

Developing a cosmetic series - results from the ESSCA network, 2009 – 2018

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Conflict of Interests

MLAS received travel reimbursement from the cosmetic industry and cosmetic industry associations. The IVDK, maintained by the IVDK e.V., of which J. Geier is an employee, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. WU has accepted honoraria for presentations or travel reimbursement from cosmetic industry associations and has received lecture fees from dermatology-related sponsors for educational lectures on contact allergy. SMW has received travel reimbursement to attend meetings with the cosmetic industry. VM declares no conflict of interest. The views expressed in this paper are the personal views of the author as an expert in the field and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authorities, the European Medicines Agency, or one of its committees or working parties. The other authors declare no COI.

Abstract

Background

There is considerable variability across European patch test centres as to which allergens are included in local and national cosmetics series.

Objectives

To propose a standardised, evidence-based cosmetic series for Europe based on up-to-date analysis of relevant contact allergens.

Methods

We collated data from the European Surveillance System on Contact Allergies (ESSCA) from 2009-2018 to determine which cosmetic allergens produce a high yield of contact allergy. Contact allergens with a prevalence of >0.3% that were considered relevant were included. Rare contact allergens were excluded if deemed no longer relevant or added to a supplemental cosmetic series for further analysis.

Results

Sensitisation prevalence rates of 39 cosmetic contact allergens are tabulated. Thirty of these allergens yield >0.3% positive reactions and are therefore included in our proposed European Cosmetic Series. Six are considered no longer relevant and therefore excluded. Three are included in a supplementary European cosmetic series. An additional 9 allergens are included in either the core or supplemental European cosmetic series following literature review.

Conclusion

We have derived a potential European cosmetic series based upon the above methods. This will require ongoing investigation based upon the changing exposure profiles of cosmetic allergens as well as new and evolving substances.

Key words: contact allergy; cosmetic; Europe; patch testing; preservative; antioxidant; emollient; antiseptic; emulsifier; surfactant

1. Introduction

Many chemicals used within cosmetic products are potent contact allergens. Contact dermatitis secondary to cosmetics is common. It frequently affects the face and can have a significant impact upon quality of life.¹ The appropriate identification of relevant cosmetic allergens is therefore of great importance.

Patients who report a presumed allergy to cosmetics may in fact suffer from 'sensitive skin'. This is a separate entity defined as 'the occurrence of unpleasant sensations (stinging, burning, pain, pruritus and tingling sensations) in response to stimuli that normally should not provoke such sensations'.² It is not immunologically driven and should not be confused with allergic contact dermatitis.

While trends, geographical differences and subgroup analyses with the allergens of the (European) baseline series have been a prior focus, another previous analysis has addressed patch testing beyond the baseline series, namely, by analysing results with a "rubber series".^{3 4 5} Following this example, the present analysis includes allergens which are part of various "cosmetic series" from centres in the ESSCA.⁶

There is significant variation across Europe with regards to cosmetic series. Some countries have nationally agreed cosmetic series but individual centres may patch test with different allergens. In addition, recent results suggest that frequently tested cosmetic allergens have a low yield of positive reactions or are of historical interest only.⁷ There is a need to develop an evidence-based cosmetic series to standardise the test substances, thereby improving diagnosis whilst maintaining cost effectiveness.⁶

This article reviews current results across Europe from centres contributing to ESSCA with regards to cosmetic patch test series. We aim to collate information on the prevalence of contact allergy as well as reviewing relevant literature with a view to recommending a potential European cosmetic series.

2. Methods

The primary aim of this study is to determine the frequency of reactions to cosmetic contact allergens not already included in the European baseline series 2019 which are tested as part of local or national cosmetic series in European dermatological centres.⁸ The secondary aim is to propose a European patch test cosmetic series. To achieve the primary aim, we analysed the database of the European Surveillance System on Contact Allergies (ESSCA) (www.essca-dc.org) in order to determine the frequency of contact allergy to individual cosmetic allergens.

The ESSCA is a working group of the European Society of Contact Dermatitis (ESCD; <www.escd.org>) dedicated to the clinical surveillance of contact allergy.⁹ Many ESSCA participants only contribute results within the baseline series, along with pertinent demographic and clinical data, in accordance with the initial objective of ESSCA. However, some ESSCA participants collect the full scope of their patch test results. These departments use a patch test software capable of flexibly recording evolving versions of various test series, including cosmetic series, such as the WinAlldat/IVDK software used by the IVDK network, the multilingual WinAlldat/ESSCA sister version of that software, or, in the case of the British Society of Cutaneous Allergy (BSCA), a differently structured, MS Access-based relational database management system.¹⁰ Therefore, the present analysis only includes results from departments (i) using this, or equivalent, software and (ii) actually documenting the full scope of patch testing. As the only exception to this rule, results from Coimbra, Portugal, with a baseline series extended by a large number of allergens within the scope of the present analysis, were also included.

The departments included, along with some basic information such as the number of tests performed in the 10-year study period, are shown in Table 1. Following national network standards, data from these departments, as well as data from other departments not included for the reasons mentioned, are delivered in an anonymous format or a pseudonymised format, where the pseudonym cannot be related to actual personal data except in the contributing department itself. This difference is important because re-consultations of patients can be identified only with pseudonymised data, and eliminated to avoid duplicate counts of results. In the present analysis, the most recent consultation of each patient has been selected. Data were quality checked, providing an “internal report” for each contributing department for scrutiny and approval before pooling of the respective data. Data management and analysis was performed with the R software package (<www.r-project.org>; RRID:SCR_001905), version 3.6. For the calculation of 95% confidence intervals (CIs) to zero proportions the recently suggested approximation to an exact CI was used.¹¹

The purpose of the present analysis focuses on the importance of the various cosmetic allergens. Age- and sex-standardisation is normally employed to enable an unconfounded comparison across time or regions. This was deliberately not performed. However, crude prevalence rates were calculated, supplemented with exact (binomial) 95% CIs. Moreover, the share of doubtful and irritant reactions, respectively, was also calculated in order to obtain a fuller picture of the reaction spectrum to a certain allergen preparation. Regarding the scope of allergens included, “cosmetic allergens” could be understood to encompass all substances which are potentially used in cosmetics and are, in the EU, subjected to the EU Cosmetics Regulation (EC) No 1223/2009. However, as fragrances are an area of intense research, such as those 26 required to be labelled according to Cosmetics Regulation, these were not included in this analysis, although we acknowledge they are important cosmetic allergens.¹² Moreover, hair cosmetic ingredients were omitted, as they are a special sector of cosmetics dealt with separately, and recently reviewed.¹³ As UV filters usually, but not exclusively, cause photo contact allergy rather than contact allergy, results have not been collected by ESSCA, because results of photo patch tests are not available in this network.¹⁴ Conversely, some of the allergens included in the present list of cosmetic allergens may have been tested in a different context, that is, not a particular “cosmetic” test series, but a more general “preservatives” series or another special test series with partial overlap.

