



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Cosmetovigilance in the Netherlands 2014-2015

RIVM Letter report 2015-0216
M. Woutersen | M.I. Bakker



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Colophon

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Huidklachten door cosmetische producten in Nederland 2014-2015

Cosmetica zijn in principe veilig, maar kunnen soms huidklachten veroorzaken, zoals roodheid en jeuk. Het RIVM beheert sinds 2009 een monitoringssysteem waarin deelnemende dermatologen ongewenste en allergische reacties na gebruik van cosmetica kunnen registreren (CESES, Consumer Exposure Skin Effects and Surveillance). Net als in voorgaande jaren melden de dermatologen vooral klachten op het gezicht en de handen na gebruik van huid/gezichtsverzorgingsproducten en haarproducten. De meest gestelde diagnose is contactallergie. Net als in voorgaande perioden veroorzaakten de conserveringsmiddelen isothiazolinonen en geurstoffen de meeste allergische reacties.

Dit blijkt uit een overzicht van de 38 meldingen die binnen CESES tussen oktober 2014 en 2015 zijn afgerond. Om te bepalen welk ingrediënt de klacht veroorzaakt, voeren dermatologen bij deze patiënten een allergieonderzoek uit, indien nodig met specifieke ingrediënten uit het verdachte product.

Isothiazolinonen zijn bekende veroorzakers van contactallergie. Momenteel evalueert de Europese Commissie opnieuw het toegestane gebruik en de concentratielimiet van methylisothiazolinon (MI) in cosmetica, omdat deze stof veel klachten veroorzaakt. Als de toegestane concentratie MI wordt verlaagd, kan de komende jaren met behulp van CESES worden vastgesteld of deze contactallergie daardoor minder vaak voorkomt. Als MI wordt vervangen door andere conserveringsmiddelen is het belangrijk te meten of deze stoffen geen ongewenste reacties veroorzaken.

Om CESES nauwkeuriger te maken wordt aanbevolen om meer meldingen te verzamelen, bijvoorbeeld door het aantal deelnemende dermatologen uit te breiden, in Nederland of daarbuiten. Tevens wordt aanbevolen om het mogelijk te maken ook klachten te melden bij tatoeages en 'nazorgproducten' voor tatoeages. Strikt genomen zijn dit geen cosmetische producten, maar ze bevatten soms ook allergene stoffen en er bestaat nog geen monitoringssysteem voor deze producten.

Kernwoorden: cosmetica, huidklachten, monitoring, cosmetovigilance, contactallergie

Synopsis

Cosmetovigilance in The Netherlands

2014-2015

Cosmetics are in principle safe for use. In some cases however, cosmetic products may lead to undesirable reactions, such as itching and erythema. RIVM has set up a monitoring system in which participating dermatologists can register undesirable and allergic reactions caused by cosmetics (CESES, Consumer Exposure Skin Effects and Surveillance). Just as in previous years, undesirable and allergic reactions mainly occurred on the face and hands after using skin/facial care and hair products. Most patients were diagnosed with contact allergy. Isothiazolinones (preservatives) and fragrances were the cosmetic ingredients causing most allergic reactions, similar to previous years.

This report provides an overview of the notifications received within CESES in the period October 2014 - October 2015. In this period, 38 reports of dermatologists were received. Dermatologists carry out patch tests and, where necessary, tests with specific ingredients of the associated cosmetic product.

Isothiazolinones are widely recognised as an important cause of contact dermatitis. At the moment the allowed use and concentration limit of methylisothiazolinone (MI) are under re-evaluation in the European Commission, because this substance causes a high incidence of contact allergy. In the coming years CESES can be used to determine the effect of the expected new policy on MI on the incidence of contact dermatitis caused by this substance. If MI is replaced by different preservatives, CESES may be used to monitor whether these substances cause undesirable reactions. To make CESES a more sensitive instrument, it is recommended to collect more reports in the project, for example by increasing the number of participating dermatologists, either nationally or internationally.

