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

# Cosmeto-vigilance in The Netherla

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*Trend report 2011 - 2012*

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Trend report 2011 - 2012

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# Abstract

**Cosmetovigilance in The Netherlands**
Trend report 2011 - 2012

Cosmetic products may lead to undesirable reactions, such as itching and erythema. RIVM has set up a monitoring system in which undesirable reactions caused by cosmetics can be registered (CESES). As in the previous years, these undesirable reactions are mainly reported after the use of hair products, skin products and make-up, including primarily those products intended to use on or around the eyes, such as eye contour cream, eye make-up and eye-make-up remover. Furthermore, relatively many reported undesirable reactions concerned sunscreens. Also, allergic reactions due to fragrances and so-called isothiazolinones, a preservative in cosmetics, are frequently reported.

**Trends in 2011 and 2012**
In addition to these on-going issues, some new trends are noted in 2011 and 2012. It turns out that octocrylene, a UV filter used in sunscreens, is able to cause allergic reactions. Over the last years more and more reports of (photo)allergic contact dermatitis are presented. Furthermore, relatively many hairdressers reported contact dermatitis after coming into contact with ammonium persulfates in hair bleaching products.

These results are presented in the trend report 2011 - 2012 of CESES (Consumer Exposure Skin Effects and Surveillance). RIVM acknowledges the value of monitoring undesirable reactions attributable to cosmetics and cosmetic ingredients. This information could contribute to the assessment of whether current EU legislation on cosmetics provides adequate protection. In addition, risks for workers, such as exposure to ammonium persulfates in hairdressers, can be identified.

**CESES**
Within CESES, general practitioners, dermatologists, and consumers in The Netherlands completed questionnaires on reported undesirable effects to cosmetics. Dermatologists also carried out patch tests and, where necessary, tests with specific batch ingredients of the associated cosmetic product. A website and a public awareness campaign were launched to encourage consumers to report undesirable effects.

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

# Rapport in het kort

**Huidklachten door cosmetische producten**
Trendrapportage 2011 - 2012

Cosmetische producten veroorzaken soms huidklachten, zoals roodheid en jeuk. Het RIVM beheert een systeem waarin huidklachten en andere overgevoeligheidsreacties na het gebruik van cosmetica kunnen worden geregistreerd (CESES). Net als in voorgaande jaren worden dergelijke klachten vooral gemeld na het gebruik van haarproducten, huidverzorgingsproducten en make-up; vooral bij producten die speciaal zijn bedoeld voor gebruik op of rond de ogen, zoals oogcontourcrème, oogmake-up en oogmake-upremover. Daarnaast zijn er relatief veel klachten binnengekomen over zonnecosmetica. Ook worden regelmatig allergische reacties gemeld als gevolg van geurstoffen en zogeheten isothiazolinonen, een conserveringsmiddel in cosmetica.

**Trends in 2011 en 2012**
Behalve deze aanhoudende trends vallen in 2011 en 2012 een aantal zaken op. Zo blijkt het UV-filter octocrylene, dat in zonnebrandcrèmes zit, allergische reacties te veroorzaken. De laatste jaren neemt het aantal meldingen van contacteczeem door deze stof toe. Verder hebben opvallend veel kappers contacteczeem gemeld nadat ze in aanraking waren gekomen met ammoniumpersulfaten in haarbleekmiddelen.

Deze resultaten blijken uit de trendrapportage 2011 - 2012 van CESES (Consumer Exposure Skin Effects and Surveillance). Het RIVM vindt het belangrijk om ongewenste effecten van cosmetische producten en ingrediënten in cosmetica te monitoren. Deze monitoring kan gebruikt worden om na te gaan of Europese wetgeving en handhaving voldoende beschermt. Ook worden risico's voor werknemers, zoals blootstelling aan ammoniumpersulfaten bij kappers, hiermee geïdentificeerd.

**CESES**
Binnen het registratiesysteem CESES wordt op twee manieren informatie ingewonnen. Ten eerste kunnen consumenten zelf hun klacht melden op de website www.cosmeticaklachten.nl. Daarnaast registreren deelnemende dermatologen huidklachten van patiënten waarbij cosmetica de mogelijke oorzaak zijn. Bij deze patiënten wordt vervolgens een allergieonderzoek uitgevoerd om vast te stellen welk(e) productingrediënt(en) de klacht veroorzaakt.

Trefwoorden:
cosmetica, huidklachten, monitoring, cosmetovigilance, contactallergie

# Contents

# Summary

According to the definition, cosmetic products include any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity. Most people use cosmetic products on a daily basis for hygiene, for beautification or for skin protection purposes. EU legislation and enforcement notwithstanding, consumers may encounter undesirable reactions after using cosmetic products. These reactions are primarily localised on the skin and comprise symptoms such as itching and erythema. In rare cases however, undesirable reactions can be more severe and lead to dizziness, nausea or even loss of consciousness. As these undesirable reactions may lead to acute and chronic health impairment, RIVM initiated, by order of NVWA, the CESES project aiming at collecting data on undesirable reactions attributed to cosmetic products. These data could contribute to the assessment of whether current EU legislation on cosmetics provides adequate protection.

For that purpose, in the CESES project reports on undesirable reactions of cosmetic products via different routes were collected, being the consumer route, the general practitioner route and the dermatologist route. Furthermore, within the CESES project, the products and ingredients causing the undesirable reactions were identified (in the dermatologist route), and NVWA was alerted in cases of a potential health concern. In addition, the project provided a forum for information exchange by stakeholders, including consumers, general practitioners, dermatologists, governmental agents, and inspectorates.

In the period May 2011 – October 2012, 659 consumer reports and 93 reports of dermatologists were received. In addition, general practitioners provided 90 reports over the year 2011. Most undesirable reactions were reported by women. The average age was between 35 and 40 years, but reports were received from all ages. A considerable number of people who reported an undesirable reaction suffered from an underlying skin condition (n=155 (24%) public route, n=18 (19%) dermatologist route, n=28 (31%) GP route), such as contact eczema or atopic dermatitis; or an allergy (n=260 (39%) public route, n=17 (18%) dermatologist route, n=24 (27%) GP route), for example to pollen or metals.

The undesirable reactions attributed to cosmetic products were primarily localised on or around the eyes, on the face or on the hands. Dermatologists

reported furthermore relatively many undesirable reactions localised on the arms and neck. Reported symptoms included mainly erythema and itching, but 4-11% of the reported symptoms were more severe with pain (1-6%) being most common. The most frequently reported product categories were make-up, skin products and hair products, and included mainly products intended to use on or around the eyes, such as eye contour cream and eye make-up, or on the face/scalp, such as leave-on day and night creams and hair styling products. In addition, relatively many reports concerned sunscreen/tanning products.

Patch testing with the European baseline series complemented with some additional substances, including methylisothiazolinone, by dermatologists in the period July 2009 – October 2012 revealed that most patients tested positive for isothiazolinones (23%), fragrance mix I (23%), nickel sulphate (21%) and fragrance mix II (18%). In addition, a specific pattern of positive responses was observed for hairdressers of whom 63% (n=31) tested positive for ammonium persulfate, 35% (n=17) for p-phenylenediamine (PPD), and 12% (n=6) for isothiazolinones. Patch testing with the batch-specific ingredients of the cosmetic product(s) showed that 42% of the 36 patients with a positive response developed a reaction to surfactants and/or emulsifying agents, 25% to preservatives and 19% to fragrances. Two patients who had an undesirable reaction attributed to sunscreens had a positive response to the relatively new UV filter octocrylene.

The data presented in the current report clearly illustrate the need to closely monitor the prevalence of isothiazolinone-induced allergic contact dermatitis. In addition, the maximum permitted level of MI in cosmetics and the overall use of MI in consumer products should be evaluated. Fragrance ingredients remain also a frequent cause of undesirable reactions to cosmetic products. The outcomes of CESES support the opinion of the Scientific Committee on Consumer Safety to restrict the use of the fragrance ingredient HICC (Lyral®) in consumer products. For hairdressers, ammonium persulfates may be as important as PPD for the development of occupational dermatitis. Furthermore, due to its (photo)sensitising properties, it is highly recommended to re-assess the sensitising properties of octrocylene and its use in cosmetic products, especially as UV filter in sunscreens.

# 1 Introduction

According to the definition displayed in the Cosmetic Products Directive (76/768/EEC), cosmetic products include: any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition. Most people use cosmetic products on a daily basis for hygiene, for beautification or for skin protection purposes. Cosmetic products cover as such a wide variety of products including bath and shower products, fragrances, skin creams, sunscreen, make-up and toothpaste.

In Europe, the safety of cosmetic products is regulated by the Cosmetic Products Directive (76/768/EEC) which is to be replaced by the Cosmetic Products Regulation (EC No 1223/2009) in July 2013. The European Directive is implemented in the national legislation and requires manufacturers to ensure the safety of their cosmetic products in normal and under reasonably foreseeable conditions, and national market surveillance authorities to monitor compliance with the legislation. Since 2004, the cosmetics industry is furthermore obliged to provide data, upon consumers' request, on the composition of the cosmetic product concerning hazardous substances as defined in the CLP Directive[1] as well as on serious undesirable reactions when using a specific cosmetic product. When the Cosmetic Products Regulation comes into force in 2013, all European (EU) Member States should literally follow this Regulation. In the Netherlands, the Netherlands Food and Consumer Product Safety Authority (NVWA) is the market surveillance authority for food and consumer products, including cosmetics, and NVWA monitors compliance with the cosmetics regulation.

EU legislation and enforcement notwithstanding, consumers may encounter undesirable reactions after using cosmetic products. These reactions are primarily localised on the skin and comprise symptoms such as itching, erythema and/or a burning sensation. In rare cases however, undesirable reactions can be more severe and lead to burns, dizziness, nausea or even loss of consciousness. The most common undesirable reactions are irritant contact

[1] According to article 3 of the CLP Directive 1272/2008 (Classification, Labelling and Packaging)

dermatitis and allergic contact dermatitis (De Groot et al., 1993; Malten et al., 1985; Berne et al., 1996). In particular, fragrances and preservatives in cosmetics have contributed considerably to the incidence of allergic contact dermatitis (Goossens, 2011; Travassos et al., 2011; Heisterberg et al., 2010).

As undesirable reactions by cosmetic products may lead to acute and chronic health impairment, the Council of Europe (CoE) adopted a resolution in 2006 recommending that the Member States implement a system for registering undesirable reactions to cosmetic products (cosmetovigilance) directed to protecting public health (Council of Europe, 2006). In response, RIVM initiated, by order of NVWA, the CESES project aiming at collecting data on undesirable reactions attributed to cosmetic products. These data could contribute to the assessment of whether current EU legislation on cosmetics provides adequate protection.

For this purpose, undesirable reactions attributed to cosmetic products were registered via three different routes: via consumers, via general practitioners (GPs) and via dermatologists. Consumer reports were collected via an online questionnaire on a dedicated website (www.cosmeticaklachten.nl) launched by RIVM. Consumers could also use the NVWA call centre and report undesirable reactions of cosmetic products by telephone. The participating GPs were members of the Continuous Morbidity Registration (CMR) Sentinel GP Network of NIVEL, the Netherlands Institute for Health Services Research and were representative of age, gender, geographical distribution, and population density in the Netherlands. In the period 2010-2011, the sentinel GPs were asked to complete the CESES questionnaire when patients with undesirable reactions to cosmetic products visited them. Dermatologists who joined were part of eight participating dermatological centres. These participating dermatological centres included academic hospitals (UMCU, VUmc, LUMC and UMCG), peripheral hospitals (Deventer Hospital, Reinier de Graaf Hospital and St. Antonius Hospital), and a referral centre for occupational skin diseases (Centrum voor Huid en Arbeid). The focus of the Centrum voor Huid en Arbeid as opposed to the other dermatological centres is thus occupation-related contact dermatitis. The centres were spread over the Netherlands, and covered both highly urbanized and more rural parts of the country. The dermatologists reported cases of patients who presented themselves with an undesirable reaction probably attributable to cosmetic products. For diagnostic purposes and to identify potential causes of undesirable reactions, dermatologists performed patch tests with the European baseline series plus some additional substances, including methylisothiazolinone (MI), cosmetic products used and, where

necessary, with specific cosmetic test-series. Where the outcome of the standard patch test was not sufficient to identify the cause of an undesirable reaction, a patch test with batch-specific ingredients of the cosmetic product was performed.

In the current report, an overview is provided of the consumer and dermatologist reports that were received in the period 1 May 2011 - 1 October 2012. These outcomes can be found in Chapters 3 and 5, respectively. The reports of GPs in 2011 are presented and discussed in Chapter 4. In addition, the results of a questionnaire that was included in the EDEN-Fragrance Study are described in Chapter 6. An overall summary and discussion of the results is presented in Chapter 8 and Chapter 9 includes the conclusions and recommendations based on the reports on undesirable reactions attributed to cosmetic products presented in the current report.

# 2 Goal and set-up of the CESES project

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

In short, four objectives were defined within CESES:

- Providing more insight in the *incidence* and *prevalence* of undesirable reactions to cosmetics.
- Assisting in the *identification* of cosmetic products and product ingredients responsible for undesirable reactions.
- Offering information that can be used for an *intervention* in case of potential health concerns.
- Providing a forum for information exchange (*data-sharing*) (e.g. between dermatologists and NVWA).

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

In this report, also the results of the CESES questionnaire that was included in the EDEN-Fragrance Study are presented. The goal and set-up of the EDEN-Fragrance study is described in more detail below.

## 2.1 Set-up and goal of the EDEN-Fragrance study

In 2009, the European Dermato-Epidemiology Network (EDEN) has conducted the 'EDEN International Study that was aimed at providing information on the prevalence of contact allergy to fragrances' (EDEN-Fragrance Study). Their main goal was to gain insight into the prevalence of contact allergy to fragrances and other sensitizers in the general population in different geographical areas (Rossi et al., 2010). In the Netherlands, the city of Groningen and the municipality of Stadskanaal were chosen for random sampling of the population as they give the best representation of the population in the northern Netherlands. Random samples of healthy individuals aged between 18 and 74 years were taken from the population of Groningen and Stadskanaal. Exclusion criteria included 1) persons that do not speak or write the Dutch language fluently, 2) persons that are unable to give informed consent, and 3) persons with a severe and active skin condition. The set-up of the EDEN-Fragrance Study provided an opportunity to relate the outcomes of the CESES consumer questionnaire to actual patch

testing with fragrances and other allergens in cosmetics. The main goal was to investigate to what extent the consumer reports received within the CESES project could be endorsed by diagnostic patch testing. In consultation with NVWA, RIVM decided to present the CESES consumer questionnaire to the population included in the EDEN-Fragrance Study. When subjects included in the study indicated that they have ever experienced an undesirable reaction to a cosmetic product, they were invited to complete the CESES questionnaire. The questionnaire consisted of questions on demographics, occupation, medical history, description of the undesirable reaction and the responsible product, diagnosis and treatment, and complaint handling by the manufacturer or retailer. Subjects that filled in the CESES questionnaire also underwent diagnostic patch testing to check for any positive responses to allergens[2] with special attention to fragrance allergens. The patch testing was conducted according to the International Contact Dermatitis Research Group (ICDRG) guidelines. Weak (+), strong (++) and extreme (+++) reactions with an allergic morphology were considered as positive responses.

[2] An overview of the allergens included in the patch test is given in Appendix II

# 3 Overview of consumer reports

In the period 1 May 2011 - 1 October 2012, 693 cases of undesirable reactions to cosmetic products were reported by consumers via the website www.cosmeticaklachten.nl or via the NVWA call centre. Thirty-four of these reports (5%) were excluded since no detailed information on the cosmetic product was available or the product did not concern a cosmetic product. As a result, 659 cases (95%) were used for further analysis. Of these 659 cases, 614 (93%) were reported for the consumer him/herself and 45 (7%) for a relative person.

## 3.1 Number of undesirable reactions per month

Each month there were on average 39 cases of adverse reactions attributed to cosmetic products reported (Figure 3.1). Further, it can be noted that the number of reported cases increases almost linearly over the period May 2011 – October 2012. In November 2011 a strong increase is observed. This is most likely related to the publication of the previous CESES report.

