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Results of a cosmetovigilance survey in The Netherlands

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SUMMARY

Background. Cosmetic products contribute considerably to the incidence of contact dermatitis. In response to a resolution of the Council of Europe, the National Institute for Public Health and the Environment (RIVM) in The Netherlands set up a pilot project to report undesirable effects attributed to cosmetic products. **Objectives.** To provide an overview of undesirable effects attributed to cosmetic products and to identify the ingredients involved. The

information could contribute to the assessment of whether current EU legislation on cosmetics provides adequate protection.

Patients/methods. General practitioners, dermatologists and consumers in The Netherlands completed questionnaires on reported undesirable effects of 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.

Results. Between July 2009 and May 2011, the RIVM received more than 1600 reports. Severe undesirable effects were claimed in 1–4% of the cases. The most frequently reported cosmetic products were make-up and moisturisers, and the most frequently identified allergens were isothiazolinones and fragrance ingredients. Three patients tested positive for co-polymers/cross-polymers.

Conclusions. Further investigations are recommended on the prevalence of isothiazolinone-induced allergic contact dermatitis and the allergenic potential of copolymers/cross-polymers.

Cosmetic products cover a wide range of hygiene and personal care products, including bath and shower products, fragrances, deodorants, and skin creams. Most people make use of cosmetic products on a daily basis: for hygiene, such as soap; for beautification, such as make-up and hair dyes; or for protection, such as sunscreen 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 (1, 2). This legislation requires manufacturers to ensure the safety of their cosmetic products in normal use and under reasonably foreseeable conditions, and national market surveillance authorities to monitor compliance with the regulation.

EU legislation and enforcement notwithstanding, consumers may encounter undesirable effects after using cosmetic products. These effects are mainly localized on the skin, and include symptoms such as erythema, itching, scaling, and a burning sensation. Although rare, severe reactions may also occur, such as burns, blistering, hair loss, or even loss of consciousness. The most common undesirable effects are irritant contact dermatitis and allergic contact dermatitis (3–5). In particular, fragrances and preservatives in cosmetics have contributed considerably to the incidence of allergic contact dermatitis (6–9).

As undesirable effects of cosmetic products may lead to acute and chronic health impairment, the Council of Europe adopted a resolution in 2006 recommending that the Member States implement a system for registering undesirable effects of cosmetic products (cosmetovigilance) directed to protecting public health (6). In response, the Netherlands Food and Consumer Product Safety Authority (NVWA) requested the National Institute for Public Health and the Environment (RIVM) to initiate a pilot project to register and evaluate reports of undesirable effects of

cosmetic products. The pilot project with the acronym CESES (Consumer Exposure, Skin Effects and Surveillance) is aimed at providing an overview of undesirable effects attributed to cosmetic products. These data could contribute to the assessment of whether current EU legislation on cosmetics provides adequate protection.

The project collected reports on undesirable effects of cosmetic products, identified the products and ingredients causing the undesirable effects, and alerted the NVWA in cases of a potential health concern.

Furthermore, the project provided a forum for information exchange by stakeholders, including consumers, general practitioners (GPs), dermatologists, government agents, and inspectorates (10).

In this article, the authors describe how the CESES project was set up, and provide an overview of the reported undesirable effects attributed to cosmetic products in the period between July 2009 and May 2011.

PATIENTS AND METHODS

Participating GPs and dermatologists

Undesirable reactions to cosmetic products were registered by GPs and dermatologists in the period between July 2009 and May 2011. The GPs participate in the Continuous Morbidity Registration (CMR) Sentinel GP Network of the Netherlands Institute for Health Services Research (NIVEL). The Dutch CMR Sentinel GP Network comprises 61 GPs in 42 general practices, representative of age, sex, geographical distribution and population density in The Netherlands. The patients registered in these practices account for 0.8% of the Dutch population, and are distributed evenly throughout the country¹. In the last 2 years, the sentinel GPs reported regularly on the occurrence of undesirable effects of cosmetic products (11, 12). Dermatologists also contributed to the CESES pilot project. In July 2009, four dermatological centres participated and three more centres joined in July 2010. These participating dermatological centres included academic hospitals (VUMC, UMCG, and UMCU), peripheral hospitals (St Antonius Hospital, Reinier de Graaf Hospital, and Deventer Hospital), and a referral centre for occupational skin diseases (Centrum voor Huid en Arbeid). The centres were spread over The Netherlands, and covered both highly urbanized and more rural parts of the country.

