

Contact sensitization to cobalt – multifactorial analysis of risk factors based on long-term data of the Information Network of Departments of Dermatology

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Summary

Background. Cobalt contact sensitization in consecutively tested patients is common. The sources of exposure, and thus clinical relevance, are mostly unclear.

Objective. To examine (i) long-term time trends of sensitization, (ii) risk factors that may point to relevant exposures, and (iii) coupling with nickel sensitization.

Methods. Data of all patients patch tested with cobalt(II) chloride hexahydrate (1% pet.) between 1992 and 2012 (n = 185 050) in the Information Network of Departments of Dermatology (IVDK, www.ivkd.org) were subjected to descriptive stratified and Poisson regression analysis.

Results. The overall prevalence of positive patch test reactions was 5.23% (95% confidence interval 5.13–5.33%). Regarding time trends, there were significant increases for males aged 18–44 years and for females aged ≥45 years, and a significant variation of co-reactivity with nickel over time. Female sex almost doubled the risk of sensitization; age ≥45 years was associated with a 30% decrease in the risk of positive patch test reactions to cobalt, and atopic eczema with an approximately 20% increase.

Conclusions. Notwithstanding some diagnostic difficulties with the test preparation, a persistent, notable proportion of cobalt sensitization, isolated or coupled with nickel allergy, can be observed. This warrants further in-depth research into causative exposures, both at the workplace and in consumers.

Key words: cobalt; contact sensitization; risk factors; time trend.

Nickel, cobalt and chromium are common allergens, and are therefore included in baseline series throughout the world. In the case of nickel and chromium, the exposures

responsible for induction of contact sensitization and elicitation of allergic contact dermatitis, respectively, have been relatively well described, and, on the basis of this knowledge, effective interventions have been established in Europe, in terms of, for example, nickel regulation and restriction of the concentration of hexavalent chromium in cement (1) and, coming soon, leather (amendment to Annex XVII of REACH) (2). However, regarding cobalt, causative exposures are less well known, despite the fact that it has been identified as a strong sensitizer in the guinea-pig maximization test (3).

Although cases of sensitization to cobalt are sometimes related to identifiable occupational exposures (4), a large number of 'non-occupational' cases have also been seen,

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not infrequently linked to nickel sensitization. As 'putative non-occupational sources of cobalt exposure', jewellery, belts, accessories, make-up, tattoo ink, nail lacquer, pigments, orthopaedic or dental implants and cleaners and detergents (5) have been mentioned, although, for the last of these, very low levels of 5 or even 1 ppm are thought to be achievable in the production process, and are probably safe for the majority of sensitized individuals (6). Animal experiments on cross-reactivity between nickel and cobalt have given negative results (7), whereas an oral provocation study with nickel yielded flare-up reactions of previous cobalt chloride patch test sites in 7 of 14 cobalt-allergic (and mostly also nickel-allergic) patients (8). Hence, coupled sensitization can result from either coupled exposure with independent sensitization, be it by the same pathway, for example via human Toll-like receptor-4 (9), or (partly) from immunological cross-reactivity. In conclusion, it appears interesting to examine the pattern of risk factors (as more or less specific exposure surrogates) associated with cobalt sensitization, and to compare these with nickel sensitization risk factors (10). Moreover, any time trend during the study period covering 21 years is of interest.

Methods

The Information Network of Departments of Dermatology (IVDK), which is a network dedicated to the clinical surveillance of contact allergy, has been described elsewhere (11). Briefly, the participating departments are predominantly located in Germany ($n = 59$), but also in Switzerland ($n = 4$) and Austria ($n = 1$). All centres are members of the German contact dermatitis research group, and adhere to international patch test guidelines (12), which have been slightly refined (13). The members collect patch test data along with clinical data and important items of the patient's history electronically, and transmit these data twice yearly to the data centre in Göttingen. After a quality check, data from departments fulfilling the quality requirements (14) are pooled and analysed. For the present analysis, data of all patients patch tested with cobalt(II) chloride (1% in pet.) between 1992 and 2012 in the course of 185 050 consultations were considered. The test material was supplied by Hermal/Trolab/Almirall (Reinbek, Germany) during the entire study period. In cases of multiple consultations by an individual patient, only the first consultation was chosen. The annual number of patients tested in this period varied from 6128 in 1992 to 11 325 in 2010, owing to (i) the increase in the number of members of the network, and (ii) generally fluctuating numbers of patients. Cobalt(II) chloride hexahydrate (1% pet.) was part of the German baseline series throughout the entire study period.