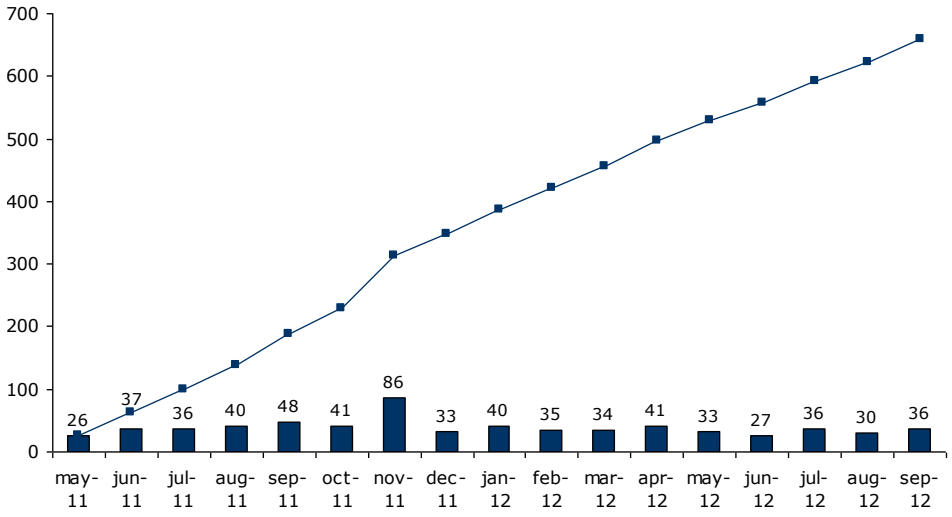



*Figure 3-1 Number of usable reports per month and cumulative number between 1 May 2011 and 1 October 2012.*

## 3.2 Demographics

As also observed in the previous report, far more undesirable reactions were reported by women (93%, n=616) than by man (7%, n=43). The age distribution of the consumer population that reported an undesirable reaction is displayed in Figure 3-2. Although most consumers were between 20 and 60 years of age, almost 10% of the reports concerned children or young adults (aged 0-19 years) and 10% of the reports related to people older than 59 years.

Moreover, a slight increase in reports for children <10 years (3%) is observed when compared to the previous report (1%). The average age of the consumer population is 39 years with the youngest person zero years of age and the eldest person 87 years.

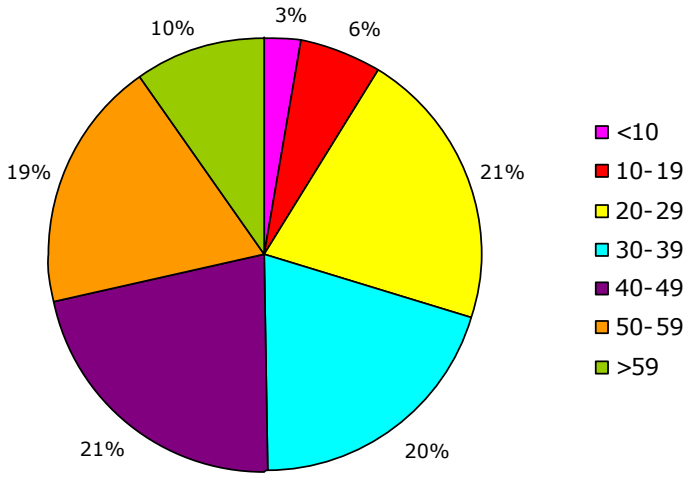



*Figure 3-2 Percentage of reports of undesirable reactions per age category (n=659).*

## 3.3 Occupation

Consumers were asked to fill in their occupation because, in some cases, occupational exposure may be involved in the development of undesirable reactions to cosmetic products. Twenty-one of the consumers reporting an undesirable reaction to cosmetic products (3%) noted that their occupation is or is most likely related to the undesirable reaction. However, as the specific occupation was only mentioned in a very few cases, it is not possible to analyse the impact of occupation on the development of undesirable reactions in more detail.

## 3.4 Description of the undesirable reaction

Undesirable reactions to cosmetic products occurred on various body regions and may occur simultaneously at several locations on the body. Also various symptoms are described.

### *3.4.1 Symptoms*

Most reported symptoms included itching (17%, n=482) and erythema (17%, n=475) followed by a burning sensation (14%, n=392), see also Figure 3-3. Severe reactions, such as blistering, nausea, pain, breathing problems, burns, hair loss and dizziness, were responsible for 11% (n=321) of the reported symptoms. Of these severe reactions, pain was most common with 6% (n=178).

Most consumers of this group (74%) have not experienced an undesirable reaction before.

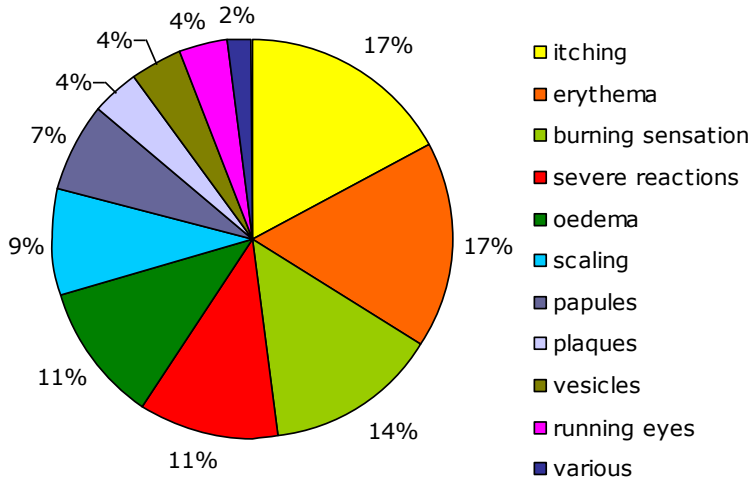



*Figure 3-3 Reported symptoms of undesirable reaction after cosmetics use in % (n=2819). The category various includes among others hyperkeratosis. Severe reactions include blistering, nausea, pain, breathing problems, burns, dizziness and hair loss.*

### 3.4.2 *Location*

Figure 3-4 shows that most undesirable reactions occurred on or around the eyes (29%, n=427). In addition, relatively often the face (17%, n=251) was mentioned as location where undesirable reactions appeared. Again, this is comparable to what was observed in the previous report, namely that most undesirable reactions attributed to cosmetics use occur on or close to the head (i.e. face, eyes, neck, scalp). Cosmetic products were primarily used on the face, eyelids/-lashes, hair and neck, as illustrated in Figure 3-5. Keeping in mind that products applied on the face or hair can also result in the development of undesirable reactions on or around the eyes and on the scalp and vice versa, the occurrence of undesirable reactions to cosmetic products is in many cases directly related to the application site of the cosmetic products.

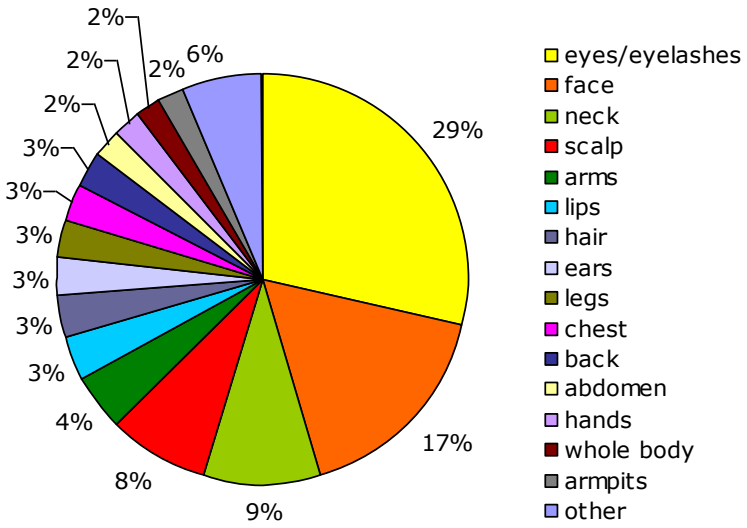



*Figure 3-4 Reported location of undesirable reaction after cosmetics use in % (n=1497). The category other includes among others buttocks, feet and oral cavity.*

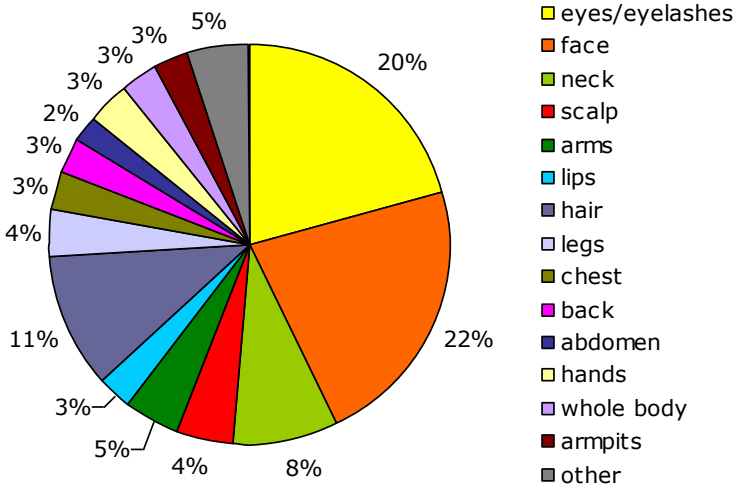



*Figure 3-5 Reported location of cosmetic product use in % (n=1041). The category other includes among others teeth, nails and oral cavity.*

### *3.4.3 Development and current status of the undesirable reaction*

Most consumers (70%, n=460) pointed out that the undesirable reaction developed on the same day as they had applied the cosmetic product. For 15% (n=99) the undesirable reaction began within 30 minutes after application. About 190 consumers (29%) have had an undesirable reaction to the same cosmetic product before. The current reaction was for approximately a fifth of this group (21%) more severe than the previous reaction. In 73% of the cases (n=131) both reactions were equally severe. When filling out the CESES questionnaire, 69% (n=452) of the consumers still experienced an undesirable

reaction. Of the consumers where the undesirable reaction had disappeared, the duration of the reaction had varied from one day to months. However, for more than half of the consumers, the undesirable reaction was gone within approximately one week.

## 3.5 Product information

Of the consumers, 91% (n=601) was able to report one or more cosmetic product(s) that probably caused the undesirable reaction. In total, 647 products were mentioned (Figure 3-6). The most frequently reported product categories were skin products (31%, n=198), make-up (30%, n=197) and hair products (21%, n=135).

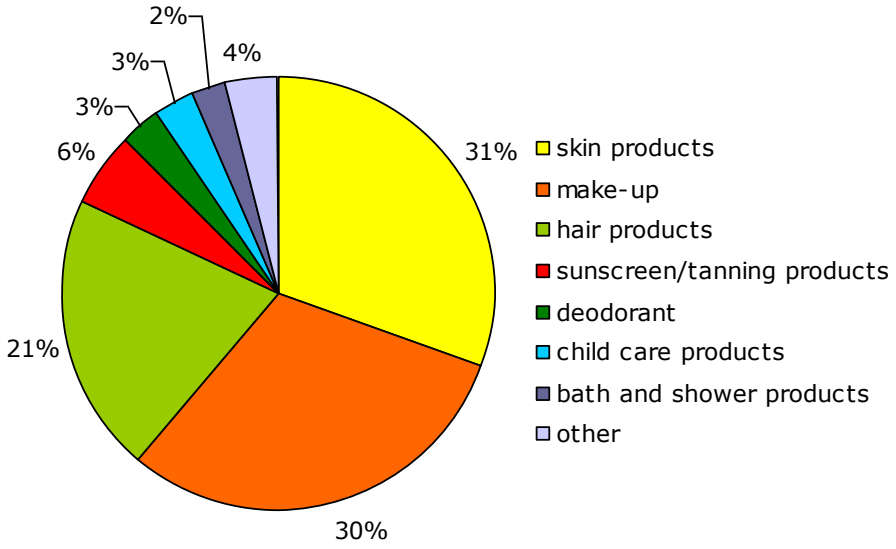



*Figure 3-6 Reported product categories that probably caused undesirable reaction in % (n=647). The category other includes among others perfumes and shaving products.*

Within the product category skin products, 73% concerned facial care products (n=144) and 14% facial cleaning products (n=27). More specifically, within the subcategory facial care products it were mainly the leave-on day and night creams (76%, n=109) and products for the delicate eye area (17%, n=25), such as eye-contour creams, that were described as responsible for the undesirable reaction. Two lines of day and night creams from two different brands led to a relatively high number of reported undesirable reactions, see also Chapter 7. For one brand, even 16% of all reports about day and night creams (n=17) concerned that specific brand. For the other brand, only four cases were reported in the consumer route in the current report, but an additional case was observed in the dermatological route in which the patient actually tested positive for the night cream. In addition, eight additional cases were found among the cases of the previous report. Furthermore, within the

subcategory facial cleaning products, the relatively high number of cleansing wipes (22%, n=6) was noteworthy.

Reported cosmetic products within the product category make-up were generally designed for application on or around the eyes (77%, n=152) and mainly included mascara (34%, n=52) and eye shadow (29%, n=44). Relatively many undesirable reactions were also reported for eye-make-up remover (13%, n=19). In addition, a significant number of undesirable reactions were reported for a lipstick from a specific brand (n=6, 30% of all lipsticks reported), see also Chapter 7.

Besides that the product category hair products was the third largest group, it is also an interesting product category because most severe reactions were attributed to products within this category. Moreover, in comparison with the previous report, much more cases concerned hair dyes (69%, n=93), mostly permanent hair dye products (81%). The other reports within the category hair products mainly concerned hair care products (28%, n=38), especially shampoos (79%).

Noteworthy, as also mentioned in the previous report, perfumes were seldom (only six cases) reported as the cause of the undesirable reaction. On the other hand, relatively more consumer reports about child care products have been received. In seven cases (47%), this concerned sunscreen/tanning products specific for children and in six cases (40%) skin products.

In Table 3-1, an overview is provided of the market shares of the different product categories and the number of undesirable reactions per product category, as reported by consumers, when corrected for their market share. Based on this overview, it can be observed that still relatively many undesirable reactions were reported about make-up, followed by sunscreen/tanning products and skin products. This results in a different top 3, than when only looking at the absolute number of undesirable reactions per product category, namely 1) skin products; 2) make-up; and 3) hair products.

*Table 3-1 Relative contribution of product categories when corrected for market share (Source: NCV, 2011).*

| Product category | Market share (%) | Number of undesirable reactions CESES (%) | Corrected for market share (%) |
|---|---|---|---|
| Skin products | 20 | 31 | 17.1 |
| Make-up | 15 | 30 | 23.0 |
| Hair products | 16 | 21 | 14.2 |
| Sunscreen/tanning products | 3 | 6 | 22.7 |
| Deodorant | 7 | 3 | 4.7 |
| Bath and shower products | 8 | 2 | 3.6 |
| Shaving products | 1 | 1 | 12.9 |
| Perfumes | 17 | 1 | 0.6 |
| Dental care products | 7 | 1 | 1.2 |
| Soap | 2 | 0 | 0 |

## 3.6 Other skin conditions and allergies

Other factors, such as skin condition, allergies and medication, may also have played a role in the development of an undesirable reaction. Of the consumers reported 24% (n=155) to suffer from an underlying skin disease and 39% (n=260) from an underlying allergy. The most frequently reported skin diseases were allergic or irritant contact dermatitis (35%, n=54) and atopic dermatitis (24%, n=37). The data furthermore show a clear age effect concerning underlying skin conditions. Consumers suffering from acne and atopic dermatitis were younger than the average age (39 years) of the consumer population. On the other hand, the average age of consumers with psoriasis and dry skin was higher than the average of the CESES population.

Underlying allergies were mainly allergies for pollen (22%, n=110) and metals like nickel (16%, n=82). Allergies for fragrances, food products and drugs were mentioned in 13% (n=66), 13% (n=65) and 12% (n=58) of cases, respectively.

## 3.7 Other factors influencing the reaction

It was recognized in the previous report that most consumers are unfamiliar with the use-by date on the package of cosmetics. This knowledge has not improved as it was confirmed for 42 products (6%) only that an expiration symbol or date was present. In the other cases it was unknown or not filled in. Misuse of cosmetics, i.e. for example use after the use-by date, may contribute to the development of an undesirable reaction. Nevertheless, consumers declared that 561 products (78%) were used according to the indications on the package.

