

Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug-utilization research (CE-DUR) approach

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Clinical epidemiology (CE) is considered unable to estimate morbidity concerning either contact sensitization (CS) or allergic contact dermatitis (ACD) at the population level. Drug-utilization research (DUR) methods estimate the morbidity of suitable diseases based on prescription data for disease-specific drugs. Our objective was to estimate population figures for incidence and prevalence of ACD and CS based on sales data for patch test material in Germany and on patient data from the Information Network of Departments of Dermatology (IVDK). Approximately 600,000 standard series are sold per year in Germany, according to the 2 main manufacturers. This raw sales figure was corrected for certain effects (discarded preparations, proportion of formerly patch-tested patients, proportion of patients with ACD seeking medical advice) to obtain an estimate of the denominator of patients eligible for patch testing annually, and combined with patch test results from the Information Network of Departments of Dermatology (IVDK). In 17.8% (of 9,266 IVDK patients) ACD was established. Extrapolated to the general population, an incidence of ACD of between 1.7 and 7 per 1000 per year was estimated, depending on whether conservative or more liberal assumptions concerning the above effects were made. Of 78,067 IVDK patients tested between 1992 and 2000, 46.8% had at least 1 positive reaction (+ to +++), and 22.7% had at least 1 stronger positive reaction (++ or +++). The 9-year prevalence of CS was estimated to lie between 4.0% and 16.6% for the first outcome, and between 2.0% and 8.1% for the second. Concerning single allergens, 1.9–4.5 million individuals are probably sensitized to nickel, and 1.4–3.4 million to fragrance mix among the German population of 82 million inhabitants. The morbidity data found in this study are in good accordance with data from population-based epidemiological studies. In comparison to these, the CE-DUR approach seems to be an economically feasible method to estimate *continuously* the population impact of ACD and CS.

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Both contact sensitivity (CS) and its clinical manifestation, allergic contact dermatitis (ACD), have been the subject of epidemiological studies (reviews 1–3). These can be divided into 2 categories: population-based and patient-based (4, 7). Population-based studies on contact dermatitis yield results on the frequency of hand eczema (various causes) in the general population (5) or in occupationally defined subgroups (6, 7), on the frequency of contact dermatitis irrespective of etiology or site (8), and, more rarely, on the frequency of allergic contact dermatitis (9). Recently, sensitization to the most common contact allergens has been studied in the general population (10–14).

However, in the field of CS and ACD, clinical epidemiology, i.e. studies using epidemiological methods in a clinical population of patients, has been the preferred method (4) to obtain information on the most important allergens or subgroups at risk (15, 16).

Generally, the results of clinical epidemiology cannot be generalized directly to the general population: although acknowledged to give valuable hints on the impact of certain allergens (17, 18) clinical epidemiology is considered to be unable to estimate morbidity concerning either CS or ACD in the general population (19).

For some years, a new method has been increasingly preferred above others to estimate the frequency of a disease in the general population, namely drug-utilization research (DUR). Drug-utilization is formally defined by the WHO as: 'The marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences' (20). The number of diseased persons is calculated based on specific drug consumption (sales and defined daily drug dose per person), data which are delivered by, for example, pharmacy databases (21). This approach is best applied to study patients taking drugs exclusively used to treat one single disease, like epilepsy (22).

The DUR approach can, in principle, be applied not only to the therapeutic background, but also to diagnostics, if (i) similar data on consumption (application) are available and (ii) additional assumptions concerning several factors (see below) are made. Thus, we have applied the DUR methodology to obtain estimates of ACD and CS morbidity, and the prevalence of contact sensitization to important allergens in the standard series, respectively, and present the first results in this paper.

Materials and Methods

Several heterogeneous sources of data have been used for the expansion of the DUR approach (CE-

DUR), namely sales data for commercial patch test material suppliers, patch test data, demographic data, and relevant scientific literature.

