



Current trends in patch testing – new data from the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK)

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Summary

Background and objectives: The relevance of contact allergens is subject to constant change due to changing exposures according to consumers' preferences and legal requirements. The objective of this paper is to present trends in contact sensitization from the DKG and IVDK patch test clinics, which have led to changes in the DKG standard series (as of 1.1.2014), as well as the current legal framework which has influenced these trends and the way patch testing is performed.

Patients and methods: The patients from 56 DKG and IVDK patch test clinics from 2010 (n = 13,117), 2011 (n = 13,320) and 2012 (n = 12,529) were analyzed with regard to frequencies of sensitization (hit list) to contact allergens as well as the location of allergic contact dermatitis.

Results: With a sensitization rate of 15 % nickel is still the most frequently recognized contact allergen. An increase can be observed for fragrance mix I (9.1 %), the preservative composition of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (4.5 %) and methylisothiazolinone (MI) alone (6.8 %). A decline is present for potassium dichromate from above 6 % (2007) to 3 % (2012) and for bufexamac (currently at 0.6 %). Backgrounds, legal requirements and resulting changes to the DKG standard series are illustrated.

Conclusions: The indicated trends demonstrate the relevance of clinical epidemiology and the "sentinel function" of DKG and IVDK with regard to public health and prevention of contact allergies.

Introduction

The incidence of allergic contact eczema is estimated to amount to 1.7–7 cases per 1000 inhabitants per year in Germany [1]. The prevalence of allergic contact dermatitis is approximately 7% in the general population (German Health Survey [Bundesgesundheitsurvey] 1998) [2]. Between 15% and 20% of the general population show sensitization to ≥1 of the commonly recognized allergens tested in the standard series [2, 3]. Experimental studies have shown that preexistent irritative contact dermatitis promotes the development and severity of allergic contact dermatitis, as induction of an

acquired specific immune response requires an initial activation of the non-specific innate immune system [4]. Although causative and regulative mechanisms of allergic contact dermatitis have been studied extensively and a number of scientific approaches are aiming to restoration of immunotolerance through direct activation of regulatory T-cells and IL-10 production, so far no curative medical treatment option is available to reverse an acquired sensitization [5]. Avoidance of allergens is still the only curative approach towards allergic contact dermatitis. Identification of the causative allergen through allergological diagnostic procedures is thus critical for successful therapy of allergic contact dermatitis.

Patch testing by a dermatologist or allergist according to current guidelines is the present diagnostic gold standard [6, 7]. For quality assurance of inter-individual variance in patch test reading and interpretation, a validated training for patch test reading has been developed by the German Contact Dermatitis Research Group (DKG), which is freely available at <http://dkg.ivdk.org> for training purposes.

The clinical relevance of specific contact allergens changes constantly and is mainly influenced by consumer preferences, product formulations and legal regulations. To recognize these developments and their influence on contact allergies in a timely fashion, active members of the DKG and the Information Network of Departments of Dermatology (IVDK) collect patient histories, clinical data and patch test results in a standardized fashion, and transmit the data in anonymized form to the IVDK database at Göttingen University.

The data are submitted to a quality control [8] and analyzed for certain research questions including clinical and epidemiological trends. All 56 dermatology departments affiliated with the IVDK are members of the DKG. DKG is a scientific society devoted to contact dermatitis under the mantle of the German Dermatologic Society (DDG). Full DKG membership requires a certified training in the field of contact dermatitis. Most members actively practice at clinical dermatology departments where their responsibility includes the allergy department. Other forms of membership are available for legal bodies, societies and sponsoring members.

In close cooperation the DKG and IVDK have compiled a "Top 25" list of frequent contact allergens, which is presented along with the most common sites of allergic contact dermatitis and the current complex legal frameworks.

Patients and Methods

Standardized checked data collected from patients ($n = 38\,878$) tested between 2010 and 2012 ($n = 38\,966$ tests) were analyzed. Details regarding the participating centers, patch test procedure and supply sources for testing materials are available in the online supplement (see online Supporting Information).

Results

Top 25 most frequent contact allergens and epidemiological trends

Nickel

Among the "Top 25" of contact allergens (Table 1), nickel has assumed position #1 for years, with a sensitization rate of >15% in the unselected patch test patient collective of the

Table 1 Current "hit list" (Top 25) of contact allergens in the patch test cohort tested 2010 to 2012 in the hospitals contributing to the DKG-IVDK consortium (age- and gender-standardized, database status: 8th November 2013).

Year	2010	2011	2012
No. of patients	13,117	13,320	12,529
Nickel(II) sulfate	14.9 %	15.6 %	15.3 %
Fragrance mix	7.4 %	8.1 %	9.1 %
Balsam of Peru	5.9 %	7.1 %	7.2 %
Cobalt chloride	4.4 %	5.2 %	5.8 %
Fragrance mix II	4.9 %	4.4 %	4.6 %
MCI / MI (e.g. Kathon CG)	3.1 %	3.8 %	4.5 %
Rosin	3.7 %	4.0 %	3.9 %
Propolis	2.0 %	2.7 %	3.7 %
Potassium dichromate	2.5 %	3.4 %	3.0 %
MDBGN	2.2 %	2.6 %	2.7 %
Ylang-Ylang oil (I + II)	NT	2.3 %	2.4 %
Wool alcohols	2.4 %	2.6 %	2.2 %
Thiram mix	2.3 %	2.1 %	2.1 %
HICC (e.g. Lyrall®)	1.8 %	1.9 %	1.8 %
Epoxy resin	1.3 %	1.5 %	1.4 %
Formaldehyde	0.9 %	0.9 %	1.3 %
Compositae Mix*	1.2 %	1.6 %	1.2 %
Jasmine absolute	NT	1.4 %	1.2 %
Sandal wood oil	NT	1.4 %	1.1 %
Cetyl stearyl alcohol	0.7 %	1.0 %	1.0 %
Paraben Mix	0.5 %	0.7 %	0.8 %
Bronopol	0.5 %	0.8 %	0.7 %
Turpentine	2.9 %	1.7 %	0.6 %
Bufexamac	1.0 %	0.9 %	0.6 %
*from 2012: Compositae Mix II			

