9,10). A summary of the existing legal requirements can be found in Table 4.

Although a recommendation has been proposed to ban MI in leave-on cosmetics (11,12), the rate of MI-reduction in those products is difficult to evaluate at present and various EU-countries still keep on reporting devastating increases in their rates of MI-allergic patients, both in adults and in children (13). In our patch-test units in Antwerp and Leuven as high as 9% of patients tested between January 2014 and June 2014 have been sensitized to MI, with a relevance rate of about 80%, and with MI-containing cosmetics as the major culprit sources

(14). At this moment (March 2015), this % is still as high. Apart from leave-on cosmetics, which are held responsible for inducing MI-allergy, also rinse-off cosmetics, detergents and paints have gained attention as important MI-containing sources, mainly in eliciting contact dermatitis (2,15). On the other hand, detergents, and even rinse-off cosmetics, might act as "leave-on" products, when used repetitively (e.g. cleaning agents used by a cleaner, shampoo used by a hairdresser) or in a cumulative way, hence possibly inducing contact allergy (16,17). Furthermore, airborne sensitization from paints is well-known (18). Therefore, the MI-content in detergents and paints should be lowered, perhaps even restricted to 15 ppm, as was already advised for rinse-off cosmetics in the aforementioned SCCS-Opinion (11). However, the cosmetic industry considered the latter not to be feasible (personal communication dr. I.R. White, ESCD Barcelona, 28 June 2014).

Recently, some studies have reported on the presence of isothiazolinones in paints (9,10), but only few have looked into their true content 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, (iii) or even the use of forbidden isothiazolinones (BIT and OIT) in cosmetics (2, 5, 19). Occasionally, we were able to make similar observations, e.g. 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 (20). Similar findings have been reported for formaldehyde as well, being present in extremely high concentrations in certain cosmetic products (21,22), or in products that were found to be incorrectly labelled, i.e. stating no formaldehyde(releasers) present (23).

Cosmetics

With regard to the observed MCI/MI-levels and the origin of the higher MI-content in some cosmetics, the most important sensitization source, 3 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 n° 1 in Table 2, containing MCI 8 ppm and MI 4 ppm). This, however, seems highly unusual, since the mixture of MCI/MI as a 3:1 ratio is commercially available as Kathon CG ® (e.g. Rohm and Haas, Croydon, UK) and we are not aware of any products on the market today 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, which has been previously reported (9,10) and which was also confidentially confirmed to us by at least one Belgian paint manufacturer. When only considering the label of a cosmetic product, stating the presence of MCI and MI, one cannot tell whether MI was supplementary added to MCI/MI or not (24). 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 of 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-content of a given MI- or MCI/MI-containing product, possibly without the cosmetic manufacturer being aware of this.

When we elaborate further on this: some patients we have examined at our patch-test units showed extreme reactions (3+) to their own leave-on cosmetics containing MI (Fig. 1), with little or no reactions to the mixtures of MCI/MI 100 ppm aq. or 200 ppm aq. (containing only 25 or 50 ppm of MI, respectively), though reacting to MI as tested at 500 or, more recently, 2000 ppm aq. Besides their leave-on character, or, with regard to rinse-off cosmetics due to their repetitive or cumulative use, these very high concentrations of MI are liable to facilitate contact sensitization even more.
Furthermore, it is interesting to compare our results to 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 already high MI concentrations (3/4 of products > 50 ppm and 1/4 of products > 95 ppm), yet still below the maximum limit of 100 ppm (25). However, the majority of the examined products in that study, and at that time, were rinse-off cosmetics, as opposed to mainly leave-on cosmetics being analysed in the present study. As already suggested (24), the use of MI as a preservative in cosmetics, also in leave-on products, may well have increased substantially since 2010 and the present study –taking into account some limitations (see below)- points out that certain leave-on cosmetics, at least on the Belgian market, do contain too high MI-values.