Sales data

The numbers of patch test sets of the standard series were supplied by the 2 main manufacturers in Germany (Hermal/Trolab, Reinbek, and Hal/Brial, Greven). In total, patch test material sufficient to test approximately 600,000 patients was sold in 1999, assuming 100 applications per syringe. This figure was stable in the preceding years, except for the period of 1990–1994, when the number was higher (around 1 million). However, as financial incentives in the beginning of the nineties rather than medically motivated application were suspected to have caused this peak, the conservative annual sales number of 600,000 for the whole study period of 9 years (1992–2000) was chosen.

Patch test data

Methods and previous results of the IVDK have been reported (17, 18). Briefly, patch test results and a standardized patient history, including final diagnosis, are transferred from the dermatological departments participating in the IVDK to the data centre in Göttingen. For the calculation of a 9-year period prevalence of sensitization to allergens of the standard series, we used data accumulated between 1992 and 2000. For the calculation of ACD, cumulative incidence data collected in 1999 were used. Cases of ACD were defined as follows: a final diagnosis 'allergic contact dermatitis' (based on the sensitization diagnosed, the clinical picture and the relevance of the sensitization) and a positive (at least +) reaction to at least 1 of the standard series allergens.

Model factors and underlying assumptions (Fig. 1)

First of all, the proportion of patch test preparations which were purchased by dermatologists, but discarded rather than applied, is estimated to range between 10% and 20%, following the experience of a local patch test clinic at Göttingen. Thus, the number of patients actually patch tested will correspondingly be lower (Fig. 1).

The sales figures do not reflect the absolute number of diseased people: it was found that only 15–38% of patients with contact dermatitis in general seek medical consultation at all (6, 23, 24). Thus, to estimate the number of persons with suspected ACD eligible for patch testing, the number of patients patch tested per year estimated from the