DKG-/IVDK hospitals. Nickel allergies are usually acquired by exposition to costume jewelry or piercings. Therefore, nickel content and release rates have been regulated by an EU directive (94/27/EG) and have been limited to $< 0.5 \mu\text{g}/\text{cm}^2$ /week for products intended to come into direct and prolonged contact with the skin [9]. First data analyses confirmed successful results; however, since 2000 (Figure 1), the frequency of nickel allergies has been stable at an unsatisfactorily high level. Epidemiological surveillance by the IVDK suggested a still-existing significant exposure to nickel, which could be

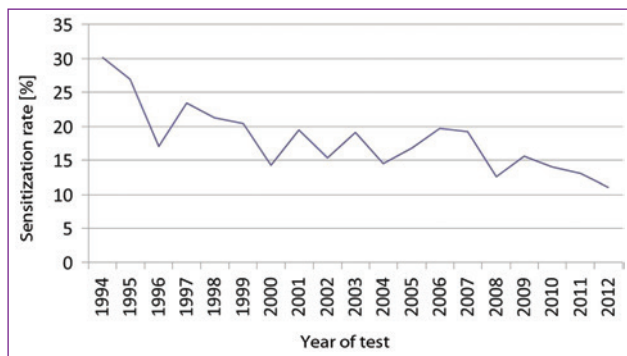


Figure 1 Sensitization to nickel in young women (1–17 years of age), data of the IVDK 1994–2012. After a significant decline, the sensitization rate has persisted on a high level due to a loophole in the EU-Nickel-Directive.



Figure 2 Fourteen days after her first piercing, a 13-year-old girl developed allergic contact dermatitis. There was no past history of nickel sensitivity. In this patient, the sensitization phase was directly followed by the elicitation phase of the contact dermatitis.

confirmed by chemical analysis of >600 nickel-containing pieces of costume and piercing jewelry [10]. While the threshold value seems excessively high, even this is inadequately adhered to. Thus, the directive was adjusted in 2004, now permitting a maximum nickel release from ear studs and piercing jewelry of $<0.2 \mu\text{g}/\text{cm}^2/\text{week}$ (2004/96/EC) [11]. Preliminary stratified analyses from 2013 indicate a regressive trend for nickel allergies in young women aged 1–17, 18–30 and 31–44 years, with a significant increase in nickel sensitizations among women aged 45–60 years [12], the latter probably being due to a cohort effect in a sample that had been exposed to nickel at legally not regulated concentrations in their earlier years.

Thus, epidemiological surveillance confirmed both the success and initial partial failure of the implemented directives. Figure 2 shows a 13-year-old girl, who developed allergic contact dermatitis 14 days following a first piercing.

Fragrances

Fragrance-containing test substances (fragrance mix I, Balsam of Peru (INCI: *Myroxylon pereirae*), fragrance mix II, ylang-ylang oil I + II, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall®), jasmine absolute, sandal wood oil) are among the most frequent contact allergens with allergic response rates $>1\%$.

The most relevant allergens contained in fragrance mix I are oak moss (*Evernia prunastri*), isoeugenol and cinnamaldehyde. Following the voluntary reduction in the use and concentration of these problematic fragrances in cosmetics and body care products, the response rate to fragrance mix I in the IVDK decreased from 13.1% (1999) to 6.5% (2006–2008). During the last years, the response rate to fragrance mix I has increased again; the cause of this rise is unclear. A considerable risk of sensitization is associated not only with the 26 fragrances that are currently subject to declaration [13]. According to a Scientific Committee on Consumer Safety (SCCS) statement in June 2012, a number of other fragrances and essential oils have been identified as actual or likely contact allergens. Thus, a total of 128 fragrances/extracts will have to be declared to the consumer (SCCS plenary decision, June 2012) [14]. Among scientists and experts, the statement has been criticized, as some of the 128 listed substances have not yet been shown to be contact allergens (e.g. benzyl benzoate or camphor), while for others, a sufficient risk assessment remains to be made [15].

Preservatives

Due to high sensitization rates when used in cosmetics, MDBGN (methylchloroisothiazolinone/methylisothiazolinone) has been banned by EU directive, since 2003 from leave-on products, and since 2007 also from rinse-off products, the transitional period ending in March 2008 [16]. Response rates have not dropped as expected yet, the sensitization rate according to IVDK data is stable at 2%. Currently, alternative preservatives are increasingly used.