For diagnostic purposes and to identify potential causes of undesirable effects, dermatologists performed patch tests with the European baseline series [plus some additional substances, including methylisothiazolinone (MI) at a concentration of 0.05% aqua], cosmetic products used, and, when necessary, specific cosmetic test series. Patch test preparations were applied on the upper part of the back for 2 days (48 hr) with Van der Bend_ square chambers (Brielle, The Netherlands) with Fixomull stretch_ (Beiersdorf, Germany). Readings were performed on day 2, day 3 and (in some cases) day 6 or day 7, and conducted by well-trained dermatologists according to the guidelines of the International Contact Dermatitis Research Group. Where the outcome of the standard patch tests was not sufficient to identify the cause of an undesirable effect, the dermatologists requested the NVWA to obtain specific batch ingredients of the cosmetic product from the company responsible for bringing the product to the market.

[TABLE 1]

Consumer reports

The CESES project also included consumer reports of undesirable reactions to cosmetic products. Consumer reports were collected via an online questionnaire on a dedicated website² launched by the RIVM. Consumers could also use the NVWA call centre³ and report undesirable effects of cosmetic products by telephone.

To create consumer awareness, a media campaign was conducted that included activities such as news interviews (newspapers, radio, and television), online banner advertising, articles in women's magazines, and handouts at fairs and conventions.

Questionnaire

All participants (GPs, dermatologists, and consumers) were asked to complete a questionnaire about undesirable effects of cosmetic products. The questionnaire included: (i) general personal information (age, sex, occupation, and familiarity with underlying skin disorders and allergies); (ii) description, body region and severity of the undesirable reactions; (iii) diagnosis and treatment; and (iv) a detailed description of the cosmetic product(s) potentially responsible for the reaction, including brand name, product name, batch code, expiration date, and selling point.

In addition, specific questions were asked of each group of participants. Consumers were asked whether they had visited a GP or dermatologist. GPs were asked whether they had referred the patient to a dermatologist.

The dermatologists were asked to record the outcome of patch tests with the European baseline series, and, where applicable, the test results with batch-specific ingredients.

These reports were checked by a senior dermatologist for completeness. The potential causal relationship between the undesirable effect and the cosmetic product was established according to the COLIPA (now known as Cosmetics Europe) model (13, 14).

Assessment

All reports were analysed by the RIVM. Those reports without detailed information on the cosmetic product or that did not concern a cosmetic product were eliminated. Cases of severe undesirable effects, including hair loss, blistering, breathing problems, loss of consciousness, dizziness, skin burns, and nausea, or a high frequency of undesirable effects attributed to the same cosmetic product, were reported to the national competent authority.

RESULTS

Reported cases

In the period between July 2009 and May 2011, a total of 1294 cases of undesirable effects of cosmetic products were reported by consumers, 153 cases were reported by sentinel GPs, and 163 cases were reported by participating dermatologists (Table 1). In total, 38% (n = 494) of consumers who reported an adverse skin reaction after using a cosmetic product visited their GP, and 12% (n = 158) consulted a dermatologist for further treatment and/or diagnostic patch testing. Before giving consideration to consulting a doctor, a considerable number of consumers (62%, n = 797) had applied selftreatment, such as treating the affected skin with a soothing

(fatty) cream. The data show that 17% (n = 205) of consumers reported the problem to the product retailer, and 10% (n = 120) contacted the manufacturer.

In most cases, manufacturers were apparently unaware of adverse skin reactions caused by cosmetic products.

Furthermore, the number of consumer reports increased after each event in the media campaign launched to create consumer awareness (data not shown).

