

Contact allergy to ingredients of topical medications: results of the European Surveillance System on Contact Allergies (ESSCA), 2009–2012

Wolfgang Uter^{1*}, Radoslaw Spiewak², Susan M. Cooper³, Mark Wilkinson⁴, Javier Sánchez Pérez⁵, Axel Schnuch⁶ and Marie-Louise Schuttelaar⁷

¹Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany

²Department of Experimental Dermatology and Cosmetology, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

³Department of Dermatology, Churchill Hospital, Oxford, UK

⁴Department of Dermatology, Chapel Allerton Hospital, Leeds, UK

⁵Department of Dermatology, Hospital Universitario la Princesa, Madrid, Spain

⁶Information Network of Departments of Dermatology (IVDK), University Medicine Göttingen, Göttingen, Germany

⁷Department of Dermatology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands

ABSTRACT

Purpose The aim of this study was to give an overview of the prevalence of contact allergy to active ingredients and excipients of topical medications across Europe.

Methods Retrospective analysis of data collected by the European Surveillance System on Contact Allergies (www.essca-dc.org) with substances applied to consecutively patch tested patients, 2009–2012, in 54 departments in 12 European countries.

Results In view of the varying composition of the baseline series used in the previously mentioned departments and countries, between 58 833 (lanolin alcohols) and 16 498 patients (sodium metabisulfite) were patch tested with the topical agents covered in this study. Among these, positive (allergic) reactions were most commonly observed to sodium metabisulfite (3.12% positive), followed by propolis (2.48%), Compositae mix (1.73%), lanolin alcohols (1.65%) and caine mix III (benzocaine, cinchocaine and tetracaine; 1.27%).

Conclusions Several of the substances warrant routine screening for contact allergy, i.e. patch testing in a baseline series. However, in view of a vast number of other topical agents, additional patch testing with the suspect topical drug preparations (including natural remedies and cosmetics) is warranted. In the event of a positive test to the (pharmaceutical) product, single ingredients should be tested individually to precisely identify the hapten(s). Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—contact allergy; adverse event; patch testing; clinical epidemiology; topical drugs; pharmacoepidemiology

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*Correspondence to: W. Uter, University of Erlangen/Nürnberg, Department of Medical Informatics, Biometry and Epidemiology, Waldstr. 4-6, 91054 Erlangen, Germany. E-mail: wolfgang.uter@fau.de

The following members of the European Surveillance System on Contact Allergies network contributed data to this analysis (in alphabetical order, by country): Austria: Werner Aberer, Graz; Switzerland: Andreas Bircher, Basel, Dagmar Simon, Bern, Barbara Ballmer-Weber, Zürich, Philip Spring, Lausanne; Germany: Peter Frosch, Dortmund, Thomas Fuchs, Göttingen, Jochen Brasch, Kiel, Andrea Bauer, Dresden, Peter Elsner, Jena, Swen Malte John, Osnabrück, Vera Mahler, Erlangen, Elke Weisshaar, Heidelberg AKS; Denmark: Jeanne Duus Johansen, Gentofte/Copenhagen; Spain: Ana Giménez Arnau, Barcelona IMAS, Javier Sánchez-Pérez, Madrid Princesa, Juan Fco. Silvestre, Alicante, Juan García-Gavín, Virginia Fernández-Redondo, Santiago de Compostela, José Carlos Amario-Hita, Cádiz, Pedro Mercader, Murcia, Inmaculada Ruiz, León; Finland: Riitta Jolanki, Maria Pesonen, Helsinki, Tapio

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INTRODUCTION

Topical medications encompass a heterogeneous group of sometimes complex products. Ingredients include the active ingredient as well as variable excipients such as preservatives, buffers, matrix components and fragrances, including natural extracts, and other plant materials. Alternative, so-called natural topicals and cosmetics may have an even more complicated formulation. Topical medications encompass a wide range of products, of which many are supplied without a prescription, including emollients, corticosteroid creams, antiseptics, antibacterial creams, haemorrhoid creams and anti-inflammatory creams. Thus, there is a wide variety of potential causes of allergic contact dermatitis, i.e. haptens. If a patient with contact dermatitis suspected to be due to such ingredients consults a dermatologist, which may not always be the case, the existence of contact allergy to one or more of the ingredients is usually assessed in a diagnostic patch test.¹ The aim is to identify the culprit hapten to enable the patient to avoid future skin or mucous membrane contact, and thus relapses of allergic contact dermatitis.