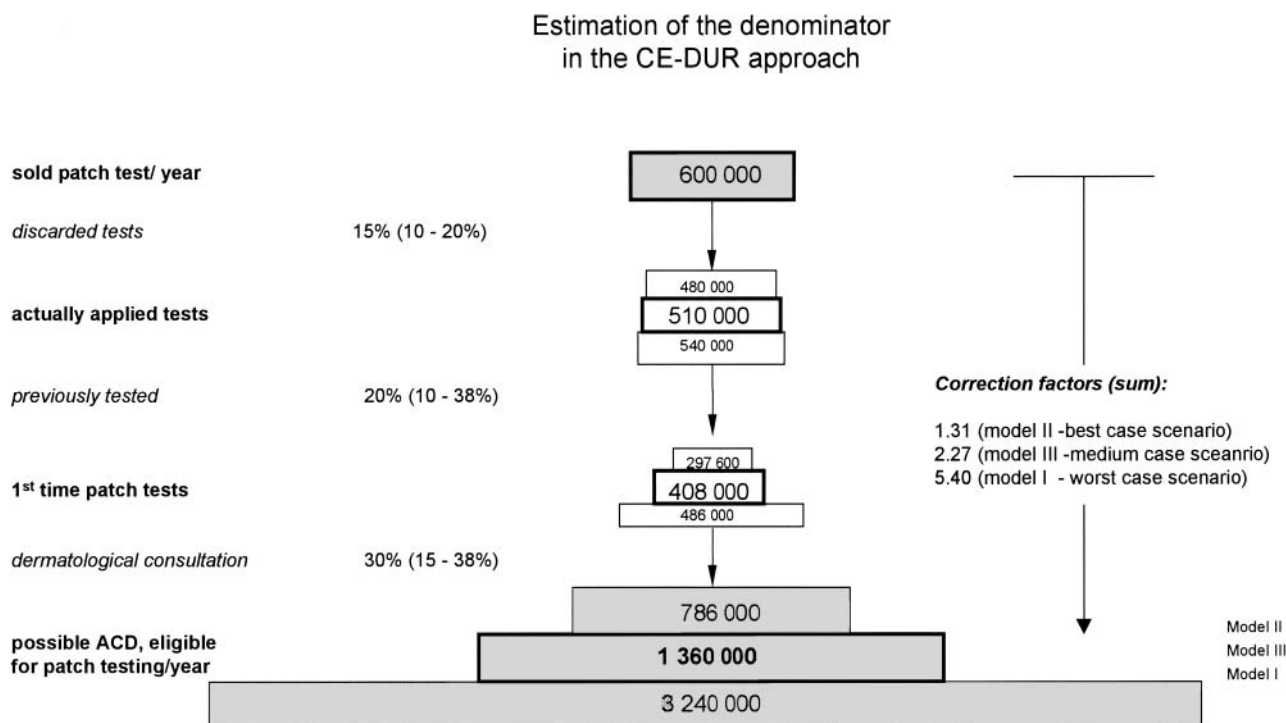


Fig. 1. Stepwise estimation of number of patients eligible for patch testing, based on number of patch tests sold annually and published evidence concerning the selection process. With model III, following a more conservative estimation process, the number of patients eligible for patch testing would be 1.36×10^6 /year. With model I, a worst case scenario, the number would be 3.24×10^6 /year

sales figures quoted above has to be multiplied by a particular factor (see Fig. 1).

Some patients had already been tested elsewhere – up to 38% according to the statistics of the Göttingen department. As a consequence, the true number of newly diagnosed cases of CS will be lower, and the estimate has to be corrected downwards (Fig. 1).

One major assumption is that the probability of a patient who presents with suspected ACD of being patch tested is similar in the IVDK and in the remaining dermatologists' offices. A consequence of this assumption is that the effect of different selection processes prior to presentation in one of the specialised IVDK centres, as opposed to presentation in institutions of primary dermatological care, does not need to be additionally accounted for.

All in all, the crucial figure, i.e. the absolute number of people with suspected ACD eligible for patch testing, has to be estimated. For this estimation process, we used correction factors based on the different assumptions outlined above in 3 different scenarios presented in Fig. 1. In model I, the absolute number of cases being patch tested would be 3.24 million (worst case scenario), in model II, 786,000 (best case scenario), and in model III (a probable medium scenario) 1.36 mil-

lion. The total population in 1992–2000 was some 82 million in Germany.

For the estimation of the incidence of ACD, we related the proportion of patients with this final diagnosis, as defined above, registered in the IVDK to the 3 absolute numbers mentioned above. For the estimation of prevalence we related the proportion of patients with at least one + reaction registered during a 9-year period (1992–2000) to the 3 different absolute numbers multiplied by 9 (years). For the estimation of prevalence of each individual CS, different models were chosen. In order to account for possible diagnostic uncertainties considered relevant for at least some allergens, the prevalence of sensitization was additionally separately calculated on the basis of ++ and +++ reactions only.

Results

Incidence of ACD

Altogether, 9,266 patients were patch tested with the standard series in the departments of the IVDK in the year 1999. In 1,648 of them (17.8%) the final diagnosis ACD was established. The incidence of contact allergy (cases per 1000 per year) as calculated with model I would be 7, with model II, 1.7 and with model III, 3.0 (Table 1)

Table 1. Incidence of allergic contact dermatitis, and 9-year prevalence of contact sensitization according to different scenarios (see Fig. 1)

Scenario	Incidence [per 1000 per year]	9-year-prevalence I, + to +++ reactions (%)	9-year-prevalence II, ++/+++ reactions (%)
Worst case	7	16.6	8.1
Best case	1.7	4.0	2.0
Medium	3.0	7.0	3.4

Table 2. Frequencies of sensitization to allergens of the standard series tested over a 9-year period (1992–2000) in the IVDK (n = 78,067). Allergens added or omitted during this time are not included in the list. Frequencies of sensitization in the general population were estimated on the basis of model I, probably a worst case scenario, and model III, the medium scenario (see Materials and methods) and related to the total population of Germany (82,000,000). To address potential diagnostic uncertainties of the + patch test reactions, the frequencies of unequivocal allergic reactions (++++) are also presented.