Far more adverse reactions were reported by women (78–91% of reports) than by men. The average age was ~41 years (Table 1), but reports were received for all ages, with the youngest person being <1 year old and the oldest person 92 years old. A considerable number of people (15–26%) who reported an adverse reaction were familiar with an underlying skin disease, such as contact eczema or atopic dermatitis, and 20–39% reporting having an underlying allergy (e.g. pollen, metals, or food allergens; Table 1).

Localisation and symptoms

Undesirable reactions to cosmetic products were reported in various body regions, and occurred simultaneously at several locations. Reports from consumers, sentinel GPs and dermatologists showed that most undesirable reactions attributed to cosmetic products occurred on or around the eyes and eyelids, and on the face and neck (Fig. 1). More undesirable reactions on the hands were reported by dermatologists (17%, n = 49) than by consumers and sentinel GPs. Generally, the body regions affected were directly related to the application site of the product.

Most reported symptoms included erythema and itching (Fig. 2). Pain was reported in 2% and 6% of the cases reported by dermatologists and consumers, respectively. Severe undesirable effects, including hair loss, blistering, breathing problems, dizziness, skin burns, and nausea, were claimed in 1–4% of the cases reported.

Loss of consciousness was reported in two cases: one case was reported by a GP and concerned a hair dye product, and the other case was reported by a dermatologist and concerned a hair bleach product. Undesirable effects were shown to develop quickly, and occurred within 30 min in 16% (n = 202) of the consumer reports and in 6% (n = 8) of the reports by GPs. Most reports from dermatologists did not include information on the time elapsed between the moment of exposure and the development of undesirable effects.

[FIGURE 1 AND FIGURE 2]

Reported product categories

The most frequently reported product categories were make-up and moisturisers (Fig. 3). Undesirable effects of make-up products were predominantly reported by consumers and GPs, and mainly concerned products designed for use on or around the eyes, such as mascara, eye shadow, and eye make-up remover. Moisturisers were mainly leave-on body and face care products such as body lotions/creams and day and night creams. In total, 13% (n = 42) of consumer reports on face care products concerned eye contour creams, and 12% (n = 8) of moisturisers reported by dermatologists concerned non perfumed ointments.

Dermatologists reported more cases than consumers and GPs of undesirable effects of hair care products (23%, n = 51) and soaps (22%, n = 49). Hair care products were

predominantly shampoos (82%, $n = 42$), and bath and shower products constituted 61% ($n = 30$) of reports on soaps. Hair dye products responsible for the most severe undesirable effects encompassed 4% (dermatologists) to 6% (GPs) of the total number of reports (Fig. 3). Although fragrance ingredients are known allergens in cosmetic products, hydroalcoholic products such as perfumes were mentioned as a potential cause of undesirable effects in only 2–3% of cases reported.

Patch test results

In 96% ($n = 156$) of cases reported by dermatologists, a patch test with the European baseline series was performed. Most patients (97%, $n = 151$) tested positive for one or more allergens or substances/products (Table 2). The most commonly reported allergens in these patients were isothiazolinones (23%), fragrance mix I (21%), cocamidopropyl betaine (CAPB; 21%), and fragrance mix II (18%). The hair dye ingredient *p*-phenylenediamine and the fragrance ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) caused positive reactions in 9% and 6% of the tested patients, respectively. The preservatives quaternium-15 and formaldehyde, which is also a marker of contact allergy to formaldehyde releasers, caused positive reactions in 4% and 3% of the tested patients, respectively.

[FIGURE3]

On the basis of these test results, the causal relationships between the undesirable effects and specific cosmetic products were assessed. In cases where the allergen that tested positive was found to be an ingredient in the cosmetic product, a causal relationship between the reported reaction and the cosmetic product was assessed as being likely or very likely (Table 2). In those cases where the product did not contain the allergen that tested positive, a causal relationship was unlikely. However, a direct causal relationship between the positively tested allergen and the cosmetic product could not be confirmed in cases where the product ingredient lists were not provided and the dermatologist had not provided a clarification for the assumed causality. A causal relationship between the cosmetic product and the undesirable effect was not assumed in cases of positive test results for allergens, such as nickel sulfate, methylidibromo glutaronitrile (MDBGN), and cobalt chloride. These positive test results should be interpreted with caution, because these allergens are prohibited in cosmetic products under the Cosmetic Products Directive (76/768/EEC).