In order to propose a standardised European Cosmetic Series (our secondary aim), it was necessary to analyse the above information in the context of a literature search. Allergens within the European baseline series typically produce a frequency of >0.5-1% allergic reactions in those tested.¹⁵ In order to minimise the risk of missing relevant cosmetic allergens, we proposed a threshold for inclusion of 0.3% for a European cosmetic series. This threshold does not refer to consecutively tested patients, but to the (often large) subset with suspected cosmetic-related allergic contact dermatitis. Proven common contact allergens (based upon an equal to or higher than 0.3% share of positive reactions) qualified for inclusion within our proposed European cosmetic series. Contact allergens that yielded less than 0.3% positivity rate were scrutinised. A PubMed search was performed to highlight relevant publications pertaining to these allergens in order to determine their modern day relevance. We took into account the fact that certain substances may rarely produce contact allergy but are associated with a wide exposure profile; these allergens were still considered for inclusion. We also took into account the fact that exposure profiles may vary dependent on geography; therefore, we have highlighted allergens which provoke a high yield of reactions in certain countries for inclusion in a supplementary cosmetic series.

3. Results

ESSCA database analysis yielded information on cosmetic patch test allergens from 26 departments and covering seven countries across Europe (Table 1). Information regarding the frequencies of

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reactions to cosmetic allergens tested was collated from 6 countries (results from Portugal added to the overall results, where available) and this is summarised in Table 2. In this table we have highlighted the cosmetic allergens which can be considered more suited for inclusion within a supplementary cosmetic series and those which are probably no longer suitable for inclusion in a cosmetic series.

Online supplemental Table 3 shows the distribution of reaction strength from ?+ to +++ and those interpreted as irritant.

In addition, we have reviewed the relevance of cosmetic allergens in sunscreen, hairdressing and nail aesthetic products. We have recommended inclusion of important contact allergens in these particular groups within the proposed European cosmetic series. We have also considered emerging contact allergens with the potential to be of relevance to cosmetic contact dermatitis and have recommended inclusion in the supplementary cosmetic series.

4. Discussion

Allergens (haptens) to be included in a cosmetic series with >0.3% positive reactions during aimed testing, where the reactions were considered relevant over a wide geographic area were suggested for the proposed series. They are categorized into the following subsets: preservative, antioxidant, antiseptic, emollient, emulsifier/ surfactant/ vehicle and special functions (Hydroabietyl alcohol and shellac). Few other allergens were relevant for sun protection and nail aesthetics.

The listed preservatives are well known and important contact allergens in cosmetics.¹⁶ Antioxidants are increasingly used in cosmetics and the incidence of contact allergy to propyl gallate in particular is reported to have increased.¹⁷ Skin conditioning treatments can contain high concentrations of fatty alcohols such as cetearyl alcohol which is known to be a sensitizing emollient.¹⁸ Surfactants such as cocamide diethanolamine (DEA) and lauryl glucoside, and emulsifiers such as decyl glucoside are known contact allergens and are frequently implicated in facial contact dermatitis. The use of alkyl glucosides in cosmetic products is increasing. Recent studies have shown that the prevalence of alkyl glucoside induced allergic contact dermatitis is high and that concomitant reactions between different alkyl glucosides are common.¹⁹

The following allergens were scrutinized based upon a lower than 0.3% rate of positive contact allergy reactions. Following literature review, they have been classed as:

- 1) Relevant contact allergens and for inclusion in a European cosmetic series
- 2) Relevant and for inclusion in a supplementary cosmetic series
- 3) Not relevant and therefore not for routine testing.

4.1 Preservatives

Disodium EDTA 1% pet.

Disodium EDTA is a chelating agent used ubiquitously in many products including cosmetics and sunscreens. It is tested in local cosmetic series in centres across Europe and is part of a national cosmetic series in the United Kingdom.⁶ It is a known contact allergen.^{20 21 22 23} However, reports of contact allergy to disodium EDTA in cosmetics are relatively infrequent.^{24 25} Data from four European countries that test for this allergen demonstrate a low percentage of positive reactions (0.07% amongst a total of 7023 patients tested). It therefore does not seem appropriate to include disodium EDTA in a European cosmetic series.

4.2 Antioxidants

BHT 2% pet.

BHT is a toluene based ingredient used as a preservative in cosmetics. In 1990, Flyvholm et al. surveyed 1336 eczema patients patch tested with BHT and reported no positive reactions.²⁶ In 1998,

a report of contact dermatitis from tertiary-butylhydroquinone in hair dye was reported, with cross-sensitivity to BHA and BHT.²⁷ There are very few case reports in the literature of contact allergy with BHT in cosmetics. Eight countries in Europe report testing for this in either national cosmetic, local cosmetic or local baseline series.⁶ ESSCA data analysis from six countries demonstrates a 0.13% share of positive patch test reactions to BHT (n=29716 tested). Three of these countries report no positive reactions. We would therefore suggest that this is not included in a European Cosmetic Series.

Tocopheryl acetate 10% pet.