Allergen/Reactions	Clinical patients		Population (%)			
	+/+++	++/++++	Model I		Model III	
			+/+++	++/++++	+/+++	++/++++
Nickel sulfate	15.5	8.3	5.5	3.0	2.3	1.2
Fragrance mix	11.7	4.0	4.2	1.4	1.8	0.6
Myroxylon Pereirae resin	8.5	2.5	3.0	0.9	1.3	0.4
p-Phenylenediamine	4.6	2.0	1.6	0.7	0.7	0.3
Potassium dichromate	4.2	1.6	1.5	0.6	0.6	0.2
Colophonium	3.9	1.75	1.4	0.6	0.6	0.3
Lanolin alcohol	3.8	0.9	1.4	0.4	0.6	0.1
MDBGN/PE*	2.0	0.75	0.4	0.15	0.2	0.06
	4.2	1.2	0.7	0.2	0.3	0.08
Thiuram mix	2.7	1.1	1.0	0.4	0.4	0.2
Neomycin	2.7	0.8	1.0	0.3	0.4	0.1
MCI/MI**	2.5	0.8	0.9	0.3	0.4	0.1
Formaldehyde	2.0	0.5	0.7	0.2	0.3	0.1
Oil of turpentine	2.0	0.5	0.7	0.2	0.3	0.1
Benzocaine	1.6	0.65	0.6	0.2	0.2	0.1
Paraben mix	1.5	0.3	0.5	0.1	0.2	0.05
Epoxy resin	1.2	0.6	0.4	0.2	0.2	0.1
Cetearyl alcohol	1.2	0.3	0.4	0.1	0.2	0.05
p-tert.-Butylphenol-formaldehyde resin	1.0	0.4	0.36	0.1	0.15	0.06

*MDBGN/PE (methyltribromo glutaronitrile/phenoxyethanol) was tested in 2 different concentrations (0.5 and 1.0%) in 1992–1996 and 1997–2000, respectively.

**MCI/MI = methylchloroisothiazolinone (+) methylisothiazolinone.

Prevalence of CS

Between 1992 and 2000, a total of 78,067 patients were tested with the standard series. 36,551 of them (46.8%) had at least 1 weak positive reaction (+), and 17,682 (22.7%) at least 1 stronger positive reaction (++). The sales figure for patch test preparations during the 9-year period was taken as 5.4 million. On the basis of all allergic patch test reactions, the 9-year prevalence of CS was therefore 16.6% (model I), 4.0% (model II), and 7.0% (model III), respectively. The respective proportions based on ++++ reactions were: 8.1%, 2.0% and 3.4% (Table 1).

The 9-year prevalences of important individual allergens of the standard series are calculated following models I and III, assuming that these models represent a worst case scenario and a medium scenario and are presented in Table 2. It is

noteworthy that 4.5 or 1.9 million persons of the German population (depending on the underlying model assumptions) are sensitized to nickel, and 3.4 and 1.4 million, respectively, to fragrances. Furthermore, (several) hundred thousands of persons are sensitized to a number of other allergens.

Discussion

In this study we used data from clinical epidemiology and – encouraged by methods applied in drug utilization research – sales figures of patch test preparations to estimate the incidence of ACD and the prevalence of CS. Sales figures for patch test preparations are a good indicator of how often patch testing was performed in the total population, equivalent to how often ACD was suspected. With a multiparametric model of different factors affecting the actual incidence and prevalence of

ACD and CS, respectively, a sensitivity analysis was performed to address the potential influence of these factors on morbidity estimates, resulting in worst case (model I), best case (model II), and medium case (model III) scenarios. Based on a comparison of the 3 models with previously published results, we conclude that the latter model is probably suitable for the estimation of incidence of ACD (3.0 cases per 1000 persons per year), whereas model I is more in accordance with previously published prevalence estimates concerning CS (16.6%), as outlined in the following sections.