The rate of type IV sensitizations to the preservative mixture methylchloroisothiazolinone/methylisothiazolinone (MCI/MI at 3 : 1) has constantly increased in the DKG standard series from 2009 to 2012, as did the rate of single-substance sensitization to MI alone in the DKG preservative series [17, 18]. This is probably due to an increase in primary sensitizations to MI due to a change in exposure, with a subsequent immunologic cross reaction to MCI. In 2012, the sensitization rate for MCI/MI (100 ppm in water) was 4.5%. The majority of IVDK centers have patch tested MI (0.05% in water) in parallel to the DKG standard series (Nov 01, 2011–June 30, 2013; 6,176 patients at 19 centers); detecting a response rate of 6.8%.

About two-thirds of MI positive patients are MCI/MI positive in a patch test, resulting in one-third of MI sensitized

patients not being identified by patch testing the mixture of MCI/MI.

The German cosmetics directive (Verordnung über kosmetische Mittel, KosmetikV) permits the use of MCI/MI at 15 ppm (0.00015 %), while due to assumed lower sensitization rates, the threshold for MI in cosmetics is still at 0.01% [16]. Sensitization to MI affects mostly patients using MI-containing cosmetics as well as varnishers, beauticians and geriatric nurses. Painters are frequently affected, with sensitization rates of >15%, as MI is increasingly used as a preservative in paints [19]. The current increase in sensitization rates over the last three years has been dramatic [17, 19].

The preservative iodopropynyl butylcarbamate (IPBC) shows a sensitization rate of 2.2% when tested in parallel to the DKG standards series. Sensitization rates to other preservatives tested in the standard series (bronopol, paraben mix) are <1%.

Bufexamac

Bufexamac is an anti-inflammatory agent used to treat eczema as well as in antihemorrhoidal products and wound healing ointments. Due to its unfavorable efficacy and side effect profile, a data-based IVDK initiative led to a market withdrawal with no transition period for bufexamac used in medical products by the European Medicines Agency (EMA) and the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) effective May 5, 2010. Since bufexamac-containing pharmaceutical products have been withdrawn from the European market [20], sensitization rates have decreased slowly.

Potassium dichromate

Among the “Top 25” contact allergens, the response rate to potassium dichromate has fallen from more than 6% (2007) to 3% (2012). IVDK data show that sensitization rates have fallen especially in patients working in the construction industry, i.e. bricklayers, tilers and construction workers with occupational skin diseases. Efforts to reduce the chromate content of cement, with a voluntary industry agreement in 2000 followed by an EU regulation, are responsible for this development. According to EU directive 2003/53/EC of January 1, 2005, the maximum chromate content for cement intended to be handled is 2 mg/kg [21].

Epoxy resins are the second most frequent allergen in the construction industry, with currently increasing response rates of 13.7% [22]. These data show the positive effect of a threshold for chromate content in cement, but also clearly indicate the necessity for a revision of current preventive measures for the use of epoxy resins. This underlines the relevance of clinical epidemiology and contact dermatitis surveillance for occupational safety.

While in the DKG and IVDK patch test cohort sensitization rates to potassium dichromate have fallen in middle-aged men (reduced exposition in cement), sensitization rates in young women are currently rising because of the wearing of non-lined leather garments. For working gloves, the threshold of 3mg/kg according to DIN EN 420 [23] is close to detection level. For shoes to receive the EU Ecolabel, a maximum of 10 mg/kg of chrome (VI) is tolerated. Nevertheless, and in spite of a corresponding recommendation from the German Federal Institute for Risk Assessment (Bundesinstitut fuer Risikobewertung, BfR), no general threshold for leather products has been issued yet [24]. The BfR recommends, according to state-of-the art analytics, a ban of chrome (VI) from consumer goods [24]. At the time of the BfR statement, detection of chrome (VI) was possible at a threshold of 3 mg/kg. Current analytical methods allow a detection of chrome (VI) at ≥ 1 ppm, to which the threshold should be adjusted.

Rubber allergens

Rubber allergens in gloves play an important role in occupational contact allergies, where often gloves are worn for protection but may cause problems themselves. Accelerator-free gloves have been developed by a number of manufacturers and are commercially available, but are not yet widely used. Current IVDK analyses failed to show any relevant changes in the spectrum of typical allergens, with thiuram dominating by far [25]. The sensitization typically affects healthcare professionals, cleaners, mechanics, machinists and hairdressers. This analysis demonstrates another important function of the surveillance system, namely providing proof of a persistent problem and urging a primary preventive measure (replacement of a common allergen).

Update of the DKG standard series (as of November 11, 2013)

The first standard series was designed by Bonnevie before World War II, and has, over the centuries, been subjected to numerous deletions and supplementations [26]. Taking into account current trends and developments, the DKG updated their standard series on November 11, 2013, to take effect by January 1, 2014. Due to increasing sensitization rates, methylisothiazolinone (MI) 0.05 % and iodopropynyl butylcarbamate (IPBC) 0.2 % were included, while bufexamac 5 %, bronopol 0.5 % and 4-tert-butylphenol formaldehyde resin 1 % will, in response to decreasing sensitization rates, no longer be in the standard series from January 1, 2014. All sensitizers in this list are tested in petrolatum. The latter will be available for patch testing in the following series: “DKG: Other pharmaceuticals” (bufexamac), “DKG: Preservatives” / “DKG: Industrial biocides” (bronopol) and “DKG: Leather and Shoes” (4-tert-butylphenol formaldehyde resin).