In addition, it is recommended to expand CESES with undesirable reactions to tattoos and tattoo aftercare products. Although strictly speaking these are not cosmetics, they are known to cause allergic reactions and are not monitored elsewhere.

Keywords: cosmetics, undesirable reactions, monitoring, cosmetovigilance, contact allergy

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Summary

This report provides an update with the notifications received from the clinical route of the CESES project during 2014-2015. The notifications describe undesirable reactions attributed to the use of cosmetics under normal, foreseeable, circumstances. Between October 2014 and October 2015, 38 notifications were finalized, of which 21 were also initiated in this period. As earlier, the symptoms erythema, scaling, and itching were reported most often. Also as described in previous CESES reports, skin and hair products were the most reported product types and most reactions were on the face and hands.

Patch tests confirmed that isothiazolinones and fragrance mix I were still responsible for the majority of the undesirable reactions (38% and 26% of the cases, respectively).

Isothiazolinones are widely recognised as an important cause of contact dermatitis. Recently, a SCCS opinion has been published confirming that the current concentration limit of 0.01% methylisothiazolinone (MI) in cosmetics is too high to prevent the induction of sensitization. Currently the concentration limits of isathiozolinones are re-evaluated in the EU. In addition, a dossier has been submitted to the European Chemicals Agency (ECHA) for the harmonised classification of MI, which includes classification for skin sensitization. The expected reduction in the allowed use/concentration of MI may lead to an increased use of other preservatives, which may also give rise to contact allergy in humans. Continuous monitoring in CESES is advised to pick up the effects of the proposed changes in concentration limits on the incidence of contact dermatitis caused by MI. In order to make CESES a more sensitive instrument, it is recommended to increase the number of reports in the project, for example by increasing the number of participating dermatologists, either nationally or internationally.

In addition to the monitoring of undesirable reactions to cosmetics, CESES may also be used to monitor dermal reactions to other specific products. Of particular interest are tattoos and tattoo aftercare products, which are known to sometimes cause (severe) allergic reactions, but for which there is currently no monitoring system.

1 Introduction

The Consumer Exposure Skin Effects and Surveillance (CESES) project was initiated by RIVM in 2009, on request of the Netherlands Food and Product Safety Authority (NVWA) and the ministry of Public health, Welfare and Sport (VWS). The aim of the project is to monitor undesirable reactions attributed to cosmetic products. These monitoring data are used to gain insight in the incidence and prevalence of undesirable reactions to cosmetics and assist in the identification of cosmetic products and product ingredients responsible for these reactions. This knowledge can contribute to the regulation of cosmetics in the EU. A complete overview of the background of the CESES project can be found in previous reports (Salverda-Nijhof et al. 2011; de Wit-Bos et al. 2012).

In 2014, a complete overview was made of the results of all consumer notifications and notifications of dermatologists received in the first five years of CESES (de Wit-Bos et al. 2014b). For this reason, the notifications of 2009-2014 are not included in the current report. This report provides an update with the notifications finalised in the period 1 October 2014 – 1 October 2015. As the public route for complaints on cosmetics is not longer organized by the RIVM but by the Dutch Food and Consumer Product Safety Authority (NVWA), only dermatologist notifications will be presented.

The goal and set-up of the CESES-project are extensively described in a previous report and in a scientific paper (Salverda-Nijhof et al. 2011; Salverda et al. 2013).

In this report, a change has been made in the way the results are presented in comparison with previous years. Hitherto, two groups of results were presented, one with the general results of all notifications started and finalised in the preceding year, the second with the results of the patch tests collected over all years (2009-time of report). In the current report, the results are presented of all notifications, including patch tests, finalised in the last year, regardless of the year in which they were started. The advantage of this new approach is that it includes notifications that were started in one year and finalised in the next.

Dermatologists who reported undesirable reactions in the past year were part of six participating dermatological centres. These dermatological centres included five academic hospitals (Erasmus MC, UMCU, VUMC, LUMC and UMCG) and a peripheral hospital (Van Weel-Bethesda Hospital). Two other participating centres (Deventer Hospital and the Centrum voor Huid en Arbeid in Arnhem) did not report finalized cases in 2015.