## 3.8 Diagnosis and treatment

More than half (59%, n=388) of consumers applied self-treatment, mainly by removing the product or stopping its use either followed by replacement with an

alternative product or not (37%) and by applying a soothing (fatty) cream (29%). However, after refraining from using the cosmetic product, 23% (n=151) of consumers still suffered from the undesirable reaction. As also mentioned in the previous report, this may indicate that a relatively long period should pass before the reaction has completely disappeared. It may also be possible that the cosmetic product was not responsible for the development of the undesirable reaction. Another explanation may be that the cosmetic product(s) that was used as an alternative resulted in the same kind of undesirable reactions.

The GP was visited by 37% of the consumers (n=242) and treatment was recommended in 204 cases (85%). In total, 165 of the 204 consumers (81%) received a prescription for medication by the GP. Treatment entailed included mainly a prescription for a corticosteroid cream or antihistamines or a combination of both.

Eventually, 11% (n=70) have visited a dermatologist. Of these consumers, 50 (71%) received some sort of treatment. The type of therapy was known for 45 consumers. Medication, being mainly a corticosteroid cream or antihistamines, was prescribed for 63% (n=44) of the consumers. In addition, 70% (n=49) of consumers underwent patch testing and 36 of them (73%) were tested positive for one or more allergens. Of these positive test outcomes, five consumers (14%) were found to have a positive response to isothiazolinones, eleven (31%) to fragrances, eight (22%) to nickel, and six (17%) to PPD.

### 3.9 Reaction of the manufacturer and retailer

A relatively small group of consumers returned to the retailer or contacted the manufacturer about their undesirable reaction. The retailer was visited in 103 cases (14%) and the manufacturer contacted in 65 cases (9%).

**Results Consumers *abstract***

- In the past year and a half, 659 consumers reported an undesirable reaction via the website www.cosmeticaklachten.nl or via the NVWA call centre.
- The number of reported undesirable reactions increased after moments of media attention.
- Most undesirable reactions (93%) were reported by women.
- Most reported symptoms included erythema and itching (both 17%) and burning sensations (14%) and occurred mainly on or around the eyes (29%) and on the face (17%).
- Severe reactions accounted for 11% of the reported symptoms. Pain was the most common severe reaction with 6%.
- Skin products (31%), make-up (30%) and hair products (21%) were the most frequently reported product categories. It concerned mainly leave-on day and night creams, eye make-up and hair dyes.
- There are relatively many undesirable reactions reported about products for application on or around the eyes, such as eye contour cream, eye make-up and eye-make-up remover products.
- Compared to the previous report, relatively more consumer reports about child care products, especially sunscreens and skin products, were received.
- When looking at sales figures, sunscreen or tanning products were relatively often mentioned as the alleged cause of the undesirable reactions.
- About a third of the consumers visited a general practitioner and about a tenth consulted a dermatologist with the undesirable reaction.
- Only in 14% respectively 9% of the cases, the retailer or manufacturer were contacted.

# 4 Overview of reports from the CMR Sentinel General Practice Network

Since January 2010, the 42 general practitioners (GPs) participating in the CMR Sentinel GP Network of NIVEL reported undesirable reactions possibly caused by the use of cosmetic products by completing a questionnaire. This chapter provides an overview of reports from GPs in the period from January 2011 to December 2011 and a comparison between the years 2010 and 2011.

## 4.1 Number of undesirable reactions

Between January 2011 and December 2011, the participating GPs have completed 108 questionnaires of which 90 were suitable for further analysis. The remaining 18 questionnaires were excluded because the reported product did not concern a cosmetic product or detailed information on the cosmetic product was lacking. There were less undesirable reactions reported in 2011 (n=90) compared to 2010 (n=153).

## 4.2 Demographics

By far, most of the undesirable reactions (87%, n=78) reported by the GPs concerned women. Undesirable reactions after cosmetic use may occur at all ages as the age of the patients reporting an undesirable reaction ranged from 8 to 89 years. In Figure 4-1, the age distribution of the patients that visited a GP with an undesirable reaction attributed to the use of cosmetics is presented. Although the relative contribution per age categories differs between 2010 and 2011, the average age remained largely the same namely 41 and 40 years, respectively.

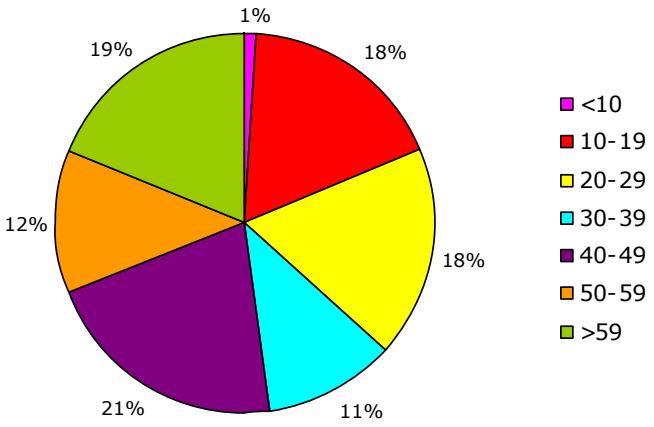



*Figure 4-1 Percentage of reports of undesirable reactions per age category (n=90).*

## 4.3 Occupation

As in 2010, the occupation of the patient was only reported in relatively few cases (38%, n=34). Although for most of these cases occupational exposure was probably not involved, for three reports (9% of known cases) occupation may have contributed to the development of the undesirable reaction. These patients were hairdresser or cosmetician. Within these professions, daily exposure to cosmetics or related products is common.

## 4.4 Description of the undesirable reaction

### *4.4.1 Symptoms*

The undesirable reactions, as presented in Figure 4-2, were mainly expressed by itching (32%, n=77), erythema (23%, n=56), burning sensation (14%, n=34) and scaling (12%, n=29). Severe reactions constituted only 1% (n=3) of the reported symptoms and included pain in all three cases. The reported symptoms show in general a similar picture when comparing the symptoms reported in 2010 with those reported in 2011.

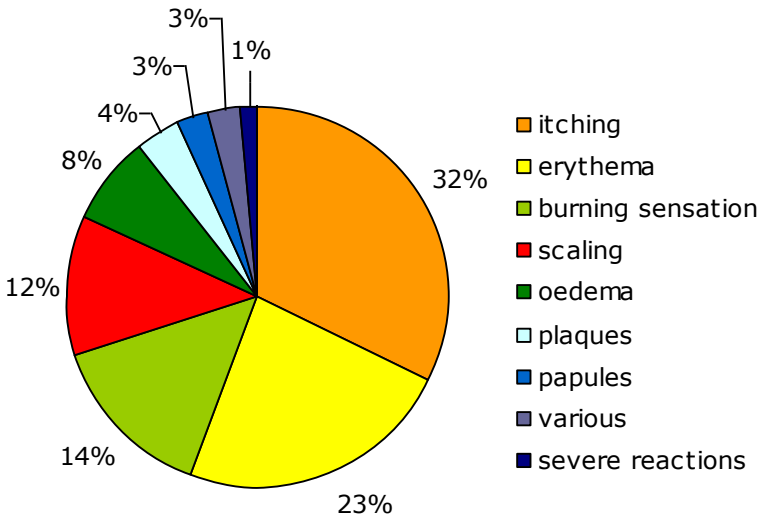



*Figure 4-2 Reported symptoms of undesirable reaction after cosmetics use in % 2011 (n=239). The category 'various' includes among others running eyes. Severe reactions include blistering, nausea, pain, breathing problems, burns, dizziness and hair loss.*

### *4.4.2 Location*

About a third of the reported undesirable reactions (n=42) was located on or around the eyes and about a fifth on the face (n=29), see Figure 4-3. There were relatively more undesirable reactions reported by GPs on these locations in 2011 than in 2010.

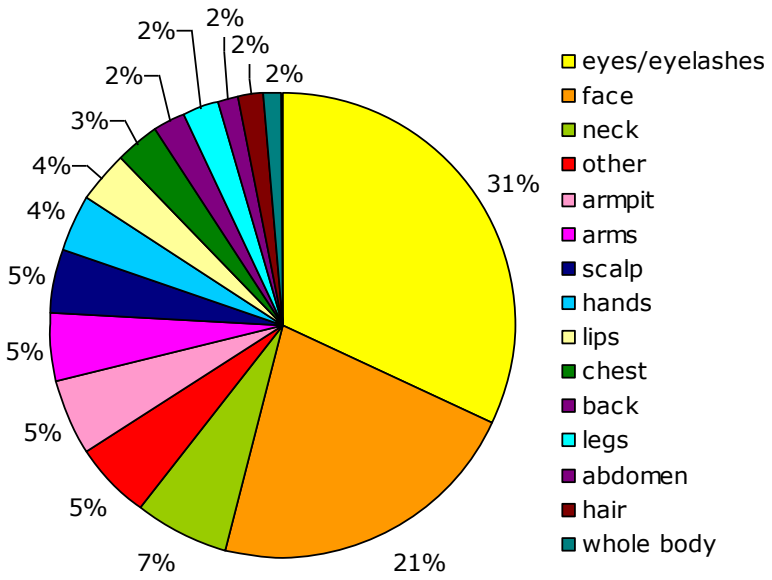



*Figure 4-3 Reported location of cosmetic product use in % (n=132). The category 'other' represents the total sum of other locations, such as nails and feet.*

## 4.5 Product information

Of all patients, 83% (n=75) reported one or more product categories that most likely caused the undesirable reaction. In total, these patients mentioned 83 cosmetic products, see Figure 4-4. In most cases, the reported undesirable reactions were attributed to the use of skin products (32%, n=26) or make-up (30%, n=25). Of the make-up products, the largest part comprised eye make-up products such as mascara, eye pencil and eye shadow. Furthermore, skin products mainly included leave-on products, such as day and night creams. This explains the fact that most of the undesirable reactions were located on or around the eyes or on the face, as these products are used on these locations. The other product categories were too diverse or too small to identify specific subgroups of products.

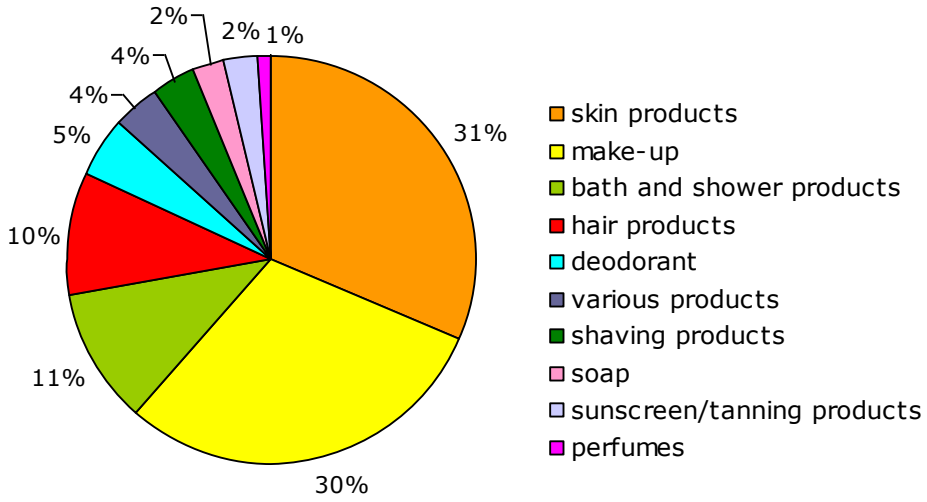



*Figure 4-4 Reported product categories that probably caused undesirable reaction in % (n=83). The product category 'other' includes among others child care products.*

## 4.6 Other skin conditions and allergies

Most patients did not have a history with skin problems (n=62; 69%) or other allergies (n=66; 73%). Of 17 patients (19%) is known that they display an allergic reaction or irritation reaction on other substances and materials, including metals, fragrances, detergents, rubber, food products or medicinal salve.

## 4.7 Diagnosis and treatment

Setting a final diagnosis for the undesirable reaction can only be done by dermatologists performing a patch test. In several cases though, GPs expressed a diagnosis. In total, 76 patients (84%) were diagnosed with allergic contact dermatitis. Urticaria was diagnosed in only one case (1%). Furthermore, two patients (2%) were suffering from two conditions such as allergic contact dermatitis together with constitutional eczema or with another condition.

GPs advised medical treatment to 76 patients (84%), and mainly included the application of hydrocortisone cream or salve. In 6% of the cases (n=5), GPs referred their patients to the dermatologist. More patients were thus referred to a dermatologist in 2010 (14%) than in 2011 (6%).

**Results Sentinel GPs *abstract***

- In total, 90 usable reports were received from GPs in 2011.
- Mainly women (87%) sought medical advice for an undesirable reaction.
- Undesirable reactions were primarily characterised by erythema, itching, burning sensations and scaling and were comparable between both years. The reactions were mainly located on or around the eyes and on the face with relatively more reactions on these locations reported in 2011 than in 2010.
- Severe reactions accounted only for 1% of the reported symptoms. In all cases the severe reaction consisted of pain.
- Most frequently reported product categories were skin products (32%) and make-up (30%) and concerned mainly leave-on skin care products and eye make-up.
- More patients were referred to a dermatologist in 2010 (14%) than in 2011 (6%).

# 5 Overview of reports from dermatologists

For the general analysis (i.e. demographics, occupation, description of the reaction, product information) of the undesirable reactions reported by dermatologists in the current report, it was decided to include only those reports that were initiated and finalised in the period between 1 May 2011 and 1 October 2012. In this way, a trend comparison between the current report and the CESES report of 2011 can be made.

For the analysis of the patch tests with the European Baseline series and for the patch test with batch-specific ingredients of the cosmetic products, including the causality assessment, all reports of undesirable reactions received in the period July 2009 (the start of the CESES project) and 1 October 2012 were included.

## 5.1 Number of undesirable reactions

Between 1 May 2011 and 1 October 2012, dermatologists initiated and finalised 95 reports of undesirable reactions. Of these 95 reports, two were excluded because the reported products did not concern cosmetics.

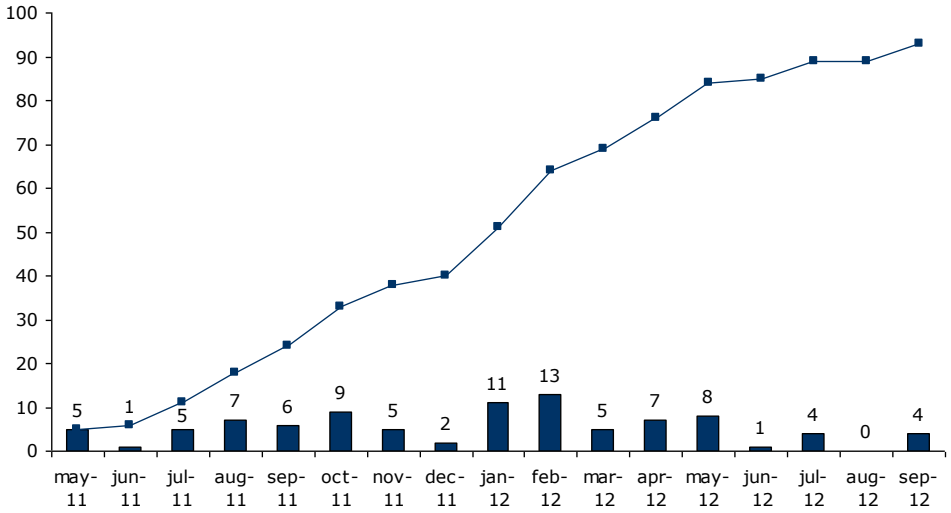
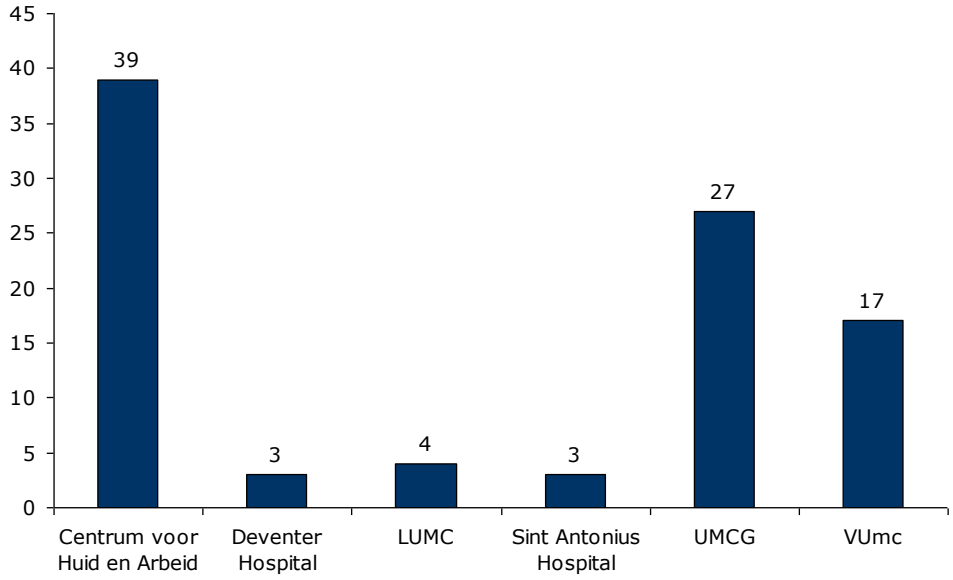