Figure 3 Acute facial edema, as well as pruritus and erythema of the scalp and ears after dyeing her hair brown. No wheals, no dysphagia, no shortness of breath, no signs of infections were present. No previous intake of drugs was reported. In strongly PPD-sensitized individuals the clinical picture of an acute contact dermatitis in its early stage may resemble angioedema. In the patch test done 8 weeks after the above mentioned symptoms very strong (+++) positive test reactions were detected for p-phenylenediamine, p-toluenediamine, p-aminophenol, p-aminoazobenzene, disperse orange 3 after 72 hours. Strong positive (++) positive test reactions were detected for 4,4'diaminodiphenylmethane. The patient had had obtained a henna tattoo during a holiday in Croatia at the age of 7.

When the license for patch testing has been obtained, p-phenylenediamine (PPD) 0.3 % in petrolatum will be included in the standard series [27]. Following clear evidence of iatrogenic sensitizations by PPD at higher concentrations (1%), it was excluded from the standard series in 2005, and has since then been tested exclusively within the “Hairdressing Chemicals” series. This is not the case for PPD at reduced concentrations [28, 29]. PPD is not only used in hair dyes, but added at much higher concentrations to black henna for temporary tattoos, to make them look more like permanent tattoos. These higher concentrations often induce severe allergic contact dermatitis to PPD and structurally related substances. Figure 3 shows extensive facial swelling in a 13-year-old girl after a hair coloring procedure, who had been sensitized by a henna tattoo at 7 years of age.

Localization of allergic contact dermatitis

Using the DKG standard series, the DKG-/IVDK centers patch tested a total of 38,878 patients (38,966 tests) between 2010 and 2012. Because a recent new sensitization was suspected, 88 patients were tested twice. The test cohort is characterized according to the MOAHLFA index [30] (Table 2).

Table 2 Characterization (MOAHLFA-Index) of the 38.878 patients patch tested 2010 to 2012 in the hospitals contributing to the DKG-IVDK consortium.

		Number	Percentage
Male	M	13 957	35.9
Occupational disease	O	6 287	16.2
Atopic Dermatitis	A	8 278	21.3
Dermatitis of the Hands	H	10 665	27.4
Dermatitis of the Legs	L	4 093	10.5
Dermatitis of the Face	F	6 103	15.7
Age ≥ 40 years	A	28 412	73.1

In 10,221 patients (26.3%), allergic contact dermatitis was diagnosed (1st or 2nd final diagnosis). Table 3 shows the most frequent sites for dermatitis in patients with final diagnosis of allergic contact dermatitis and being sensitized to one or more allergens of the standard series. The hands are the most frequent sites for both occupational dermatoses and contact allergies.

Influence of legislation on patch testing

Current German legislation regulating patch test allergens exerts strong influences on

(i) the epidemiological surveillance and sentinel function of the IVDK network and thus preventing the early recognition of novel, important allergens and (ii) moreover the individual diagnostic work-up necessary for secondary prevention which would allow the patient to be symptom-free. The background information is briefly summarized:

With its 12th amendment in 2004, the German Medicinal Products Act (The Drug Law) (Arzneimittelgesetz, AMG) section 4, sub-section 5 defines allergens as “medicines containing antigens or haptens, which are intended to, in humans or animals, detect specific antibodies or protective substances (test allergens), or which contain substances to be used to reduce a specific immunologic hypersensitivity with an antigen-specific mechanism (therapeutic allergens)”. This has been the implementation of the existing EU directive 2001/83/EC into national (german) law [31]. Test allergens (patch or prick test substances) and therapeutic allergens (substances for allergen immunotherapy) are subject to the same authorization requirements as, for example, chemotherapeutic agents. Large epidemiological studies with putative novel contact allergens, which usually precede clinical registration trials, cannot be achieved under AMG-conditions. After the transitional period ended in 2005, no new patch test substances have been registered, resulting in an increasing

Table 3 The most frequent locations in patients with allergic contact dermatitis (n = 10 221) and diagnosed type IV-sensitization to one or several contact allergens of the DKG standard series. All other locations of the body were affected in less than 1 %.

	Number	Percentage
Hand/hands	2,159	21.1
Face	1,324	13.0
Periocular/lids	731	7.2
Lower leg	724	7.1
Generalized	553	5.4
Scalp	455	4.5
Palmar region	436	4.3
Torso	345	3.4
Leg/legs	252	2.5
Arm/arms	246	2.4
Foot/feet	235	2.3
Back of the hand	203	2.0
Forearm	164	1.6
Neck	155	1.5
Oral mucosa	145	1.4
Anal region	110	1.1
Abdomen	110	1.1
Genital region	105	1.0
Axilla/axillae	100	1.0

diagnostic gap. A critical statement from nine professional societies led by Axel Schnuch highlighted this problem [32].

A recent (2012) statement from the EU Commission Directorate General for Health and Consumers clarified that AMG regulations for clinical studies are applicable to clinical registration trials for test allergens, but not to epidemiological studies designed to assess sensitization prevalence to a new antigen.

This statement was confirmed by representatives of the the German Federal Ministry of Health (Bundesministerium für Gesundheit, BMG) and the Paul Ehrlich Institute (PEI) in an expert round table discussion between the German Dermatologic societies (ABD, ÄDA, DGAKI, DKG, IVDK), the Paul Ehrlich Institute (PEI), the German Federal Ministry of Health (Bundesministerium für Gesundheit, BMG), the German Employers' Liability Insurance associations (Berufsgenossenschaften, BGW) and allergen manufacturers at their meeting in July 2012.