Dermatologists requested specific batch ingredients of cosmetic products used by 62 patients (38%). However, the NVWA was able to obtain the requested ingredients from the manufacturer for only 20 patients (32%). Fifteen patients (75%) tested positive for one or more batch ingredients, including surfactants/emulsifiers ($n = 7$), fragrance ingredients ($n = 4$), and preservatives ($n = 3$).

Three of the 15 patients who tested positive developed a reaction to copolymers/cross-polymers, including C30–38 olefin/isopropyl maleate/MA copolymer used in a sunscreen.

Diagnosis

On the basis of the medical history and the results of diagnostic patch testing, patients were most frequently diagnosed with allergic contact dermatitis (56%, $n = 86$) or a combination of allergic contact dermatitis and atopic dermatitis (19%, $n =$

29). Fourteen (9%) patients were diagnosed with a combination of allergic and irritant contact dermatitis. None of the patients was diagnosed with irritant contact dermatitis alone.

Causality assessment and notifications

Assessment of the relationship between undesirable effects and cosmetic products showed that causality was unlikely, questionable or unknown in 18% of cases (n = 30) reported by dermatologists, but was confirmed and assessed as likely in 52% of cases (n = 84) and very likely in 30% of cases (n = 49).

The RIVM notified the NVWA about a specific cosmetic product in six cases. In these cases, the RIVM had received a considerable number of reports on a specific batch of a cosmetic product, or the seriousness of the undesirable effects reported required the RIVM to alert the NVWA.

In response, the NVWA contacted the manufacturer or importer in The Netherlands to carry out an inspection of the safety dossier. The inspections did not lead to product withdrawals from the market. In one case, the manufacturer considered product reformulation.

[TABLE 2]

DISCUSSION

As cosmetic products have a global market, the CESES results were compared with the results from other cosmetovigilance systems in the EU. Cosmetovigilance systems are or have been operational in Norway, Sweden, Belgium, Denmark, Germany, France, and Italy (3, 15–21).

Cosmetovigilance systems vary with regard to: (i) the method of registration (voluntary or legal requirement); (ii) the participants (dermatologists, pharmacists, dentists, or consumers); and (iii) agencies responsible for the cosmetovigilance system (government, public health agency, consumer organisation, or industry). To the best of our knowledge, the CESES project is the first cosmetovigilance system that also includes a specific website dedicated to the collection of consumer reports.

Even though these reports are not validated by medical professionals, and are based on consumer perception, they provide insights into the occurrence of undesirable effects of cosmetic products, and are early signals for attention to a specific cosmetic product or ingredient. Since 2003, the Netherlands Pharmacovigilance Centre (Lareb) has also been accepting patient reports on undesirable effects of drugs. Lareb has recently reported that consumer reports provided a valuable contribution in addition to healthcare professional reports (22).

From the start of the CESES project in July 2009 until May 2011, the RIVM received more than 1600 reports (~ 73 reports/month) of undesirable effects of cosmetic products. From the reports of the sentinel GPs, it is estimated that 13 in 10 000 people or ~22 000 individuals in The Netherlands (considering 16.7 million registered inhabitants) consult a GP about undesirable skin effects attributed to cosmetic products. Consumer reports showed that, in 38% (n = 494) of the cases, a GP was consulted, implying that, annually, some 60 000 people in The Netherlands

have an undesirable reaction attributable to a cosmetic product. This is probably an underestimation, because, in most cases, consumers do not consult a GP or dermatologist, as most reactions to cosmetic products are not severe, and disappear soon after discontinuation of product use or after self-treatment.

However, consumers tend not to consult a health professional even in cases of severe reactions. This was indicated by a survey conducted at the request of the Council of Europe in 2002–2005, showing that only 25–36% of people consult a GP if they experience highly undesirable effects (6). The problem of undesirable effects caused by cosmetic products is also underestimated, as not every consumer is willing to report. To encourage consumers to register undesirable effects, the CESES project included a public awareness campaign, and each media activity resulted in a direct increase in the number of consumer reports.