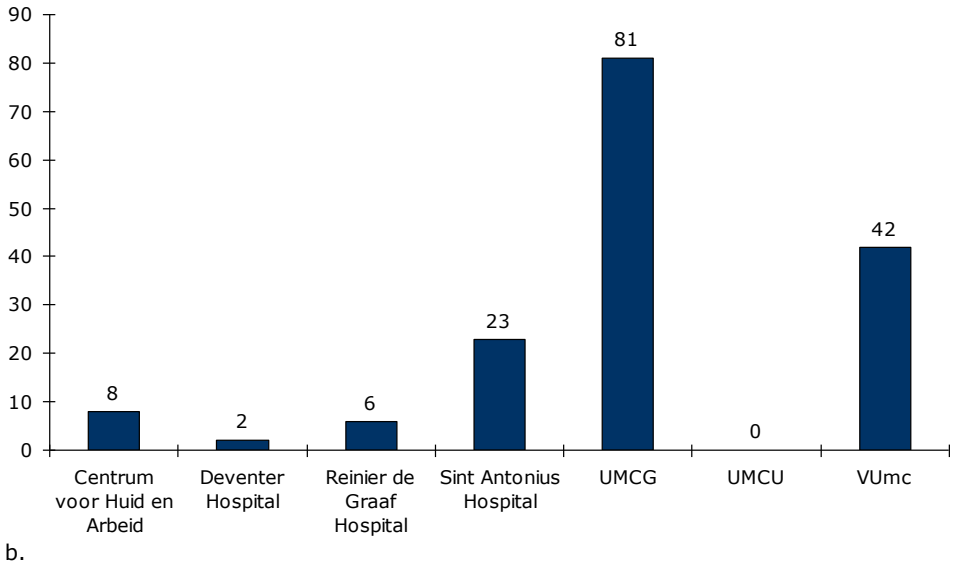

*Figure 5-1 Number of usable reports per month and cumulative numbers between 1 May 2011 and 1 October 2012.*

Figure 5-1 provides an overview of the number of undesirable reactions reported by dermatologists per month. On average, dermatologists reported per month five undesirable reactions; the actual numbers varied between zero and thirteen. In Figure 5-2, an overview is provided of the number of reported cases per participating dermatological centre included in the current report (Figure 5-2a), and for comparison this is also shown for the previous report (Figure 5-2b). As

shown, for the current report, most reports were received from the Centrum voor Huid en Arbeid (42%, n=39), UMCG (29%, n=27) and VUmc (18%, n=17).




a.




b.

*Figure 5-2 Number of usable reports per dermatological centre a. between 1 May 2011 and 1 October 2012; b. between July 2009 and 1 May 2011.*

## 5.2 Demographics

Most of the patients who visited the dermatologist with an undesirable reaction were women (85%, n=79). This image is comparable to that observed in the consumer and in the GP route. The age distribution of the patients is presented in Figure 5-3. Noteworthy, about half of the patients was relatively (very) young (<30 years of age), with the youngest patient being five years old. This is also reflected in the average age of the patients (35 years), which is lower than seen in the consumer and GP route. The eldest patient with an undesirable reaction was 72 years old.

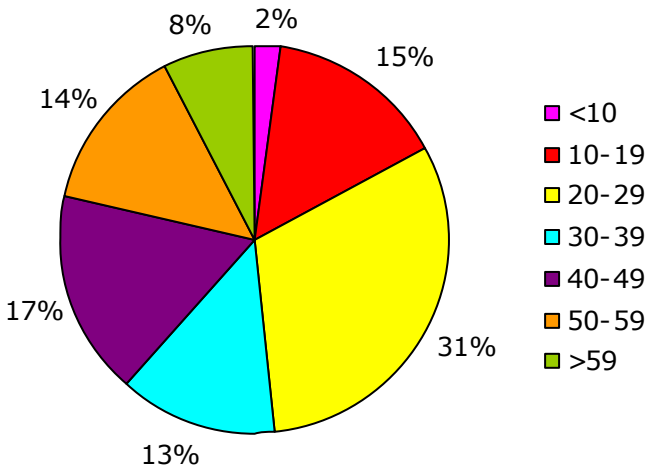



*Figure 5-3 Percentage of reports of undesirable reactions per age category (n=93).*

## 5.3 Occupation

An occupation was reported for 87 patients (94%). In 46% of the cases (n=43), the dermatologist pointed out that occupational exposure is or may be related to the development of the undesirable reaction. Among these cases, 35 patients are hairdresser and two are beautician.

## 5.4 Description of the undesirable reaction

### *5.4.1 Symptoms*

The undesirable reactions mainly included erythema (24%, n=82) and itching (22%, n=76), followed by scaling (17%, n=60). Severe reactions were observed in 4% of the reported symptoms (n=14), and included primarily pain (n=8) but also two cases of breathing problems and one case of unconsciousness were reported.

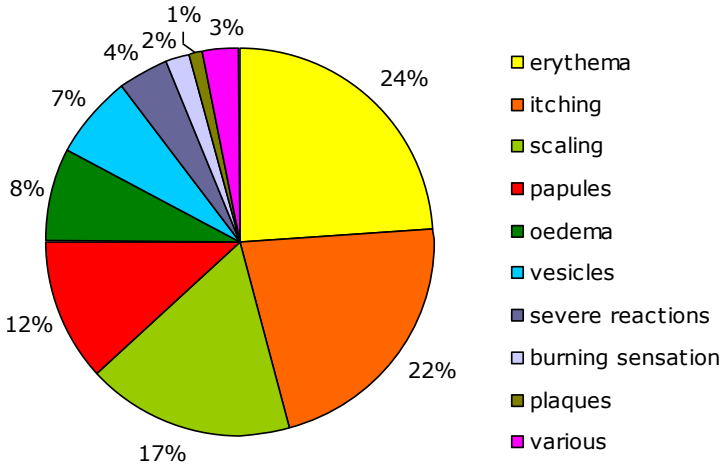



*Figure 5-4 Reported symptoms of undesirable reaction after cosmetics use in % (n=345). The category various includes among others hyperkeratosis. Severe reactions include blistering, nausea, pain, breathing problems, burns, dizziness and hair loss.*

### 5.4.2 *Location*

As in the consumer route, the dermatologists reported that their patients had undesirable reactions in various body regions and simultaneously at several locations. In contrast to what is noticed in the consumer and GP route, the dermatologists' reports showed that most undesirable reactions attributed to cosmetic products occurred on the hands (26%, n=48). Furthermore, relatively many reactions were observed on the face (21%, n=38) and on the arms (10%, n=19). Undesirable reactions located around the eyes were observed in 7% of the cases (n=13).

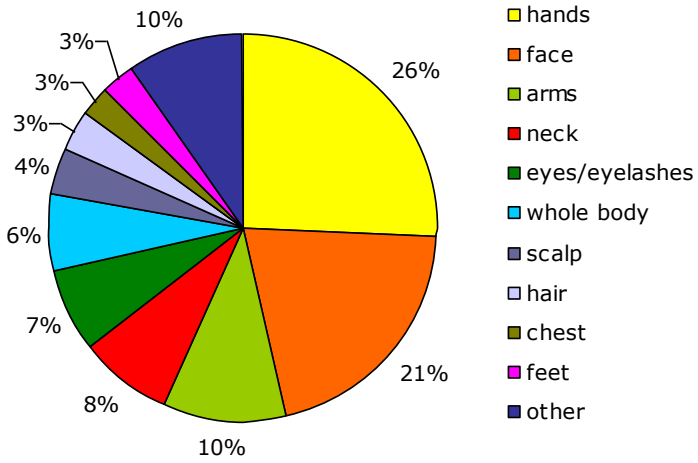



*Figure 5-5 Reported location of undesirable reaction after cosmetics use in % (n=185). The category other includes among others ears, legs and back.*

## 5.5 Product information

For 96% (n=89) of the cases, dermatologists reported one or more cosmetic products to be allegedly responsible for the undesirable reaction. In total, 246 products were mentioned. The most frequently reported product categories were hair products (76%, n=188) followed, at a large distance, by skin products (9%, n=23).

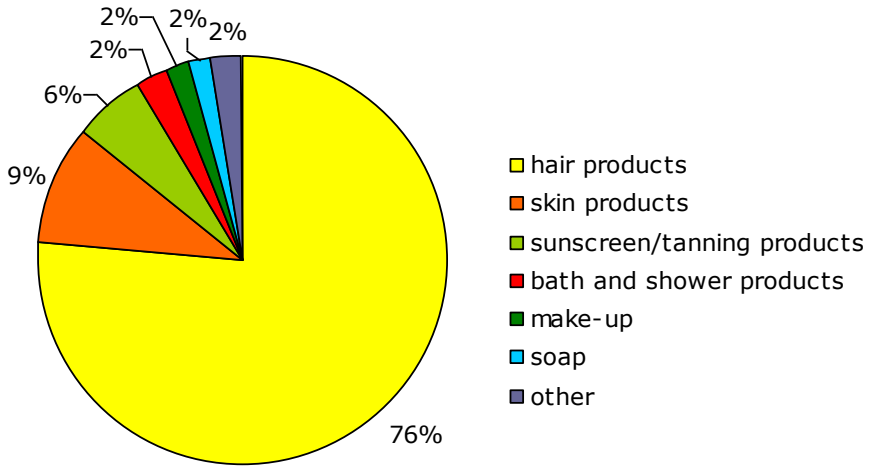



*Figure 5-6 Reported product categories that probably caused undesirable reaction in % (n=246). The category other includes among others perfumes and shaving products.*

Undesirable effects to hair products comprised predominantly styling products (46%, n=87). Hair care products, such as shampoos, and hair dyes were mentioned in 23% (n=43) and 31% (n=58) of the cases, respectively.

Skin products attributed to the development of undesirable reactions were generally leave-on facial care products (70%, n=16), such as day and night creams and eye-contour creams.

## 5.6 Other skin conditions or allergies

Of the patients that visited the dermatologist with an undesirable reaction attributed to cosmetics, 19% (n=18) suffers from an underlying skin condition, 18% (n=17) from an allergy and 4% (n=4) from both. Atopic dermatitis (89%) was the most frequent underlying skin condition. The predominant allergies were to fragrances (47%) and metals (29%), such as chromium or nickel.

## 5.7 Diagnosis and treatment

Based on the medical history, physical examination and the results of diagnostic patch testing, allergic contact dermatitis (44% (n=41)) was the main diagnosis made by dermatologists. In addition, 18 patients (19%) were diagnosed with a combination of allergic and irritant contact dermatitis and 12 patients (13%)

with a combination of allergic contact dermatitis and atopic dermatitis. For 11 patients (12%), the final diagnosis was a combination of all three forms of dermatitis.

The final diagnosis led in 18 cases (19%) to an adjustment in the treatment or the start of a new treatment. In these cases, therapy consisted of refraining from using the cosmetic product and/or ingredients or usage of medication. One patient was advised to consider a career change. This concerned a masseuse/ former beautician who reacted positively to massage oil, fragrance mix I and several separate fragrance allergens.

## 5.8 Patch tests

In the period July 2009 – 1 October 2012, patch testing with the European baseline series and the cosmetic product was performed in 327 patients (98%). Of these patients, 312 patients (95%) showed a positive response to one or more allergens. The main allergens for which patients were tested positive mainly included MCI/MI and/or MI to which 23% (n=72) of the patients showed a positive response, and fragrance mix I to which also 23% (n=71) showed a positive response (see Table 5-1). Nickel sulphate led in 21% of the cases (n=65) to a positive response and fragrance mix II in 18% of the cases (n=58).

*Table 5-1 Results patch test with European baseline series complemented with additional substances for patients reported by dermatological centres in the period July 2009 – 1 October 2012 (top 10).*

| Allergen | % positive |
|---|---|
| methyl(chloro)isothiazolinone (MI and Kathon CG ® (MCI/MI)) | 23% |
| fragrance mix I [3] | 23% |
| nickel sulphate | 21% |
| fragrance mix II [4] | 18% |
| cocamidopropyl betaine (CAPB) | 15% |
| p-phenylene diamine (PPD) | 14% |
| ammonium persulfate | 10% |
| methyldibromo glutaronitrile (MDBGN) | 10% |
| hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyral ®) | 8% |
| colophonium | 7% |

The same analysis was conducted for the 93 patients who are specifically included in the current report (period 1 May 2011 – 1 October 2012). All these patients underwent patch testing with the European baseline series and the cosmetic product. For 96% of these patients (n=89), the patch test resulted in a positive response to one or more allergens. Of the patients with a positive response, 26% (n=23) tested positive for MCI/MI and/or MI, 26% (n=23) for

[3] Fragrance mix I contains cinnamyl alcohol, cinnamaldehyde, eugenol, alpha-amyl-cinnamaldehyde, hydroxycitronellal, geraniol, isoeugenol and *Evernia prunastri* (oak moss absolute).
[4] Fragrance mix II contains alpha-hexyl-cinnamaldehyde, citral, citronellol, farnesol, coumarin and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral ®).

PPD and 26% (n=23) for fragrance mix I (see Table 5-2). Furthermore, 25% (n=22) tested positive for nickel sulphate and 25% (n=22) for ammonium persulfate. Fragrance mix II led to positive responses in 21% of the cases (n=19).

*Table 5-2 Results patch test with European baseline series complemented with additional substances for patients included in current report (top 10).*

| Allergen | % positive |
|---|---|
| methyl(chloro)isothiazolinone (MI and Kathon CG ® (MCI/MI)) | 26% |
| p-phenylene diamine (PPD) | 26% |
| fragrance mix I | 26% |
| ammonium persulfate | 25% |
| nickel sulphate | 25% |
| fragrance mix II | 21% |
| hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyral ®) | 12% |
| cocamidopropylbetaine (CAPB) | 11% |
| rubber | 10% |
| myroxylon pereirae (perubalsem) | 10% |

Especially the many positive responses to ammonium persulfate are noteworthy. In the previous report only five cases (3%) of positive responses to ammonium persulfate were recorded, which amounted to only 3%. In one case, the response to ammonium persulfates resulted in an anaphylactic shock. When all undesirable reactions reported by dermatologists in the period July 2009 – October 2012 are taken into account, positive responses to ammonium persulfate were observed in 32 patients (10%) of which most cases were seen in the period described in the current report.

For some ingredients mentioned in Tables 5-1 and 5-2, such as MI and PPD, concentration limits are established. MI may be used in cosmetic products up to a maximum concentration of 0.01% and the combination MCI/MI (3:1) up to concentrations of 0.0015%. PPD can be used in cosmetics at a maximum concentration of 2% (calculated as free base). Use of the fragrance ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyral ®) must be mentioned in the list of ingredients on the label of the cosmetic product when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products. This obligation also applies to 25 other fragrances, such as cinnamyl alcohol and eugenol, for the same concentration limits.

Other allergens are forbidden in cosmetics. In the Cosmetic Products Directive (76/768/EEC), it is stated that the use of nickel sulphate and methyldibromo glutaronitrile in cosmetics is prohibited, which means that these reactions are not the result of using cosmetics at the present time.

A new patch test with the batch-specific ingredients of the cosmetic product was requested for 146 of the 334 cases (44%) reported in the period July 2009 - October 2012. For 43 patients (29%), this specific patch test was performed up to now and resulted in positive responses to one or more of the tested ingredients in 84% of the cases (n=36). The results of the specific patch test show that 15 patients (42%) developed a reaction to surfactants and/or emulsifying agents, nine patients (25%) to preservatives and seven patients (19%) to fragrances (see Appendix III for a more detailed overview of the outcomes of the batch-specific patch tests). In the previous report, there was special attention for co/cross polymers, including the C30-38 olefin/isopropyl maleate/MA copolymer, i.e. three of the 15 patients were tested positive for these cosmetic ingredients. In the current period, no new cases of contact allergy to co/cross polymers were observed.

