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REVIEW ARTICLE

Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK)

A. Schnuch[1], J. Geier[1], H. Lessmann[1], R. Arnold[1] & W. Uter[2]

[1]Information Network of Departments of Dermatology, University of Göttingen, Göttingen; [2]Department of Medical Informatics, Biometry and Epidemiology, University Erlangen-Nürnberg, Erlangen, Germany

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Correspondence
Prof. Dr. Axel Schnuch, IVDK-Zentrale, Institut an der Universität Göttingen, Von Siebold Str. 3, 37075 Göttingen, Germany.
Tel.: +49 551 396439
Fax: +49 551 396095
E-mail: aschnuch@med.uni-goettingen.de

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Abstract

Contact allergy (CA) surveillance networks provide information to a multitude of stakeholders, which is indispensable for evidence-based decision-making in the field of prevention. Methods and results of the German surveillance system on CA are reviewed and discussed with reference to other systems. The German network structure comprises 56 departments of dermatology and includes all patients who are patch-tested for suspected CA. Data analysis considers the results of patch testing and further pertinent information for each patient. Following aspects are addressed: (i) the description of the clinical population, (ii) evaluation of patch test reactions, (iii) relationship between patch test results and population characteristics. Trend analyses on chromate (decreasing), epoxy resin (increasing) and nickel (heterogeneous) served as examples for surveillance system analyses, with the identification of sentinel events, as well as proof of success or failure of prevention. In addition, external data sources can be used such as sales data of patch test preparations to estimate frequencies of sensitization on a population level. National prescription data of drugs and statistics of labelling of preservatives on cosmetics can be included, the latter two approaches allowing for risk estimates conferred by specific allergens.

Contact allergy (CA), comprising allergic contact dermatitis (ACD) as a clinical entity and underlying delayed-type sensitization as a latent condition, is triggered by natural or man-made chemicals of usually low molecular weight (contact allergens or haptens) in private or occupational settings. Substantial progress has been made in understanding the pathophysiologic mechanisms underlying ACD (1), but chasing the responsible provocating agent(s) for each individual patient remains a difficult task. Occupational CA represents a substantial socio-economic burden in Germany and in other countries, requiring steady monitoring to target in-depth research and preventive action, respectively. Management of this disease must consider its particular characteristics (2). In this review, we focus on epidemiological and preventive aspects.

Contact allergies as a public health and occupational safety problem

The main reasons to perform surveillance of CA are manifold.

1 Although the symptoms of ACD can be treated, for example, with glucocorticoids, 'silent' sensitization can hitherto not be cured. Sensitized individuals are at permanent risk of a relapse of ACD upon each sufficient contact with the offending substance(s). As a consequence, the 'quality of life' as assessed by appropriate instruments was found to be reduced (3).
2 ACD is frequent in the general population. About 7% per year are affected by ACD, and between 15–20% were found to be sensitized to at least one of the major allergens (4).
3 ACD as occupational disease is associated with sick leave and potential loss of occupation – not to mention the severe individual psycho-social burden. At least in certain subgroups, for example construction workers, the prognosis was shown to be bad (5). Direct and indirect costs of occupational ACD in Germany are in the range of 700 million € per year (6); hence, it is a disease with high socio-economic impact.

These characteristics of CA, and in particular of sensitization (incurable, frequent, high costs), render prevention an important objective of public health. Because, in contrast to the majority of airway allergens, most contact allergens are man-made and skin contact to contact allergens is often determined by behaviour, CA is preventable, at least in principle.

A prerequisite for preventive intervention in this field is the unequivocal identification of the allergen and the exposure conditions leading to allergen contact. As new allergens continuously emerge and as exposure to known allergens often changes over time, continuous surveillance is mandatory to keep knowledge updated and readjust prevention, if necessary. This can be achieved with the help of a surveillance system (7).

Objectives of a surveillance system on CA

Generally, surveillance systems have several objectives: (i) to show the persistence of a real problem, (ii) to put into perspective an assumed problem, (iii) to identify emerging problems by monitoring trends (sentinel events) and (iv) to prove the success of interventions (8). The history of public health surveillance goes back to 1348 (Venice) and 1377 (Marseille), where these cities were forced to take measures (e.g. quarantine) against plague, much later followed by the surveillance of infectious diseases, occupational diseases and side effects of drugs (9). Thus, the surveillance of CA has its roots in the long history of public health.