The vast majority of active ingredients or excipients is tested in an aimed fashion, i.e. only if actual exposure is suspected. Only a limited set of haptens is applied to all patients patch tested, irrespective of their history, in the so-called baseline series. Haptens are usually included in the baseline series if they have been shown to be reasonably common, e.g. with allergic reactions observed in at least 0.5–1% of consecutively tested patients,² and especially if exposure is not easily suspected based on the patient's history. Such routine application, in consecutive patients, allows comparisons between the frequencies of contact allergy to different ingredients, as it is independent from the suspicion of the attending dermatologist, which may vary considerably.

The aim of this study is to investigate the prevalence of positive patch tests to the main constituents of topical medications as determined by routine diagnostic data from 12 European countries. Differences between national data will be presented, discussing findings against previous results, and exposure or regulatory information, as far as available and appropriate. Besides the substances considered here, other excipients may act as haptens, namely preservatives and fragrances. Results with these have been published elsewhere (A. Giménez Arnau, in preparation, and Frosch, Johansen and Schuttelaar³).

METHODS

The retrospective analysis is based on routine clinical data collected by the European Surveillance System on Contact Allergies (ESSCA, www.essca-dc.org) network.⁴ Briefly, clinical and demographic data, along with patch test results, of all patients patch tested in the departments participating in ESSCA for suspected allergic contact dermatitis are documented electronically in local departments. The departments use diverse data capture software and partly the multilingual software WinAlldat/ESSCA provided by ESSCA.⁵ Standardized patch testing follows international recommendations.¹ The anonymized data delivered by the participating departments are pooled in the ESSCA data centre in Erlangen for further analysis,⁶ using R (version 3.1.3) software.⁷ Considering the fact that all individual identifiers were removed from the collected data, and no quasi-unique profiles, but only aggregated results are reported, such pooled analysis was deemed compliant with European data protection requirements. Pertinent guidelines for the statistical analysis of patch test data^{8,9} were considered. The maximum patch test reaction between day 3 and day 5 (inclusive) was aggregated as patch test outcome. Reactions designated as either weak, strong or extreme positive, the symbols being +, ++ and +++, respectively, were classified as allergic, the remainder as non-allergic. The study period was January 2009 to December 2012, including 12 European countries

Table 1. Characteristics of the departments constituting the ESSCA network in 12 European countries

Country	N (depts.)	N (pats.)	% (male)	Age (5% p., Median, 95% p.)
Austria	1	1113	26.1 %	17; 48; 75
Denmark	1	2582	30.4 %	–; –; – ¹
Finland	2/1 ²	1057	37.9 %	20; 43; 67
Germany	8/2 ²	7628	40.4 %	21; 49; 77
Italy	6 ³	9267	33.4 %	5; 40; 74
Lithuania	1	865	19.5 %	21; 47; 78
Poland	3/1 ²	2828	28.9 %	19; 43; 69
Slovenia	6	5224	30.7 %	16; 44; 72
Spain	7	4257	31.7 %	18; 48; 79
Switzerland	4	4990	38.9 %	18; 49; 78
The Netherlands	2	4385	34 %	17; 43; 71
United Kingdom	13	15532	31.9 %	15; 44; 76
Overall	54	59728	33.4 %	15; 45; 75 ⁴

p., percentile of distribution.

¹Not calculable, as only aggregated data are available; the proportion of patients age 40 and above is 64.9%.

²Number of departments specialized in occupational dermatology after the slash.

³Including one purely paediatric dermatology department.

⁴Excluding Danish data.

and, in total, 54 departments (Table 1); for further details see Uter, Gefeller and Giménez-Arnau.⁴

The vast majority of departments used patch test systems in which the investigator loads the allergens in the test chambers. In the case of active ingredients and excipients considered here, all haptens are dispersed in petrolatum; for concentrations used see Table 2. Test results with the TRUE Test®, a pre-loaded test system using a hydrocellulose matrix for the haptens instead of petrolatum, are presented separately, because at least concerning some haptens,¹⁰ this test system is not considered equivalent to investigator-loaded systems. Altogether, 59 728 patients tested with the baseline series were analysed. In 2435 of these, patch tests with the TRUE Test were performed; for further details, see Uter, Gefeller and Giménez-Arnau.⁴

Concerning patch test haptens, the Compositae mix represents important haptens of this plant family, which are sometimes used in herbal topical medications, but which are also relevant from direct contact

with the plants when gardening or in an occupational context. The Compositae mix is an extract from flowers of *Arnica montana*, *Chamomilla recutita* L., *Tanacetum parthenium* L. and from leaves of *Tanacetum vulgare* L. and *Achillea millefolium*, referring to the 6% preparation from Almirall/Hermal/Trolab.¹¹ The Compositae mix from Chemotechnique (5% as well as 2.5% pet.) contains *Tanacetum vulgare* L., *Arnica montana*, *Anthemis nobilis*, *Chamomilla recutita* L. and *Achillea millefolium* extracts with 0.1% and 0.05% parthenolide added, respectively.¹²