## 5.9 Causality

Assessment of the causality between undesirable reactions and cosmetic products was conducted by a senior dermatologist based on the outcomes of the patch test with the European Baseline series and the cosmetic product, the final diagnosis, and, when performed, the patch test with batch-specific ingredients of the cosmetic product. Regarding the outcomes of the patch test with the European Baseline series, only relevant cosmetic allergens were taken into account for causality assessment. The causality between the undesirable reaction and the reported cosmetic product was clearly demonstrated in the case of 239 (83%) of the 277 patients for which the causality was established. For 134 patients (48%) this causality was likely and for 105 patients (38%) very likely. The causality was unlikely or questionable for 39 patients (14%).

When looking at the patients with a report started and finalised between May 2011 and October 2012, a clear causality between the undesirable reaction and the cosmetic product was shown for 78 (84%) of the 93 patients. In 43% of the cases (n=40), causality between the undesirable reaction and the product is likely and in 41% of the cases (n=38) even very likely. For 15 patients (16%), causality was unlikely or questionable.

A relatively large number of hair styling products as the potential cause of undesirable reactions was mentioned, see paragraph 5.5. Compared to what was observed in the previous report, this is rather noteworthy as in general hair dyes are regarded as the culprit. It is interesting is to notice though that of the 87 hair styling products only 32 products (37%) turned out to be giving a positive response in the patch test. By way of comparison, of the hair dyes 43 products

(74%) gave a positive response. In terms of causality, hair dyes are important contributors to the development of undesirable reactions attributed to cosmetic products.

The participating dermatologists indicated that the specific patch test with batch ingredients contributed largely to making a final diagnosis.

**Results Dermatologists *abstract***

- Dermatologists reported 93 usable and finalised reports of undesirable reactions between 1 May 2011 and 1 October 2012.
- Mainly women (85%) visited a dermatologist with the undesirable reaction, and half of the patients were aged under 30.
- In 46% of the cases, occupational exposure is or may be related to the development of the undesirable reaction.
- Reported symptoms of the undesirable reaction included predominantly erythema (24%), itching (22%) and scaling (17%) and occurred mainly on hands (26%) and on the face (21%).
- Severe reactions accounted for 4% of the reported symptoms. Pain was the most common severe reaction.
- Hair products were by far the most frequently reported product category (76%) and included mainly styling products.
- For 312 patients (95%) seen by dermatologists since the start of CESES, the patch test conducted with the European baseline series and the cosmetic product resulted in positive responses to one or more allergens. Of these patients, 23% had a positive response to MCI/MI or MI and/or fragrance mix I. Furthermore, 21% were tested positive for nickel sulphate but this ingredient is not relevant for cosmetic products.
- A specific patch test with batch ingredients was performed for 43 patients. Thirty-six of these displayed a positive response to at least one of the tested ingredients. No new cases of positive responses to co/cross polymers were observed. Fifteen patients (42%) developed a reaction to surfactants and/or emulsifying agents, nine patients (25%) to preservatives and seven patients (19%) to fragrances.
- The relationship between the cosmetic product and the undesirable reaction was considered likely or very likely in 84% of the 93 cases.

# 6 Overview of reports of the EDEN-Fragrance Study

The EDEN-Fragrance Study was set up to gain insight into the prevalence of contact allergy to fragrances and other sensitizers in the general population. As such, it provided an opportunity to relate the CESES consumer questionnaire to actual patch testing with fragrances and other allergens in cosmetics. In total, 120 subjects that had experienced an undesirable reaction to a cosmetic product during their lifetime were interviewed and patch tested within the EDEN-Fragrance Study stated. These people completed the CESES questionnaire. Of these 120 subjects, four were excluded because the product responsible for an undesirable reaction did not concern a cosmetic product. Consequently, 116 respondents were used for further analysis.

## 6.1 Demographics

When looking at demographic characteristics, 63% of the subjects (n=73) were female and 37% (n=43) were male. Compared to the people that reported undesirable reactions on the consumer and clinical route of the CESES project, this population consisted of relatively a large group of men. Figure 6-1 presents the number of reports of undesirable reactions per age group. This figure shows that there is no specific age category in which more undesirable reaction were reported than in other categories. The mean age of the subjects was 36 years of age. The youngest subject was 19 years old and the eldest 70 years old, which was in line with the inclusion criteria of the EDEN-Fragrance Study.

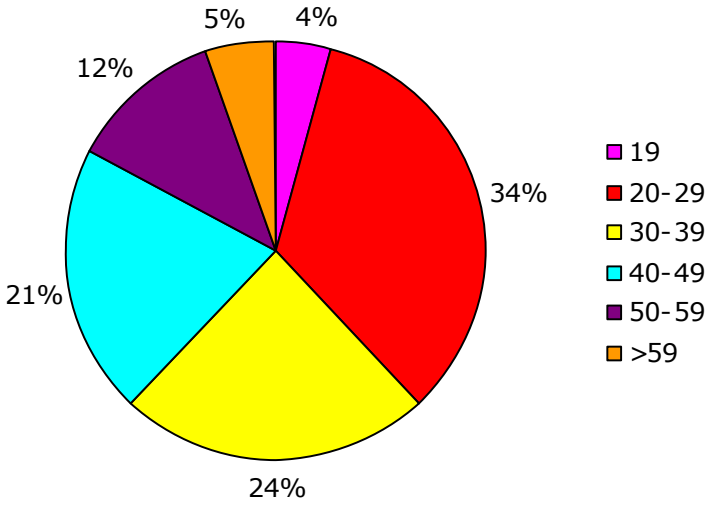



*Figure 6-1 Percentage of reports of undesirable reactions per age category (n=116).*

## 6.2 Description of the undesirable reaction

### *6.2.1 Symptoms*

The undesirable reactions are presented in Figure 6-2 and included mainly itching (26%, n=82), erythema (24%, n=77) and a burning sensation (15%, n=47). In 6% of the cases the undesirable reaction was more severe with reports of pain (n=14), breathing problems (n=3), dizziness (n=1), blistering (n=1) and nausea (n=1). This concerned 17 subjects, which is 15% of the total population included.

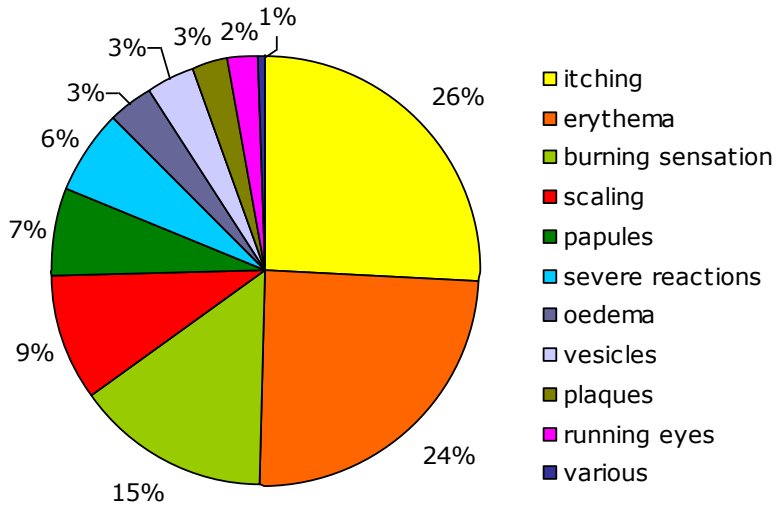



*Figure 6-2 Reported symptoms of undesirable reaction after cosmetics use in % (n=317). The category 'various' includes among others hypokeratosis.*

### *6.2.2 Location*

The undesirable reactions attributed to cosmetic products reported in the questionnaire were located at a wide variety of body regions and locations. Most undesirable reactions occurred on the face (13%, n=32) or under the armpits (13%, n=31). This is graphically depicted in Figure 6-3. Undesirable reactions on or around the eyes were mentioned in 10% of the cases (n=24).

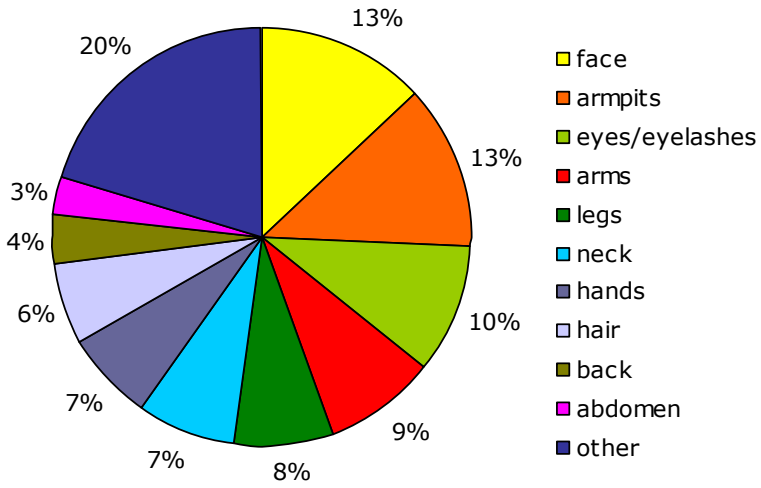



*Figure 6-3 Reported location of cosmetic product use in % (n=243). The category 'other' represents the total sum of other locations, such as tongue and feet.*

## 6.3 Product information

The question which cosmetic product or products probably caused the undesirable reaction was answered by 89 subjects (77%). The respondents mentioned 106 cosmetic products in total. When the products are subdivided in product categories, most products mentioned fall into the categories deodorants (20%, n=21) and skin products (18%, n=19), see Figure 6-4. Within the category skin products mainly products for facial care (n=12), such as cream or lotion, were reported.

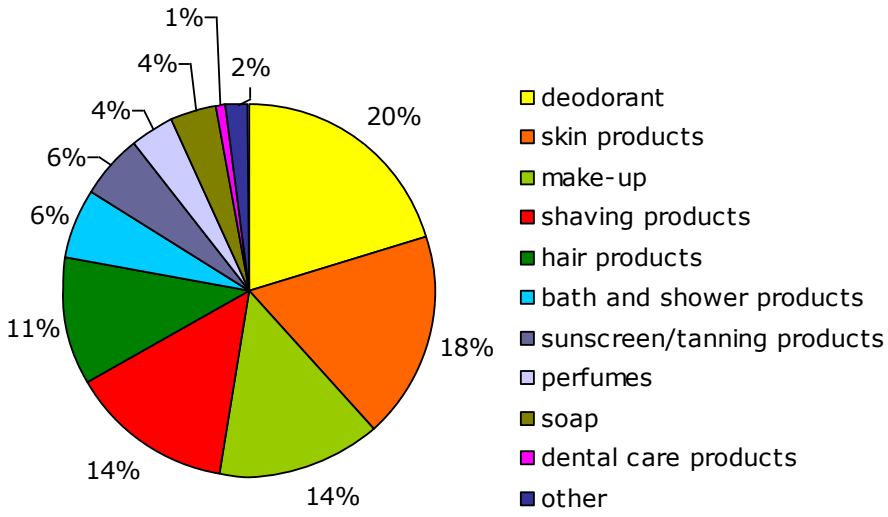



*Figure 6-4 Reported product categories that probably caused the undesirable reaction in % (n=106).*

The location of product use (Figure 6-3) are well in line with the reported product categories that probably caused the undesirable reaction, e.g. the

finding that most undesirable reactions were reported to occur on the armpits correlates well with the frequent reports on deodorants.

## 6.4 Patch tests

All 116 subjects who filled in a CESES questionnaire because they have had at least once an undesirable reaction to a cosmetic product during their lifetime have undergone patch testing with several allergens (see Appendix II). Positive patch tests, meaning a positive response (+, ++ or +++) to one or more of the allergens tested, were obtained in 33% (n=38) of the subjects. Within this group of subjects with positive responses, 18 (47%) showed a positive response to allergens that can be present in cosmetics of which eight subjects had a strong or extreme response (++ or +++). When focussing only on fragrance allergens, six subjects had a positive response to fragrances of which four with a strong to extreme response. Of the 38 subjects, 22 (58%) showed a positive response to nickel sulphate. Nickel is an important contact allergen, but its use is forbidden in cosmetics. Therefore, this allergy is most probably not related to cosmetics use. An overview of the results of the patch tests itemized per allergen type (cosmetic versus non-cosmetic allergen) is provided in Figure 6-5.

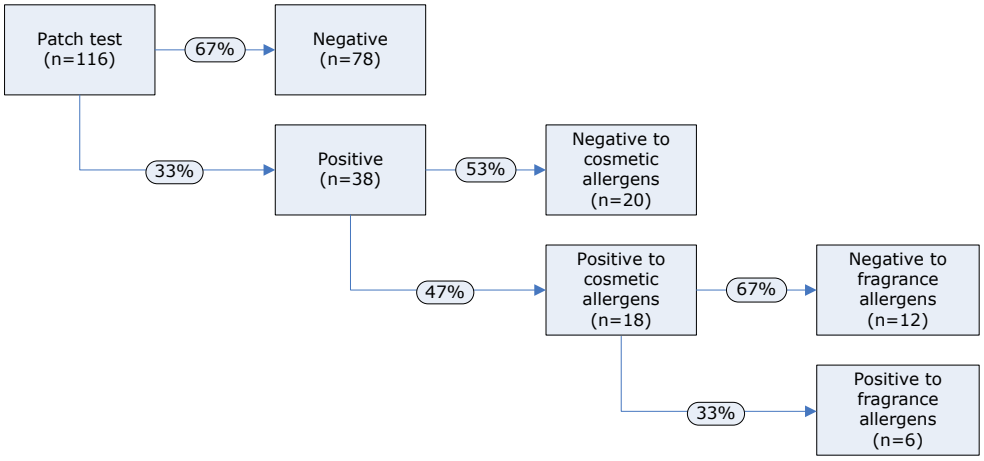



*Figure 6-5 Overview of the results of patch testing itemized per type of allergen.*

Figure 6-6 describes the number of subjects showing a positive response per allergen that can be present in cosmetics (n=39). Of all positive responses to these allergens, most responses were observed to fragrance allergens (n=23, 59%), see also Figure 6-7. These positive responses to fragrance allergens were observed in six subjects (33%).

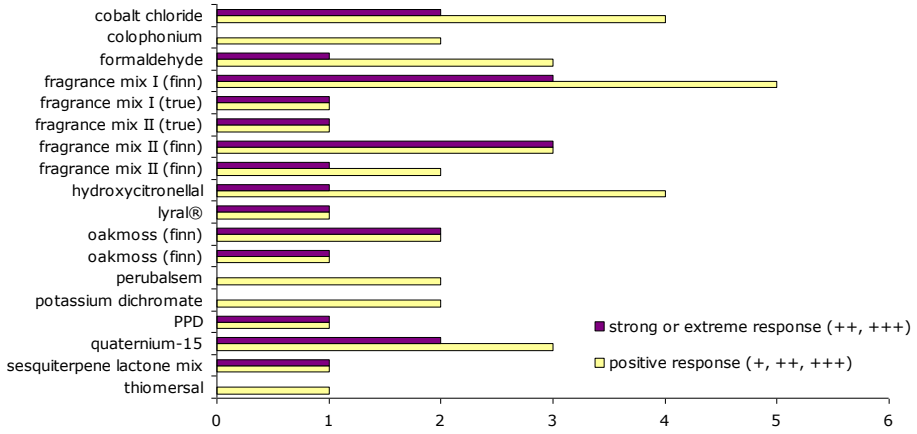



*Figure 6-6 Number of positive responses itemized per allergen that can be present in cosmetics (n=39) recorded for 18 subjects. Note: fragrance mix I and II and oak moss were tested at various concentrations using either the TRUE test (true) or with Finn chambers® (finn) and are thus presented more than once. See also Appendix II.*

It can be observed that 60% of the responses (n=21) to allergens that can be present in cosmetics are strong or extreme responses (represented by the purple bars). For example, in the case of the reactions to oak moss (n=2 and 1 for the different concentrations, respectively), all positive responses were strong or extreme. On the other hand, for perubalsem only weak positive responses (+, n=2) and no strong or extreme responses were seen. Regarding fragrance allergens exclusively (figure 6-7), strong to extreme positive responses were registered in 15 of the 23 cases (i.e. 65%).