The main objective of surveillance of CA is the provision of valid, up-to-date data as a basis for evidence-based prevention. Several aspects referring to the strategies outlined above can be distinguished:

1 What is the current *importance of known allergens*? The importance, possibly relative to other, related compounds, can be identified by means of a quantitative description of the persistence or time trend of a recognized allergen.
2 Which *new allergens* are emerging? 'Emergence' can be identified in terms of a predefined *sentinel event* above a threshold of concern, for example a certain number of cases (in certain subgroups).
3 Which *exposure conditions* are associated with CA to a specific allergen? These may comprise occupational and nonoccupational exposures to allergenic chemicals or products.
4 Which sensitizations are associated with a specific (occupational or nonoccupational) exposure (*Allergen pattern of a certain exposure*)?

Methods of the CA surveillance system IVDK

Surveillance systems are described along the 'Guidelines for Evaluating Surveillance Systems' of the Center of Disease Control (CDC), Atlanta, Georgia (8, 10), which refer to public health importance, objectives, elements and attributes such as sensitivity, timeliness, representativeness, accuracy, completeness and flexibility and which have been discussed in detail elsewhere (7).

Structural elements of the surveillance system

The consortium includes 56 departments of dermatology from Germany, Switzerland and Austria, which participate in the surveillance system IVDK (participants mentioned under acknowledgements; for further details, see http://www.ivdk.org/de/ueber-den-ivdk/mitglieder).

Patients are not specifically recruited for the purpose of surveillance. Instead, all patients who consult the departments of the network in the context of routine care are included, namely those patients who are patch-tested for suspected CA. Thus, the surveillance system does not entail costs for case recruitment as other epidemiological projects may do. Data generation for the surveillance system is an almost 'automatic by-product' of the departmental data documentation. Data are electronically stored by means of the proprietary software (WinAlldat/IVDK). Data comprise the following:

1 results of patch testing, with type and strength of reactions as well as their time course and including also all negative reactions. Patch testing is performed according to national and international guidelines (11).
2 data from the patients' history (with information on occupation and suspected causal exposures categorized using a catalogue of more than 50 'contactants' such as textiles, glues, paints etc.) and
3 clinical data (final diagnosis, for example irritant or ACD, anatomical site of the dermatosis, atopic dermatitis).

Data of all patch-tested patients are transferred in an anonymous format twice yearly to the data centre in Göttingen. In subsequent analyses, cases of interest are identified within the pooled data. While passive surveillance systems rely on the motivation of those reporting, for example in systems on adverse drug effects or on occupational diseases, and are thus hampered by serious underreporting (12), the active approach of the IVDK ensures the completeness of the database. [Completeness and timeliness are important 'attributes' of a surveillance system (7).]

Data analysis

All anonymous data are stored in the data centre in Göttingen. Data management and analysis is performed with the statistical program package SASTM (version 9.2; SAS Institute, Cary, NC, USA). After each of the twice-yearly data transmissions, the quality is checked with a standard report, which is reviewed in the data centre, and delivered and discussed with the participating departments. For further, scientific analyses, only data fulfilling internal quality standards (13) are considered. Methods of data analyses follow statistical guidelines (14). In the following sections, the most pertinent approaches are briefly presented.

Description of the clinical population

The basic and overall most important characteristics of patients patch-tested are described following the lines of the MOAHLFA index (15), which was recently extended to

include the percentage age of patients positive to at least one baseline series allergen (16): M (men), O (occupational dermatitis), A (atopic dermatitis), H (hand dermatitis), L (leg dermatitis), F (face dermatitis) and A (age >40). These characteristics have a proven and profound impact on the allergen spectrum. Thus, consideration of these characteristics will help to explain differing results from different centres (15), for example high frequencies of sensitization to epoxy resin in a population with many occupational cases ('O') or high prevalences of sensitization to topical medications in departments providing care to many elderly patients, possibly with leg dermatitis ('L') (17). Furthermore, generalization of the results beyond the specific subgroup or an undue comparison between studies is put into perspective by the differing main population characteristics. Meanwhile, the MOAHLFA index is widely used in studies of clinical epidemiology of CA (18). The MOAHLFA index has primarily evolved as an array of simple descriptive measures. However, the patient characteristics assembled in the index are so important that they are also used as adjustment factors, for example, for standardization (Table 1) (15) and in multifactorial analyses (Table 5) (19).