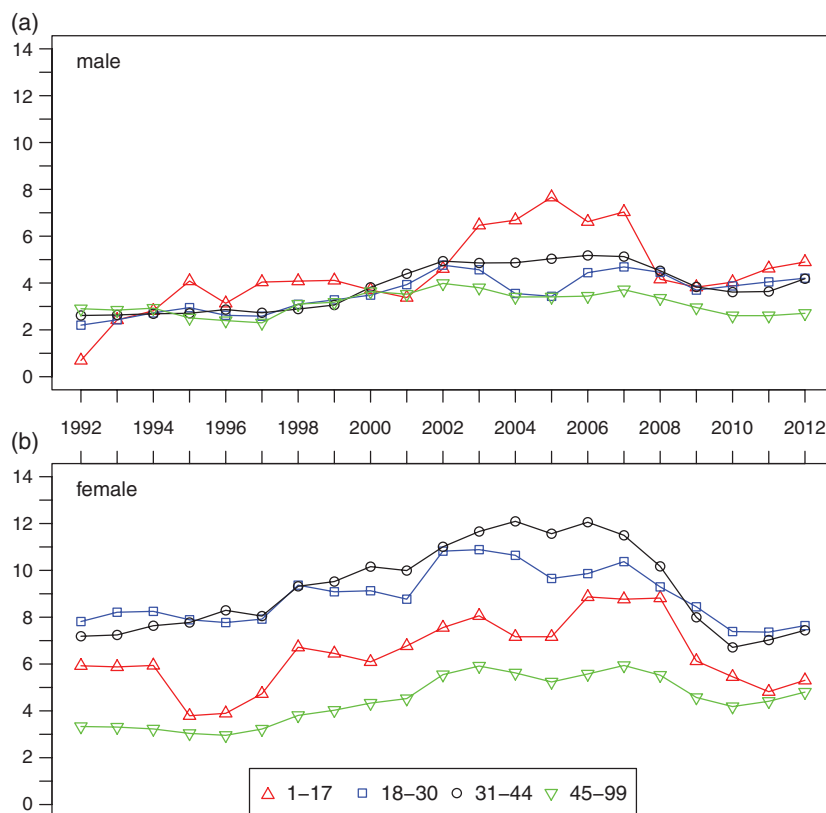
The annual prevalence of positive cobalt patch test reactions was descriptively analysed, stratified for sex and four age groups corresponding to the categorization used in a previous analysis (15), that is, up to 17 years, 18–30 years, 31–44 years, and older than 44 years. Within each of these eight strata, the Cochran Armitage test for trend was employed to assess monotonic temporal changes in these prevalence rates. It should be noted that, owing to very large variations in subsample sizes, the statistical power to detect a trend as significant varied between the eight strata. To address potential risk factors for cobalt sensitization in this clinical sample, a Poisson regression analysis was performed. As an outcome, reactions to cobalt chloride were dichotomized into positive, comprising + to +++ reactions, and non-positive, comprising negative, irritant and doubtful reactions. As an alternative, a three-level outcome was defined, contrasting + and ++/+++ reactions, respectively, with non-positive reactions. The following explanatory factors were considered: (i) age in four categories as above, (ii) sex, (iii) previous or current atopic eczema, (iv) anatomical site of contact dermatitis, aggregated to six categories as shown in Table 5a and missing or 'other' site, respectively, (v) year of the patch test, and (vi) occupation, aggregated to 49 job titles as shown in Table 5b. Up to three so-called 'contactants', that is, product categories considered to be probably causative for the current episode of contact dermatitis, chosen from a list of 54 categories, are routinely documented in the IVDK, and were additionally considered for descriptive analyses. For data management and analysis, R statistical software, version 3.0.1, was used (16), following pertinent guidelines (17).