In theory, it is thus possible to conduct epidemiological studies with novel contact allergens manufactured in a licensed pharmacy (section 13 AMG), given the consent of the local ethics committees and the German Central Authority of the Federal States for Health Protection (Zentralstelle der Länder für Gesundheitsschutz, ZLG)/Regional Administrative Council (Regierungspräsidium). Few specialized pharmacies are licensed accordingly. The ZLG/Regional Administrative Councils are independent in their decisions, rendering the abovementioned positions of the BMG and PEI non-binding.

The first draft of the 16th amendment of the German Medicines Act which comprises an amendment of the German Pharmaceuticals and Active Agent Manufacturing Ordinance (Arzneimittel- und Wirkstoffherstellungsverordnung, AMWHV, section 1, sub-section 3 sentence 4), included imminent consequences for already authorized patch test substances which is outlined in more detail in the online supplement [32, 33] (see online Supporting Information).

With the 15th (and unaffected by the 16th) amendment of the German Medicinal Products Act (2009), practicing physicians may “manufacture pharmaceuticals for personal use in an individual patient” according to section 13, sub-section 2b, e.g. for diagnostic use (patch/prick/intracutaneous testing of personal substances such as occupational contactants, medicines or food). Notification and supervision is regulated by section 67 AMG (General notification requirement). The supervising authority in charge varies with the respective federal state within the German federal state. A list of GCP Inspectorates is available at <https://www.zlg.de/zlg/aktuelles/meldung/article/liste-der-gcp-inspektorate-aktualisiert.html>.

For notifications in accordance with section 67 AMG, the transitional period ended by February 1, 2010 (section 144, sub-section 7 AMG). Since then, testing without prior notification is considered a regulatory offence. According to section 64, sub-section 3 AMG, the responsible administrative authority is obliged to conduct site visits at regular intervals, to a reasonable extent and with special respect to potential risks. Site visits at centers and offices are thus to be expected and have taken place in certain federal states. Prior announcement of a site visit is at the discretion of the responsible authority. An official catalog of screening criteria is not available.

Documentation of standardized patch testing and the storage and dilution of the substances does not differ for patient-specific substances as compared to commercially available patch test substances with regard to test procedures and liability-related consequences [6]. Test substance manufacturing must be in accordance with state-of-the-art scientific and technical procedures [34, 35] and has to be documented as such. Standard operating procedures are useful [36]. There

is a tendency of complex allergologic diagnostic procedures to be relocated to specialized centers.

Discussion

Both individual predisposition and private and occupational exposures determine the development of allergies [37, 38]. Exposure is determined by supply and consumer demand, valid legal regulations and surveillance of compliance with these. Consumer demand is shaped by changing life styles: Since 1995, the “eclectic consumption-dependent” group has evolved, demanding an extensive variety of cultural and consumer goods. Free of the explicitly stressed demand for inner maturation and self-development, which were characteristic of the 1980s, they are extravagant consumers with a wide range of exposures [39]. Enjoyment of changing combinations and aesthetic awareness without rational argumentation are characteristics of this trend [39]. At the same time, increasing consumer demand e.g. for hair dye products or henna tattoos for optical enhancement without risk awareness is notable especially in younger age groups (Figure 3). The EU commission estimates that in 2004 more than 60% of women and 5–10% of men dyed their hair [40].

Legal regulations concerning threshold values and analytical procedures have been effective for chromate in cement, as seen by falling sensitization rates. At the same time, the EU nickel directive in its current form has failed to achieve similar results, with stable, high sensitization rates. With sensitization rates of >4% in Germany and Europe [41, 42], a ban of MDBGN from cosmetics was necessary and reasonable and led to a decrease of sensitization rates to <3%, while, however, alternative preservatives are increasingly used.

MI was initially rated as a less-potent contact allergen when compared to MCI, with higher concentrations being permitted. This has led to a dramatic increase in MI sensitizations in exposed subjects. It has thus been shown that the currently permitted concentration in cosmetics is too high and needs to be immediately adjusted.

To take account of current developments of sensitization rates in the cohort tested at DKG/IVDK centers, the DKG standard series has been updated as of January 1, 2014.

These trends in contact allergy development demonstrate the relevance of clinical epidemiology and the sentinel function of DKG and IVDK regarding the prevention of contact allergies and, thus, public healthcare, including primary prevention of sensitization in occupational fields at risk [38, 43–46]. Personal skin protection measures are critical in preventing sensitization. Once contact allergy has manifested, patient information forms the basis of successful secondary and tertiary prevention to preserve ability to work and freedom of eczema symptoms. An online supplement

summarizes negative consequences of the current AMG amendments on epidemiologic studies with novel contact allergens and thus the sentinel function of the DKG and IVDK (see online Supporting Information).

Given the current framework conditions of the AMG, a deficiency in clinical monitoring of novel contact allergens and, on the other hand, a number of practical obstacles to individual diagnostic procedures forecast a diagnostic gap in elucidation of contact allergies. To close this gap in a timely fashion, epidemiological studies with putative novel contact allergens and when of confirmed frequent recognition, the registration of new test substances for novel important contact allergens is imperative. Therefore, DKG and IVDK continue to seek the dialogue with responsible administrative institutions.