RESULTS

Table 2 provides an overview of the overall patch test results with ingredients of topical preparations in the ESSCA network. As a representation of indications for topical use, the ATC codes (http://www.whocc.no/atc_ddd_index/, last accessed 21 June 2016) are shown for the active ingredients. A subdivision of test results by country is shown in Table S1 in the

Table 2. Overall results with the haptens used as active ingredient or excipient in topical medications, and partly in cosmetics

Hapten	ATC code(s)	Conc.	nr(test)	%					95% CI
				+	++/ +++	?+/ IR	pos.	pos. std.	
Benzocaine	A01AE53, C05AD03, D04AB04, R02AD01	5%	24 670	0.28	0.44	0.11	0.72	0.65	(0.55-0.75)
Caine Mix III (benzocaine, cinchocaine and tetracaine)	As above, +A01AE02, C05AD02/-04, D04AB02/-06, S01HA03/-06, S02DA04	10%	16 131	0.89	0.38	0.50	1.27	1.22	(1.05-1.39)
Budesonide	D07AC09, R01AD05, R03BA02	630 µg/cm ²	469	0.43	1.71	0	2.13	2.03	(0.55-3.51)
		0.01%	7794	1.09	0.41	2.34	1.5	1.56	(1.27-1.85)
		0.1%	21 455	0.29	0.13	0.09	0.42	0.43	(0.34-0.52)
		1 µg/cm ²	2519	0.24	0.32	1.14	0.56	0.55	(0.25-0.85)
Tixocortol-pivalate	R01AD07	0.1%	11 962	0.39	0.35	0.46	0.74	0.73	(0.58-0.88)
		1%	23 542	0.61	0.40	0.23	1.00	0.94	(0.82-1.06)
		3 µg/cm ²	2519	0.44	0.12	0.64	0.56	0.5	(0.24-0.77)
Bufexamac	D04AX03, M02AA09	5%	13 591	0.44	0.32	1.16	0.77	0.81	(0.64-0.98)
Clioquinol	D08AH30, D09AA10, G01AC02, S02AA05	5%	16 435	0.12	0.19	0.06	0.31	0.31	(0.23-0.39)
(Iodochlorhydroxyquine)									
Fusidic acid, sodium salt	D06AX01, D09AA02, S01AA13	2%	15 593	0.28	0.11	0.04	0.39	0.39	(0.29-0.49)
Neomycin sulfate	A01AB08, D06AX04, G01AA14, R02AB01, S01AA03, S02AA07, S03AA01	20%	28 569	0.83	0.49	0.28	1.32	1.24	(1.11-1.37)
		230 µg/cm ²	2365	0.25	0.21	0.32	0.47	0.41	(0.16-0.66)
Compositae mix	n.a.	2.5%	13 842	0.48	0.61	0.07	1.09	1.02	(0.86-1.18)
		5%	11 994	1.00	0.73	1.28	1.73	1.57	(1.35-1.79)
		6%	2079	0.34	0.34	0.10	0.67	0.47	(0.22-0.72)
Sesquiterpene lactone mix	n.a.	10%	25 719	0.39	0.32	0.20	0.72	0.72	(0.62-0.82)
Propolis *	n.a.	10%	28 474	2.03	0.45	4.03	2.48	2.34	(2.16-2.52)
Cetostearyl alcohol	Excipient	20%	29 248	0.66	0.19	1.29	0.86	0.76	(0.66-0.86)
Lanolin (wool fat) alcohols	Excipient	30%	56 435	1.36	0.34	1.31	1.70	1.62	(1.51-1.73)
		1 mg/cm ²	2362	0.93	0.13	1.02	1.06	1.03	(0.62-1.45)
Sodium metabisulfite	Excipient	1%	16 485	2.49	0.62	0.47	3.11	3.03	(2.77-3.29)

ATC code(s), anatomical/therapeutic/chemical classification as far as pertinent for topical application on skin and mucous membranes, excluding combinations; Conc., concentration in the patch test preparation in petrolatum, except when given as mg or µg/cm²: in a hydrophilic gel matrix (TRUE Test®); nr(test), number of patients tested; %(+), proportion of weak positive allergic reactions; %(++/+++), proportion of strong (++) or extreme (+++) positive allergic reactions; %(?+/IR), proportion of doubtful (?+) or irritant (IR), i.e. non-allergic reactions; %(pos.), proportion of + to +++ allergic reactions; %(pos.std.), proportion of allergic reactions, directly age- and sex-standardized; 95%CI, 95% confidence interval to the standardized prevalence.

n.a., not applicable.