Results

The overall proportion of positive patch test reactions was 5.23% [95% confidence interval (CI) 5.13–5.33%]. The overall frequencies of the three grades of positive reactions were as follows: +, 3.47%; ++, 1.37%; and +++ reactions, 0.39%. The distributions per year of positive reactions in the four age strata for female and male patients are shown in Fig. 1a,b.

Crystallization of cobalt chloride hexahydrate has been reported to occur and to potentially cause a peculiar type of reaction with erythema and petechiae (18). As these reactions could be mistaken for erythematous and even infiltrated reactions, that is, weak positive reactions (see Discussion), a more conservative 'positive' outcome was defined, based on ++ and +++ reactions alone. The corresponding time trend analysis, stratified as above, is shown in Fig. 2a,b. No significant trend was observed in this analysis, except for a significant upward trend ($p = 0.001$)

Fig. 1. Prevalence of positive patch test reactions (+ to +++) to cobalt chloride, 1% pet., between 1992 and 2012 in the Information Network of Departments of Dermatology, stratified for four age groups [up to 17 years ($n = 5245$), 18–30 years ($n = 32\,386$), 31–44 years ($n = 40\,149$), and > 44 years ($n = 106\,535$)] and (a) male ($n = 1750$, $n = 11\,179$, $n = 16\,184$, and $n = 39\,203$, respectively) and (b) female ($n = 3495$, $n = 21\,207$, $n = 23\,965$, and $n = 67\,332$, respectively) patients. During the study period, the proportion of patients aged up to 44 years decreased, and the proportion of the older patients increased significantly ($p < 0.0001$). Annual prevalence rates were smoothed by use of a 3-year moving average centred around lag 0. Trends were significant ($p < 0.05$) for males between 18 and 44 years of age and for the oldest females (age ≥ 45 years).



in the subgroup of the oldest female patients. The proportion of +++ reactions remained almost unchanged throughout the years ($p > 0.4$), including in the subgroup of female patients ($p > 0.2$).

As cobalt sensitization often coincides with nickel sensitization, the joint distribution of patch test results for both metal haptens was analysed, with a slightly aggregated categorization of patch test reactions (Table 1). A highly significant association was found ($p < 0.0001$, χ^2 test). The overall prevalence ratio (PR, which can be interpreted as relative risk) of cobalt sensitization in the presence of nickel sensitization was 8.04 (95% CI 7.73–8.36). The PR for nickel sensitization in the presence of cobalt sensitization was 4.73 (95% CI 4.63–4.83). This means that the risk of being sensitized to cobalt in nickel-allergic patients is almost twice as high as the risk of being sensitized to nickel in cobalt-allergic patients.

The characteristics of patients sensitized to either cobalt or nickel or both were compared according to the MOAHLFA index (19) (Table 2). Patients sensitized to cobalt alone were much more often men than in the other two subgroups, and suffered slightly more often from occupational (and) hand dermatitis, with an age distribution more similar to the average than if nickel sensitization was (also) present. Table 3 shows contactants

for which a significant and positive bivariate association with cobalt sensitization was found, which is quantified by odds ratios with accompanying 95% CIs.

Besides product types considered to be causative for the current episode of dermatitis, that is, contactants, the job title of the current occupation is an important surrogate for different exposures, and was thus subjected to a bivariate analysis for those occupations with an above-average sensitization prevalence (Table 4). For illustration of the patient characteristics, the MOAHLFA index, mean age and prevalence of positive reactions to nickel in the subgroups reacting positively and negatively to cobalt were compared.