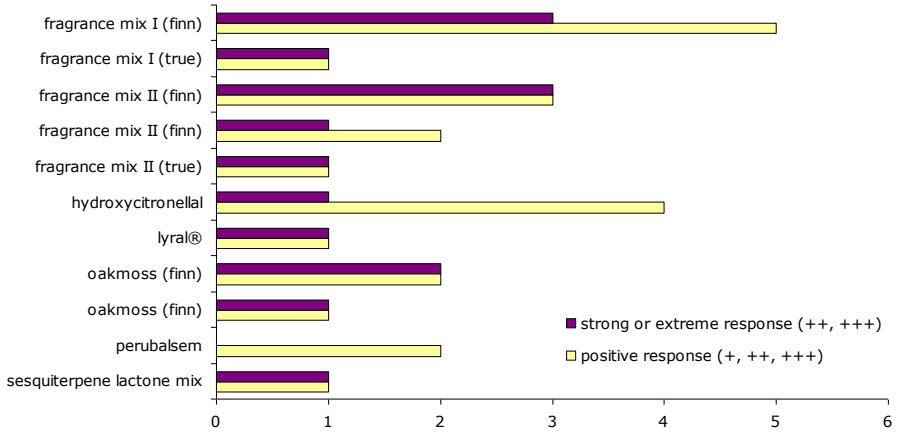



*Figure 6-7 Number of positive responses itemized per fragrance allergen (n=23) recorded for six subjects. Note: fragrance mix I and II and oak moss were tested at various concentrations using either the TRUE test (true) or with Finn chambers® (finn) and are thus presented more than once. See also Appendix II.*

## 6.5 Patch tests in relation to product information

Of the 18 respondents who had a positive response to one or more allergens that can be present in cosmetics, 14 (78%) were able to cite one or more

cosmetic products to which they have had an undesirable reaction. These products could be divided in product categories as is done in Figure 6-8. Most subjects had an undesirable reaction after deodorant use (43%, n=6). Deodorants are known to contain many fragrance ingredients. When looking at the six subjects who showed a positive response to fragrance allergens, three of them mentioned a product, of which two fell in the product category deodorant and one in the category perfumes. The other three subjects did not define a product category.

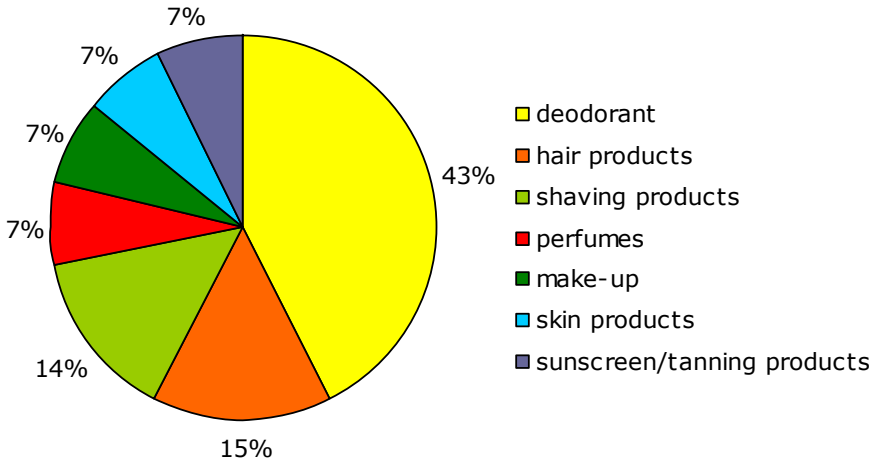



*Figure 6-8 Reported product categories that probably caused the undesirable reaction in % in subjects with a positive response to cosmetic allergens in a patch test (n=14).*

## 6.6 Diagnosis and treatment

Before considering visiting a GP or a dermatologist, 43 subjects (37%) applied self-treatment. This meant in 24 cases (56%) stopping with the cosmetic product and in 14 cases (33%) treatment with a fatty cream or salve.

Thirty-one subjects (27%) reported having visited the GP with their undesirable reaction. Treatment included mainly avoiding usage of the product or the prescription of a corticosteroid cream, which was recommended to 25 subjects (81%). Eight respondents (26%) have subsequently visited a dermatologist who also mainly prescribed a corticosteroid cream and performed patch testing in six cases (all of them were positive). Of these six subjects, the current patch test was again positive.

## 6.7 Other skin conditions and allergies

About 32% (n=37) declared that they suffer from other skin conditions. Atopic dermatitis was most prominent among this group of people (22%, n=8). Allergic contact dermatitis and irritant contact dermatitis were only mentioned in a very

few cases (n=1 and 2, respectively). On the other hand, nine subjects (24%) could not tell which skin condition they were diagnosed with.

Thirty-five subjects (30%) stated to be allergic to other substances, including metals (34%, n=12), drugs and fragrances (both 29%, n=10). Of these persons, 12 (34%) reacted actually positive to the allergens tested, including eight subjects with a positive response to allergens that can be present in cosmetics. Four of these eight subjects responded positively to fragrance allergens.

**Results EDEN-Fragrance Study *abstract***

- 116 subjects filled in the CESES questionnaire and were patch-tested.
- The population consisted mainly of women (64%). However, compared to the CESES routes relatively many men (37%) reported an undesirable reaction.
- The undesirable reactions included mainly itching (26%), erythema (24%) and a burning sensation (15%) and were located on the face (13%), under the armpits (13%) and on or around the eyes and eyelashes (10%).
- Severe reactions were seen in 15% of the subjects.
- Product categories associated with the undesirable reactions were primarily deodorant and skin products.
- A third of the subjects showed a positive response to allergens in the patch test of which nickel was the most prevalent allergen.
- Of these subjects, 47% had a strong or extreme positive response to allergens that can be present in cosmetics, which were mainly fragrance allergens (59%).
- For (at least) 50% of the subjects with a positive response to fragrances the reaction could be related to deodorant or perfumes. However, due to the low number of subjects in this group, caution is needed when interpreting these data.

# 7 Early Warning

One of the objectives of CESES is to send 'Early Warnings' to NVWA in case severe undesirable reactions or a high frequency of undesirable reactions attributed to a cosmetic product were reported.

As described in the previous report, RIVM reported six Early Warnings to NVWA during the period November 2009 - May 2011 to NVWA. Besides additional reports for existing Early Warnings, RIVM notified NVWA in four new cases in the period May 2011 – October 2012. Table 7-1 provides an overview of the Early Warnings that were either new this period or for which additional cases were reported. NVWA has given follow-up to these Early Warnings. Two cases were not followed up by NVWA. Furthermore, not all Early Warnings did result in satisfying actions taken by the manufacturers (e.g. reformulation, or better instruction).

*Table 7-1 Early Warnings based on reports of undesirable reactions by consumers and dermatologists*

| Product | Reports till May 2011 | New consumer reports till October 2012 | New reports dermatologists till October 2012 | Symptoms | Causality * | Follow up NVWA |
|---|---|---|---|---|---|---|
| Toothpaste | 5 | 4 | none | Burning sensation, erythema, vesicles, 'tongue and lips feel like being burned' | Not assessed | See first report, Salverda-Nijhof et al. 2011a. |
| Eye make-up remover | 8 | 4 | none | Itching, erythema, burning sensation, pain, running eyes, 'wounds' | Not assessed | See first report, Salverda-Nijhof et al. 2011a. |
| Udder cream | 7 | none | 1 # | Erythema, itching, scaling, vesicles, oedema | Likely - very likely, product tested positive | Contact with manufacturer who indicated to reformulate the udder cream. |
| Sunscreen | 3 | 2 | none | Erythema | Very likely, product tested positive | - |
| Day and night cream / serum | - | 17 | none | Itching, erythema, burning sensation, burns, scaling, oedema, papules | Not assessed | Contact with manufacturer who concluded that it is probably a 'launch' effect, i.e. introduction of new product. Extra quality controls are undertaken. |
| Lipstick | 9 | 6 | none | Oedema, burning sensation, erythema, itching, scaling, vesicles | Not assessed | Contact with manufacturer who indicated that reactions may be experienced when use instructions are not correctly followed, i.e. not applying the top coat leading to dry lips. In addition, cases are too diverse to draw general conclusions. |
| Day and night cream | 8 | 4 | 1 | Burning sensation, running eyes, itching, erythema, oedema | Very likely, product tested positive | - |
| Sunscreens for children | 2 | 11 | none | Itching, papules, erythema, scaling, nausea, dizziness, burning sensation, oedema, breathing problems | Not assessed | Monitoring number of reported cases concerning sunscreens for children |

* Not assessed means no patch tests for confirmation were performed since all reports were done in the consumer route.
# Same batch number as previous reports.

# 8 Summary and discussion

This chapter includes the summary and the most significant and interesting outcomes regarding reports of undesirable reactions from consumers, via GPs, and via dermatologists are discussed. Furthermore, a trend comparison is made with the observations described in the previous report. In addition, the outcomes related to the EDEN-Fragrance Study are discussed.

## 8.1 Description of undesirable reaction

In all routes, the undesirable reactions were primarily characterized by relative mild symptoms, such as itching and erythema, but 1-11% of the reported symptoms were more severe with pain (1-6%) being most common. Consumers and sentinel GPs reported that the undesirable reactions were mainly located on or around the eyes and on the face, while dermatologists reported relatively many undesirable reactions on the hands and face.

## 8.2 Cosmetic products

The most frequently reported product categories were hair products, skin products and make-up (see Figure 8-1), and included mainly products intended to use on or around the eyes, such as eye contour cream and eye make-up, or on the face or scalp, such as leave-on day and night creams and hair styling and colouring products. In addition, relatively many reports concerned sunscreen/tanning products. This is the same picture as seen in the previous report. However, dermatologists reported relatively more undesirable reactions about hair products and less about skin products and make-up. An explanation for this is the large contribution of hair products reported by the Centrum voor Huid en Arbeid, which is mainly focussed on occupational exposure. In case of undesirable reactions after occupational exposure people are more inclined to seek medical advice because it may hamper them in their profession.

The hair products reported by dermatologists included mainly styling products (46%) and hair dyes (31%). Compared to the previous report, the number of hair styling products as the potential cause of undesirable reactions is much larger. However, in terms of causality, hair dyes are important contributors to the development of undesirable reactions attributed to cosmetic products. Hair dyes may contain the cosmetic allergen PPD known to be able to cause severe reactions but also persulfate salts (see 8.5.4). In contrast to the previous report, no cases of unconsciousness caused by persulfates were reported. In a recent study in Denmark, the need for an increased focus, raised awareness and

a mindset change regarding the high degree of contact dermatitis related to occupational exposure in hairdressers was recognised (Lysdal et al., 2012). Stimulation of for example glove use may lead to a decrease of the high occurrence of hand eczema in hairdressers.

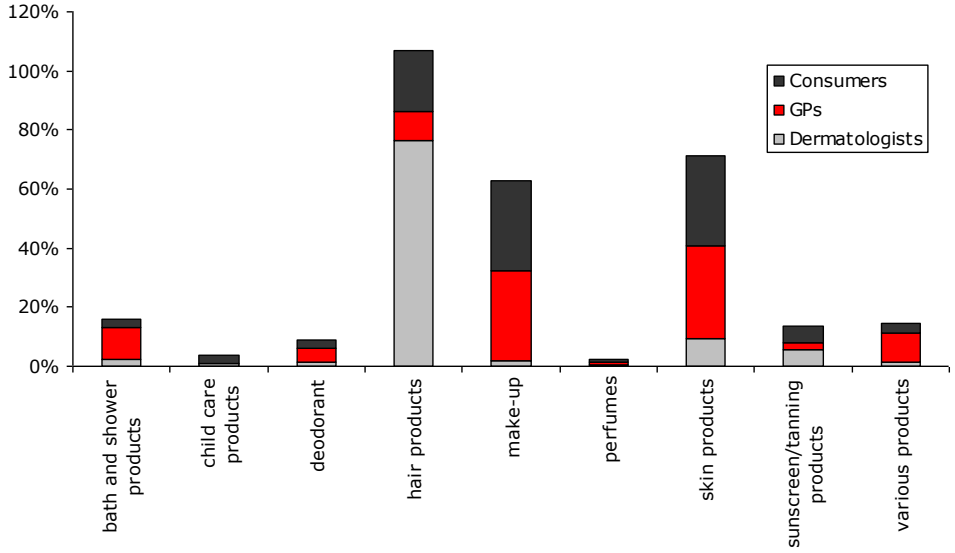



*Figure 8-1 Number of undesirable reactions (in %) per reported product category and per route. Various products include among others shaving products.*

## 8.3 Cosmetic ingredients: patch tests

Since the start of the CESES project in 2009, 312 patients (95%) had a positive response to one or more allergens when tested with the European baseline series and/or the cosmetic product. In addition, 36 (84%) of the 43 patients tested showed a positive response to one or more of the tested ingredients in the patch test with batch ingredients. Of these patients, 15 (42%) developed a reaction to surfactants and/or emulsifying agents, nine (25%) to preservatives and seven (19%) to fragrances.

In reality the number of ingredients tested positive as well as the number of patients with a positive response may be higher. Reasons for this are the fact that not all ingredients with an (possible) allergic potential were tested, because they were unavailable or that the concentration at which the ingredients were tested was not always sufficiently high, as reported by de Groot (2008), to observe a positive response.

### *8.3.1 Isothiazolinones*

The outcomes of the standard patch tests showed that isothiazolinones (including MI or the combination of MI and MCI (Kathon CG®)) were with 23% (n=72) the most frequently positively tested patch test allergens. The high

number of responses to isothiazolinones was already recognized in the previous report and supported by several publications in literature (see Amaro et al., 2011, Garcia-Gavin et al., 2010, Schnuch et al., 2011a and 2011b; Tosti et al., 2003, and Wijnhoven et al., 2008.

In short, isothiazolinones are widely used as preservatives in both industrial products as well as in cosmetics. In the early 2000s, MI was released as individual preservative for use in industrial products, and in 2005 for use in cosmetic products. Until then, MI was only used in the combination with MCI. For use in cosmetics, maximum permitted concentrations are defined being 0.0015% for the combination MCI/MI (3:1) and 0.01% for MI alone. However, currently there are no restrictions on the use of MI in industrial and cleaning products, and the use concentrations are higher than those permitted in cosmetics. It was assumed that MI would have a lower allergenic potential than the combination MCI/MI, but several studies and case reports showed that also MI alone has a high allergenic potential (Amaro et al., 2011; Lundov et al., 2010; Garcia-Gavin et al., 2010; Schnuch et al., 2011a).

A recent review of Lundov et al. (2011) showed that the prevalence of MI contact allergy is around 1.5%, based on studies in Denmark, Finland and Germany, and sources of exposure are associated with occupation, cosmetic products or household products. With the review of Thyssen et al. (2007a) in mind, in which they described that epidemics often begin with cases of contact dermatitis due to occupational exposure followed by consumer cases, an epidemic of MI-induced contact allergies may not be far away. The high prevalence of isothiazolinone-induced contact allergy was also recognized at the Workshop on Cosmetovigilance in May 2012 in Brussels and in the SCCS opinion on benzisothiazolinone (Scientific Committee on Consumer Safety (SCCS), 2012a). Exposure to MCI/MI via cosmetic products remains a persisting problem. Analysis of contact allergy surveillance data from a period of 19 years (1992-2010) by the Information Network of Departments of Dermatology (IVDK) in Germany showed a frequency of positive patch test responses of 2.3% in patients in whom cosmetics were considered as culprit exposures. Moreover, neither a significant and relevant decline in the frequency of positive responses nor a decrease in average sensitivity was observed. The apparently increased use of MI alone was suggested as possible explanation (Uter et al., 2012). A subsequent publication of Geier et al. (2012) analysing the IVDK data between 2009-2011 showed that the prevalence of sensitisation to MCI/MI has increased from 2.3% to 3.9%, allergic reactions to MI increased from 1.9% to 4.4%, and the proportion of MI-positive patients among those who reacted to MCI/MI

increased from 43.3% to 58.9%. According to the authors, these data seem to support the hypothesis that increasing exposure to MI leads to an increase in primary sensitisation to MI, and partly to subsequent immunological cross-reactivity to MCI. In most cases of contact dermatitis though, it remains unclear which preservative (MI alone or MCI/MI) was the primary sensitizer (Lundov et al., 2011; Macias et al., 2012). These developments confirm the need for closely monitoring of isothiazolinones. Furthermore, it is advisable to include MI in the European baseline series to make sure MI is monitored and taken into account as culprit for the development of undesirable reactions after cosmetics use. This is supported by several of the published articles, among others by Geier et al. (2012) and Uter et al. (2012). In addition, a reduction in the maximum use concentration of MI seems advisable.