Detergents
Detergents, including wet household wipes, often contain isothiazolinones (2), usually MI, MCI/MI and/or BIT as shown in the present study, and are the second most important allergen source of MI, the latter being 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 (16). Furthermore, since MI is a volatile allergen, as with paints (9-10, 26-28), also household detergents applied to large surfaces in-house may also give rise to airborne contact dermatitis, sometimes even with unusual clinical manifestations, as recently reported (29). Furthermore, a cleansing agent containing a high amount of MI, used to clean a dental prosthesis, was held responsible for inducing a flare-up of a quiescent oral lichen planus (30). Finally, also in this group of products, mislabelling may occur (20), as even reported for a medical device (31). In this regard it is interesting to mention that not all types of gloves seem to be able to protect against (occupational) hand dermatitis (32), and the use of thick (reusable) nitrile gloves, instead of natural rubber latex or polyvinylchloride, has thus been proposed (33).

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 during several months. In the present study, which mainly focused on cosmetics and detergents, only 4 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 considerably lower (range: 23-41 ppm) compared to 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 of MI (26), now clearly labelled by the manufacturer as “containing methylisothiazolinone which can cause allergic reactions”. Although some paint producers may only use MI, or more often MI together with BIT, one manufacturer (confidentially) confirmed us that MCI/MI may also be combined with MI and BIT (as already mentioned by others [9,10]). Furthermore, the total content may increase by the addition of other isothiazolinone-containing additives (e.g. colour pastes which are added to a

basic, colourless paint). Apart from the need to regulate isothiazolinone-concentrations and institute proper labelling, another potential health hazard which should urgently be evaluated is the addition to paints of so-called nanoparticles (measuring between 1 nm and 100 nm), such as titanium dioxide (TiO_2), which is also uses in cosmetics (e.g. sunscreens). Recently it was shown that TiO_2 increases the sensitization capacity of dinitrochlorobenzene (DNCB) in an experimental mouse model (34); hence, their exact influence on human skin sensitization is hitherto 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, or, Nutshell, http://nutshellpaints.co.uk/, Exeter, Devon, UK – see 35). 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 reference 9, may be misleading, especially with regard to the permitted MI and BIT concentrations since most analysed (and problematic) 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.

Limitations of this study

The present study, although pointing towards too high use concentrations of MI in leave-on cosmetics, has some limitations which 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 on 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 not to extrapolate these results too easily to all cosmetic products available on the market today.

Conclusion

Approximately one year after the recommendation to discontinue the use of MI in leave-on cosmetics, and reduce its content in rinse-off cosmetics, the present study demonstrates 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 observations might add to the driving force behind the escalating MI-epidemic.

With regard to paints, it seems that OIT, although considered an important occupational allergen for painters (36), 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 as good as non-existing labelling of paints –with very few modest exceptions – add to the difficulty for sensitized patients to strictly avoid this important and highly relevant allergen, both in consumer-related products as 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 correct labelling should be ensured for all these product types. This implies that authorities recognize MI as an important allergen, and by extension, as an important occupational allergen, and the installation of adequate control mechanisms on a European level.

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Figure legends

Fig. 1: A patient reacting to a cosmetic serum (+++) containing MI 188 ppm (courtesy of prof. An Goossens).

Tables

Table 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 (eyes)	<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

Table 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

Table 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

Table 4 : EU Regulation of isothiazolinones in cosmetics, detergents and paints.

Product type	Labelling	MCI/MI	MI	OIT	BIT
Cosmetics (leave-on and rinse-off)(see ref. 6-7)	Obligatory	X* *Max. 15 ppm*[#]	X* *Max. 100 ppm*	Not allowed	not allowed
Household detergents (see ref. 8)	Obligatory	X *No Max.*	X *No Max.*	X *No Max.*	X *No Max.*
Water-based paints (see ref. 9-10; 37-38)	Only rules of self-classification by the industry are in use[§]	X° *No Max.*	X° *No Max.*	X *No Max.*	X *No Max.*

MI: methylisothiazolinone
MCI: methylchloroisothiazolinone
BIT: benzisothiazolinone
OIT: octylisothiazolinone
X: allowed
No max: 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, self-defined concentration by the industry (e.g. > 0.1% or 1000 ppm) are labelled as “may cause allergic sensitisation” (37-38).