Conflict of interest

Vera Mahler is the director of the German Contact Allergy Group, a scientific non-profit organization, which, during the last years, has received donations from Almirall-Hermal and SmartPractice Germany. Vera Mahler has received honoraria for patch test reading courses from Almirall-Hermal.

Axel Schnuch is the head of the IVDK and director of IVDK e.V. For the documentation and scientific data analysis of contact allergies, IVDK has received funding from the German Federal Environmental Agency (Umweltbundesamt), the German employers' liability insurance associations (Berufsgenossenschaften), Unna foundation and IVDK e.V. (prior G.E.P.A. e.V.). Funding members of IVDK e.V. include industry unions and cosmetics companies.

Johannes Geier declares no conflict of interest.

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References

- 1 Schnuch A, Uter W, Geier J, Gefeller O. IVDK study group. Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug-utilization research (CE-DUR) approach. *Contact Dermatitis* 2002; 47: 32–9.
- 2 Schnuch A, Uter W. Die Verbreitung des Kontaktekzems in der Allgemeinbevölkerung und in verschiedenen Berufen. In: Schultze-Werninghaus G, Fuchs T, Bachert C, Wahn U (Hrsg): *Manuale allergologicum*. München: Dustri, 2004: 297–345.

- 3 Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population – prevalence and main findings. *Contact Dermatitis* 2007; 57: 287–99.
- 4 Nosbaum A, Vocanson M, Rozières A et al. Allergic and irritant contact dermatitis. *Eur J Dermatol* 2009; 19: 325–32.
- 5 Vocanson M, Hennino A, Rozières A et al. Effector and regulatory mechanisms in allergic contact dermatitis. *Allergy* 2009; 64: 1699–714.
- 6 Schnuch A, Aberer W, Agathos M et al. Deutsche Kontaktallergie-Gruppe. Durchführung des Epikutantests mit Kontakallergenen. Leitlinien der Deutschen Dermatologischen Gesellschaft; Deutschen Gesellschaft für Allergie und klinische Immunologie. *J Dtsch Dermatol Ges* 2008; 6: 770–5.
- 7 Becker D. Das allergische Kontaktekzem. *J Dtsch Dermatol Ges* 2013; 11: 607–19.
- 8 Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes „Informationsverbund Dermatologischer Kliniken“ (IVDK). *Dermatologie Beruf Umwelt* 2005; 53: 107–14.
- 9 Europäische-Gemeinschaften. Richtlinie 94/27/EG des Europäischen Parlaments und des Rates vom 30. Juni 1994 zur zwölften Änderung der Richtlinie 76/769/EWG zur Angleichung der Rechts- und Verwaltungsvorschriften der Mitgliedstaaten für Beschränkungen des Inverkehrbringens und der Verwendung gewisser gefährlicher Stoffe und Zubereitungen. *Amtsblatt der Europäischen Gemeinschaften (ABl EG) Nr. L 188*: 1.
- 10 Schnuch A, Wolter J, Geier J, Uter W. Nickel allergy is still frequent in young German females – probably because of insufficient protection from nickel-releasing objects. *Contact Dermatitis* 2011; 64: 142–50.
- 11 Europäische-Gemeinschaften. Richtlinie 2004/96/EG der Kommission vom 27. September 2004 zur Änderung der Richtlinie 76/769/EWG des Rates vom 27. Juli 1976 hinsichtlich der Beschränkungen des Inverkehrbringens und der Verwendung von Nickel für nach dem Durchstechen von Körperteilen eingeführte Erststecker zwecks Anpassung ihres Anhangs I an den technischen Fortschritt. *Amtsblatt der Europäischen Union L 301/51* vom 28.9.2004.
- 12 Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. *Contact Dermatitis* 2013; 69: 251–9.
- 13 Schnuch A, Uter W, Geier J et al. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis* 2007; 57: 1–10.
- 14 Scientific Committee on Consumer Safety (SCCS). OPINION on Fragrance allergens in cosmetic products. The SCCS adopted this opinion at its 15th plenary meeting of 26–27 June 2012. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf
- 15 Schnuch A. Comment on Scientific Committee on Consumer Safety SCCS OPINION on Fragrance allergens in cosmetic products. 2013. http://www.ivdk.org/images/stories/medien/mitteilungen/Schnuch_Comment_on_SCCS_Fragrances_opinion.pdf
- 16 Kosmetik-Verordnung in der Fassung der Bekanntmachung vom 7. Oktober 1997 (BGBl. I S. 2410); zuletzt geändert durch Artikel 1 der Verordnung vom 21. Dezember 2012 (BGBl. 2013 I S. 2). <http://www.gesetze-im-internet.de/bundesrecht/kosmetikv/gesamt.pdf>
- 17 Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; 67: 334–41.
- 18 Uter W, Gefeller O, Geier J, Schnuch A. Methylchloroisothiazolinone / methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients of 19 years. *Contact Dermatitis* 2012; 67: 125–9.
- 19 Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013; 69: 231–8.
- 20 Uter W, Schnuch A. EMA revokes marketing authorization of bufexamac. *Contact Dermatitis* 2011; 64: 235–6.
- 21 Richtlinie 2003/53/EG des Europäischen Parlamentes und des Rates vom 18. Juni 2003 zur 26. Änderung der Richtlinie 76/769/EWG des Rates über Beschränkungen des Inverkehrbringens und der Verwendung gewisser gefährlicher Stoffe und Zubereitungen (Nonylphenol, Nonylphenolethoxylat und Zement). *Amtsblatt der Europäischen Union L 178/24* vom 17.7.2003.
- 22 Geier J, Krautheim A, Uter W et al. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health* 2011; 84: 403–11.
- 23 DIN EN 420:2010–03. Schutzhandschuhe – Allgemeine Anforderungen und Prüfverfahren; Deutsche Fassung EN 420: 2003 + A1: 2009.
- 24 BfR empfiehlt, Allergie auslösendes Chrom (VI) in Lederprodukten streng zu begrenzen. Stellungnahme Nr. 017/2007 des BfR vom 15. September 2006, aktualisiert am 24. Mai 2007. http://www.bfr.bund.de/cm/343/bfr_empfiehl_allergie_ausloesendes_chrom_in_lederprodukten_streng_zu_begrenzen.pdf
- 25 Geier J, Lessmann H, Mahler V et al. Occupational contact allergy caused by rubber gloves – nothing has changed. *Contact Dermatitis* 2012; 67: 149–56.
- 26 Schnuch A, Uter W. Epikutantestung mit der DKG-Standardserie – ein Rückblick. *Allergologie* 2009; 32: 262–72.
- 27 Geier J, Ballmer-Weber BK, Dickel H et al. Monitoring contact sensitization to p-phenylenediamine (PPD) by patch testing with PPD 0.3 % in petrolatum. *Contact Dermatitis* 2013; 69: 26–31.
- 28 Becker D, Mahler V, Szliska C et al. The concentration of paraphenylenediamine (PPD) for routine patch testing in a standard series needs to be redefined. *Contact Dermatitis* 2005; 53: 186–7.
- 29 Hillen U, Dickel H, Löffler H et al. Late reactions to patch test preparations with reduced concentrations of p-phenylenediamine: a multicentre investigation of the German Contact Dermatitis Research Group. *Contact Dermatitis* 2011; 64: 196–202.
- 30 Schnuch A, Geier J, Uter W et al. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40 000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; 37: 200–9.