### *8.3.2 Fragrances*

Fragrances belong to the most important contact allergens in consumer products, including cosmetics, and subsequently, allergy to fragrances is one of the most frequently occurring types of allergic contact dermatitis (Thyssen et al., 2007b; Wijnhoven et al., 2008). As in the previous report, this is confirmed by the outcomes of the patch test with the European baseline series showing that 23% of the patients (n=71) were tested positive for fragrance mix I and 18% (n=58) for fragrance mix II.

Special attention has been given the last years to the fragrance ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyral®), which is often used in cosmetic products. HICC has been found responsible for more than 1500 cases of allergic contact dermatitis since 1999 (SCCS, 2012b). Several attempts were made to reduce the high level of exposure to HICC. In 2003, a recommendation was made to limit the use concentration of HICC in cosmetic products to 200 ppm (SCCS, 2012b). However, this was never implemented. The current EU legislation prescribes that HICC must be specifically declared on the ingredient label when present in concentrations of 0.001% in leave-on products and 0.01% in rinse-off products. Heisterberg et al. (2012) investigated the occurrence of contact allergy to HICC in Denmark and evaluated the effectiveness of the restrictions that have been made so far. The results showed that the prevalence of allergic contact dermatitis caused by HICC was about 2.5% and this figure remained stable over the past nine years. Since the start of the CESES project, 8% of the patients who had a positive patch test had a positive response to HICC. Recently, the SCCS reviewed several fragrance ingredients including HICC (SCCS, 2012b). They were of the opinion that the number of reported cases of allergy to HICC were extremely high and that

repeated exposure to HICC, even at levels below 200 ppm, should be considered unsafe. Therefore, they concluded, HICC should not be used in consumer products to prevent further cases of contact allergy to HICC and to limit the consequences for those already sensitised. The CESES data underline the SCCS conclusion.

### *8.3.3 UV filters in sunscreens*

Of the five patients seen by dermatologists reporting an undesirable reaction to sunscreens in the last eighteen months, two patients were patch tested with the sunscreen and the specific batch ingredients. The results of these tests showed that both patients had a positive response to octocrylene. Octocrylene is a relatively new cinnamate solar filter and increasingly used in sunscreens because of its spectrum efficiency, covering mostly UV-B but also short UV-A wavelengths. Octocrylene is regulated as UV filter under Annex VII/1,10 of the Cosmetics Directive. This means that the ingredient can be used as cosmetic ingredient as UV filter at a maximum concentration of 10% (expressed as acid). Octocrylene has been reviewed by the Scientific Committee on Consumer Products (SCCP) in 1994 who concluded that it could be classified as a non-irritant and non-sensitizer nor would it induce phototoxic or photoallergic reactions. A recent study discussed 50 cases and showed that octocrylene appeared to be a strong allergen leading to contact dermatitis in children and mostly photoallergic contact dermatitis in adults with an often-associated history of photoallergy from ketoprofen (Avenel-Audran et al., 2010). These observations were supported by the study of Travassos et al. (2011) in which octocrylene was by far the most frequent (photo)allergen in sun care products. It is therefore important to reassess the safety of octocrylene with respect to its sensitisation potential.

### *8.3.4 Ammonium persulfates*

Relatively many positive responses were observed to ammonium persulfates between May 2011 and October 2012, i.e. 25% of the patients showed a positive response to ammonium persulfate. Positive patch tests to the other persulfates potassium persulfate and sodium persulfate were observed in 4% of the patients. Ammonium persulfates, as well as potassium and sodium persulfates, are strongly oxidising inorganic salts used in hair bleaches and hair colouring preparations to accelerate the bleaching process (Hoekstra et al., 2012). These positive responses concerned mainly hairdressers who consulted a dermatologist. For this specific occupational group, in the period July 2009 – October 2012, the results of the patch test are presented in Table 8-1 showing a different pattern than the general population. It is interesting to note that for

hairdressers included in the CESES project, ammonium persulfate is the most important sensitising agent, i.e. 63% of the hairdressers tested positive to ammonium persulfate. This figure is much larger than that for PPD (35%). Generally, PPD is seen as the main culprit for contact dermatitis among hairdressers. However, these outcomes may indicate that in hairdressers ammonium persulfate may be equally important to monitor as PPD. In addition, other ingredients may also be more important allergens in hairdressers than in the general population, such as rubber, toluene-2,5-diamine sulfate and p-aminophenol.

*Table 8-1 Results of patch test with European baseline series complemented with additional substances for hairdressers included in CESES seen in dermatological centres in the period July 2009 – October 2012 (n=50).*

| Allergen | % positive |
|---|---|
| ammonium persulfate | 63% |
| p-phenylene diamine (PPD) | 35% |
| nickel sulphate | 22% |
| fragrance mix I | 22% |
| fragrance mix II | 20% |
| rubber | 18% |
| methyl(chloro)isothiazolinone (MI and Kathon CG ® (MCI/MI)) | 12% |
| toluene-2,5-diamine sulfate | 12% |
| p-aminophenol | 12% |

Persulfates have been reported to cause several types of skin reactions, including allergic contact dermatitis, irritant contact dermatitis, localised contact urticaria and generalised urticaria (Pang and Fiume, 2001). They may also cause immediate reactions in the mucous membranes of the bronchial system through inhalation, leading to asthma and rhinitis. Although rare, even cases of anaphylactic reactions have been reported (Hoekstra et al., 2012). Also within the CESES project, one case of unconsciousness (see previous report) was caused by an anaphylactic shock in a patient tested positive for ammonium persulfate. The exact mechanism of immediate reactions to persulfates remains unclear, however.

## 8.4 The EDEN-Fragrance Study

In addition to the CESES routes, the current report also contained the results of the patch tests and the CESES questionnaire that were presented to the population of the EDEN-Fragrance Study. The aim of this was to relate the outcomes of the CESES consumer questionnaire to the results of actual patch testing with fragrances and other allergens in cosmetics.

About 16% of the subjects who indicated to have ever reacted to a cosmetic product showed a positive response to one or more allergens that could be present in cosmetics in the patch test. This outcome may have several

explanations. A disadvantage of the set-up of the study was that the CESES questionnaire was filled in retrospectively and asked about an undesirable reaction that may have occurred in the distant past. Therefore, undesirable reactions to cosmetics may not have been remembered correctly. On the other hand, not all undesirable reactions due to cosmetic products are confirmed with patch testing or are in fact due to an irritation reaction. Since the consumer route within CESES is mainly filled in by consumers when the undesirable reaction was in the near past or is even still present, the consumer reports received within the CESES project may be more reliable than the consumer reports collected within the Eden-Fragrance Study.

The results of the patch tests showed that subjects mainly tested positive for fragrance allergens. Half of the subjects who showed a positive response to fragrance allergens reported deodorant or perfumes as the product category to which they ever had an undesirable reaction. The other half did not define a product category, but as fragrances are widely used in cosmetic products, the chance that they have reacted to a cosmetic product containing fragrances is relatively high. For (at least) 50% of the subjects with a positive response to fragrances this could thus be related to the cosmetic product, e.g. deodorants or perfumes. However, due to the low number of patients in the group, these data should be interpreted with caution.

Interestingly, compared to the 'general' CESES population, a relatively high number of men (37%) included in the EDEN-Fragrance Study filled in the CESES questionnaire. This may be explained by the fact that for the EDEN-Fragrance Study subjects were actively recruited to participate. Based on this, it can be concluded that it is useful to try to adjust the CESES communication strategy in such a way that also men are better reached.

## 8.5 Importance of CESES for cosmetovigilance

The pilot project of CESES has demonstrated its value as a cosmetovigilance tool in the Netherlands. The results obtained within CESES were shown to be comparable to the results from other cosmetovigilance systems in Europe. Additionally, at the Cosmetovigilance Workshop held on 14 and 15 May 2012 in Brussels also other European Member States expressed their appreciation for the Dutch cosmetovigilance system. CESES is unique in Europe since it monitors both validated and non-validated (consumer reports) undesirable reactions. This is important as it was recognized that the majority of the consumers do not seek medical advice in case of undesirable reactions to cosmetics. The consumer route within CESES is therefore indispensable to monitor the incidence and

prevalence of undesirable reactions and intervene quickly in case many reactions are reported for one specific cosmetic product. In addition, it became also clear at the Cosmetovigilance Workshop that the cosmetic industry is only obliged to notify Competent Authorities (CAs) in case of serious undesirable effects (SUEs). SUEs are defined as such that only extreme severe reactions will be registered by industry and notified, i.e. in case of temporary or permanent functional incapacity, disability, hospitalisation, congenital anomalies or an immediate vital risk or death. Many undesirable reactions to these cosmetic ingredients will not fall under the definition of an SUE. In this way, undesirable reactions attributed to cosmetics as described in this report will not be accessible to CAs or market surveillance monitors. In addition, trends in undesirable reactions due to occupational exposure and the prevalence of undesirable reactions attributed to specific allergens are not reported by industry. Therefore, cosmetovigilance systems are a valuable addition to the European Cosmetics Regulation and they highly contribute to consumer safety when concerning the use of cosmetics. Besides the Dutch cosmetovigilance system, also other member states have operational cosmetovigilance systems. At the Workshop, member states declared to continue to invest in maintaining (and setting up) own cosmetovigilance systems as these systems 1) provide insight in the prevalence of undesirable reactions attributed to cosmetic products and 2) identify occupation-related conditions attributed to cosmetic products.

The Cosmetovigilance Workshop furthermore clarified that the outcomes of CESES are in line with the observations in the other MS. For example, isothiazolinones were also identified in other European systems to lead to relatively high numbers of undesirable reactions. MI as such is since 2005 on the market as cosmetic ingredient and partly due to the several cosmetovigilance systems in the several Member States this preservative is now identified as an important allergen. To monitor relatively new (combinations of) cosmetic ingredients, cosmetovigilance systems as CESES are indispensable. The present industry-led cosmetovigilance system is not sufficient to monitor such trends. This also illustrates the need for monitoring patch-test results as these provide the necessary information to determine the specific cosmetic product and ingredient(s) responsible for the development of (occupation-related) undesirable reactions. In this way, occupational groups can be identified that are subject to contact dermatitis caused by cosmetic products with detrimental consequences, such as unemployment.

# 9 Conclusions and recommendations

## 9.1 Recommendations for future monitoring

- Isothiazolinones are identified as one of the most important allergens in developing undesirable reactions. Closely monitoring of isothiazolinones should be continued.
- For hairdressers, ammonium persulfates may be as important as p-phenylenediamine (PPD) in developing skin reactions. More attention should therefore be paid to these allergens.
- Both the consumer and dermatologist route are informative and complementary sources of undesirable reactions. They provide insight into the safety of cosmetics and valuable information for dissemination at the European level, for example in the Working Party and Standing Committee on Cosmetics, EU working groups and in the Scientific Committee on Consumer Safety (SCCS).
- In 2013, it is important to establish a step-by-step plan/ decision scheme that provides guidance on the sending and follow-up of Early Warnings. A step-by-step plan will facilitate the opportunity of intervention in case of potential health concerns.

## 9.2 Recommendations at the EU level

- As the prevalence of MI-induced contact allergy in Europe is still rising, it is advisable to include MI in the European baseline series to ensure adequate monitoring of isothiazolinones. In addition, current risk management options could be re-evaluated (e.g. maximum permitted levels). A request by the European Working Party on Cosmetics for a new SCCS opinion on isothiazolinones is now being prepared.
- In the recent SCCS opinion on fragrances, it was concluded that HICC should not be used in consumer products to prevent further cases of contact allergy to HICC and to limit the consequences for those already sensitised. Based on the outcomes of CESES this opinion is supported.
- Octocrylene seems to exhibit (photo)sensitising properties despite the SCCS opinion of 1994 considered octocrylene to be completely safe. As octocrylene is used as UV filter in sunscreens, it is highly recommended to update the SCCS opinion on octocrylene and re-assess the sensitising properties of octrocylene and its use in cosmetic products.
- For dissemination at the EU level, it would be of great value to present the results of the Dutch cosmetovigilance system during European meetings, such as the meeting of the Working Party and Standing

Committee on Cosmetics, the DG SANCO subgroup on Skin Allergens, or initiatives like the Workshop on Cosmetovigilance.

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# Appendix I CESES in the media

Media attention has been identified in the previous reports as an important factor within CESES to stimulate consumers to report undesirable reactions attributed to cosmetic products. The number of visitors of the CESES website www.cosmeticaklachten.nl is directly linked to media attention (Salverda et al., 2011b). In this chapter is an overview provided of the media attention given to CESES during the last year.

**Number of visitors of the website**

In the period between May 2011 and October 2012, 7626 unique visitors visited the website www.cosmeticaklachten.nl. This means that the website receives on average 449 unique visitors per month. A large peak in the number of visitors was observed for November 2011 (1287 unique visitors). This is most likely due to the presentation of the previous report accompanied by a press release. It was furthermore interesting to see that sending out the tweets was accompanied by an increase in the number of visitors.

**Communication activities: general media**

Two press reports were published by regional and national media in June 2011 and November 2011, respectively. The first press report paid attention to the release of the first report within CESES and the second press report to the second report. Several newspapers and websites, such as de Telegraaf, de Volkskrant, and nu.nl, picked up these press reports.

In September 2012, NIVEL published a press release about the role of the sentinel GPs in CESES and the results on their website in response to the publication of their annual report 2011 (see http://www.nivel.nl/dossier/jaarrapportage-2011). This press release was widely reacted on by among others de Telegraaf, de Volkskrant and gezondheidsnet.nl.

In addition, the Consumentengids paid attention to the CESES website in their magazine of July 2012 and incited their readers to report undesirable reactions due to the use of cosmetic products.

**Communication activities: social media**

Social media are media by which a large population can be reached and stimulated to take action. Another advantage is that this type of publicity is free of charge. Therefore, it is pre-eminently suitable for RIVM to bring CESES to the notice of the Dutch population.

Since May 2011 the following activities were conducted/took place to generate attention for CESES:

- Two tweets (dated 1 August 2012 and 4 October 2012) via the general RIVM Twitter account to come within reach of a larger public.
- Adding of CESES as a fixed topic on the RIVM Facebook account and on the RIVM homepage (file tab Themes).
- Two web logs (www.beautypolish.nl and www.curvacious.nl) generated attention for the CESES-website by encouraging their viewers to report undesirable reactions including a referral to the website. These web logs also put information about CESES on their Facebook and/or Twitter.
- Use of Google Adwords to make sure www.cosmeticklachten.nl is on top of the Google list when relevant search terms are used.
- Cooperation with www.gezondheidsplein.nl that will provide information about and will refer to the CESES website when relevant topics are visited. In addition, the campaign includes the use of polls and banners. This campaign is in force in the period September 2012 – December 2012. First results show that 225.339 visitors of the website have seen (part of) the campaign, i.e. the poll, the banner or the specific pages about CESES. Of these visitors, 271 visitors clicked on the link to www.cosmeticaklachten.nl. The poll 'Are you familiar with www.cosmeticaklachten.nl' was viewed by 23314 visitors. In addition, an interview with RIVM about the CESES project was placed on their website for the December theme 'Beauty during the holidays.

**RIVM toolkit undesirable reactions attributed to cosmetics**

The use of the RIVM toolkit for communication to the public is continued. The toolkit is meant to be used by anyone who gives education to the general public about illness and health, like area health authorities (GGDs), pharmacists and general practitioners. The content provides ready for use information material or semi manufactures specifically addressed to highlighting the CESES website, such as frequently asked questions (FAQs), information cards and banners. In 2012, there were 667 downloads of the content of the toolkit. For example, the banner was downloaded approximately 30 times and the FAQs almost 130 times.

**Distribution of information cards**

The information cards were furthermore distributed in hard copy together with a poster at a large part of the Dutch general practitioners (~3000 practices) and pharmacists (~1500) in October 2012. It is expected that the number of reports

of undesirable reactions via the website will increase due to the attention generated via this communication activity.