Evaluation of patch test reactions

The basic descriptive measure in the analysis of patch testing is the proportion (%) of allergic reactions out of all patients tested. The proportions are usually accompanied by the 95% confidence interval (14) to indicate precision. Reaction type (allergic *vs* irritant/doubtful) and strength (+, ++, +++) are evaluated. This allows further characterization of the reaction pattern of a given allergen by standardized methods, namely the reaction index (RI) and the positivity ratio (PR). These parameters are evaluated routinely and are now used by other groups (20).

The RI (21) describes the relation of allergic (+ to +++) to nonallergic (doubtful/irritant, that is, nonnegative) reactions, ranging from −1 to +1. The lower limit indicates that all reactions were nonallergic and the upper that all reactions were allergic. Thereby, a negative RI indicates a large number of '?' and/or irritant reactions in relation to positive reactions (owing to, for example, an inherent irritant potential of the substance or too low a test concentration). As a consequence, further research into the most adequate test preparation might be necessary. The PR (22) is the percentage of '+' reactions among all allergic reactions. A high PR, for example, >90%, together with a negative RI may indicate that some of the '+' reactions can be assumed to be not allergic, but irritant (i.e. false positive). Conversely, the patch test concentration may be too low, yielding fewer strong or extreme allergic reactions than usual. Both parameters can guide optimization of a patch test preparation and aid cautious interpretation of epidemiological data. For

Table 1 Persistence of problems: frequencies of sensitization to allergens of the baseline series in 2010

Allergen	Sensitization prevalence (%) of patients tested	95% CI	Standardized sensitization prevalence (%)	95% CI
Nickel sulphate	13.3	12.7–14.0	15.0	14.2–15.8
Fragrance mix I	8.4	7.9–9.0	7.4	6.9–7.9
Myroxylon pereirae (Balsam of Peru)	7.2	6.7–7.7	6.0	5.5–6.4
Fragrance mix II	5.5	5.1–5.9	5.0	4.6–5.4
Cobalt chloride	3.9	3.6–4.3	4.5	4.1–5.0
Colophony	3.7	3.4–4.1	3.6	3.2–4.0
MCI/MI (e.g. Kathon CG®)	3.2	2.9–3.6	3.0	2.6–3.3
Oil of turpentine	3.2	2.8–3.5	2.9	2.5–3.2
Potassium dichromate	2.6	2.3–3.0	2.6	2.2–2.9
Lanolin alcohols	2.6	2.3–2.9	2.5	2.1–2.8
MDBGN	2.5	2.3–2.9	2.2	1.9–2.5
Thiuram mix	2.2	2.0–2.5	2.2	1.9–2.5
Propolis	2.1	1.8–2.4	2.0	1.7–2.3
HICC (e.g. Lyral®)	2.1	1.8–2.4	1.9	1.6–2.2
Epoxy resin	1.5	1.3–1.7	1.4	1.1–1.6
Compositae Mix	1.4	1.2–1.6	1.2	1.0–1.4
Bufexamac	1.0	0.9–1.3	1.0	0.8–1.2
Formaldehyde	1.0	0.8–1.2	1.0	0.8–1.2
Cetostearyl alcohol	0.9	0.8–1.1	0.7	0.6–0.9
IPPD	0.7	0.5–0.9	0.7	0.5–0.9

Crude prevalences and prevalences adjusted for age and sex together with the 95% confidence intervals (CI) are displayed. A prevalence of 8% in the clinical population indicates a prevalence of >1 million in the general population of Germany, for instance (4). Thus, such routine statistics prove the persistence of problems.

MDBGN, methyldibromo glutaronitrile; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, *N*-Isopropyl-*N*′-phenyl-p-phenylenediamine.

instance, the relatively high number of 'allergic' reactions to benzalkonium chloride (BAC) can most likely be interpreted as mainly false-positive (irritant) reactions (23). Differences between centres with regard to the PR and RI of certain allergens may be due to methodological differences in patch test reading and thus indicate the need for further harmonization between centres, an aspect generally disregarded up to now.

For some years, the irritant sodium lauryl sulphate (SLS) is being tested in parallel with the baseline series. A reaction to SLS (0.25% in water) indicates a higher propensity of the individual to irritation. It thus may help interpreting weak positive reactions to allergens that are at the same time marginal irritants (under patch test conditions) and, together with RI and PR of the allergen considered, may put into perspective an 'allergic' (+) reaction in the individual case (24).

Relationship between patch test results and population characteristics

Standardization: If the proportion of positive reactions – across time, and/or in certain subgroups – is of primary interest, the confounding effect of patient characteristics associated with sensitization needs to be addressed to achieve unbiased results. As one technique, direct standardization, usually for age and sex, yields unbiased prevalence estimates (14). For example, time trend analyses without standardization of data may be misleading if the underlying population characteristics have changed over time.