Within the CESES project, an undesirable reaction is defined as any adverse effect attributed to the use of cosmetics under reasonably foreseeable conditions.

2 Overview of notifications from dermatologists

A general overview of the notifications of the dermatologists received in the period 2014 – 2015 is provided.

The results are analysed in the following ways:

- General analysis (section 2.1-2.6), which includes information that is provided in all notifications (i.e. demographics, occupation, description of the undesirable reaction, product information).
- Results of the patch tests with the European Baseline series and of the patch test with cosmetic products and their batch-specific ingredients (section 2.7-2.8).

2.1 Number of undesirable reactions

In the period between 1 October 2014 and 1 October 2015, dermatologists finalised 38 reports of undesirable reactions, of which 87% (n=33) concerned women. Most patients (84%) were between 20 and 70 years, the average age being 43.5 years.

Figure 1 shows the number of notifications initiated by dermatologists per month. Of the 38 notifications, 17 were started before October 2014, one in 2011, four in 2012, three in 2013, and nine between January and October 2014.

The 21 notifications initiated between October 2014 and October 2015 were distributed unevenly over the year.

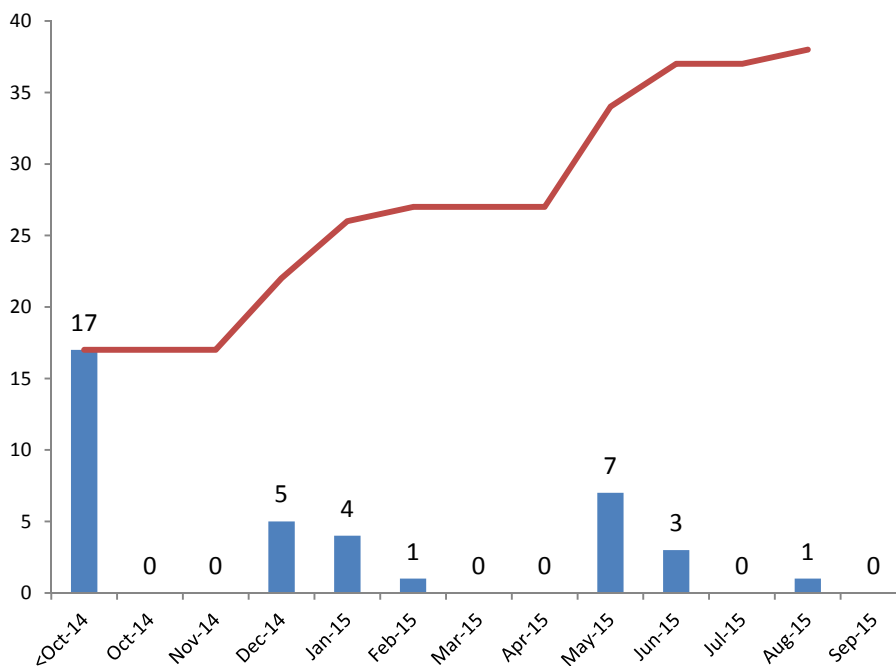


Figure 1: Number of notifications per month and cumulative numbers between 1 October 2014 and 1 October 2015.

Figure 2 shows the number of notifications per participating dermatological centre in the reported period. Most reports were finalised by the VUMC.