A considerable number of people reported suffering from an underlying allergy (20–39%) or a skin disease (15–26%). These percentages are higher than reported in the review of Wijnhoven et al. (23), possibly because undesirable reactions to cosmetic products occur more frequently in patients with contact dermatitis or atopic dermatitis (24). Moreover, people with an underlying allergy or skin disease may also be more inclined to report undesirable effects on a website or seek medical attention for further diagnosis.

The four most frequently reported cosmetic products were moisturisers, make-up, hair care products, and soaps. Eye contour creams and non-perfumed ointments constituted a specific subcategory of moisturisers frequently registered by consumers and dermatologists, respectively. Reports on moisturisers as a frequent cause of undesirable effects are in line with the findings of other cosmetovigilance systems (3, 6, 15, 17, 25–27). Most undesirable effects of make-up concerned products for use on or around the eyes and eyelids, which is in accordance with other studies (24, 25). As in other monitoring systems (3, 15, 17, 21, 24, 26), most undesirable effects were reported in women, and this may be explained by the fact that women have a high level of use of cosmetic products. In addition, cosmetic products are often associated with products such as make-up and skin cream, which are principally used by women. Women are also more inclined to seek medical attention and report health effects. Furthermore, skin sensitisation and allergic contact dermatitis are more common in women (24, 26, 28, 29).

Of the patients patch tested with the European baseline series, the largest group (23%, $n = 34$) reacted to isothiazolinones [MI or a mixture of methylchloroisothiazolinone (MCI) and MI]. In 47% of these cases (16/34), isothiazolinones were found to be the causal link between the undesirable effect and the cosmetic product (Table 2).

MI, MCI and MCI/MI are potent sensitisers that are widely used as preservatives in consumer products, such as household cleaning products and cosmetic products (23, 30, 31). The MCI/MI mixture (in a 3:1 combination) is permitted in cosmetic products up to a maximum concentration of 0.0015%, and the maximum permitted concentration of MI is 0.01% (1, 32). Since 2005, MCI/MI has often been replaced by MI alone to reduce the prevalence of allergic contact dermatitis caused by preservatives. As MI is a weaker preservative, there usually needs to be another preservative, such as phenoxyethanol, which is a rare allergen that is especially used in skin care products (9). Recent case reports have shown that MI alone can also

induce allergic contact dermatitis (31, 33, 34). The combination of allergenic potency and frequent use in consumer products means that MI and MCI/MI exposure carries a high risk for the development of allergic contact dermatitis (35) especially occupational dermatitis (31, 35). The results of the CESES project and other studies (31, 34, 36–38) indicate a need for close monitoring of the prevalence of MI-induced allergic contact dermatitis. A recent study (39) showed that a considerable number of patients reacted to an MI concentration 20 times lower than permitted in cosmetic products, and has recommended that the permitted MI concentration in cosmetic products be reduced under the Cosmetic Products Directive (76/768/EEC).

Fragrances are known allergenic substances present in cosmetic products (9, 27, 40). Estimates show that 1.0–4.2% of the general population are sensitised to fragrance ingredients, and fragrance allergy is, in addition to allergy to preservatives, a frequent cause of undesirable effects of cosmetic products (41, 42). In the CESES project, 21% of patients subjected to a patch test reacted to fragrance mix I, and 18% had a positive reaction to fragrance mix II. It is known that false-positive reactions to fragrance mix I and fragrance mix II are common.

In this regard, it is important to note here that, in most cases of a positive reaction to fragrance mix I or fragrance mix II, further breakdown testing with a fragrance series, including the separate ingredients of the two mixes, was performed. The diagnosis of fragrance allergy was based not only on a positive reaction to fragrance mix I or fragrance mix II, but also on the medical history and the reaction to individual fragrance ingredients and markers.

In the CESES pilot project, 6% ($n = 9$) of patients tested with the European baseline series were found to be positive for the fragrance ingredient HICC. Recently, the Scientific Committee on Consumer Safety (SCCS) reported that HICC has been shown to be the cause of a considerable number of cases of allergic contact dermatitis since 1999 (43). On the basis of this information, the SCCS recommended that the use of HICC in consumer products be discontinued.