- 31 Richtlinie 2001/83/EG des Europäischen Parlamentes und des Rates vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel. Amtsblatt der Europäischen Union L 311 vom 28.11.2001, S. 67.
- 32 Schnuch A, Mahler V, Elsner P et al. Der Allergie-Diagnostik mit dem Epikutantest droht das Aus. Gemeinsame Stellungnahme zur Novellierung des Arzneimittelgesetzes der DDG, DGAKI, DKG, ABD, BVDD, ÄDA, GPA, DGAUM und des IVDK. *J Dtsch Dermatol Ges* 2012; 10: 280–1.
- 33 Deutscher Bundestag. Gesetzentwurf der Bundesregierung. Entwurf eines Zweiten Gesetzes zur Änderung arzneimittelrechtlicher und anderer Vorschriften. Drucksache 17/9341. 18. 04. 2012. <http://dip21.bundestag.de/dip21/btd/17/093/1709341.pdf>
- 34 Frosch PJ, Pilz B, Peiler D et al. Die Epikutantestung mit patienteneigenen Produkten. In: Plewig G, Przybilla B (Hrsg.): Fortschritte der praktischen Dermatologie und Venerologie 1996. Berlin: Springer Verlag, 1997: 166–81.
- 35 De Groot AC. Patch Testing, 3rd Edition, acdegroot publishing, Wapserveen, 2008.
- 36 Mahler V. Epikutantests mit patienteneigenen und zugelassenen Testsubstanzen. *Dtsch Dermatologie* 2013; 61: 295–301.
- 37 Schnuch A, Westphal G, Mössner R et al. Genetic factors in contact allergy—review and future goals. *Contact Dermatitis* 2011; 64: 2–23.
- 38 Uter W, Gefeller O, Geier J et al. Untersuchungen zur Abhängigkeit der Sensibilisierung gegen wichtige Allergene von arbeitsbedingten sowie individuellen Faktoren. Bremerhaven. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Forschung, Fb 949, 2002.
- 39 Wahl A. Die Veränderung von Lebensstilen, Generationsfolge, Lebenslauf und sozialer Wandel, Campus Verlag, Frankfurt am Main 2003: 135–40.
- 40 European Commission. Commission bans 22 hair dye substances to increase consumer safety. IP/06/1047 20/07/2006. http://europa.eu/rapid/press-release_IP-06-1047_en.htm
- 41 Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br J Dermatol* 2011; 164: 1316–25.
- 42 Svedman C, Andersen KE, Brandão FM et al. Follow-up of the monitored levels of preservative sensitivity in Europe: overview of the years 2001–2008. *Contact Dermatitis* 2012; 67: 312–4.
- 43 Søstved H, Basketter DA, Estrada E et al. Ranking of hair dye substances according to predicted sensitization potency: quantitative structure-activity relationships. *Contact Dermatitis* 2004; 51: 241–54.
- 44 Uter W, Geier J, Lessmann H, Schnuch A. Unverträglichkeitsreaktionen gegen Körperpflege- und Haushaltsprodukte: Was ist zu tun? Die Informations- und Dokumentationsstelle für Kontaktallergien (IDOK) des Informationsverbundes Dermatologischer Kliniken (IVDK). *Dtsch Dermatologie* 1999; 47: 211–4.
- 45 Lessmann H, Uter W, Geier J, Schnuch A. Die Informations- und Dokumentationsstelle für Kontaktallergien (IDOK) des Informationsverbundes Dermatologischer Kliniken (IVDK). *Dermatologie Beruf Umwelt* 2006; 54: 160–6.
- 46 Geier J, Krautheim A. Das Netzwerk „Kontaktallergien durch Berufsstoffe“ – KAB-Netzwerk. *Dermatologie Beruf Umwelt* 2010; 58: 139–40.