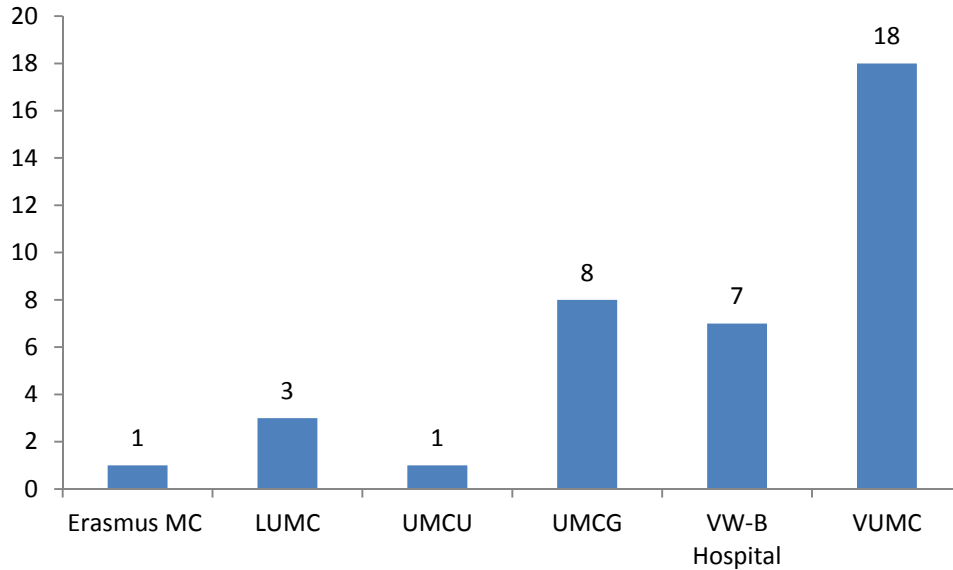


Figure 2: Number of notifications per participating dermatological centre.

2.2 Description of the undesirable reactions

The largest number of undesirable reactions were located on the face (30%, n=21), followed by the hands (16%, n=11), neck (10%, n=7) and on or around the eyes (10%, n=7) (Figure 3). This is similar to earlier reports, although the percentages on hands and arms are somewhat lower in the present report. A reason for this may be that the 'Centrum voor Huid en Arbeid' did not participate in 2014-2015. This centre reported mainly cases due to occupational exposure, which often gives reactions on the hands and arms.

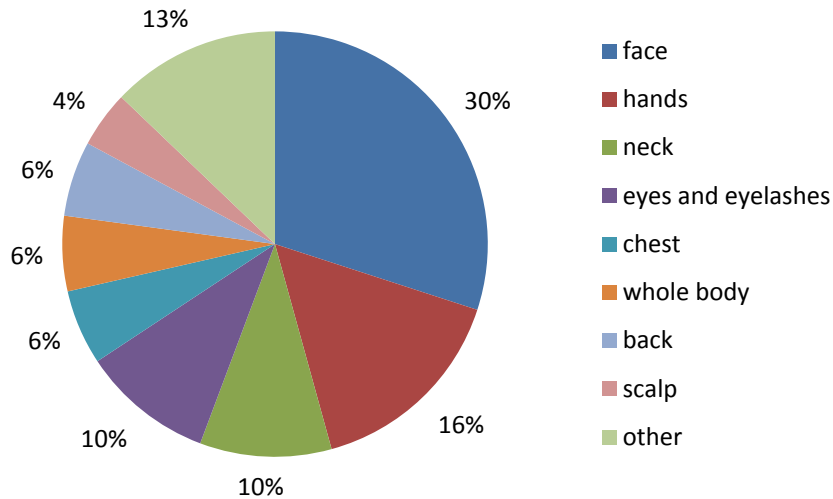


Figure 3: Reported location of undesirable reaction after cosmetics use in % (n=70). The category other includes among others armpits, arms, and legs.

The reported symptoms included mainly erythema (26%, n=33), scaling (18%, n=23) and itching (17%, n=22). Furthermore, oedema (10%, n=13), papules (9%, n=11) and burning sensation (8%, n=10) were relatively frequently reported (Figure 4). A severe reaction was observed in only one case (1%) and concerned pain.