Stratification: Subgroup-specific characteristics may be obscured by the standardization process (25). Therefore, stratification for specific subgroups (e.g. defined by different groups of age, gender, occupation or other characteristics) is a useful approach to identify subgroup-specific problems that could otherwise not be identified.

Multifactorial analyses: If the risk of sensitization to a certain allergen associated with one or more factors is of interest (e.g. occupation), potential confounders such as sex and age, but also atopic dermatitis, anatomical site of dermatitis or year of patch testing, can be confounding factors. In this situation, multifactorial analyses (logistic or Poisson regression) are performed to control for the confounding factors (Table 5) (14, 19).

Certain research questions may require additional statistical tools beyond the methods outlined above. Close cooperation between dermatologists and biostatisticians has proven extremely useful to avoid the use of inadequate statistical methods (26).

Results of the IVDK

The ever-growing database (220 339 patients up to December 2011) may be used in two different ways: (i) as a dynamic surveillance system in its proper sense, essentially updating time trend analyses each year, and (ii) as a registry, basically analysing associations between sensitization and population characteristics with satisfactory statistical power and precision. Results are presented as typical examples. The complete list of publications on the homepage of the IVDK displays the variety of research issues dealt with (http://www.ivdk.org/de/aktivitaeten/publikationslistensubmenu).

The surveillance system

The IVDK defines itself mostly as a surveillance system, the register being a welcome by-product. It is not primarily through registry data and analyses, but through continual surveillance that timely warnings and subsequent prevention are made possible. Timeliness is evidently one of the important attributes of a surveillance system dedicated to the control of rapidly spreading infections (8, 10). However, in contrast to infectious diseases, ACD has a slowly developing dynamic. Timeliness has therefore to be interpreted differently, being not in the range of days or weeks but rather several months or few years. The strategies of surveillance include, above all, the detection of sentinel events through monitoring trends, 'cornerstone objective of most surveillance systems' [Buehler (8)] (Figs 1 and 2). Other objectives should not be underestimated, such as pointing at the persistence of problems (Table 1 and Fig. 2) or offering evidence of the success of preventive interventions (Table 2). The proof of successful interventions on the level of primary prevention is not less than the late justification of occasionally expensive measures (27).

Decrease in chromate CA in the building trade: proof of successful, if belated, intervention

Since more than 100 years, the 'cement scabies' affecting construction workers is well known to occupational physicians (28), and cement dermatitis remained a serious problem for several decades (29). It had been proven that the level of hexavalent chromate [the culprit allergen in cement (30)] can be reduced by the addition of ferrous-II-sulphate (31). In Germany, the permitted threshold was set at 2 ppm only at the end of the 1990s, and according to a recent analysis, sensitization to chromate decreased significantly in construction workers in Germany employed since 1999, compared with

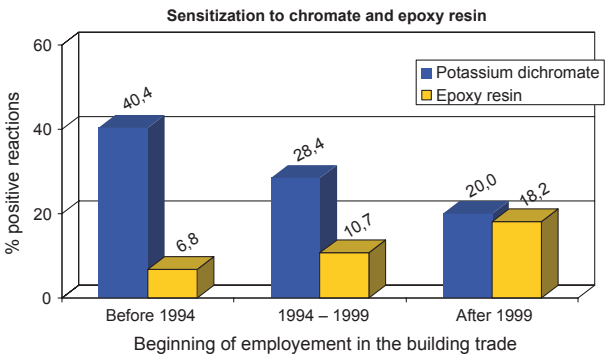

Figure 1 Time course of contact allergy to potassium dichromate and epoxy resin related to the start of employment in patients working in the building trade (as bricklayers, concrete workers, construction workers, floor layers, plasterers, terrazzo layers, tile setters) suffering from occupational dermatitis (n = 1153) (32).