*1.94% of the erythematous reactions were considered allergic.

Supporting Information. This illustrates, among other things, the important fact that, except for lanolin alcohols, the haptens are not included in each and every baseline test series in the various countries or departments. This is a consequence of the objective to adapt, nationally or locally, the baseline series so that it best reflects the spectrum of exposure to haptens. Moreover, different test concentrations of one substance may be used, most markedly in case of the two corticosteroid screening haptens, tixocortol-pivalate and budesonide. Benzocaine is still part of the recommended European baseline series¹³; however, in Finland and the UK, a mix containing benzocaine, cinchocaine and tetracaine is used instead.

The overall results show that few haptens exceed a sensitization prevalence of 1%, considering the lower 95% confidence limit, namely caine mix III, Compositae mix at 5% concentration, lanolin alcohols and, in particular, propolis and sodium metabisulfite. Sensitization to the remaining haptens was diagnosed in up to 1% of all consecutive patients. In the one hapten tested in all countries, lanolin alcohols, significant heterogeneity of sensitization prevalences between countries was noted (χ^2 test: $p < 0.0001$), with prevalences below 1% in Spain, Italy, Finland, Poland and Slovenia, and prevalences $>3\%$ in Lithuania and especially the Netherlands (Table S1).

Benzocaine, used as a marker hapten for local anaesthetics of the ester type, elicited less than 1% positive reactions. In comparison, the caine mix, which also includes tetracaine, and the amide type local anaesthetic cinchocaine [syn.: dibucaine (USAN)], yielded positive reactions more frequently, both using the investigator-loaded and the TRUE Test® system.

The two screening markers for contact allergy to corticosteroids included in the European baseline series, budesonide and tixocortol-pivalate, are tested in concentrations diverging by 1 order of magnitude by different departments. Many more patients had been tested with the higher test concentrations (Table 2). The yield of positive reactions with the pet.-based haptens was significantly higher with the lower test concentration of budesonide, but quite similar in tixocortol-pivalate. The TRUE Test® preparations resulted in very similar reaction frequencies. The analysis of coupled reactivity, considering the pet.-based haptens, showed marked discordance: among the 25411 tested with both haptens (either concentration), only 19 (0.07%) reacted to both, 236 (0.93%) only to tixocortol-pivalate and 174 (0.68%) only to budesonide. A similar observation was made with the TRUE Test® haptens, where no single patient reacted

to both, but 14 (0.51%) only to tixocortol-pivalate and 16 (0.59%) only to budesonide.

Addressing a time trend of bufexamac sensitization, the prevalence decreased from 0.97% to 0.55 between 2009 and 2012, albeit not significantly ($p = 0.058$). Clioquinol (syn.: iodochlorhydroxyquin) is a very infrequent hapten, the upper 95% confidence interval not exceeding 1%. The aminoglycoside antibiotic neomycin, which is patch tested as sulfate, caused 1.3% positive reactions overall, with quite marked geographic differences (Table S1).

In 8713 patients, both the sesquiterpenlactone mix, containing alantolactone, dehydrocostus lactone and costunolide, and the Compositae mix had been tested at 2.5% pet. While 48 patients reacted to both, 33 were diagnosed only with the Compositae mix and, vice versa, 14 only with the SL mix ($p = 0.009$; McNemar test).

DISCUSSION

The present analysis provides an overview on the frequency of a common adverse effect of topical drugs in the European population, namely contact allergy. Moreover, important ingredients also of cosmetics or 'alternative' topical therapeutics have been assessed. The results are relevant (i) for the dermatological community, in terms of informing on important routinely tested haptens, and (ii) for pharmacoepidemiological surveillance regarding an endpoint which impairs the efficacy of the medicament and is important to consider in risk-benefit considerations. Comparisons between countries provide a benchmark for national discussion in this regard.