Tocopheryl acetate is the most common form of Vitamin E in commercial skin care products. The Mayo-Clinic published results from an analysis of patch test data to determine the incidence of allergic contact dermatitis from vitamin E.²⁸ 18 patients out of a total of 2950 (0.61%) had positive reactions to tocopheryl acetate 10% pet. They concluded that vitamin E was a relatively rare contact allergen. Five centres across Europe test for tocopheryl acetate in local cosmetic series.⁶ A low prevalence of positive reactions was demonstrated from recent ESSCA record (0.02% amongst a total of 4746 patients). It would therefore seem reasonable to omit tocopheryl acetate from a European cosmetic series. However, given the widespread use of Vitamin E in cosmetic products, together with the reaction rates reported in previous publications, we suggest it is included in a supplementary cosmetic series for further investigation and clarification of its importance.

4.3 Antiseptics

p-Chloro-m-cresol 1% pet.

p-Chloro-*m*-cresol is a phenolic preservative that is used in disinfectants as well as in personal care products. On review of the literature, reports of contact allergy to *p*-chloro-*m*-cresol relate to its use in steroid creams and more historically, to chlorocresol preserved heparin.^{29 30 31} Contact urticaria has also been described.^{32 33 34} There is no recent data confirming its role in cosmetic related allergy. *p*-Chloro-*m*-cresol 1% pet. is tested in local baseline or local cosmetic series of seven countries in Europe.⁶ A 0.21% prevalence of positive reactions (n=8706) to those tested within a baseline series has been found. No positive reactions occurred amongst 925 patients who were patch tested to *p*-chloro-*m*-cresol in a special series. We therefore recommend that this allergen is not included in a current European cosmetic patch test series.

4.4 Emollients

Stearyl alcohol 30% pet. and cetyl alcohol 5% pet.

Stearyl alcohol (synonym: n-octadecanol) is a fatty alcohol. It is used as an emulsifying agent in a variety of cosmetics as well as hair products. There is limited data in the literature although; stearyl alcohol has been implicated in allergic contact dermatitis caused by wet wipes as well as Efudix cream.^{35 36} Cetyl alcohol is an emollient and lubricant found in face creams and lotions. Very few cases of contact allergy to cetyl alcohol have been reported over the last two decades.^{37 38 39 40 41} Recently, Knijp et al. performed a retrospective analysis to investigate the prevalence of contact allergy with lanolin alcohol 30% pet., as well as a supplementary series containing other lanolin derivatives including cetyl alcohol 20% pet. and stearyl alcohol.⁴² A positive reaction rate of 0.90 % was found amongst a total of 215 patients tested to both cetyl alcohol and stearyl alcohol. This study population consisted of patients for whom there was a high suspicion of lanolin contact allergy and therefore the prevalence of positive reactions to one of its derivatives is likely to be higher than that normally reported.

20 centres in Europe report testing for cetyl alcohol in either national cosmetic or local cosmetic series. There is variation in the concentration of the vehicle from 5 to 30% petrolatum. ESSCA data reports a 0.25% rate of positive patch test reactions to stearyl alcohol (n=785). The number of positive reactions with cetyl alcohol 5% pet. in local series is 0% (n=2825). In light of the literature evidence and up to date ESSCA data, we suggest that stearyl alcohol 30% pet. and cetyl alcohol 5% pet. are tested as a combination - cetearyl alcohol 20% pet. - as opposed to separate constituents.

Panthenol 5% pet.

Panthenol (dexpanthenol), the alcohol analogue of panthothenic acid, is frequently included in moisturizers, wound-healing agents, and other cosmetics. According to ESSCA data, the average total number of positive reactions amongst patients patch tested to panthenol 5% pet. in local series across Europe was only 0.19% (n= 6360). This is largely based on data from the UK and Germany who report testing a higher number of patients (n= 4485 and 1735 respectively). However, the rate of positive reactions to panthenol amongst patients tested in other European centres is much higher, ranging from 0.4 to 20%. The total numbers of patients patch tested to panthenol 5% pet. in these centres are relatively low therefore these results may be misleading. On the other hand, this variation may reflect different exposure profiles across Europe.

Over the last two decades, there are only limited reports of individual cases of hypersensitivity reactions to panthenol 5% in the literature and these do not all necessarily relate to its use in cosmetic products.^{43 44 45 46 47 48}

However, a recent article by Fernandes et al. evaluated 2171 patients to determine the frequency of allergic contact dermatitis caused by panthenol 5% pet.; they report a frequency of 1.2% positive test results.⁴⁹ Amongst those patients in whom relevance could be traced, three cases were due to moisturizers.

In light of the above evidence, we recommend that this allergen is not routinely included in a European cosmetic series, but suggest that it is observed carefully and included in our supplementary series.

4.5 Emulsifier, surfactant, vehicle

Polysorbate 80 (TWEEN 80) 5% pet.

Polysorbate 80 (Polyoxyethylene-sorbitan-20-monooleate or TWEEN 80) is a solubilizing agent used in cosmetic products as well as medical preparations and as an additive in tablets.⁵⁰ Reports of its relevance as a contact allergen are becoming increasingly rare. Only one country reported testing for this according to ESSCA data; no positive reactions were demonstrated (n=717). We suggest that this agent is not included in the European cosmetic series.

Triethanolamine 2% pet.

Triethanolamine is used as an emulsifier in cosmetics and topical medicines. Lessmann et al. performed an analysis of patch test data from The Information Network of Departments of Dermatology (IVDK) in 2009. Of 85,098 patients who had been tested with triethanolamine 2.5% pet., 323 patients (0.4%) tested positive. However, the profile was thought to be irritant rather than allergic.⁵¹

There are cases of contact sensitivity to triethanolamine in sunscreens and shampoo but its relevance as a contact allergen in cosmetic products is less frequently reported (bearing in mind that photopatch and hair products are not to be included in a combined cosmetic series).^{52 53} 18 centres in Europe report testing for triethanolamine 2-2.25% pet.⁶ Analysis of positive patch tests from three of these countries demonstrate a positivity rate of 0.11% (n=5393). This is below our recommended threshold for inclusion in a European cosmetic series. However, in light of the prevalence of reports describing its sensitising potential in other products, we would remind clinicians to consider its inclusion if it is contained within the individual's own cosmetic, sunscreen or haircare products. We have therefore included this allergen in a supplementary series.

Propylene glycol 5% pet.