Interestingly, even though fragrances are used in a variety of cosmetic products, including moisturisers, soaps, deodorants, and perfumes, there were few reports of the product category perfumes containing fragrance ingredients as a potential cause of an adverse reaction.

Possibly, consumers are aware of the allergenic potential of perfumes, and spray the product on their clothes rather than directly on the skin. Another explanation is that the exposure via scented creams and lotions is higher than that via perfumes.

The positive reaction to CAPB in 21% ($n = 32$) of patients tested with the European baseline series should be interpreted with caution. CAPB is a synthetic detergent that is widely used in cosmetic products such as shampoos, conditioners, and make-up removers (44, 45). The sensitizing properties of CAPB are subject to a scientific debate. A recent study found that patch testing with CAPB produced a large number of false-positive reactions to CAPB (46). The results of patch tests with specific product ingredients showed that 3 of 15 positively tested patients developed a reaction to co-polymers/cross-polymers, including C30–38 olefin/isopropyl maleate/MA copolymer used in a sunscreen. Co-polymers/cross-polymers are used in cosmetic products because of their film-forming, viscosity-increasing, skin-conditioning, emulsion-stabilizing and hair-fixing properties (32, 47). However, the allergenic properties of these substances are as yet unknown. The CESES results are

in line with a recent study (48) that described several cases of allergic contact dermatitis attributable to a co-polymer in a sunscreen product. The sensitising component in copolymers/ cross-polymers has not been identified, and further investigation of their allergenic potential is required (7, 47).

The positive test results for nickel sulfate, MDBGN and cobalt chloride should be interpreted with caution, because the use of these allergens in cosmetic products is prohibited. The positive results could be the consequence of historical exposure. However, traces of nickel may occur in decorative cosmetics and application tools, such as mascara brushes. A more likely cause of nickel allergy is jewellery. In 2007, a prohibition on MDBGN in cosmetics was incorporated in the Cosmetic Products Directive (76/768/EEC), and, since June 2008, products containing MDBGN have no longer been on the market.

However, MDBGN exposure via cosmetic products may result from the use of products manufactured before the prohibition. MDBGN is still used in other consumer products.

It would have been interesting to further investigate the collected consumer reports by offering diagnostic patch testing. Unfortunately, the current study setup did not allow for this. In a further study, this option could be considered.

Overall, the CESES pilot project has been shown to provide valuable information on the symptoms and the localisation of undesirable effects of cosmetic products.

Moreover, the project has contributed to the identification of products and product ingredients that cause undesirable effects. In our opinion, a cosmetovigilance system is an important tool to obtain information on the safety of cosmetic ingredients that could be used to assess whether current EU legislation on cosmetics provides adequate protection.

On the basis of the experience gained and the positive evaluation of CESES as a tool for monitoring undesirable effects of cosmetic products, the Netherlands Food and Consumer Product Safety Authority and the Ministry of Health, Welfare and Sport have decided to continue registration of undesirable effects in 2012. During this time, the potential for establishing a European cosmetovigilance network will be explored to stimulate further exchange of information between cosmetovigilance systems in Europe.

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¹ See also www.nivel.nl.

² www.cosmeticaklachten.nl. (in Dutch)

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TABLES AND FIGURES

Table 1. Characteristics of participants in the Consumer Exposure, Skin Effects and Surveillance project

Route	Participants	Number of included reports	Sex (%)		Mean age in years (range)	% underlying skin disease	% underlying allergy
			Male	Female			
Public route	Consumers	1294	9	91	41 (0–92)	26	39
Clinical route	General practitioners	153	18	82	41 (0–86)	25	20
	Dermatologists	163	22	78	40 (6–86)	15	32

Fig. 1. Localisation of undesirable reactions to cosmetic products reported by consumers, sentinel general practitioners, and dermatologists.