Addressing single active ingredients, the following aspects are worth discussing:

- Although tested in different patients, and thus not directly comparable, it is striking that benzocaine had a much lesser yield of positive reactions than the caine mix. This may be due to the fact that the latter also covers an amide type local anaesthetic, i.e. cinchocaine. Thus, substitution of benzocaine with a caine mix should be considered.¹⁴ Local anaesthetics are found in a number of burn treatment creams, creams for bee and wasp stings, haemorrhoid preparations and throat sprays. In a Finnish study, 25 of 650 patients tested with local anaesthetics reacted positively, among them 20 to cinchocaine. Local treatments for perianal conditions were the most common sensitizers.¹⁵
- Allergy to corticosteroids may be an under-recognized problem as it may present as poor response to a topical steroid treatment, rather than as typical contact dermatitis. The two corticosteroids

tested as screening haptens in the baseline series are intended to cover the spectrum of different types of contact allergy to corticosteroids. However, the classification of contact allergy to corticosteroids is a difficult topic still evolving^{16,17} and a second patch test with a number of different corticosteroids should usually follow if the screening corticosteroids yielded positive reactions, to identify the culprit(s), and safe alternatives. The fact that a lower concentration of budesonide elicited more positive reactions has been explained by lesser immunosuppression of the patch test reaction by lower doses of corticosteroid¹⁸—too low a dose to elicit a reaction is a further diagnostic pitfall.¹⁹

- Clioquinol (iodochlorhydroxyquin) is a quinoline derivative with some antifungal effect when applied topically. However, use has apparently declined, and in view of the rarity of positive reactions, it does not seem to be warranted to continue to test this hapten routinely: there were less than 1% allergic reactions, and past exposure to the substance can easily be identified from the patient's history.
- Neomycin sulfate is the only aminoglycoside antibiotic, and in fact, the only antibiotic, recommended to be patch tested routinely.¹³ In the USA, where various topical drugs containing neomycin, often together with bacitracin and/or corticosteroids, are available over-the-counter, routine testing is useful and yielded e.g. 7.1% positive reactions in consecutive patients.²⁰ Cross reactions to other aminoglycosides are common.²¹ Previously, based on similar surveillance data 1998–2003, the decreased exposure to neomycin, at least in Germany, was found to be mirrored by a slight but significant reduction in sensitization prevalence.²² Neomycin may be found in topical creams as well as a number of ear and eye drops. In view of available therapeutic alternatives and because of the sensitization potency and frequency, a withdrawal of the marketing authorization should be considered.
- Clinical surveillance in Germany had found contact allergy to bufexamac a considerable problem, which had been grossly under-estimated based on notifications on adverse events, and had moreover identified a number of individual risk factors.²³ Based on this, and a generally unfavourable risk-benefit balance, the marketing authorization for bufexamac has been withdrawn by the European Medicines Agency in 2010.²⁴ In the present data, a trend for a decline in sensitization prevalence is seen, in line with the sharp reduction in exposure, although this is certainly diluted by patients in whom this contact

allergy was relevant for a previous episode of allergic contact dermatitis, but not for contact dermatitis leading to current dermatological consultation.

- Fusidic acid has only been tested in the UK, as sodium salt. The rather low prevalence of positive reactions of around 0.4%, together with perhaps a reasonable chance to identify previous exposure and possible sensitization from the patient's history, renders this compound a less obvious candidate for inclusion in a baseline series.

Among the excipients are the following:

- Sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$) is widely used as antioxidant, disinfectant and preservative agent, including foodstuff. By this route, systemic allergic contact dermatitis may be elicited.²⁵ The rather high prevalence of positive patch test reactions in consecutively tested patients, in the UK and especially in Amsterdam, the Netherlands, seems to warrant inclusion in a baseline series. Indeed, a recent prospective study, employing three different patch test concentrations and exposure and relevance assessment concluded that (i) sodium metabisulfite contact allergy appears to be relevant for most patients and (ii) 1% pet. is the optimum patch test concentration.²⁶ Moreover, other sulfites may cross react,²⁷ following a putative protein modification mechanism involving nucleophilic attack by sulfite dianions on target electrophilic centres in skin proteins.²⁸
- Lanolin alcohols are a natural mixture of emulsifying alcohols of various chain lengths and structures, and they are weak haptens contained in wool fat or wool wax (lanolin) produced from sheeps' wool. Considering the relatively wide use of lanolin and lanolin alcohols, the frequency of sensitization is relatively low (Table 2). Efforts have been made to reduce allergenicity, e.g. by limiting the concentration of alcohols in lanolin or purification processes in general. In contrast, modification in terms of hydrogenation historically increased the allergenic potential.²⁹
- Cetearyl alcohol (CAS no. 8005-44-5), another emulsifying agent, is not a part of the European baseline series¹³ but is tested in countries participating in the IVDK network (www.ivdk.org), i.e. Austria, Germany and Switzerland, as well as Lithuania and the UK. The frequency of positive reactions might merit inclusion in a baseline series. However, positive patch test reactions to cetearyl alcohol have been found to be (i) poorly reproducible and (ii) hard to verify by a use test³⁰; hence, it may not be generally recommendable to include cetearyl alcohol in a baseline series.