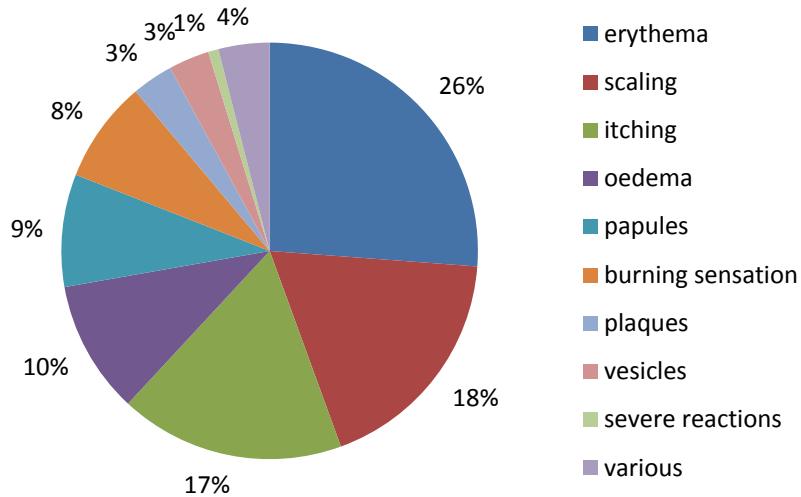


Figure 4: Reported symptoms of undesirable reaction after cosmetics use in % (n=126). The category various includes among others hypokeratosis. Severe reactions include pain.

Most patients (72%, n=26) stated that they did not know when the undesirable reaction has started, and about one third of all patients still suffered from the reaction when they visited the dermatologist. For 35% (n=12) it was not the first time they had an undesirable reaction to the respective cosmetic product. In these cases, the reaction was either equal in severity or more severe than previously (50% for both options).

2.3 Cosmetic products

For all patients, the dermatologists could report one or more cosmetic products to be allegedly responsible for the undesirable reaction. They reported, in total, 49 products. The most frequently reported product category was skin products (35%, n=17) followed by hair products (20%, n=10), see Figure 5. Sunscreen/tanning products and bath/shower products were both reported 4 times (8%), all other products only one or two times.

The largest group of skin products contributing to the development of undesirable reactions were leave-on facial care products (41%, n=7), such as day and night creams. The hair products that induced most reactions were hair care products, such as shampoo (60%, n=6).

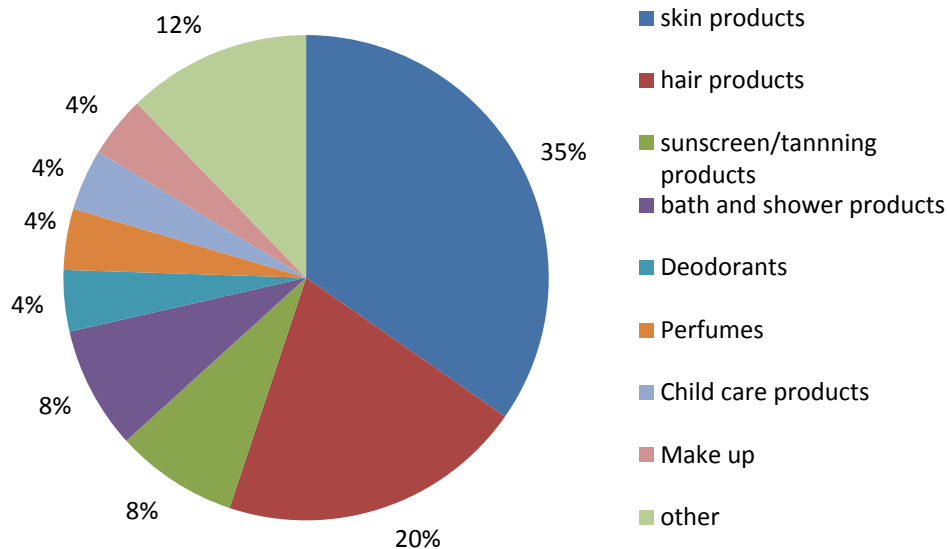


Figure 5: Reported product categories that probably caused undesirable reaction in % (n=49). The category other includes among others shaving products and soaps.

2.4 Factors possibly related to the undesirable reaction

Of the 38 notifications received, only in 5% of the cases (n=2) a causal relation was reported between the reaction and occupation (hairdressers) and in one case this relation was possible (laboratory employee).

14 patients (37%) suffered from an underlying skin problem, mostly atopic dermatitis, and 10 patients (28%) from an allergy. Of these patients, 3 suffered from both an underlying skin problem and an allergy.