Incidence of ACD

There are no reports on the incidence of ACD in the general population. For contact dermatitis in general, i.e. irrespective of etiology, an incidence of 7.9 cases per 1000 person-years was observed in the Netherlands (25). Incidence rates of ACD in specific occupational subgroups with increased risk of occupational skin disease are clearly much higher (7, 26, 27), but are unsuitable for comparison when referring to the general population. In a student population, the dermatology clinic utilization incidence was studied (28), with ACD amounting to an incidence of 2.8 per 1000. More recently, the referral rate for patch testing from a predominantly urban population to a contact dermatitis unit in the UK was analysed and an estimate of ACD incidence based on the diagnostic outcome was given (0.6 cases per 1000 persons per year) (29). After adjusting this rate for the impact of non-consulting and pre-tested patients according to model III (Fig. 1), an estimated adjusted incidence rate of 1.6/1000 per year results. However, even this figure is probably an underestimation, as the density of dermatologists is much lower in the UK than in Germany, and thus, with a clear consumer-provider interaction in health care seeking behaviour (30, 31), a lower total consultation rate in the UK will ensue.

Prevalence of sensitization to individual allergens

We evaluated the sensitization to allergens of the standard series diagnosed during a 9-year period of patch testing in the IVDK. We are fully aware of the fact that (i) during a relatively long period the underlying population (the denominator) is not stable, if births, deaths and other migration effects are considered, and (ii) the patients registered by the IVDK are only a relatively small subset of the numerator of diseased, and that even all patients patch tested within 1 year in Germany are only a subset of all persons with CS. However, with an increasingly large window of observation, it can

be assumed that more and more sensitized persons with a relevant sensitization – causing ACD – will consult a dermatologist, both concerning primary dermatological care providers and IVDK centres. In contrast, latent sensitization which never caused ACD will not be detected by this method, or only if another CS causes ACD and results in the patient consulting a dermatologist, latent CS then being detected as a chance finding.

If the outcome was defined as at least 1 positive reaction to an allergen of the standard series in the total test population of 78,067, prevalences of 16.6, 4.0 and 7.0%, respectively, were found employing the 3 alternative parameter settings (Table 1). If different population characteristics are taken into account, e.g. leading to a higher proportion of nickel-sensitive subjects, results of the 2 successive Glostrup allergy studies in Denmark, which found a prevalence of sensitization to at least 1 allergen of the standard series of 15.2% (10) and 18.6% (11), respectively, these estimates are again similar to estimates obtained with our approach. Finally, in a recent population-based study in cooperation with the MONICA III survey (Monitoring of Trends and Determinants of Cardiovascular Diseases) in Augsburg/Germany, in which 1,537 individuals were patch tested, the frequency of at least 1 positive reaction to allergens of the standard series was 28.0 % (95% CI: 26.6–29.4) (14). However, the results of this study cannot be generalized fully, essentially because of different selection criteria (e.g. only a particular age segment of the population (25–79 years) with generally higher prevalence was studied). All in all, there is conclusive evidence that between 15% and 20% of the general population are sensitized to 1 or more of the most important allergens

Nickel

The 9-year prevalence of nickel sensitization in our study (2.3% and 5.5%, respectively) is considerably lower (by a factor of 2–5) than in studies in the general population (10, 12–14). The bias of our study population towards less nickel CS may be explained presumably by the phenomenon that individuals sensitized to nickel only, who at most suffer from dermatitis caused by imitation jewellery, jeans studs, etc., have become aware of their allergy by themselves and do not seek medical advice with subsequent patch testing to the same extent (e.g. 30%) – if ever – as those with other CSs. This presumptive, albeit plausible, phenomenon may also explain the differences between the global CS prevalence found in our analysis (7.0% and 16.6%, respectively) and population-based studies (15–20%) – the contribution of the high proportion of

nickel CS is overwhelming with regard to the overall CS prevalence.