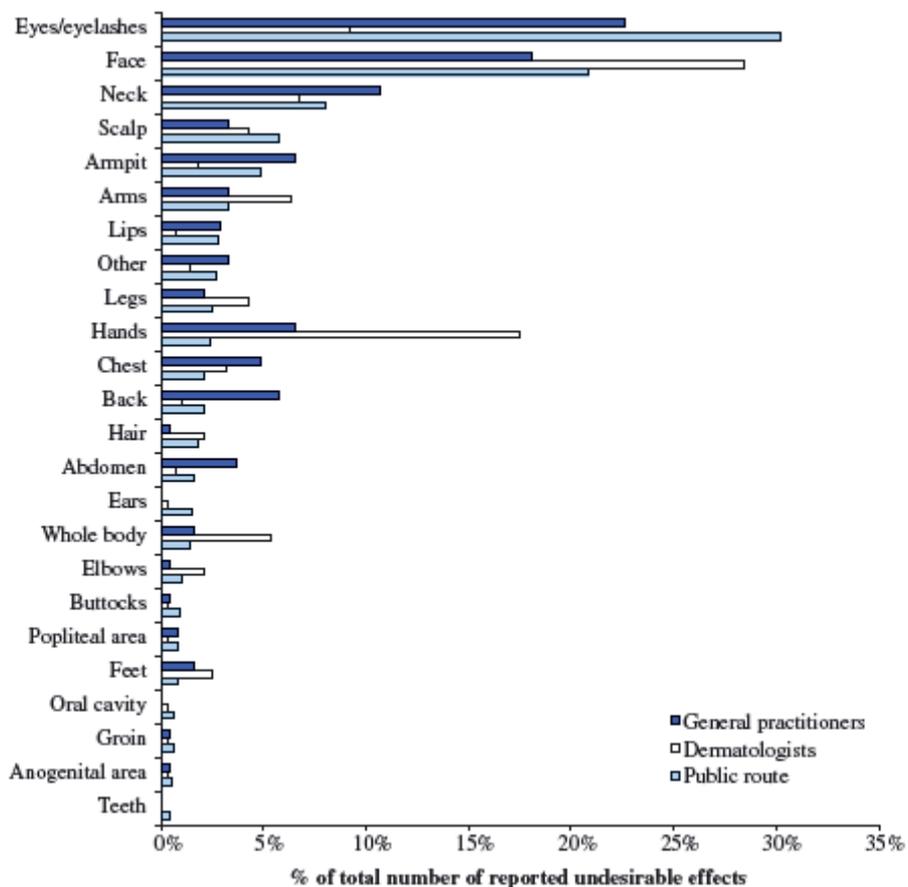


Fig. 2. Undesirable reactions to cosmetic products reported by consumers, sentinel general practitioners, and dermatologists.