2.5 Diagnosis and treatment

The final diagnosis was filled in for 82% of the notifications (n=31). Based on the medical history, physical examination and the results of diagnostic patch testing, 77% of these patients (n=24) were diagnosed with one condition, which was irritant contact dermatitis in one case and allergic contact dermatitis in all others. The other 7 patients were diagnosed with a combination of allergic contact dermatitis and other allergies or skin conditions.

A treatment was described for 32 patients. Often, a combination of treatments was prescribed. The prescribed treatments usually included local corticosteroids, avoidance of the allergen, and/or emollients.

2.6 Patch tests

All 38 patients were patch tested with the European baseline series and 89% (n=34) of these patients had a positive response to one or more allergens. Positive responses were mainly to the mixture of methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) (Kathon CG ®) and/or MI (35%, n=12 counting patients reacting to both substances as one positive) and fragrance mix I (24%, n=8). All

other allergens caused 9% of the reactions (n=3) or less (see Table 1). The use of nickel sulphate and cobalt (di)chloride in cosmetics is prohibited, meaning that these reactions are likely not the result of using cosmetics. Disperse blue 106 and 124 are not used in cosmetics, but are quite common textile dyes.

Table 1: Patch test results with European baseline series and additional substances in patients seen by participating dermatologists reported in the period 2014-2015 (top 10)

Allergen	% positive
MI and/or MCI/MI (Kathon CG ®)	35%*
fragrance mix I	26%
cocamidopropylbetaine	12%
myroxylon pereirae	9%
amerchol L 101	9%
cobalt chloride	9%
nickel sulfate	9%
colophonium	9%
methylidibromo glutaronitrile (MDBGN)	6%
back rubber mix (CPPD, DPD)	6%
disperse blue 106	6%

* four patients (12%) were sensitised to both MI and MCI/MI, five to MCI/MI (15%) and three to MI only (9%)

An additional patch test with the batch-specific ingredients of the cosmetic product was performed in 7 cases. Only in 3 cases, one or more ingredients tested positive. Of these 3, one patient responded to disperse blue 124, another to butyrospermum parkii butter, C12-15 alkyl benzoate, C30-38 olefin/isopropyl maleate/macopolymer, dimethicone, and octocrylene, and one to a combination of titanium dioxide + butyl hydroxytoluene (bht) + ricinus communis seed oil.

2.7 Causality assessment

A senior dermatologist assessed the likelihood that an ingredient in the product caused the undesirable effects. This assessment was based on the outcomes of the European Baseline patch test series, information on the ingredients of the cosmetic product and, when performed, the patch test with batch-specific ingredients of the cosmetic product. Regarding the outcomes of the European Baseline patch test series, only relevant cosmetic allergens (i.e. allergens used in cosmetics) were taken into account for causality assessment. A causal relationship between the undesirable reaction and the reported cosmetic product could be established for 27 (71%) of the 38 patients. For 9 patients (33%) this causality was likely and for 17 patients (63%) very likely. The causality was unlikely or questionable for 1 patient (4%).

3 Discussion and conclusions

3.1 Number of notifications

This report includes 38 notifications that were finalised by dermatologists between October 2014 and October 2015, bringing the total number of finalised notifications to 484. In the period 2013-2014 the number of notifications was similar (40), but in earlier years it has been higher (ranging from 72-118). It is known that there are more undesirable reactions to cosmetics which are not reported, e.g. due to the limited number of dermatologists in the CESES project. We hope to increase the fraction of reported reactions in the future, as trends can only be seen when numbers have a critical mass. When we want CESES to be a tool able to pick up trends and new allergens, it's necessary to increase the number of reports. For this reason it is recommended increase the number of dermatologists in the CESES-network, either nationally or internationally.

In the report the results were presented of all notifications, including patch tests, finalised in the last year, regardless of the year in which they were started. This is a change compared to previous years, when the results of the patch tests were determined of all years since the start of CESES.