Fragrance mix

The prevalence of sensitization to the fragrance mix is estimated (from model III and model I, respectively) to be 1.8% and 4.2% of the total population or, in absolute terms: 1.4–3.4 million persons in Germany are sensitized to fragrances. This prevalence estimate is in good agreement with prevalences reported from Denmark (10, 12, 13), namely, 1.1%, 1.8% and 2.9% (the latter standardized for sex from Bryld (12), Table 16). However, similarly to nickel, the consultation of 30% assumed in the medium scenario may also be too high for ACD caused by fragrances, as suggested by a Danish report on the frequency of dermatological complaints after the use of perfumed products (32). This assumption is supported by the fragrance allergy prevalence found in the KORA study, which is surprisingly high (11.4%) (14).

For the fragrance mix there is concern that a relatively large proportion of weakly positive (+) reactions are false-positive, i.e. irritant. We therefore included a more conservative definition of the specific CS outcome, considering only ++ and +++ reactions as allergic. The results reflect the respective absolute minimum prevalence. On the basis of these ++ and +++ reactions, the 9-year CS prevalence is still high (0.6%, or some 500,000 persons) (Table 2, model III).

General remarks

It would not be worthwhile to develop the extended CE-DUR model addressing ACD and CS with its set of underlying assumptions, if there was not 1 major drawback with population-based studies on ACD and CS morbidity which supports the usefulness of our approach. This drawback is the limited diagnostic performance of patch testing in a population with low disease prevalence, i.e. the general population; namely, a low positive predictive value and a high proportion of false-positive results (33). Furthermore, if patch testing is performed in persons with no previous or current symptoms indicative of ACD, i.e. not in patients, the issue of active sensitization becomes ethically important, because this risk is not counter-balanced by diagnostic benefit to the individual. Although the risk of active sensitization to allergens of the standard series is generally considered small, a recent study raised a warning at least regarding p-phenylenediamine (34). There may be additional concern about the diagnostic validity of patch testing in population-based studies, if for the sake of

feasibility the standards of patch testing are compromised, e.g. if results are only read once, after 2 days (11), which is known to introduce a total error of some 40%, mainly in terms of false-negative results (35).

Finally, some general critical remarks have to be made concerning our adaptation of the CE-DUR approach to ACD and CS: it presupposes that both the characteristics of patients consulting departments of dermatology and dermatologists working in an office, respectively, and the indication for patch testing do not differ. The indication for patch testing by practising dermatologists probably does not cause concern regarding potential selection bias. The patch test results of 5,766 patients from a large multicentre study in Germany, comprising 21 dermatological offices, with mostly higher CS prevalences, even point to a more restrictive indication for patch testing in (these) offices (36). In summary, our approach to estimating the number of patients patch tested on the sales figures of patch test material seems justified, with no hint of overtesting.

The CE-DUR approach integrates information from different sources. In future studies the assumptions underlying our estimates (e.g. proportion of patients (i) with suspected ACD, (ii) eligible for patch testing, (iii) who consult a dermatologist) will need to be confirmed. The fact that our results are largely consistent with other, population-based data, namely, those from Denmark, is reassuring, assuming that allergen exposure in Denmark and Germany does not differ substantially (and there is indeed no indication of this). and vice versa: it was questioned (e.g. in debates concerning EU regulatory issues) whether data from Denmark, a country with a rather small target population of some 5 million, could be regarded as representative of the whole of Europe with its more than 300 million inhabitants. Our study, based on a population of 82 million, does support the Danish results. Furthermore, our study may be taken as an additional argument for performing CS surveillance on a European level, as intended by the European Surveillance System on Contact Allergies (ESSCA), which has now started (37). Last but not least, the CE-DUR approach is not only economically feasible, but also adds further value to the clinical epidemiology of contact allergy by continuously estimating the population impact of ACD and CS.

References

1. Menné T, Christophersen J, Maibach H I. Epidemiology of allergic contact sensitization. *Monogr Allergy* 1987; 21: 132–161.