Although the stratified analyses offered some insights into variation in cobalt sensitization prevalence with sex, with age, over time, and in categories of contactants and occupations, a Poisson regression analysis aimed at identifying risk factors for cobalt sensitization in a more detailed and mutually adjusted manner, following previous similar analyses, for example regarding nickel (10) or methylisothiazolinone (20) (Tables 5a and 5b; the presentation of results of the three models is split into two tables for better readability), was performed. First, no steady time trend was found, in accordance with the descriptive results shown in Figs. 1 and 2a,b. Hence, it

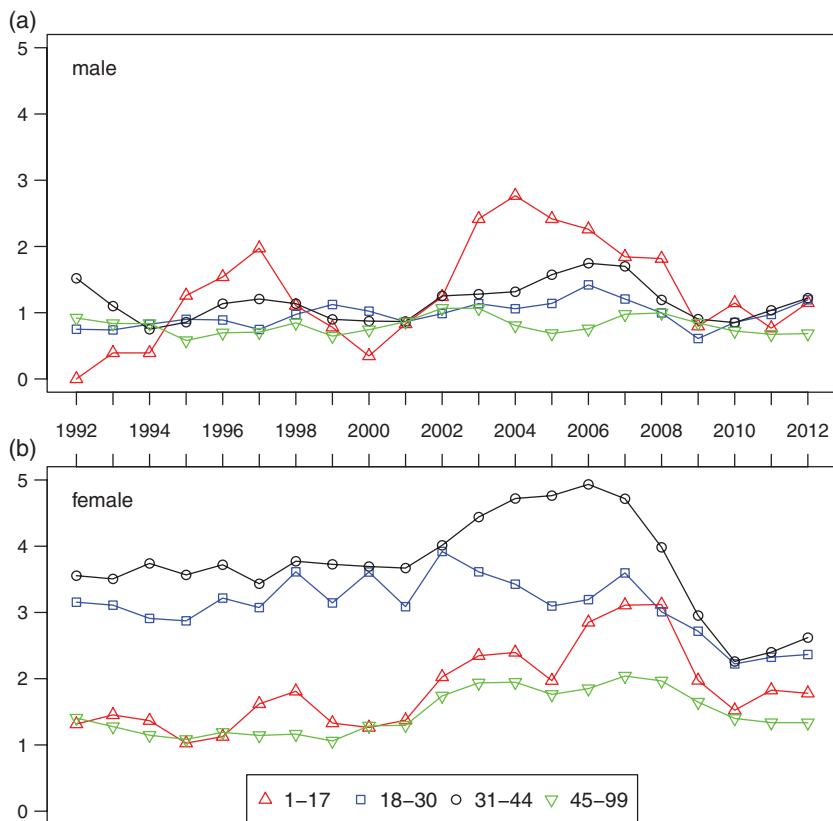


Fig. 2. (a,b) Prevalence of positive patch test reactions (++ or +++) to cobalt chloride, 1% pet., between 1992 and 2012 in the Information Network of Departments of Dermatology, stratified and smoothed as in Fig. 1. An increasing trend was significant ($p < 0.05$) for the oldest females (age ≥ 45 years).

is appropriate to include the year of patch test as a factor, and not as a linear term, in the Poisson modelling. Female patients had an almost doubled risk of being sensitized to cobalt. As compared with the youngest age group chosen as the reference, the risk of cobalt sensitization in the two 'middle-aged' groups was slightly, but not significantly, increased, and was significantly lower in patients aged ≥ 45 years. Past or current atopic eczema was associated with an approximately 20% increase in the risk of cobalt sensitization. Regarding anatomical sites of dermatitis (at or prior to presentation for patch testing), the trunk served as an arbitrary reference. As compared with this body region, hand dermatitis was strikingly associated with cobalt sensitization ($\sim 50\%$ increase in risk), whereas dermatitis of the arms and of the head (including, in this aggregation, the earlobes) was only weakly associated with cobalt sensitization.