Results from a study by Mahler and Dickel looked at IVDK databases to identify important contact allergens in hand eczema.⁵⁴ A total of 56,170 patients were patch-tested between 2014 and 2018. They identified 6820 patients with hand eczema without occupational dermatitis. In this cohort, propylene glycol 20% water ranked 26th among the 30 most common contact allergens with a 1.1% positivity rate (n=5312). The use as dispersant and solvent in cosmetics, personal care products and household cleaners has often been suspected as clinically relevant exposure.

ESSCA data from three European countries suggests a variation in the relevance of propylene glycol 5% pet. as a contact allergen. Some departments report no positive reactions, whereas one country reports a 0.37% positivity rate (n= 2157). On the other hand, the majority of centres testing with propylene glycol 20% water reported a high positive reaction rate, averaging 1.16%. We recommend therefore that propylene glycol 20% water is included in the proposed European cosmetic series. However, patch test reactions to propylene glycol 20% water may cause irritant or false-positive reactions and should be interpreted with care; retesting with propylene glycol 5% pet. may be recommended in the individual case.⁵⁵

4.6 Further considerations

Allergens studied were not exhaustive and relevant allergens in a cosmetic series may include common sunscreen and hairdressing allergens, as well as those contained within nail cosmetics.

Sunscreen allergens

The European multicentre photopatch test study (EMCPPTS) Taskforce provided information on the relative frequency of both allergic contact dermatitis and photoallergic contact dermatitis to common allergens, many of which are ubiquitous in cosmetics.⁵⁶ The UV absorbers octocrylene, benzophenone-3 and butyl methoxydibenzoylmethane are frequently implicated in photoallergic contact dermatitis. These results are reflected by Gonçalo et al. in their recommendations for a European photopatch test baseline series.⁵⁷ Although benzophenone-3 is declining in use, octocrylene use in sunscreens is increasing over time. These three substances were also common inducers of allergic contact dermatitis, according to EMCPPTS data. Methylene bis-benzotriazolyl tetramethylbutylphenol is reported as a frequent cause of allergic contact dermatitis but this has been attributed to the role of the added surfactant decyl glucoside, which is already included in the proposed European Cosmetic Series.⁵⁸ In addition, benzophenone-4, an allergen permitted in sunscreens but mainly used in other cosmetics to prevent photodegradation has a high positive pick-up rate according to data from the UK and Ireland.⁵⁹

Based on the above literature, we propose including octocrylene, benzophenone-3, benzophenone-4 and butyl methoxydibenzoylmethane in our European Cosmetic Series.

Hairdressing allergens

Substances used in cosmetic treatments of hair may cause contact allergy and result in allergic contact dermatitis often involving the face. The majority will be relevant in the context of contact dermatitis in hairdressers and will be tested in the separate hairdressing series. Glyceryl monothioglycolate, however, may also cause contact allergy amongst consumers.^{60 61} Although acid perming is currently less fashionable it may still warrant continued monitoring and we have therefore added this to the supplementary series.

Nail aesthetic allergens

With regards to allergens in nail cosmetics, acrylates are frequently used and are an important cause of allergic contact dermatitis. The majority of reactions are associated with 2-hydroxyethylmethacrylate (HEMA). This is tested within the European Baseline Series.⁶²

Tosylamide/formaldehyde resin (TFR) is a thermoplastic resin which hardens as it dries and facilitates adhesion in the application of nail polish to nail. It is the main allergen responsible for contact dermatitis to conventional nail polish, classically causing eyelid dermatitis. It has been reported as positive in up to 6.6% of patch tests.^{63 64 65} We have therefore included this in the proposed European Cosmetic Series.

In addition, contact allergy to phthalic anhydride/trimellitic anhydride/glycols copolymer and adipic acid/neopentyl glycol/trimellitic anhydride copolymer in nail varnish are becoming increasingly relevant. This was first reported by Moffitt and Sansom in 2002.⁶⁶ Subsequent case reports of contact dermatitis to copolymers have highlighted their importance as an allergen in nail varnish.^{67 68} These copolymers have high molecular weights and the exact nature of the haptens involved is not yet

known.⁶⁹ We therefore recommend including this in a supplementary European Cosmetic Series for further review and analysis as routine testing has largely been undertaken in the UK and they are not available as commercial allergens.⁷⁰

Emerging cosmetic allergens

A recent paper highlighting updates to the British Society of Cutaneous Allergy Facial Series discussed new cosmetic ingredients and emerging facial allergens.⁵⁶ Ethylhexylglycerin, a fixative with antimicrobial properties, is used ubiquitously in cosmetic products and there are increasing reports of contact allergy.^{71 72 73} We have therefore included this allergen in the supplementary cosmetic series for further investigation.

Incorporating the above, a final list of allergens suggested to test routinely in those suspected of cosmetic allergy is shown in table 4 ('Proposed European Cosmetic Series') along with those allergens suggested for further study ('Supplementary European Cosmetic Series').

It will be important to validate this series and to continually review and update as new evidence emerges. The final sequence of allergens tested however should take into account the exposure profile of the individual. It may therefore be necessary to test a patient's own products (remembering that may give rise to false negative reactions due to the lower concentration of allergen in the product). We must also consider the fact that many cosmetic products contain fragrances which may, in addition, be allergens in 'natural' plant cosmetics.

Different exposure profiles with regards to cosmetic allergens in Europe may exist. A European cosmetic series should take this into account and could be supplemented by national cosmetic series dependent on local exposure. Allergens that are largely historic or not of current relevance should be avoided.

The allergens chosen for inclusion have predominantly been included on the basis of the frequency of reactions to them and presumed relevance. In further refining this series, patch test preparations should ideally be non-irritant to avoid misinterpretation. Referring to online supplemental table 3, patch test reactions in over 2% of patients were interpreted as being irritant to: propolis 10% pet., caprylyl gallate 0.3% pet., propylene glycol 20% water, cocamidopropyl betaine 1% water, oleamidopropyl dimethylamine 0.1% water, cocamide DEA 0.5% pet., lanolin alcohol plus paraffinum liquidum (amerchol L-101™) 50% pet., tertiary butylhydroquinone (TBHQ) 1% pet. and shellac 20% ethanol. It is therefore clear that some allergen preparations may require reformulation to reduce the risk of misinterpretation whilst maintaining the sensitivity of the test.