The remaining haptens are pertinent to phytotherapeutics:

- The Compositae mix, in its two slight variants concerning the extracts included, is a natural mixture covering several of the main sensitizing components, mainly the sesquiterpene lactones, but also other sensitizers. This explains why more patients react to the Compositae mix but not to the SL mix containing just three selected sesquiterpene lactones (costunolide, alantolactone and dehydrocostus lactone in equal parts) than vice versa. However, despite the advantage of covering even more sesquiterpene lactones and other, albeit less frequent Compositae haptens, being a natural mixture, the Compositae mixes are difficult to standardize. The potential relevance of Compositae haptens has been demonstrated repeatedly.^{31,32}
- Propolis has been identified as a regionally important hapten, depending e.g. on the regional exposure to food supplements or folk medicines containing propolis.^{32,33} In the latter, it is used for its alleged antibacterial, antifungal and antiviral properties, amongst others. Apart from use in topicals, it may also be found in cosmetic products including shampoo, conditioners, lipsticks, nail varnishes and toothpastes; International Nomenclature on Cosmetic Ingredients names include propolis cera, propolis wax and propolis extract.³⁴ Propolis consists of more than 300 ingredients, and its composition is region-dependent. In central Europe, where poplar trees grow, caffeates are the main responsible haptens in propolis contact allergy.³⁵ The properties, composition and aspects of contact allergy have recently been reviewed.³⁶ In the current recommended patch test concentration of 10% pet., the prevalence of positive reactions (age- and sex-standardized) is proportionally high, and moreover, a large proportion of the weaker, merely erythematous reactions have been considered as weak allergic reactions (Table 2), which may point to a borderline low patch test concentration unable to elicit a full allergic response in some of the sensitized. In several countries, propolis is included in the baseline series, for example the UK³³, Germany³⁵ and Poland.³⁷ The high prevalence of positive patch test reaction might warrant inclusion in the baseline series of even more European countries.

After the single results discussed earlier, some more general considerations should be addressed. First of all, it should be mentioned that the simple, albeit age- and sex-standardized, descriptive analyses are a first step when addressing the risk of contact allergy associated with active ingredients or excipients.

Particularly high contact allergy prevalences in one country should prompt investigation into possible reasons. Subsequent action could include re-evaluation of risk–benefit of the substance concerned, in comparison to other substances with a similar therapeutic effect. Sensitization prevalences found in patients, as in the present analysis, have been extrapolated to the population level to give a better impression on the burden of morbidity.³⁸ More importantly, morbidity should best be related to an exposure denominator, e.g. in terms of defined daily doses, to arrive at a proper, comparative risk assessment of ingredients.³⁹ Such exposure data are not available on a European level, but the German results cited can probably be generalized.

An important limitation of all these approaches is, however, the fact that only a relatively small fraction of active principles as well as excipients are readily available as patch test haptens. Many other agents, especially those which are still under patent protection, are difficult or virtually impossible to obtain for commercially compounding patch test substances. Hence, as an important addition to routine diagnostics, the topical preparations, including alternative remedies and also e.g. transdermal therapeutic systems, the patient had been using and which may possibly have caused allergic contact dermatitis should also be tested. This is usually possible by just applying the topicals ‘as is’, i.e. without further dilution; pertinent guidelines should be followed.¹ In case of a positive patch test reaction to such a product, the single active ingredients and excipients of the product should be patch tested individually, in order to identify the actual hapten. Reporting of such results will contribute to a growing body of evidence concerning this rarely serious, but restrictive adverse reaction to topical pharmaceutical products and thereby supplement large-scale epidemiological surveillance as presented in this report. Ideally, a suitable risk assessment concerning contact allergy should be integrated into the pharmaceutical development and be part of registration and licensing requirements to avoid contact allergy in the first place; unfortunately, current guidance in terms of ICH Q8R2 and the QWP guideline on transdermal patches does not address this endpoint. Full labelling of excipients, along the lines of the Cosmetics Regulation EC 1223/2009 in Europe,⁴⁰ would greatly help in diagnosis and management of allergic patients.

CONFLICT OF INTEREST

A. S. works as *ad hoc* consultant for the cosmetic industry, partly remunerated. R. S. is shareholder and scientific adviser as the Polish representative of

Chemotechnique Diagnostics. W. U. accepted travel reimbursement and partly honoraria for presentations given to cosmetic industry (associations) and received a lecture fee from Almirall Hermal for educational lectures on contact allergy. M. W. attended a drug advisory board meeting for GlaxoSmithKline (alitretinoin). The other authors do not declare any conflicts of interest pertinent to this study.