2. Smit H A, Coenraads P J. Epidemiology of contact dermatitis. *Monogr Allergy* 1993; 31: 29–48.
3. Schnuch A. Die Verbreitung des Kontaktekzems in der Allgemeinbevölkerung und in verschiedenen Berufen. In: Fuchs E, Schulz K H, eds. *Manuale Allergologicum* Munich-Deisenhofen: Dustri-Verlag, 1994: v.n.b.2: 1–42.
4. Schnuch A. Evaluating surveillance systems in contact dermatitis. In: Schwindt D A, Maibach H I, eds. *Cutaneous Biometrics*. New York: Kluwer Academic, Plenum Publishers, 2000: 243–255.
5. Meding B. Epidemiology of hand eczema in an industrial city. *Acta Derm Venereol Stockh Suppl* 1990; 4 (Suppl 153): 2–43.
6. Smit H A, Burdorf A, Coenraads P J. The prevalence of hand dermatitis in different occupations. *Int J Epidemiol* 1993; 22: 288–293.
7. Uter W. *Epidemiologie und Prävention von Handekzemen in Feuchtberufen am Beispiel des Friseurhandwerks*. Osnabrück: Universitätsverlag Rasch, 1999.
8. Johnson M-L T, Roberts J. Skin conditions and related need for medical care among persons 1–74 years. United States 1971–74. Hyattsville, Maryland: National Center for Health Statistics. *Vital and health statistics*, Ser 11, No. 212. 1978: 1–72.
9. Hermann-Kunz E. Allergische Krankheiten in Deutschland. Ergebnisse einer repräsentativen Studie. *Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz*, 2000; 43: 400–406.
10. Nielsen N H, Menné T. Allergic contact sensitization in an unselected Danish population – the Glostrup allergy study, Denmark. *Acta Derm Venereol (Stockh)* 1992; 72: 456–460.
11. Nielsen N H, Linneberg A, Menné T, Madsen F, Frolund L, Dirksen A, Jorgensen T. Allergic contact sensitization in an adult Danish population: two cross-sectional surveys eight years apart (The Copenhagen Allergy Study). *Acta Derm Venereol* 2001;81: 31–34.
12. Bryld L E. *A Genetic-Epidemiological Study of Hand Eczema in Young Adult Twins*. Copenhagen: University of Copenhagen, 2000.
13. Mortz C G, Lauritsen J M, Bindslev-Jensen C, Andersen K E. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001; 144: 523–532.
14. Uter W, Ludwig A, Balda B-R, Schnuch A, Schäfer T, Wichmann HE, Ring J. Prävalenz von Kontaktsensibilisierungen gegen Allergene der ‘Standardreihe’ – Vergleich von KORA-Studiendaten mit dem IVDK-Register. *Allergo J* 2001; 10: 326–328.
15. Schnuch A, Uter W. The role of clinical epidemiology in the study of occupational contact dermatitis. In: Kanerva L, Elsnér P, Wahlberg J E, Maibach H I, eds. *Handbook of Occupational Dermatology* Berlin: Springer, 2000: 17–26.
16. Geier J, Schnuch A. A comparison of contact allergies among construction and nonconstruction workers attending contact dermatitis clinics in Germany – results of the Information Network of Departments of Dermatology from November 1989 to July 1993. *Am J Contact Dermatitis* 1995; 6: 86–94.
17. 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: 200–209.
18. Uter W, Schnuch A, Geier J, Frosch PJ. Epidemiology of contact dermatitis: the information network of the departments of dermatology (IVDK) in Germany – a surveillance system on contact allergies. *Eur J Dermatol* 1998; 8: 36–40.
19. Prystowsky S D, Allen A M, Smith R W, Nonomura J H, Odom R B, Akers W A. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine – relationships between age, sex, history of exposure, and reactivity to standard patch tests and use tests in a general population. *Arch Dermatol* 1979; 115: 959–962.
20. Lunde P K M, Andrew M, Baksaas I. Drug utilization studies – an instrument in drug research. In: Kewitz H, Roots I, Voigt K, eds. *Epidemiological Concepts in Clinical Pharmacology*. Berlin: Springer, 1987: 57–72.