Conclusion

We propose a core European Cosmetic Series containing allergens of relevance that should be tested in all dermatology patch test centres on patients who present with suspected contact allergy to cosmetics. We have also constructed a separate list of supplementary allergens which are of potential but not definite relevance. These should be tested in all tertiary patch test centres as part of a cosmetic series and their relevance should then be closely observed and evaluated.

Table 1: Characteristics of departments* contributing at least 100 patch tests with a cosmetic series.

	Country	Department	Contribution	n(test)	n(test baseline)	n(test cosmetic)
1	AT	Graz	2009–2018	2400	2376	1492
2	CH	Basel	2009–2018	2346	2107	957
3	CH	Bern	2009–2018	3384	3321	2657
4	CH	Zürich & Luzern	2009–2018	6733	6368	5087
5	CH	Aarau	2014–2018	563	511	337
6	DE	Dortmund	2009–2018	1849	1555	1170
7	DE	Göttingen	2009–2018	1215	1153	906
8	DE	Kiel	2009–2018	2754	2613	2041
9	DE	Dresden	2009–2018	3365	2303	1515
10	DE	Jena	2009–2018	2551	2360	1766
11	DE	Mainz	2009–2018	491	466	260
12	DE	Osnabrück	2009–2018	3522	3383	2739
13	DE	Erlangen	2009–2018	3132	2766	2130
14	DE	Heidelberg	2010–2018	1927	1917	1379
15	DE	Hannover	2015–2018	1095	1019	931
16	DE	Bochum	2016–2018	960	838	834
17	ES	Barcelona	2009–2018	4284	4253	966
18	ES	Madrid	2009–2018	1337	1337	281
19	ES	Alicante	2009–2014	1303	1257	492
20	ES	Santiago de Compostela	2009	284	284	278
21	ES	Murcia	2010–2016	458	416	108
22	ES	León	2011–2016	901	153	352
23	NL	Groningen	2009–2018	3675	3232	2156
24	NL	Amsterdam	2009–2018	8634	8318	1930
25	PT	Coimbra	2017–2018	733	733	–
26	UK	Leeds	2009–2018	8707	8707	5869

*AT; Austria, CH; Switzerland, DE; Germany, ES; Spain, NL; The Netherlands, PT; Portugal, UK; United Kingdom

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Table 2: Substances that have been employed in a cosmetic series in at least one department in Europe. Patch test reactions to cosmetic allergens obtained in the contributing departments, stratified for country.