Appendix

Patients/ Materials and Methods: participating centers, patch test procedure and supplier information for patch test material

From 2010–2012, the following 50 Departments of Dermatology from Germany, Austria and Switzerland participated: Aarau, Augsburg, Basel, Berlin Charité, Bern, Bielefeld, Bochum St. Josefs-Hospital, Bochum IPA, Dessau, Detmold, Dortmund, Dresden, Erlangen, Essen, Falkenstein, Freudenberg, Gera, Graz, Greifswald, Göttingen, Halle, Hamburg BUK, Hamburg Dermatologikum, Hamburg UKE, Hannover, Heidelberg Univ.-Hautklinik, Heidelberg Abt. klin. Sozialmedizin, Heilbronn, Homburg/Saar, Jena, Lausanne, Leipzig, Luebeck, Mainz, Mannheim, Marburg, Minden, Munich LMU, Munich Schwabing, Munich TU, Muenster, Nuremberg, Oldenburg, Osnabrück, Rostock, Stuttgart, Tübingen, Ulm, Wuerzburg, Zurich.

Patch testing was done in accordance with AWMF guideline 013-018 „Patch testing with contact allergens“ [6]. Patch test substances were supplied by Almirall Hermal, Reinbek, Germany, SmartPractice Germany, Barsbüttel, Germany and Chemotechnique, Vellinge, Sweden. As test chamber systems, 46 centers used Finn Chambers on Scanpor (SmartPractice Germany), two centers used Haye's Test Chambers [HAL Allergie, Duesseldorf, Germany] and one center each used IQ Chambers [Chemotechnique, Vellinge, Sweden] or Curatest F [Lohmann & Rauscher, Neuwied, Germany]. Patch exposure time was 24h in eight centers (3 953 patients) and 48h in 42 centers (34 925 patients). Test reading was done after 48 and 72 hours. In a few single cases, test reading was done after 96h instead of 72h. According to current guidelines, tests were read as negative, allergic (positive), questionable or irritant. In the list of the TOP 25 most frequent contact allergens, only allergic reactions (+, ++, +++) were included [6]. Patch test data were transferred to the IVDK in anonymized form together with final diagnoses, eczema localization, medical history of atopic dermatitis, allergic rhinitis, allergic bronchial asthma, occupation, age and gender.

Influence of legislation on patch testing: Imminent effects of the draft for the 16th amendment to the AMG

According to the draft bill for the 16th amendment to the AMG issued in December 2011, comprising an amendment to the German Pharmaceuticals and Active Agent Manufacturing Ordinance (Arzneimittel- und Wirkstoffherstellungsverordnung, AMWHV, section 1, sub-section 3 sentence 4), GMP conditions would have been valid for the raw material manufacturing of contact allergens. This would have neces-

sitated a market withdrawal of all patch test substances, as worldwide no GMP-certified production of consumer substances (hair dyes, rubber accelerators, fragrances etc.) exists. For contact allergen manufacturing, this is neither necessary nor reasonable. Following a joint initiative of the allergologic societies [32] and a mediation by the Paul Ehrlich Institute, the 16th amendment to the AMG effective October 26, 2012 excludes the manufacture or production of raw materials for patch test substances from GMP requirements according to the EG GMP guideline, ensuring the continued production of registered patch test substances.

The abovementioned specification of patch test substances is listed in printed matter 17/9341 of April 18, 2012 (Statement of grounds, B. special section regarding article 10 [Amendment to the German Pharmaceuticals and Active Agent Manufacturing Ordinance] concerning sentence 1 [section 1], letter c; pp. 73–74) [33].

Effects of AMG amendments on epidemiologic studies with novel contact allergens

The AMG amendment negatively influences epidemiologic studies with new contact allergens and thus compromises the abovementioned sentinel function of the DKG/IVDK cooperation regarding relevant new contact allergens, as currently these, although the general public is exposed to them on a daily basis, cannot be monitored.

Given the current legal conditions, new relevant contact allergens cannot be identified in epidemiologic studies, and subsequently will not be registered as patch test substances, with an ever-widening diagnostic gap as a result. The Scientific Committee on Consumer Products has, for example, identified 229 hair dye components as potential allergens, suggesting a ban on 93 [43]. In contrast, 11 hairdressing substances are listed in the DKG hairdressing series. An epidemiologic study with potential new contact allergens in hairdressing products has been prepared, but could not be initiated due to conflicting interpretations of the current legal framework by the ZLG. Currently, individual testing with patient-owned substances can partly bridge this diagnostic gap. In singular cases, products can be identified, however, the individual allergen cannot be identified and thus not be avoided in other products in the future. A request for single components from the manufacturers is time-consuming and often completely unsuccessful due to cooperation issues. For components of cosmetics, the German Information and Documentation Center for Contact Allergies (Informations- und Dokumentationsstelle für Kontaktallergien, IDOK) provides support for ordering test substances and information on suitable test concentrations [<http://www.ivdk.org/de/ueber-den-ivdk/portrait/10-allgemein/17-idok>] [44, 45], while comparable resources for occupational allergens are not available anymore [46].