# Appendix II Allergens patch-tested in the EDEN-Fragrance Study

| **Abbreviation** | **Allergen** | **Present in cosmetics** |
|---|---|---|
| finn1cinnamic | cinnamiyl alcohol | yes |
| finn2cinnamic | cinnamal | yes |
| finn3amylcinn | amylcinnamyl alcohol | yes |
| finn4geraniol | geraniol | yes |
| finn5hydroxyc | hydroxycitronellal | yes |
| finn6eugenol | eugenol | yes |
| finn7isoeugen | isoeugenol | yes |
| finn8oakmoss | Evernia prunastri extract (oakmoss) | yes |
| finn9oakmoss | Evernia prunastri extract (oakmoss) | yes |
| finn10fragranc | fragrance mix I: amylcinnamal, cinnamal, cinnamyl acohol, eugenol, Evernia prunastri extract, geraniol, hydroxycitronellal, isoeugenol | yes |
| finn11citral | citral | yes |
| finn12citronel | citronellol | yes |
| finn13coumar | coumarin | yes |
| finn14farneso | farnesol | yes |
| finn15hexyl | hexyl connamal | yes |
| finn16lyral | hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, Lyral ®) | yes |
| finn17sorbitan | sorbitan ester | yes |
| finn18fraganc * | fragrance mix II: hydroxyisohexyl 3-cyclohexene carboxaldehyde(Lyral ®), citral, farnesol, coumarin, citronellol, a-hexylcinnamal | yes |
| finn19fraganc * | fragrance mix II: hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral ®), citral, farnesol, coumarin, citronellol, a-hexylcinnamal | yes |
| finn20sesquit | sesquiterpene lactone mix | yes |
| true1nickelsu | nickel sulfate | no |
| true2woolalco | lanolin alcohol | yes |
| true3neomyc | neomycin sulfate | no |
| true4potassiu | potassium dichromate | yes |
| true5cainemix | anaesthetics | no |
| true6fragranc | fragrance mix I variant | yes |
| true7colophon | colophonium (rosin) | yes |
| true8epoxy | epoxy resin | no |
| true9quinoline | clioquinol and chloquinaldol | no |

| | | |
|---|---|---|
| true10balsam | perubalsam, Myroxylon pereirae resin | yes |
| true11ethylene | ethylenediamine | no |
| true12cobalt | cobalt chloride | yes |
| true13ptert | para-tertiary butylphenol formaldehyde resin | no |
| true14paraben | methyl-, ethyl-, propyl-, butyl- and benzyl-paraben | yes |
| true15carba | dithiocarbamates and diphenylguanidine | no |
| true16black | black rubber mix | yes |
| true17ClMeiso | Cl + Me-isothiazolinone | yes |
| true18quatern | quaternium-15 | yes |
| true19mercapt | mercaptobenzothiazole (MBT) | no |
| true20pPhenyl | 4-phenylenediamine base (PPD) | yes |
| true21formald | formaldehyde | yes |
| true22mercapt | mercaptobenzothiazole | no |
| true23thiomer | thiomersal | yes |
| true24thiuram | thiuram mix | yes |
| true25diazoli | diazolidinyl urea | yes |
| true26imida | imidazolidinyl urea | yes |
| true27budeso | budesonide | no |
| true28tixocor | tixocortol pivalate | no |
| true29hydroc | hydrocortisone-17-butyrate | no |
| nix50newfragr | fragrance mix II variant | yes |

* different concentrations

# Appendix III Outcomes CESES-specific patch testing with batch ingredients performed by dermatologists

Overview of products and ingredients tested positive divided by product and patient number. – negative response, ? doubtful response, + positive response, ++ strong positive response, NT not tested. * from literature # concentration set by working group on test concentrations

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| 535 | Shampoo | | | 5% aq* (open test) | - | + | NT |
| | magnesium chloride | viscosity controlling | 5% aq* | 5% aq* | - | Irritation | NT |
| | piroctone olamine | preservative | 1% pet | 1% pet* | ? | - | NT |
| | sodium laureth sulfate (Emal) | surfactant | | 0.5% aq | - | ? | NT |
| | sodium laureth sulfate (Genapol) | surfactant | | 0.5% aq | - | ? | NT |
| 545 | Cream | | | | - | - | NT |
| | butyrospermum parkii butter | skin conditioning/ emollient | 30% mo | 30% mo | - | + | + |
| 545 | Body milk | | | as is* | - | + | - |
| 553 | Cream | | | as is* | | | + |
| 563 | Lotion | | | pure | + | ++ | NT |
| | Peg-7 hydrogenated castor oil | emulsifier/ surfactant | 30% pet* | 10% PET | + | + | NT |
| | peg-45/dodecyl glycol copolymer | emulsion stabiliser | 5% pet* | 2.0% PET | + | + | NT |
| | benzyl alcohol | preservative/ solvent | 5% pet* | 1.0% PET | ? | + | NT |
| | polymer/peg-2 hydrogenated castor | emulsifier | 20% pet n.a. | 5.00% | - | + | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | oil/so | | | | | | |
| 565 | Sunscreen | | | as is* | + | ++ | NT |
| | c30-38 olefin/isopropyl maleate/ma copolymer | surfactant, emulsion stabiliser | | 5% pet | + | + | NT |
| | benzophenone-3 | UV filter | 2% pet* | 10% pet | ++ | ++ | NT |
| 565 | Tonic | | | as is* | - | ++ | NT |
| 569 | Shampoo | | | | - | - | NT |
| | CI 17200 | cosmetic colouring agent | 1% pet* | 1% pet* | - | ? | NT |
| | sodium laureth sulfate | surfactant/ detergent/ foam layer | 0.5% aq+ | 5% aq | + | + | NT |
| 587 | Shampoo | | | 5% aq (open test) | - | + | NT |
| | sodium cocoyl glutamate | surfactant/ detergent | 1% aq | 1% aq | - | + | NT |
| | sodium coco-sulfate | surfactant/ detergent / emulsifier | | 1% aq | ? | - | NT |
| 596 | Cleansing gel | | | | NG | NG | NT |
| | acrylates/c10-30 alkyl acrylate crosspolymer | film former | 1% pet | 2% aq | - | + | + |
| | styrene/acrylates copolymer | opacifying | | 10% aq | - | + | + |
| 602 | Gel/cream | | | 5% aq* (open test) | - | + | - |
| | coco-betaine | surfactant/ detergent/ foam layer | used conc. | 6% aq | - | ? | - |
| | sodium laureth sulfate | surfactant/ | 0.5% aq+ | 2% aq | - | ? | ? |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | | detergent/ foam layer | | | | | |
| 611 | Shaving cream | | | 5% aq (open test)* | ? | + | NT |
| | limonene | fragrance | 2% pet* | 2% pet* | - | ? | NT |
| | sodium lauryl sulfate | surfactant/ detergent/ foam layer | 0.5% aq+ | 0.1% aq* | ? | + | NT |
| | sodium cetyl sulfate/sodium lauryl sulfate/sodium myristyl sulfate/sodium stearyl sulfate/laureth-10 | combination of functions, like emulsifier, surfactant, detergent, foam layer | | 1% aq | ? | + | NT |
| 685 | Cream | | | as is* | ? | + | NT |
| | methylisothiazolinone | preservative | used conc. | 0.1% aq | + | ++ | NT |
| 711 | Sunscreen | | | as is* | ? | + | NT |
| | tocopherol | antioxidant/ skin conditioner | 10% pet* | 10% pet* | ++ | + | NT |
| 713 | perfume (fragrance) | fragrance | 10% pet | 10% pet | ++ | ++ | ++ (day 6) |
| | cocamidopropyl betaine | boosting | 1% aq | 1% aq | ? | + | + (day 6) |
| 735 | Soap | | | | - | - | NT |
| | tetrasodium edta | chelate | 1% pet* | 1% aq* | ? | - | NT |
| | perfume (fragrance) | fragrance | 10% pet | 10% pet* | - | + | NT |
| | geraniol | fragrance/ tonic | 5% pet* | 5% pet* | - | + | NT |
| 737 | Shampoo | | | | - | - | NT |
| | polyquaternium-7 | antistatic/ film former | 0.1% aq* | 1% aq | - | ? | - |
| | linalool | deodorants/perfu | 10% pet* | 10% pet* | ? | - | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | | me compound | | | | | |
| 737 | Douche and shower gel | | | 5% aq* (open test) | - | - | + |
| | specific ingredient | | | 5% aq* (open test) | - | ? | NT |
| | polyquaternium-7 | antistatic/ film former | 0.1% aq* | 0.1% aq* | ? | - | NT |
| | perfume (fragrance) | fragrance | 10% pet | 10% pet* | ? | - | NT |
| 785 | citronellol | masking | 2% pet* | 2% pet* | - | + | NT |
| | limonene | fragrance | 2% pet* | 2% pet* | - | + | NT |
| 789 | Cleansing gel (face) | | | 5% aq* (open test) | + | + | NT |
| | potassium behenate | cleansing/ surfactant | | 1% aq | - | + | NT |
| | potassium laurate | emulsifying/ surfactant | 1% aq | 1% aq | - | + | NT |
| | potassium myristate | emulsifying/ surfactant | 1% aq | 1% aq | - | + | NT |
| | potassium palmitate | emulsifying/ surfactant | | 1% aq | - | + | NT |
| | sodium methyl cocoyl taurate | surfactant/ cleansing/ foaming | 0.5% aq | 0.5% aq | + | + | NT |
| 791 | Sunscreen | | | as is* | + | + | NT |
| 791 | Sunscreen | | | as is* | + | + | NT |
| 793 | Shampoo | | | 5% aq* (open test) | ? | ? | ? |
| | cocamidopropyl betaine | boosting | 1% aq | 1% aq | ? | + | + |
| 793 | Body milk | | | as is* | - | + | + |
| 797 | Eye pencil | | | | - | - | NT |
| | ascorbyl palmitate | antioxidant | 30% pet* | 30% pet* | + | + | NT |
| 811 | Body cream | | | as is* | + | + | NT |
| | sucrose stearate | emulsifying/skin | 20% pet+ | 3% aq/alc | + | + | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | glyceryl stearate | conditioning emollient/ emulsifying | 20% pet* | 30% pet* | ? | + | NT |
| | sorbitan tristearate | emulsifying | 5% m.o.* | 5% mo | + | + | NT |
| | stearic acid | emulsifying/ emulsion stabiliser/ refatting? | 5% pet* | 5% pet* | - | + | NT |
| 899 | Cream | | | as is* | + | + | + |
| | cetyl alcohol | emollient/ emulsifying/ opacifying/ viscosity controlling | 30% pet* | 20% pet | ? | - | + |
| | perfume | | | 10% pet* | + | + | + |
| | peg-20 stearate | emulsifying/ humectant/ surfactant | | 30% aq/alc | - | + | + |
| | stearyl alcohol | emollient/ emulsion stabilisers/ opacifying/ viscosity controlling | 30% pet* | 30% pet* | ? | + | + |
| 901 | Shampoo | | | 5% aq* (open test) | ? | + | NT |
| | decyl glucoside | surfactant/ emulsion stabilisers | 1% aq | 1% aq | + | + | NT |
| | perfume | | | 10% pet* | + | + | NT |
| 915 | Shampoo | | | 5% aq* | ? | + | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | cocamidopropyl betaine | boosting surfactant/ cleansing/ foaming | 1% aq | 1% aq* | - | + | NT |
| | sodium laureth sulfate | | 0.5% aq+ | 2% aq* | ? | + | NT |
| 915 | Soap | | | 5% aq* | - | + | NT |
| | sodium laureth sulfate (24) | | | 0.5% aq | ? | + | NT |
| | sodium laureth sulfate (25) | | | 0.1% aq | + | + | NT |
| 949 | Shampoo | | | 5% aq* (open test) | - | + | NT |
| | perfume | | | 10% pet* | - | + | NT |
| | sodium benzoate | preservative | 5% pet* | 5% aq* | - | ? | NT |
| 951 | Hair conditioner | | | 5% aq | ? | + | NT |
| 957 | Cleansing product | | | as is | - | + | + (day 6) |
| | citrus aurantium oil/citrus grandis oil/citrus nobilis oil/lavandula angustifolia oil/lavandula etc. | combination of functions, like astringent/ tonic/ masking | | 5% pet | + | + | + (day 6) |
| | limonene | fragrance | 2% pet* | 2% pet* | ? | + | + (day 6) |
| 959 | Cream | | | as is* | + | ++ | ++ |
| | geraniol | fragrance/ tonic | 5% pet* | 5% pet* | + | + | + |
| | limonene | fragrance | 2% pet* | 2% pet* | + | + | + |
| | perfume | | | 10% pet* | ? | + | ? |
| 961 | Eye contour cream | | | as is* | + | + | + |
| | methylisothiazolinone | preservative | used conc. | 0.05% aq | + | + | + |
| 963 | Cream | | | as is* | - | + | + |
| | capryloyl salicylic acid | skin conditioning | | 1% alc | - | + | + |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | paraffinum liquidum/cera microcristallina/paraffin | combination of functions, like antistatic/ emollient/ solvent/ skin?/ binding/ emulsion stabilisers/ opacifying/ viscosity controlling | pure* | pure | ? | + | + (day 6) |
| | sorbitan tristearate | emulsifying | 5% m.o.* | 5% mo* | - | + | + |
| | tocopherol | antioxidant/ skin conditioning | 10% pet* | 10% pet* | ? | + | + (day 6) |
| 973 | bis-ethylhexyloxyphenol methoxyphenol triazine | UV absorbers/UV filter | | 2% pet | + | ++ | NT |
| | butyl methoxydibenzoylmethane | UV absorbers/UV filter | 2% pet* | 10% pet* | + | + | NT |
| | octocrylene | UV absorbers/UV filter | 1% pet* | 10% pet* | - | ++ | NT |
| | octocrylene | UV absorbers/UV filter | 1% pet* | 1% pet* | + | + | NT |
| | bis-ethylhexyloxyphenol methoxyphenol triazine | UV absorbers/UV filter | | 3% pet | + | + | NT |
| | butyl methoxydibenzoylmethane | UV absorbers/UV filter | 2% pet* | 2% pet | + | + | NT |
| | drometrizole trisiloxane | UV absorber | | 0.05% pet | - | + | NT |
| | peg-30 dipolyhydroxystearate | emulsifying | 30% pet+ | 2% pet | - | + | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | tocopherol | antioxidant/ skin conditioning | 10% pet* | 10% pet* | - | + | NT |
| 995 | Shampoo | | | 5% aq* (open test) | ? | + | + (day 6) |
| | potassium sorbate | preservative | 5% pet* | 5% pet* | - | ? | |
| | sodium benzoate | preservative | 5% pet* | 5% pet* | ? | ? | ? |
| 1001 | Douche and shower gel | | | 5% aq* (open test) | + | + | NT |
| 1001 | Shampoo | | | 5% aq* (open test) | - | + | NT |
| | disodium lauroamphodiacetate/sodium chloride | combination of functions, like antistatic/ surfactant/ viscosity controlling | 1% aq* | 1% aq | + | + | NT |
| | piroctone olamine | preservative | 1% pet | 1% pet | - | + | NT |
| 1045 | Body milk | | | as is* | + | + | NT |
| | citronellol | masking | 2% pet* | 2% pet* | + | + | NT |
| | hydroxycitronellal | perfume compound/ masking | 2% pet* | 2% pet* | + | + | NT |
| 1045 | Douche gel | | | 5% aq*(open test) | ? | + | NT |
| | linalool | deodorants/ perfume compound | 10% pet* | 10% pet* | + | + | NT |
| 1089 | Sunscreen | | | as is* | + | ++ | NT |
| | octocrylene | UV absorbers/UV filter | 1% pet* | 10% pet* | + | + | NT |
| 1091 | Cream | | | as is* | + | + | NT |
| | diazolidinyl urea | preservative | 2% pet* | 2% pet* | + | + | NT |
| | perfume | | | 1% alc | + | + | NT |
| 1107 | Shampoo | | | 5% aq* (open test) | ? | + | NT |

| Patient number | Tested product or ingredient | Substance type | Reference concentration | Test concentration | Outcome after 2 days | Outcome after 3 days | Outcome after 7 days |
|---|---|---|---|---|---|---|---|
| | cocamidopropyl betaine | boosting | 1% aq | 1% aq* | ? | + | NT |
| | cocamidopropyl betaine | boosting | 1% aq | 1% pet | - | ? | NT |
| | sodium benzoate | preservative | 5% pet* | 0.2% aq | - | ? | NT |

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