Allergen	Conc.	Context	AT	% pos	(95% CI)	CH	% pos	(95% CI)	DE	% pos	(95% CI)	ES	% pos	(95% CI)	NL	% pos	(95% CI)	UK	% pos	(95% CI)	total	% pos	95% CI
Preservative																							
Benzyl alcohol	1	Sp	1381	0.72	(0.35–1.33)	11566	0.27	(0.18–0.38)	14637	0.25	(0.18–0.35)	1141	0.35	(0.1–0.9)	1479	1.08	(0.62–1.75)	5861	0.27	(0.16–0.44)	36065	0.32	(0.26–0.38)
Chloroacetamide	0.2	Sp	1426	0.91	(0.49–1.55)	9023	0.49	(0.35–0.65)	14482	0.39	(0.29–0.5)	947	0.11	(0–0.59)	2164	0.18	(0.05–0.47)	2049	0.05	(0–0.27)	30091	0.4	(0.33–0.47)
Disodium EDTA	1	Sp	86	0	(0–3.42)	590	0.17	(0–0.94)	488	0.2	(0.01–1.14)	0	0		0	0		5859	0.05	(0.01–0.15)	7023	0.07	(0.02–0.17)
TBHQ (tert-Butylhydroquinone)	1	Sp	1335	1.2	(0.69–1.94)	8016	2.08	(1.78–2.42)	13789	2.34	(2.09–2.6)	0	0		0	0		4492	0.53	(0.34–0.79)	27632	1.91	(1.76–2.08)
2-Bromo-2-nitropropane-1,3-diol	0.5	B	1475	0.81	(0.42–1.42)	6391	0.89	(0.68–1.15)	9685	0.82	(0.65–1.02)	3199	0.69	(0.43–1.04)	3554	0.37	(0.19–0.62)	8707	0.51	(0.37–0.68)	33011	0.69	(0.6–0.78)
	0.5	Sp	540	0.93	(0.3–2.15)	4047	0.4	(0.23–0.64)	7466	0.5	(0.35–0.68)	45	2.22	(0.06–11.77)	62	3.23	(0.39–11.17)	0	0		12160	0.5	(0.38–0.64)
DMDM hydantoin	2 _a)	B	0	0		0	0		0	0		2421	1.16	(0.77–1.67)	0	0		3998	0.13	(0.04–0.29)	6419	0.51	(0.35–0.72)
	2 _a)	Sp	1352	0.59	(0.26–1.16)	8241	0.46	(0.33–0.63)	13665	0.37	(0.27–0.48)	339	0.29	(0.01–1.63)	64	0	(0–4.57)	3156	0.16	(0.05–0.37)	26817	0.38	(0.31–0.46)
Diazolidinyl urea	2	B	0	0		0	0		1353	0.22	(0.05–0.65)	5954	0.42	(0.27–0.62)	11632	0.77	(0.62–0.95)	8707	0.4	(0.28–0.56)	27646	0.55	(0.47–0.65)
	2	Sp	1298	1	(0.53–1.71)	7149	0.59	(0.42–0.79)	11017	0.51	(0.38–0.66)	1458	0.96	(0.53–1.61)	0	0		0	0		20922	0.6	(0.5–0.71)
Imidazolidinyl urea	2	B	75	0	(0–3.92)	15	0	(0–18.1)	1673	0.12	(0.01–0.43)	6043	0.36	(0.23–0.55)	11629	0.78	(0.63–0.96)	8705	0.22	(0.13–0.34)	28873	0.47	(0.4–0.56)
	2	Sp	1352	0.89	(0.46–1.55)	8240	0.42	(0.3–0.59)	12833	0.44	(0.34–0.58)	1479	0.95	(0.52–1.58)	0	0		0	0		23904	0.49	(0.41–0.59)
Iodopropynyl butylcarbamate	0.2	B	966	0.93	(0.43–1.76)	6667	1.35	(1.09–1.66)	11974	1.02	(0.85–1.22)	3800	0.42	(0.24–0.68)	8077	3.66	(3.27–4.1)	4893	0.22	(0.11–0.4)	36377	1.5	(1.37–1.63)
	0.2	Sp	878	1.94	(1.13–3.08)	4554	1.16	(0.87–1.52)	6945	1.57	(1.29–1.89)	23	4.35	(0.11–21.95)	52	1.92	(0.05–10.26)	3156	0.29	(0.13–0.54)	15608	1.22	(1.05–1.4)
Sodium metabisulfite	1	B	75	4	(0.83–11.25)	15	0	(0–18.1)	321	0.93	(0.19–2.71)	0	0		8078	6.04	(5.53–6.58)	8707	2.21	(1.91–2.54)	17557	3.98	(3.67–4.28)
	1	Sp	140	3.57	(1.17–8.14)	3582	3.82	(3.22–4.51)	2863	2.51	(1.97–3.16)	112	1.79	(0.22–6.3)	0	0		0	0		6697	3.23	(2.82–3.68)
Phenoxyethanol	1	B	0	0		197	1.02	(0.12–3.62)	794	0.13	(0–0.7)	342	0	(0–0.87)	8078	0.61	(0.45–0.8)	4537	0.04	(0.01–0.16)	13948	0.39	(0.29–0.5)
	1	Sp	77	1.3	(0.03–7.02)	390	0	(0–0.77)	1884	0.48	(0.22–0.9)	0	0		0	0		3156	0.06	(0.01–0.23)	5507	0.22	(0.11–0.38)
Sodium benzoate	5	B	0	0		0	0		0	0		0	0		0	0		3998	0.33	(0.17–0.56)	3998	0.33	(0.17–0.56)
	5	Sp	1148	0.52	(0.19–1.13)	7362	0.8	(0.61–1.03)	8979	0.39	(0.27–0.54)	0	0		0	0		0	0		17489	0.57	(0.47–0.7)
Sorbic acid	2	Sp	1351	0.3	(0.08–0.76)	8197	0.51	(0.37–0.69)	13710	0.73	(0.59–0.89)	921	0.11	(0–0.6)	2067	0.53	(0.27–0.95)	5869	0.15	(0.07–0.29)	32115	0.52	(0.44–0.6)
Antioxidant																							
BHA	2	Sp	1335	0.22	(0.05–0.66)	8013	0.47	(0.34–0.65)	13813	0.46	(0.36–0.59)	821	0.12	(0–0.68)	2090	0.1	(0.01–0.35)	5869	0.14	(0.06–0.27)	31941	0.36	(0.3–0.44)
BHT	2	Sp	1335	0	(0–0.22)	7986	0.19	(0.11–0.31)	13827	0.15	(0.09–0.23)	664	0	(0–0.45)	35	0	(0–8.2)	5869	0.05	(0.01–0.15)	29716	0.13	(0.09–0.18)
Propyl gallate	1	Sp	0	0		0	0		0	0		787	1.14	(0.52–2.16)	0	0		5869	0.58	(0.4–0.81)	6656	0.65	(0.47–0.87)
Caprylyl gallate	0.3	Sp	1327	2.41	(1.66–3.39)	8015	1.24	(1–1.5)	13824	2.07	(1.84–2.32)	65	9.23	(3.46–19.02)	266	7.52	(4.65–11.37)	0	0		23497	1.89	(1.72–2.07)
Tocopheryl acetate	10	Sp	0	0		0	0		0	0		256	0	(0–1.16)	0	0		4490	0.02	(0–0.12)	4746	0.02	(0–0.12)
Antiseptic																							
Methenamine (Hexamethylentetram	1	Sp	301	0	(0–0.99)	1739	0.58	(0.28–1.05)	3848	0.42	(0.24–0.67)	32	0	(0–8.94)	130	0.77	(0.02–4.21)	0	0		6050	0.45	(0.29–0.65)
	2	Sp	0	0		0	0		0	0		805	0.37	(0.08–1.09)	0	0		0	0		805	0.37	(0.08–1.09)
p-Chloro-m-cresol	1	B	0	0		0	0		0	0		0	0		0	0		8706	0.21	(0.12–0.33)	8706	0.21	(0.12–0.33)
	1	Sp	0	0		0	0		0	0		925	0	(0–0.32)	0	0		0	0		925	0	(0–0.4)
Chlorhexidine digluconate	0.5 _a)	Sp	1633	0.55	(0.25–1.04)	13859	0.45	(0.35–0.58)	16111	0.27	(0.19–0.36)	478	0.84	(0.23–2.13)	15	0	(0–18.1)	2483	0.04	(0–0.22)	35312	0.35	(0.29–0.42)
Triclosan	2	Sp	1352	0.44	(0.16–0.96)	8236	0.47	(0.34–0.65)	13711	0.4	(0.3–0.52)	915	0	(0–0.33)	28	0	(0–10.15)	2484	0.08	(0.01–0.29)	26726	0.38	(0.31–0.46)
Emollient																							
Lanolin (Amerchol L-101™)	50	B	0	0		0	0		1353	1.7	(1.08–2.54)	0	0		8939	7.15	(6.62–7.7)	8707	0.48	(0.35–0.65)	19732	3.63	(3.38–3.9)
	50	Sp	1335	5.47	(4.31–6.83)	7999	3.89	(3.47–4.33)	12972	3.72	(3.4–4.06)	900	0.89	(0.38–1.74)	708	13.84	(11.38–16.61)	2713	0.29	(0.13–0.58)	26627	3.68	(3.46–3.91)
Cetearyl alcohol	20	B	2367	1.06	(0.68–1.56)	12154	0.93	(0.77–1.12)	19660	0.95	(0.82–1.1)	0	0		0	0		8707	0.14	(0.07–0.24)	42888	0.79	(0.7–0.87)
	20	Sp	0	0		0	0		0	0		86	1.16	(0.03–6.31)	687	2.04	(1.12–3.4)	0	0		773	1.94	(1.09–3.18)
Stearyl alcohol	30	Sp	0	0		0	0		0	0		785	0.25	(0.03–0.92)	0	0		0	0		785	0.25	(0.03–0.92)
Cetyl alcohol	5	Sp	0	0		0	0		0	0		785	0	(0–0.38)	2040	0	(0–0.15)	0	0		2825	0	(0–0.13)
Panthenol (dexpanthenol)	5	Sp	5	20	(0.51–71.64)	88	2.27	(0.28–7.97)	1735	0.4	(0.16–0.83)	47	2.13	(0.05–11.29)	0	0		4485	0.02	(0–0.12)	6360	0.19	(0.1–0.33)
Propolis	10	B	2370	6.54	(5.58–7.61)	12196	4.17	(3.82–4.54)	19687	3.35	(3.1–3.61)	0	0		230	2.61	(0.96–5.59)	8707	0.95	(0.76–1.18)	43551	3.26	(3.09–3.43)
	10	Sp	0	0		0	0		25	12	(2.55–31.22)	476	1.05	(0.34–2.43)	611	3.11	(1.88–4.81)	0	0		1112	2.43	(1.61–3.51)
Emulsifier, surfactant, vehicle																							
Polysorbate 80 (TWEEN 80)	5	Sp	0	0		0	0		0	0		717	0	(0–0.42)	0	0		0	0		717	0	(0–0.51)
Sorbitan sesquioleate (SSO)	20	B	1681	1.55	(1.01–2.26)	3517	0.97	(0.67–1.35)	11104	0.84	(0.68–1.03)	0	0		8077	2.44	(2.11–2.8)	0	0		24379	1.44	(1.29–1.59)
	20	Sp	33	9.09	(1.92–24.33)	356	2.81	(1.36–5.11)	1455	2.13	(1.45–3.01)	1116	0.72	(0.31–1.41)	2037	0.88	(0.52–1.39)	5869	0.14	(0.06–0.27)	10866	0.72	(0.57–0.9)
Cocamide DEA	0.5	Sp	1335	1.35	(0.8–2.12)	8008	0.7	(0.53–0.91)	13790	0.64	(0.51–0.79)	0	0		0	0		4492	0.16	(0.06–0.32)	27625	0.61	(0.52–0.71)
Cocamidopropyl betaine	1 _a)	Sp	1334	1.57	(0.98–2.4)	8480	1.46	(1.22–1.74)	13680	1.89	(1.67–2.14)	426	0.23	(0.01–1.3)	2056	2.04	(1.48–2.75)	4489	0.02	(0–0.12)	30465	1.47	(1.34–1.61)
Oleamidopropyl dimethylamine	0.1 _a)	Sp	0	0		0	0		0	0		106	0.94	(0.02–5.14)	2319	1.98	(1.46–2.64)	4492	0.04	(0.01–0.16)	6917	0.71	(0.52–0.94)
Triethanolamine	2.5	Sp	1393	0.79	(0.39–1.41)	8202	0.24	(0.15–0.38)	14434	0.41	(0.31–0.53)	27	0	(0–10.5)	61	0	(0–4.79)	0	0		24117	0.37	(0.3–0.46)
	2	Sp	0	0		0	0		0	0		875	0.23	(0.03–0.82)	26	0	(0–10.88)	4492	0.09	(0.02–0.23)	5393	0.11	(0.04–0.24)
Decyl glucoside	5	B	0	0		0	0		0	0		0	0		230	2.61	(0.96–5.59)	1073	0.37	(0.1–0.95)	1585	0.77	(0.37–1.41)
	5	Sp	54	0	(0–5.4)	795	0.75	(0.28–1.64)	1236	1.7	(1.05–2.59)	232	0.43	(0.01–2.38)	0	0		2263	0.93	(0.58–1.42)	4580	1.07	(0.79–1.41)
Lauryl glucoside	3	Sp	0	0																			