The role of occupational exposure, as crudely reflected by the current job title, is evident from the second half of the Poisson regression analysis shown in Table 5b. As no natural reference category for a nominally scaled variable such as job title exists, a 'medium-risk' reference group, namely teachers, was chosen. Although the numerical values of the risk estimates (PRs) depend on

Table 1. Coupled reactivity between cobalt and nickel (absolute numbers): the upper percentages refer to row percentage, i.e. the proportions of graded nickel reactions in the strata of cobalt reactions; the lower percentages refer to column percentage, i.e. the proportion of graded cobalt reactions in the strata of nickel reactivity

Cobalt	Nickel			
	Negative	IR/?	+	++/+++
Negative	144 432	3048	10 583	9141
	86.4%	1.8%	6.3%	5.5%
	94.9%	73.5%	80.2%	67.4%
IR/?	4064	884	790	774
	62.4%	13.6%	12.1%	11.9%
	2.7%	21.3%	6%	5.7%
+	2800	164	1521	1803
	44.5%	2.6%	24.2%	28.7%
	1.8%	4%	11.5%	13.3%
++/+++	955	53	306	1835
	30.3%	1.7%	9.7%	58.3%
	0.6%	1.3%	2.3%	13.5%

IR, irritant reaction; ?, doubtful reaction.

this choice, the ranking of risk, and its variation (by a factor of almost 4), is definite. The top four occupations, with significantly elevated adjusted risk as compared with the

Table 2. MOAHLFA factors in all patients tested with cobalt chloride and nickel sulfate ($n = 183\ 153$) as compared with patients positive only for cobalt, for nickel and cobalt, and only for nickel

Factor	% overall $n = 183\ 153$	% Co only $n = 3972$	% Co and Ni $n = 5465$	% Ni only $n = 21\ 288$
Male	37.3	40.4	12.8	13.2
Occupational	15.1	23.7	20.1	17.5
Atopic eczema	18.4	24	23.4	21.4
Site: hand	28.3	40.5	36	30.3
Site: leg	11	9.1	4.2	5.9
Site: face	15.6	10.1	16.3	18.4
Age ≥ 40 years	66	63.7	48.5	51.4

reference category, were construction workers, metal surface treaters, cashiers, and printers.

As there may have been time trends in the use of cobalt or nickel, and as there are subsequent downward trends of nickel allergy at least in subgroups of patients (15, 21), a supplemental logistic regression analysis was performed, involving the same variables as before (Tables 5a and 5b), but also nickel sensitization (dichotomous) and an interaction term between nickel sensitization and the (factorized) year of patch testing. Highly significant associations ($p = 0.00001$) between all factors considered, including the interaction between year of patch test and nickel reactivity on cobalt reactivity, were found in this analysis. Hence, the association between cobalt and nickel sensitization varied significantly between the years.

Discussion

The present analysis includes patch test data collected for a large number of patients ($n = 185\ 050$) during a study period of 21 years. Hence, any time trend, even in a relatively small subgroup, should become evident. However, although considerable variation was noted over time, no downward trend was observed. On the contrary, all significant trends seen in some subgroups were upwards (Fig. 1). Consideration of only ++ and +++ reactions (Fig. 2) shows a similar pattern, albeit evidently with a lower level of prevalence. Considering just extreme positive reactions, the proportion remained stable in our data, in contrast to a long-term Danish analysis identifying a significant decrease (22); the reason for this is unknown. The more or less pronounced 'hump' in the years 2002–2007 is difficult to explain; a similar, albeit smaller, study in Italy found a similar increase and subsequent decrease in cobalt sensitization (23), and a Danish study covering 1992–2009 found a similar increase towards the end of the study period (24).

Regarding the validity of positive patch test reactions to 1% cobalt chloride hexahydrate in pet. – as used in