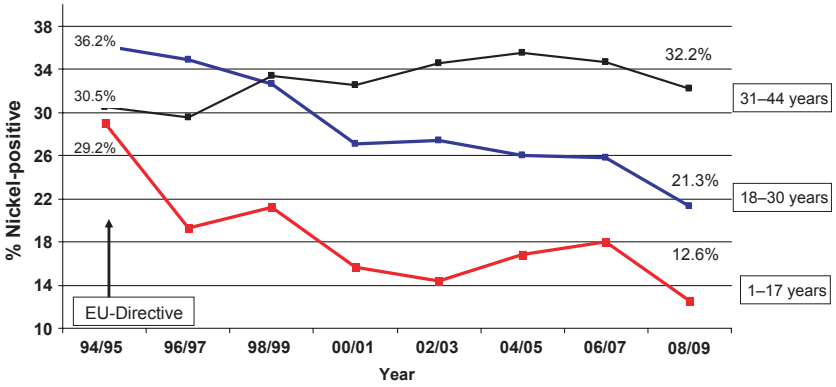

Figure 2 Nickel allergy in women of different age groups. Data from the IVDK 1994–2009, number of patients tested: 2357, 13 936 and 16 478, respectively. Decreasing and increasing trends significant (Cochrane–Armitage trend tests: <0.0001). Most remarkably, nickel allergy in the age group 1–17 did not decrease significantly between 2000 and 2009, indicating a failure of the directive, as the vast majority of this age group came into contact with potentially nickel-containing objects only after nickel regulation (40).

Table 2 Proof of success of primary prevention targeting the noxious agent, provided by IVDK studies and partly also by studies of other networks

Allergen/exposure	a (%)	Intervention	b (%)	Ref. IVDK	Other studies
Glycerylmonothioglycolate ('acid' permanent wave) in young female hairdressers	46	Withdrawal from the market	0	(27)	
Nickel (costume jewellery) in women <30 years of age	37	EU N ickel directive Limit 0.5 μg/cm^2/week	26	(38)	(39)
MCI/MI in men exposed to paints	11	Limitation to 15 ppm (EU and German EPA)	4	(27)	
Fragrances (FM I)	13	Among other changes, reduction of use concentrations following IFRA recommendations	7	(71)	(70)
MDBGN	4	Use prohibited	2	(74)	(69)
Chromate (in construction workers)	40	Limitation to 2 ppm in cement	20	(32)	(33)

a = Sensitization *before* intervention in the IVDK data.
b = Sensitization *after* intervention in the IVDK data.
MDBGN, methyldibromo glutaronitrile; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.

workers exposed to cement before 1994 (Fig. 1) (32). Early reports from Scandinavia (33) and, finally, Germany (32) may be regarded as the proof of success of a rather costly regulation.

Increase in epoxy resin allergies in the building trade: a sentinel event in a surveillance system

Contact allergy to epoxy resin systems is often acquired through occupational exposure in the building trade, where they are increasingly used, for example, as two-component adhesives or in floor coating. In previous analyses, it had been shown that construction workers and painters are particularly at risk of becoming sensitized (Tables 3 and 4) (34). Recently, a time trend analysis considering not only the years of patch testing but (for the first time) the years in which the patients started working in the building trade revealed that patients who started to work after 1999 had higher percentages of epoxy resin sensitization than those with an earlier start [18.2%, compared to 10.7% (start in 1994–1999) and 6.8% (start before 1994)] (Fig. 1) (32).

Heterogeneous trends in nickel allergy: success and failure of regulation

For decades, allergy to nickel remained the most frequent CA in patch-tested patients (15, 35) as well as in the general population (4, 36). The main cause is exposure to costume jewellery. After the EU nickel regulation in 1994, limiting the exposure to nickel through nickel-containing objects (37), a substantial decrease in nickel allergy ensued (Fig. 2) (38, 39). In subsequent analyses, however, no further decrease could be noted (Fig. 2), and it became clear that nickel allergy had persisted as a health problem (40). The concern raised by our epidemiological findings prompted state agencies to analyse samples of costume jewellery, showing that a substantial number of objects still did release high amounts of nickel (40). In line with these findings, studies from Europe, United

Table 3 Exposure patterns of allergens as expressed by an increased risk quantified by the prevalence ratio (PR) of sensitization conferred by occupations and occupational groups after multiple Poisson regression analyses (19)

Occupation	PR	95% CI
Allergen: chromate		
Construction worker	3.79	(3.18–4.51)
Metal coater	3.07	(1.82–4.84)
Metal ore processor	2.03	(1.18–3.24)
Miner, stonemason	2.02	(1.13–3.32)
Office worker	1.00	(reference)
Allergen: epoxy resin		
Construction and mining workers	4.08	(2.81–6.00)
Painter, carpenters, ceramic workers	3.76	(2.52–5.63)
Chemical plant operators	2.70	(1.73–4.20)
Metal workers	1.43	(0.99–2.09)
Service occupations NEC	1.00	(reference)
Allergen: thiuram mix		
Rubber manufacturers, vulcanizers	4.49	(1.61–10.95)
Physician, dentist and related	2.43	(1.46–4.32)
Nurses	2.09	(1.30–3.62)
Construction worker	1.90	(1.12–3.43)
Waiter, bartender, etc.	1.00	(reference)

CI, confidence interval; NEC, not elsewhere classified.