Table 4: Allergens to be included in a European Cosmetic Series and a Supplementary European Cosmetic Series

Proposed European Cosmetic Series		Supplementary European Cosmetic Series	
Allergen	Conc.	Allergen	Conc.
Preservative			
Benzyl alcohol	1	Tocopheryl acetate	10
Chloroacetamide	0.2	Panthenol (dexpanthenol)	5
<i>TBHQ</i> (<i>tert</i> -Butylhydroquinone)	1	Triethanolamine	2.5
2-Bromo-2-nitropropane-1,3-diol	0.5	<i>Glyceryl thioglycolate</i>	1
DMDM hydanoin	2 _{a)}	<i>PTG* copolymer</i>	1
Diazolidinyl urea	2	<i>AA** copolymer</i>	1
Imidazolidinyl urea	2	Ethylhexylglycerine	5
Iodopropynyl butylcarbamate	0.2		
Sodium metabisulfite	1	*Phthalic anhydride/trimellitic anhydride/glycols copolymer	
Phenoxyethanol	1	**Adipic acid/neopentyl glycol/trimetallic anhydride copolymer	
Sodium benzoate	5		
Sorbic acid	2		
Antioxidant			
BHA	2		
Propyl gallate	1		
Caprylyl gallate	0.3		
Antiseptic			
Methenamine (Hexamethylenetetramine)	1		
Chlorhexidine digluconate	0.5 _{a)}		
Triclosan	2		
Emollient			
Lanolin (Amerchol L-101™)	50		
Cetearyl alcohol	20		
Propolis	10		
Emulsifier, surfactant, vehicle			
Sorbitan sesquioleate (SSO)	20		
Cocamide DEA	0.5		
Cocamidopropyl betaine	1 _{a)}		
Oleamidopropyl dimethylamine	0.1 _{a)}		
Decyl glucoside	5		
Lauryl glucoside	3		
Propylene glycol	20 _{a)}		
Special functions			
Hydroabietyl alcohol (Abitol)	10		
Shellac (natural resin)	20		
Sunscreen allergens			
<i>Benzophenone-3</i>	10		
<i>Benzophenone-4</i>	10		
<i>Octocrylene</i>	10		
<i>Butyl methoxydibenzoylmethane</i>	10		
Allergens in nail aesthetics			
<i>Tosylamide /formaldehyde resin (TFR)</i>	10		