KEY POINTS

- Allergic contact dermatitis is a common adverse effect of topical treatments.
- Potential causes of contact allergy comprise active ingredients of topical drugs (e.g. antibiotics or corticosteroids), as well as excipients, such as preservatives, fragrances, emulsifiers and others.
- Not only prescription drugs but also over-the-counter topicals and cosmetics may cause contact allergy, including natural remedies and products branded as ecological, hypoallergenic, for sensitive skin or allergen-free.
- In the (limited) set of agents tested routinely, in all patients, comparisons of contact allergy prevalences are possible.
- Patch testing suspected culprit products as is often necessary as there is a limited number of test haptens commercially available. If positive, this should be followed by break down testing to all the individual ingredients to identify the hapten (contact allergen) for future secondary prevention.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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AUTHOR CONTRIBUTION

W. U. performed data management and statistical analyses. All authors have given significant input, take responsibility for the contents and have approved the final submitted version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website.

Table S1 Results with the haptens used as active ingredient or excipient in topical medications, and partly in cosmetics, patch tested in petrolatum, stratified for country. Only those allergens tested are included which have been tested in consecutive patients in more than one country. Results from the 2 German departments using 24 h patch test exposure are presented separately: 'DE (1 day)'. The p-values after the allergen test preparations are the result of a test for heterogeneity. %(pos.), proportion of + to +++ allergic reactions ' %(pos.std.)', proportion of positives, directly age- and sex-standardised; 95% CI, 95% confidence interval to the standardised prevalence.

Table S1: Results with the haptens used as active ingredient or excipient in topical medications, and partly in cosmetics, patch tested in petrolatum, stratified for country. Only those allergens tested are included which have been tested in consecutive patients in more than one country. Results from the 2 German departments using 24 h patch test exposure are presented separately: 'DE (1 day)'. The *p*-values after the allergen test preparations are the result of a test for heterogeneity.
 %(pos.), proportion of + to +++ allergic reactions ' %(pos.std.) ', proportion of positives, directly age- and sex-standardised;
 95% CI, 95% confidence interval to the standardised prevalence.

a) Neomycin sulfate, 20% pet. (*p*<0.001)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
DK	2569	34	1.32	1.21	(0.48–1.94)
ES	3361	37	1.1	1.01	(0.67-1.34)
FI	542	15	2.77	2.46	(1.2-3.73)
IT	4673	21	0.45	0.43	(0.25-0.62)
LT	865	10	1.16	1.03	(0.35-1.72)
NL	2823	37	1.31	1.26	(0.85-1.68)
PL	2827	84	2.97	2.82	(2.22-3.42)
UK	10909	138	1.27	1.21	(1-1.41)

b) Benzocaine, 5% pet. (*p*<0.001)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
CH	991	6	0.61	0.71	(0.1-1.32)
DK	2572	9	0.35	0.38	(0.02–0.8)
ES	2952	38	1.29	1.09	(0.74-1.44)
IT	9238	50	0.54	0.54	(0.39-0.69)
LT	865	21	2.43	2.14	(1.17-3.11)
PL	2828	20	0.71	0.66	(0.37-0.96)
SI	5224	25	0.48	0.47	(0.28-0.65)

c) Caine mix III (Benzo-,Dibu-,Tetracaine), 10% pet. (*p*=0.185)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
FI	544	3	0.55	0.52	(0-1.12)
UK	15587	202	1.3	1.25	(1.08-1.42)

d) Budesonide, 0.1% pet. ($p=0.06$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
DK	2574	17	0.66	0.65	(0.09–1.22)
ES	2359	12	0.51	0.52	(0.22-0.82)
IT	690	0	0	0	(0-0.43)
LT	863	8	0.93	0.85	(0.23-1.47)
NL	1453	5	0.34	0.34	(0.04-0.64)
UK	13516	54	0.4	0.38	(0.27-0.48)

e) Budesonide, 0.01% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
ES	1374	17	1.24	1.11	(0.57-1.65)
FI	544	6	1.1	1.32	(0.25-2.39)
IT	224	0	0	0	(0-1.33)
LT	2	0	0	0	(0-77.64)
NL	2823	22	0.78	0.76	(0.44-1.08)
PL	2827	72	2.55	2.74	(2.1-3.38)

f) Tixocortol-pivalate, 1.0% pet. ($p=0.1$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
DK	2571	17	0.66	0.7	(0.12–1.3)
ES	1702	10	0.59	0.59	(0.2-0.97)
LT	864	5	0.58	0.48	(0.04-0.92)
NL	2815	35	1.24	1.24	(0.82-1.66)
UK	15590	160	1.03	0.99	(0.83-1.14)