States and East Asia (from which costume jewellery is often imported into the EU) also showed a high percentage of products releasing considerable amounts of Nickel (41–43). Thus, a partial failure of the nickel directive has been identified. This failure remained unnoticed by regulatory authorities owing to a lack of systematic outcome control regarding the effect of regulations (40).

Registry-based analyses

Identification of high-risk occupations with regard to specific sensitization

Certain occupations are associated with specific sensitizations (Tables 3 and 4). This information is indispensable for successful secondary prevention in finding alternative occupations suitable for sensitized workers. The risk to be sensitized to allergens of the baseline series conferred by occupations has been evaluated systematically and comprehensively in the context of a project commissioned by the national agency of occupational health and safety (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin) (19).

Sources of exposure associated with sensitization: the case of p-phenylenediamine (PPD)

The question of interest in this analysis was whether sensitization to PPD is mostly due to hair dyeing, as generally assumed (44). Data analysis was based on more than 3000 patients sensitized to PPD, probably the largest study group on this topic so far (45). The MOAHLFA index of patients sensitized to PPD revealed that 'F' (face dermatitis) was underrepresented, in contrast to what might be expected. Taking a closer look, we defined groups of cases according to clinical items (e.g. site of eczema: face) and according to suspected causal exposures (e.g. contactant 'hair cosmetics' or 'textiles' or work as hairdresser). Finally, 22% of PPD-positive patients could be allocated to hair dyeing in clients [comparable to results of larger multicentre studies in Europe (20%) (46)] and 23% to occupational exposure, mostly by hair dressing (47), and 44% of patients with positive patch test reactions to PPD could not be allocated to any of the subgroups, as a probable causal exposure could not be identified. One of the several possible explanations of such 'unexplained' PPD sensitization may be active sensitization (48). Naturally, in these cases, relevance (of the patch test reaction) cannot be established (48). This descriptive analysis is corroborated by multiple regression analyses (Table 5). Besides hairdressing being a major risk factor for PPD CA, two other occupations bear a significant risk of sensitization, presumably mediated by crossreactive para-aminoarylic rubber compounds (Table 5). In conclusion, an exclusive focus on hair dyeing in the prevention of PPD allergy will miss further opportunities for intervention.

Susceptibility to contact sensitization: a clinical phenotype

In a number of analyses based on the large database, polysensitization (defined as sensitization to at least three unrelated allergens included in the baseline series) was found to be an important risk factor for sensitization to any given allergen – more important than, for example, occupation or

Table 4 Allergen pattern of exposure: sensitization associated with a specific (occupational) exposure: for example construction worker

Allergen	Total tested	Percent positive: Construction workers	Percent positive: Remainder	*P*-value
Potassium dichromate	74203	20.18	3.97	<0.0005
Cobalt chloride	74147	8.56	4.91	<0.0005
Epoxy resin (DGEBA)*	74243	5.94	1.20	<0.0005
Thiuram mix	74211	5.38	2.67	<0.0005
N-Isopropyl-*N*′-phenyl-p-phenylenediamine (IPPD)	68207	2.12	0.93	0.0006

Sensitization prevalence in construction workers compared with all other occupations (34).
*Diglycidyl ether of bisphenol A.

Table 5 Independent factors associated with an increased risk of sensitization to PPD

Effect	OR	95% CI	
Female sex	1.15	1.05	1.26
Age ≥ 40	1.23	1.13	1.33
Medicolegal opinion/occupational cause *vs* other reasons for assessment	2.14	1.9	2.41
Anatomical site *vs* Ref*			
Head–neck	1.39	1.22	1.60
Hand–arm	1.26	1.10	1.43
Occupation (Groups†) *vs* Ref‡			
Hairdresser	3.24	2.70	3.90
Construction	1.52	1.15	2.01
Farming/animal care	1.33	1.01	1.76
Polysensitization			
Additional reactions 1 *vs* 0	2.22	2.02	2.45
Additional reactions 2 *vs* 0	3.29	2.96	3.66
Additional reactions 3 *vs* 0	4.25	3.74	4.84
Additional reactions 4 *vs* 0	6.93	6.11	7.85

Only significant associations displayed. Results of multiple regression analysis (45).