The advantage of this new approach is that it includes notifications that were started in one year and finalised in the next, which is often the case. As these were previously included in the total overview, they were diluted by the large number of results reported in earlier years. The disadvantage is that the number of patch test results reported in one year is quite small, which makes it more difficult to determine significant trends. Especially substances that give relatively low incidences may be overlooked due to the limited number of notifications in one year. This may be solved in future reports by either using both methods, or by giving the results of all years individually.

3.2 Cosmetic ingredients: patch tests

There are two groups of allergens responsible for the majority of reactions in the patch tests, namely isothiazolinones and fragrance mix I. Both were also responsible for a large part of the undesirable reactions in previous years. For these reasons it is recommended to continue the monitoring of these substances in the CESES project.

Isothiazolines, usually MI or MCI/MI, are wide-spectrum preservatives used in cosmetics as well as other products, such as cleaning agents, paint and other do-it-yourself products. In the Cosmetics Directive concentrations limits are set for MI and MCI (EC No 1223/2009). MI may be used in leave-on and rinse-off cosmetic products up to a maximum concentration of 0.01% and the combination MCI/MI (3:1) up to concentrations of 0.0015%. However, the concentration limit of MI of 0.01% has been identified by the SCCS (Scientific Committee on Consumer Safety) as unsafe (SCCS 2015), as is further explained in Section 3.2.1.

Fragrances are a well-known group of contact allergens. Due to their allergenic properties, fragrances such as hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyrall[®]), cinnamyl alcohol, and eugenol, must be included in the list of ingredients on the label of the cosmetic product when their concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products. In addition to fragrance mix I, also several individual fragrances were noted as causing undesirable reactions, including HICC, isoeugenol, and vanillin. These all concerned individual cases.

The reaction of one patient to C30-38 olefin/isopropyl maleate/macopolymer (emulsifier) is noteworthy, as co/cross-polymers are usually considered to not penetrate the skin. As reported in De Wit-Bos et al 2014a, this particular polymer is nevertheless occasionally responsible for contact dermatitis.

This year, one case was reported of a positive response to octocrylene. As discussed in the previous report (De Wit-Bos et al. 2014b), adults are usually sensitised to octocrylene via photosensitisation to the anti-inflammatory drug ketoprofen. This problem was discussed in the Working Group of the European Committee on Cosmetic products in 2014. Member states were asked to provide cosmetovigilance data on the prevalence of positive responses to octocrylene. Unfortunately, no data were reported and the Commission concluded that the available data were insufficient to initiate additional measures on octocrylene.

3.2.1 *Isothiazolinones*

In the past year, there were 4 reports of patients sensitised to both MI and MCI/MI, 5 to MCI/MI and 3 to MI. In addition, there was one notification of a reaction to octylisothiazolinone (OIT). High incidences of allergic reactions to isothiazolinones have also been reported in other countries, including but not limited to Belgium (Aerts et al. 2014), Denmark (Lundov et al. 2013; Madsen & Andersen 2014), France (Hosteing et al. 2014), Germany/Austria/Swiss (Schnuch et al. 2011), the UK (Johnston GA 2014), and Australia (Boyapati et al. 2013). Particularly worrying is the induction of contact dermatitis in children. In a study by Quenan et al (2015), 4 cases were described of children 6-9 years of age, who were sensitised to isothiazolinones. In addition, the study by Aerts et al (2014) mentioned a case of a 4 year old with contact allergy to MI. An important source of exposure to isothiazolinones of both children and their parents is the use of wet wipes (Higgins et al. 2013).

Because of the increasing incidence of allergic contact dermatitis, the isothiazolinones have been under scrutiny for the past few years and the concentration limits for isothiazolinones in cosmetic products are still under discussion.

As MCI/MI has been known to be a very potent sensitizer for a longer time, its use in cosmetics has already been reduced to a maximum of 0.0015% (15 ppm) in rinse-off products and banned in leave-on products. MI is still allowed in both leave-on and rinse-off products up to a concentration of 0.01% (100 ppm). The reason for this higher limit is that MI alone is a less potent skin sensitizer than MCI/MI in both human and animal tests. For example, MI's potency was lower by a factor 30 in

the Human Repeat Insult Patch Test (HRIPT) and a factor 50 in the Open Epicutaneous Test (OET) compared to MCI/MI. In a version of the Local Lymph Node Assay, the PC₂₀₀ (the concentration giving 2 fold proliferation response over controls) for MI was 1506 µg and for MCI it was 11 µg (SCCNFP 2003).