g) Tixocortol-pivalate, 0.1% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
ES	1731	5	0.29	0.27	(0.02-0.53)
FI	544	14	2.57	2.36	(1.09-3.64)
NL	4276	37	0.87	0.84	(0.57-1.11)
PL	2826	29	1.03	0.98	(0.62-1.34)
UK	2585	4	0.15	0.15	(0-0.3)

h) Clioquinol (iodochlorhydroxyquin), 5% pet. ($p=0.011$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
DK	2570	12	0.47	0.41	(0.01–0.81)
ES	2127	4	0.19	0.19	(0-0.38)
LT	865	7	0.81	0.57	(0.14-1)
NL	2823	11	0.39	0.35	(0.14-0.56)
PL	2826	12	0.42	0.43	(0.18-0.68)
SI	5224	9	0.17	0.15	(0.05-0.24)

i) Bufexamac, 5% pet. ($p=0.131$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
AT	1113	10	0.9	0.79	(0.29-1.29)
CH	4998	29	0.58	0.57	(0.35-0.79)
DE	5555	53	0.95	1.11	(0.79-1.44)
DE (1 day)	1925	12	0.62	0.61	(0.22-0.99)

j) Propolis, 10% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
AT	1109	63	5.68	5.05	(3.77-6.34)
CH	4979	204	4.1	3.77	(3.23-4.3)
DE	5532	154	2.78	2.59	(2.14-3.03)
DE (1 day)	1906	55	2.89	2.52	(1.78-3.27)
IT	2085	42	2.01	1.95	(1.36-2.54)
LT	130	0	0	0	(0-2.28)
PL	992	36	3.63	3.54	(2.36-4.71)
UK	11741	153	1.3	1.25	(1.05-1.45)

k) Compositae mix, 2.5% pet. ($p=0.102$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
FI	592	11	1.86	1.99	(0.8-3.17)
UK	13250	140	1.06	0.98	(0.82-1.14)

l) Compositae mix, 5% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
AT	1113	29	2.61	2.41	(1.5-3.32)
CH	3501	60	1.71	1.56	(1.15-1.97)
DE	3964	81	2.04	1.79	(1.38-2.21)
DE (1 day)	1348	24	1.78	1.38	(0.78-1.98)
FI	463	4	0.86	0.83	(0-1.67)
IT	1605	9	0.56	0.62	(0.21-1.03)

m) Sesquiterpenlactone mix, 0.1% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
DK	2561	33	1.29	1.09	(0.43–1.74)
ES	4277	12	0.28	0.31	(0.12-0.49)
LT	865	9	1.04	1.14	(0.26-2.02)
NL	4279	43	1	0.96	(0.67-1.25)
PL	2827	16	0.57	0.57	(0.28-0.85)
UK	10910	86	0.79	0.72	(0.57-0.88)

n) Lanolin alcohols, 30% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
AT	1109	32	2.89	2.88	(1.82-3.94)
CH	4981	124	2.49	2.48	(2.02-2.94)
DE	5540	163	2.94	2.95	(2.46-3.44)
DE (1 day)	1901	35	1.84	1.3	(0.85-1.74)
DK	2568	17	0.66	0.63	(0.09–1.16)
ES	3361	23	0.68	0.62	(0.36-0.88)
FI	1055	3	0.28	0.32	(0-0.7)
IT	9248	78	0.84	0.85	(0.66-1.04)
LT	865	26	3.01	2.93	(1.72-4.14)
NL	2823	144	5.1	5.24	(4.4-6.08)
PL	2182	19	0.87	0.83	(0.45-1.22)
SI	5224	50	0.96	0.92	(0.66-1.18)
UK	15578	219	1.41	1.38	(1.2-1.57)

o) Cetearyl alcohol, 20% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
AT	1109	12	1.08	0.93	(0.39-1.46)
CH	4979	54	1.08	1.01	(0.73-1.3)
DE	5529	56	1.01	0.89	(0.64-1.13)
DE (1 day)	1904	41	2.15	1.65	(1.1-2.2)
LT	130	1	0.77	0.53	(0-1.58)
UK	15597	87	0.56	0.51	(0.4-0.62)

p) Sodium metabisulfite, 1% pet. ($p<0.001$)

Country	nr(test)	nr(pos.)	%(pos.)	%(pos.std.)	95% CI
NL	2815	148	5.26	5.2	(4.36-6.03)
UK	13670	365	2.67	2.57	(2.31-2.84)