OR, odds ratio; CI, 95% confidence interval; PPD, p-phenylenediamine.

*Reference site: trunk.

†The occupational groups were aggregated as in a former analysis (19).

‡Reference occupation: office worker, teacher.

atopic dermatitis (for example, see Table 5) (49). This clinical phenotype may be useful to identify and advise susceptible individuals on avoiding, for example, occupations associated with a high risk of inducing further contact allergies, in the sense of individual primary prevention. Furthermore, the subgroup of susceptible patients is particularly suitable for studies on the genetics of CA (50).

Complementary use of external data sources

The use of additional external data to complement data of a surveillance system may be particularly fruitful (8). Some examples illustrate this.

The 'Clinical Epidemiology – Drug Utilization Research' (CE-DUR) approach

Clinical epidemiology does not allow direct estimation of sensitization prevalence in the general population, as patients patch-tested are evidently a subgroup of the general population selected for morbidity. Some investigators have used the sales or prescription figures of certain drugs exclusively used to treat one specific disease, such as antiepileptics, to estimate the prevalence of the disease in the general population (51). Transferring this 'drug utilization research' approach to CA, the use of sales data on patch test preparations of the standard series might be a suitable indicator, as patch test preparations are exclusively used in patients with suspected CA (4). On the basis of patch tests sold – data were provided by the main manufacturers – and after correction for a number of factors, most notably the percentage of individuals not consulting a dermatologist (at least two-third experiencing contact reactions) (4), we estimated the total population eligible for patch testing. As this population fulfilled the same selection criteria as the population tested in our network ('suspected CA'), the frequencies of sensitization (%) found in the surveillance system can be applied on the 'total patch test population' and thus extrapolated to the general population. The validity of the approach was corroborated by epidemiological studies in the general population, yielding, for instance, similar prevalences of fragrance mix I allergies (1.6% and 1.8%, respectively) (4, 52). Likewise, frequencies of sensitization to at least one allergen, indicating roughly the total sensitization prevalence, were found being similar (17% and 18%, respectively) (4, 53). This method was repeatedly used (45, 54–56) and may be useful in health reporting and policy advice (56).

Risk assessment of contact sensitization from topical drugs

The CE-DUR model was applied to frequencies of sensitization to topical drugs documented in the IVDK network between 1995 and 2005 in order to estimate the prevalence in the general population (54). In general, topical aminoglycosides showed the highest CA frequencies. According to the CE-DUR medium model, 1-year incidence rates ranged from 29.2 (neomycin sulphate) to 1.0 persons/100 000 (hydrocortisone-17-butyrate) in the general population. Regarding topical antibiotic drugs, more persons were shown to be sensitized, for example, to gentamicin sulphate ($n = 2077$) than to kanamycin sulphate ($n = 1336$). Based on these data, the impact of CA to gentamicin appears higher. However, the risk of becoming sensitized also depends on the amount of exposure. Information on exposure in terms of national prescription data [defined daily doses (DDDs) of topical drug specialties] was provided by the AOK Research Institute, WIdO, Bonn, Germany. The DDDs (in millions) of ophthalmic drugs containing gentamicin were 43.3 and 15.4 in case of kanamycin. By relating sensitization frequencies to the quantities of use, a relative incidence was calculated. The relative incidence of kanamycin (8.7) turned out to be higher than that of gentamicin (4.8). It was thus concluded that the risk of CA associated with kanamycin is higher compared with gentamicin (55).

The 'sensitization exposure quotient' of preservatives used in cosmetics

Unfortunately, standardized and comprehensive exposure data as in the case of topical pharmaceuticals are available only as an exception. Hence, a different, crude approach was used to estimate the risk to be sensitized to preservatives used in cosmetics (57), relying on (i) sensitization prevalences to preservatives documented between 2006 and 2009 in the IVDK data set and (ii) the Chemical and Veterinary Investigation Office (CVUA) in Karlsruhe, Germany, documentation on the labelling of preservatives of 3541 leave-on products during the same period. A 'sensitization exposure quotient'

Table 6 Overview on currently active contact allergy networks, not including multicentre studies of national contact dermatitis groups that are not based on a formal, pre-existing IT-based network [for details, see (58)]