21. Leveille S G, Gray S, Black D J, LaCroix A Z, Ferrucci L, Volpato S, Guralnik J M. A new method for identifying antibiotic-treated infections using automated pharmacy records. *J Clin Epidemiol* 2000; 53: 1069–1075.
22. Shackleton D P, Westendorp R G, Kasteleijn-Nolst-Trenite D G, deBoer A, Herings R M. Dispensing epilepsy medication: a method of determining the frequency of symptomatic individuals with seizures. *J Clin Epidemiol* 1997; 50: 1061–1068.
23. Wallenhammar L-M, Örtengren U, Andreasson H, Barregard L, Björkner B, Karlsson S, Wrangsjö K, Meding B. Contact allergy and hand eczema in Swedish dentists. *Contact Dermatitis* 2000; 43: 192–199.
24. Schlesinger T, Revermann K, Schwanitz H J. Dermatosen bei Auszubildenden des Friseurhandwerks in Niedersachsen. Ein Vergleich zwischen 1989, 1994 und 1999. *Derm Beruf Umwelt* 2001; 49: 185–192.
25. Lantinga H, Nater J P, Coenraads P J. Prevalence, incidence and course of eczema on the hands and forearms in a sample of the general population. *Contact Dermatitis* 1984; 10: 135–139.
26. Smit H A, Coenraads P J. A retrospective cohort study on the incidence of hand dermatitis in nurses. *Int Arch Occup Environ Health* 1993; 64: 541–544.
27. Smit H A, van Rijssen A, Vandenbroucke J P, Coenraads P J. Individual susceptibility and the incidence of hand dermatitis in a cohort of apprentice hairdressers and nurses. In: Smit H A, eds. *Work related hand dermatitis – Epidemiological studies in occupational dermatology*. Groningen: Proefschrift Rijksuniversiteit Groningen, 1992: 97–120.
28. Shenefelt P D. Dermatology clinic utilization incidence and prevalence of contact dermatitis in a University student population. *Am J Contact Derm* 1996; 7: 62 (Abstract no. 12).
29. Bhushan M, Beck M H. An audit to identify the optimum referral rate to a contact dermatitis investigation unit. *Br J Dermatol* 1999; 141: 570–572.
30. Gesler W M, Meade M S. Locational and population factors in health care-seeking behavior in Savannah, Georgia. In: DeFries G H, Ricketts T C III, Stein J S, eds. *Methodological Advances in Health Services Research*. Ann Arbor: Health Administration Press, 1989: 67–86.
31. Kuder J M, Levitz G S. Visits to the physician: an evaluation of the usual-source effect. In: DeFries G H, Ricketts T C III, Stein J S, eds. *Methodological Advances in Health Services Research*. Ann Arbor: Health Administration Press, 1989: 193–210.
32. Johansen J D, Andersen T F, Thomsen L K, Kjoller M, Menné T. Rash related to use of scented products. A questionnaire study in the Danish population. Is the problem increasing? *Contact Dermatitis* 2000; 42: 222–226.
33. Diepgen T L, Coenraads P J. Sensitivity, specificity and positive predictive value of patch testing: the more you test, the more you get? *Contact Dermatitis* 2000; 42: 315–317.
34. Devos S A, van-der-Valk P G M. The risk of active sensitization to PPD. *Contact Dermatitis* 2000; 42: 273–275.
35. Uter W, Geier J, Schnuch A. Good clinical practice in patch

- testing: readings beyond D2 are necessary – a confirmatory analysis. *Am J Contact Dermatitis* 1996; 7: 2331–237.
36. Scheuer B, Rüther T, v. Bülow V et al. Häufige Kontaktallergene – Eine praxisorientierte Multicenterstudie. *Akt Dermatol* 1992; 18: 44–49.
37. Uter W, Perrenoud D, Shaw S, Wilkinson J D, Schnuch A. Computers in the management of contact dermatitis. In: Rycroft R J G, Menné T, Frosch P J, Lepoittevin J P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 1015–1027.
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