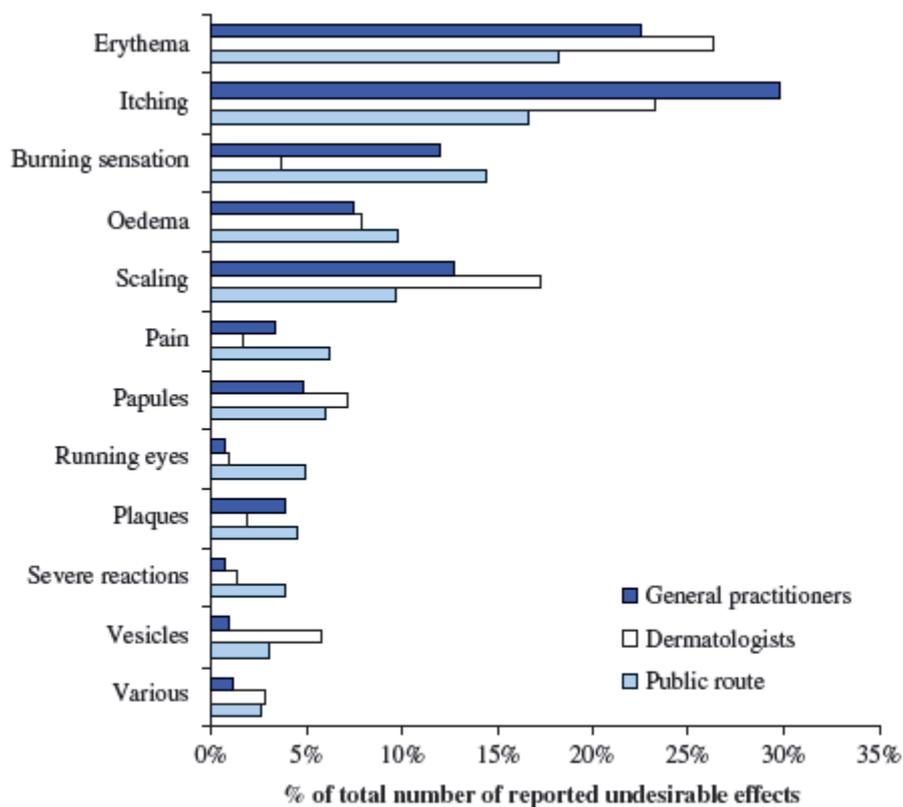


Fig. 3. Product categories reported to cause undesirable effects registered by consumers, general practitioners, and dermatologists.

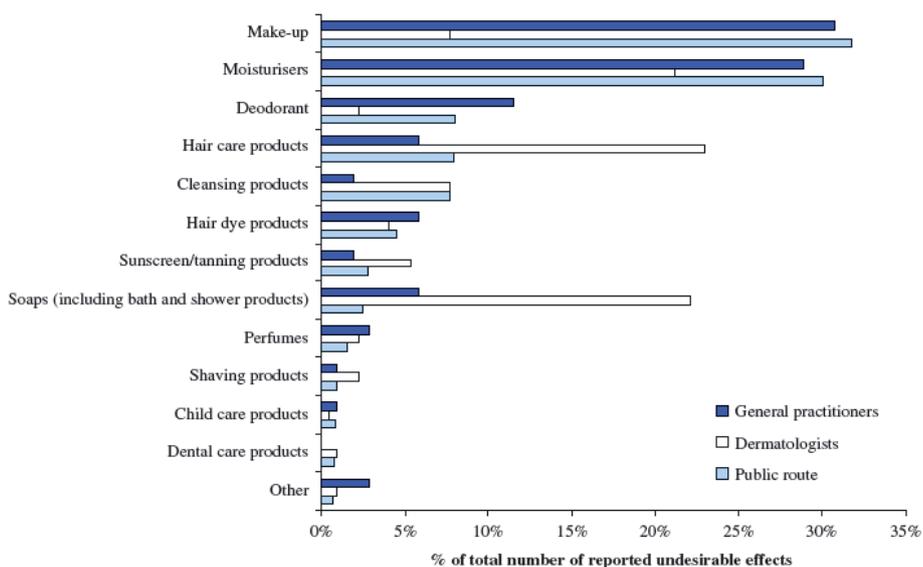


Table 2. Allergens in the European baseline series (plus some additional substances) to which participants tested positive

Allergen	Causality assessment			% that could not be confirmed (n)
	% of patients who tested positive (n)	% likely or very likely (n)	% unlikely (n)	
Isothiazolinones (MI or MCI/MI mix)	23 (34)	47 (16)	53 (18)	0 (0)
Fragrance mix I	21 (31)	52 (16)	29 (9)	19 (6)
Cocamidopropyl betaine	21 (32)	63 (20)	25 (8)	13 (4)
Nickel sulfate*	20 (30)	NA	NA	NA
Fragrance mix II	18 (27)	41 (11)	37 (10)	22 (6)
Methyldibromo glutaronitrile*	13 (20)	NA	NA	NA
<i>p</i> -Phenylenediamine	9 (13)	38 (5)	46 (6)	15 (2)
Colophonium	7 (10)	10 (1)	50 (5)	40 (4)
Cobalt chloride*	7 (10)	NA	NA	NA
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	6 (9)	67 (6)	11 (1)	22 (2)
Quaternium-15	4 (6)	17 (1)	50 (3)	33 (2)
Formaldehyde	3 (5)	20 (1)	20 (1)	60 (3)

MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NA, not assumed.

Data are presented as percentages of the total number of patients who tested positive (n = 151).

*Ingredients prohibited in cosmetic products in Europe.