Network (area covered)		Published outcomes (examples)
BCDS (UK)	British Contact Dermatitis Society	(63)
DCDG (DK)	Danish Contact Dermatitis Group	(18, 69)
ESSCA (Europe)	European Surveillance System on Contact Allergies (39 participants from 11 countries)	(60)
GEIDAC-REVAC (E)	Grupo Español en Investigación de Dermatitis de Contacto y Alergia Cutánea (*Spanish Contact Dermatitis Group*) – Red Espanola de Vigilancia en Alergia de Contacto (*Spanish Surveillance System on Contact Allergies*)	(64, 67)
IVDK (D, CH, A)	Informationsverbund Dermatologischer Kliniken (*Information Network of Departments of Dermatology*)	This publication
NACDG (USA, CAN)	North American Contact Dermatitis Group	(59)
NEICDG (I)	North-East Italy Contact Dermatitis Group	(75)
REVIDAL-GERDA (F, B)	Réseau de Vigilance en Dermato-Allergologie (*Surveillance network in Dermato-Allergology*) – Groupe d'Études et de Recherche en Dermato- Allergologie (*French research group in dermatoallergology*)	(68)
SIDAPA (I)	Società italiana dermatologica allergologica professionale e ambientale (*Italian society for allergic, occupational, and environmental dermatology*)	(58)

(SEQ) was calculated as the quotient of the relative frequency of sensitization and the relative frequency of use, a higher SEQ thus indicating a higher risk of sensitization. Again, a divergence between frequency of sensitization and risk was noted. For example, the sensitization prevalence was 1.2% in case of the parabens, whereas sensitization frequencies to imidazolidinyl urea and diazolidinyl urea (both formaldehyde releasers) were much lower (0.6% each). However, for the widely used parabens, the SEQ was much lower compared with the formaldehyde releasers (0.35 *vs* 1.6), showing that the parabens confer a very low risk of sensitization. Overall, the SEQs varied greatly: from phenoxyethanol (SEQ: 0.06) with a negligible risk to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (SEQ 9.0) and 2-bromo-2-nitropropane-1,3-diol (SEQ 13), with a considerable risk. Interestingly, there was a good correlation between the ranking of substances according to potency (hazard) based on data from the local lymph node assay and the ranking of the SEQ (risk).

Conclusion and perspectives

This review focusses on a well-established surveillance system in Central Europe. A number of other networks are active in Europe and North America (Table 6) (58, 59) publishing regularly or, as in the case of *ad hoc* multicentre studies, sporadically, the results of patch testing. As CA surveillance approaches, these networks follow the same objectives as outlined above, but differ essentially with regard to the size of the population studied, the scope of data generated, continuity over larger time periods, timeliness and completeness. Nevertheless, all certainly meet the objectives of surveillance systems: the 'persistence of problems' was shown by European (60, 61) and North American (59) as well as national networks, from Sweden (46), Denmark, (18), Italy (62), UK (63) and Spain (64). The 'emergence of allergens' (sentinel events) was noted regarding methyldibromo glutaronitrile (MDBGN) in Europe (65), methylisothiazolinone in Finland (66), nickel in Spain (67) and octocrylene in France (68). Finally, the 'success of preventive interventions' was proven, in the cases of nickel (39), chromate (33), MDBGN (63, 69) and fragrances (70).

Thus, the usefulness of CA surveillance networks for public health purposes has unequivocally been proven. Surveillance in this sector will become even more important, once alternative ('*in vitro*') methods with yet unproven validity will replace current hazard assessment via animal testing (72). Multinational networks such as the European Surveillance System on Contact Allergies (ESSCA, www.essca-dc.org) provide an even broader base for comparisons, exploiting the variation of morbidity (and exposure), which is larger than those within one country. Moreover, established network structures can be used as a platform for dedicated studies addressing study-specific questions such as safe-use concentrations by performing ROATS (73) or to the genetics of CA by studying polymorphisms possibly relevant for the development of CA (50).

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Authors' contribution

This article is a report (review) on the structure, function and results of a data network. All authors involved in the conception, design and build-up of the network; drafting of the article or revising it critically for important intellectual content; and approval of the final version of the manuscript to be published. In particular, A. Schnuch involved in the conception, design and interpretation of the study and drafting the article. J Geier involved in the acquisition, analysis and interpretation of data and revising it critically. R. Arnold involved in the build-up of the network structure and function, and acquisition of data. H. Lessmann involved in the acquisition, analysis and interpretation of data and revising it critically. W. Uter involved in the conception, design, analysis and interpretation of data, drafting the article and revising it critically.

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