However, the ban of MCI/MI in leave-on products led to a strong increase in the use of MI, which in turn caused the current increase in the incidence of contact dermatitis to MI. It may be noted that, in addition to cosmetics, MI may be also present in cleaning agents, paint and other do-it-yourself products (e.g. Danish EPA 2015).

In response to the alarming increase in allergic reactions to MI throughout Europe, the SCCS published a re-evaluation of MI in 2013, with a revision in 2014, in which it was concluded that the concentration limit of 0.01% is not sufficiently protective. Instead, the SCCS derived a safe limit in rinse-off products of 0.0015%, similar to MCI/MI. For leave-on products, no safe limit could be derived.

These conclusions remained the same in an updated SCCS opinion adopted in June 2015, which included additional cosmetovigilance data provided by industry (SCCS 2015).

As a consequence of the outcome of the SCCS opinions and the high prevalence of reactions shown by cosmetovigilance studies, the allowed use and concentration limit of MI are currently under re-evaluation in the European Commission.

In addition to the evaluation under the cosmetics regulation, also a proposal for harmonised classification and labelling of MI within the scope of the CLP Regulation has been submitted by Slovenia (ECHA 2015). This proposal contains amongst others a classification as Category 1A skin sensitizer with a specific concentration limit (SCL) of 0.06% (600 ppm). This would have the consequence that products containing more than 0.06% MI have to be labelled as skin sensitizers and MI has to be listed in the list of ingredients if it is present in a concentration of 0.006% or more. The public consultation of this proposal was in the summer of 2015. As high levels of allergic contact dermatitis are induced even under the concentration limit of 0.01%, many parties, including the SCCS and the Netherlands, have commented that the proposed SCL is too high. It is expected that the Risk Assessment Committee (RAC) will publish its opinion on MI in 2016. Afterwards, the Commission will decide on the final classification.

3.2.2 *Monitoring of tattoos and tattoo aftercare products*

Until now, CESES has only been used to monitor undesirable reactions to ingredients of cosmetic products. However, it might also be useful to monitor other specific groups of products that are related to cosmetics. A particular group that recently received a surge in attention are tattoos and tattoo aftercare products. The popularity of tattoos is increasing and there are indications they may induce a relatively high rates of adverse reactions, including allergic contact dermatitis (Bassi et al. 2014; Brady et al. 2015).

One of the difficulties is that there is still limited information on the prevalence and nature of these undesirable reactions, which is why their inclusion in CESES could provide valuable information. Moreover, both tattoos and aftercare products often contain sensitizing ingredients that are also used in cosmetics. Thus, elicitation of allergic contact dermatitis

by a cosmetic ingredient may have been induced by exposure to the same substance in a tattoo or vice versa. A well-known example is PPD, which is used in both black henna tattoos and hair dyes. The concentration of PPD in tattoos is often much higher than that is allowed in oxidative hair dyes. In addition, the contact time is much longer and the substances is either brought in direct contact with the skin (temporary tattoos) or injected in the skin (permanent tattoos). These factors make the induction of skin sensitization more likely to occur. Elicitation of allergic reactions occurs often at a dose lower than the induction those. Hence, subsequent use of hair dyes, which contain lower concentrations of PPD, may elicit contact allergy in the already sensitized subjects (de Groot 2013).

In addition, tattoos sometimes contain strong sensitizers that may not be used in cosmetics, such as mercury salts, nickel sulfate, cobalt (salts), or azo dyes (Khunger et al. 2015). Although most of these compounds are nowadays also not allowed in tattoos, they are still found on the market (NVWA 2014).

The most practical way to include these products in CESES is to add them as a product group in the CESES questionnaire.

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