All allergens in pet., except where indicated otherwise: a), water; b), ethanol.
Additional allergens relevant to sunscreen, hairdressing and nail aesthetics highlighted in italics

Allergen	Conc.	Context	n(test)	% +	% ++/+++	% ?+	% IR	% pos.	(95% CI)
Preservative									
Benzyl alcohol	1	Sp	36065	0.27	0.05	0.91	0.98	0.32	(0.26–0.38)
Chloroacetamide	0.2	Sp	30091	0.27	0.15	0.41	0.33	0.4	(0.33–0.47)
<i>TBHQ</i> (<i>tert</i> Butyl hydroquinone)	1	Sp	27632	1.3	0.89	2.84	2.41	1.91	(1.76–2.08)
2-Bromo-2-nitropropane-1,3-diol	0.5	B	33011	0.54	0.21	0.84	0.71	0.69	(0.6–0.78)
	0.5	Sp	12160	0.42	0.08	0.57	0.46	0.5	(0.38–0.64)
DMDM hydantoin	2 ^{a)}	B	6419	0.25	0.91	0	0.04	0.51	(0.35–0.72)
	2 ^{a)}	Sp	26817	0.34	0.07	0.75	1.12	0.38	(0.31–0.46)
Diazolidinyl urea	2	B	27646	0.51	0.12	0.53	0.01	0.55	(0.47–0.65)
	2	Sp	20922	0.45	0.15	0.65	0.41	0.6	(0.5–0.71)
Imidazolidinyl urea	2	B	28873	0.45	0.14	0.45	0.01	0.47	(0.4–0.56)
	2	Sp	23904	0.41	0.08	0.59	0.59	0.49	(0.41–0.59)
Iodopropynyl butylcarbamate	0.2	B	36377	1.52	0.17	2.93	0.46	1.5	(1.37–1.63)
	0.2	Sp	15608	1.32	0.14	3.36	1.53	1.22	(1.05–1.4)
Sodium metabisulfite	1	B	17557	5.27	0.55	2.07	0.02	3.98	(3.69–4.28)
	1	Sp	6697	2.21	1.02	1.51	0.73	3.23	(2.82–3.68)
Phenoxyethanol	1	B	13948	0.52	0.03	1.62	0.01	0.39	(0.29–0.5)
	1	Sp	5507	0.43	0	1.67	1.01	0.22	(0.11–0.38)
Sodium benzoate	5	B	3998					0.33	(0.17–0.56)
	5	Sp	17489	0.49	0.08	1.04	1.73	0.57	(0.47–0.7)
Sorbic acid	2	Sp	32115	0.51	0.09	0.8	0.53	0.52	(0.44–0.6)
Antioxidant									
BHA	2	Sp	31941	0.35	0.07	0.68	1.36	0.36	(0.3–0.44)
Propyl gallate	1	Sp	6656	0	1.14			0.65	(0.47–0.87)
Caprylyl gallate	0.3	Sp	23497	1.7	0.18	8.57	7.82	1.89	(1.72–2.07)
Antiseptic									
Methenamine (Hexamethylentetramine)	1	Sp	6050	0.31	0.13	0.7	1	0.45	(0.29–0.65)
	2	Sp	805	0.25	0.12			0.37	(0.08–1.09)
Chlorhexidine digluconate	0.5 ^{a)}	Sp	35312	0.33	0.04	0.76	1.31	0.35	(0.29–0.42)

Triclosan	2	Sp	26726	0.32	0.09	0.95	0.75	0.38	(0.31–0.46)
Emollient									
Lanolin (Amerchol L-101™)	50	B	19732	6.15	0.28	4.93	0.07	3.63	(3.38–3.9)
	50	Sp	26627	3.5	0.56	3.03	3.33	3.68	(3.46–3.91)
Cetearyl alcohol	20	B	42888	0.68	0.27	1.16	0.71	0.79	(0.7–0.87)
	20	Sp	773	1.68	0.26	3.31	0	1.94	(1.09–3.18)
Propolis	10	B	43551	3.06	0.79	3.71	3.1	3.26	(3.09–3.43)
	10	Sp	1112	1.53	0.9	6.96	0	2.43	(1.61–3.51)
Emulsifier, surfactant, vehicle									
Sorbitan sesquioleate (SSO)	20	B	24379	1.3	0.13	3.74	0.25	1.44	(1.29–1.59)
	20	Sp	10866	1.18	0.22	3.89	0.62	0.72	(0.57–0.9)
Cocamide DEA	0.5	Sp	27625	0.58	0.12	2.11	2.04	0.61	(0.52–0.71)
Cocamidopropyl betaine	1 ^{a)}	Sp	30465	1.59	0.13	3.71	5.84	1.47	(1.34–1.61)
Oleamidopropyl dimethylamine	0.1 ^{a)}	Sp	6917	1.86	0.08	2.41	3.49	0.71	(0.52–0.94)
Decyl glucoside	5	B	1585	1.3	1.3	4.35	0.43	0.95	(0.53–1.56)
	5	Sp	4580	0.99	0.22	2.18	0.35	1.07	(0.79–1.41)
Lauryl glucoside	3	Sp	4300	0.28	0.56			0.81	(0.57–1.13)
Propylene glycol	20 ^{a)}	Sp	28995	1.22	0.16	2.17	2.09	1.16	(1.04–1.29)
	5	Sp	3080	0.26	0	0.9	0.33	0.26	(0.11–0.51)
Special functions									
Hydroabietyl alcohol (Abitol)	10	Sp	6762	1.16	0.64	0.6	0.06	1.52	(1.24–1.84)
Shellac (natural resin)	20	Sp	83	0	1.2			1.2	(0.03–6.53)
	20 ^{b)}	Sp	3277	3.06	1.75	8	8	0.64	(0.4–0.98)

Online supplemental Table 3: Patch test reactions to cosmetic allergens obtained in the contributing departments. From the UK department (Leeds) and the PT department (Coimbra), only information on allergic vs. non-allergic reactions were available, hence these figures are not included in the detailed description of reaction grades; note that, thereby, percentages of + and ++/+++ reactions may or may not add up to total % positive. All allergens in pet., except where indicated otherwise: a), water; b), ethanol.