the present study and in baseline series throughout the world – some authors have advised caution. Hausen and Schubert (18) observed, under the microscope, relatively large, sea urchin-like crystals in the test allergen preparation a few months after manufacture. The test preparation can be re-homogenized to its initial state with only fine particles by running it through a roller mill several times, and then refilling the syringe; however, it is unclear whether this advice has been taken up. If the test preparation with these large crystals is applied occlusively in a patch test, a reddish discolouration, with follicular accentuations appearing like petechiae, is often observed. Several years earlier, Fischer and Rysted published similar clinical observations obtained with standard metal patch test preparations, including cobalt chloride in pet. (25), but, unfortunately, no laboratory analyses of the test material. In their analysis in 853 hard-metal workers, in 77 of those with a history of occupation-related hand dermatitis, more 'poral' or pustular reactions (12.1%) were observed than morphologically allergic reactions (7.3%) or erythematous reactions without infiltration (3.5%). None of the 99 patients with 'poral' reactions who could be re-tested subsequently with serial dilution testing had an allergic reaction, whereas, in 44 of 99, this peculiar type of reaction was confirmed – much more often with pet.-based than with water-based allergen preparations. From the morphological description, it appears likely that the crystallization process described later may have been the cause of the observed reactions. Concerning weak allergic reactions, only 3 of 19 initial + reactions were reproduced upon re-testing (25). A histopathological study on patch test reactions to 1% cobalt chloride in pet. macroscopically resembling closely the peculiar reactions observed by Hausen and Schubert and probably the 'poral' reactions observed by Fischer and Rysted showed that this metal salt has a toxic effect on the eccrine acrosyringium (26). In conclusion, concerning the patch test data underlying the present analysis, and any other such data, for that matter, it is possible that such non-specific irritant reactions, which sometimes appear as slightly papular, may have been classified by some dermatologists as + in a certain, possibly small, but indeterminable proportion of all documented + reactions (not likely in case of ++ or +++ reactions).

The above phenomenon makes the observed prevalence rates (of + reactions) somewhat uncertain, and should possibly prompt a reconsideration of how cobalt sensitization is patch tested for. Notwithstanding this limitation, the observed variability, for example between patients working in different occupations, also if + reactions are included, illustrates that false-positive reactions

Table 3. Contactants versus cobalt sensitization, based on data of 153 593 patients who (i) were tested with cobalt chloride and (ii) had at least one contactant documented; up to three contactants can be documented

Contactant	n (test)	% positive	OR	95% CI
Newly built houses	37	16.22	3.44	1.43–8.25
Jewellery, watches etc., non-metal	187	14.97	3.13	2.09–4.68
Jewellery, watches etc., metal	2277	12.17	2.46	2.17–2.79
Metal, other, e.g. coins	3987	11.79	2.37	2.15–2.62
Leather, excluding gloves	3436	8.67	1.69	1.50–1.91
Building materials	3400	8.59	1.67	1.48–1.89
Shoes, boots (all materials)	3379	8.29	1.60	1.41–1.81
Metal, as work materials (e.g. in turners)	4137	7.37	1.41	1.25–1.59
Gloves (all materials)	10 398	7.31	1.40	1.30–1.51
Food (additives)	3233	6.53	1.24	1.08–1.43
Disinfectants	10 505	6.49	1.23	1.13–1.33
Hair cosmetics	6394	6.47	1.23	1.11–1.36
Household and other cleaners	5073	6.07	1.15	1.02–1.29
Rubber, excluding gloves	10 475	5.83	1.10	1.01–1.20

CI, confidence interval; OR, odds ratio.

may cause some 'statistical noise' but do not make the results meaningless.

The analysis of the distribution of MOAHLFA factors offers the first insights into different profiles of cobalt sensitization that may exist: patients sensitized only to cobalt were much more often men, and an occupational context was more common, whereas patients sensitized to cobalt and nickel tended to be more similar to patients sensitized only to nickel; however, this was not a very pronounced difference. The mutually adjusted multifactorial regression analysis was primarily aimed at identifying risk factors (exposure surrogates) for cobalt sensitization, and was thereby not repeating a previous analysis that concentrated on a limited set of risk factors associated with solitary or coupled sensitization to cobalt, nickel, and chromium (27).

In line with the sex-stratified and age-stratified results (Figs. 1 and 2), patients aged <45 years had a similar risk of cobalt sensitization according to the Poisson regression analysis, whereas those aged ≥45 years had a substantially reduced risk of being sensitized, this being mainly driven by female patients. Significant variation, but no consistent, clear time trend, was observed for the temporal development of cobalt sensitization over the period of investigation. The evaluation of the temporal development was further complicated by the significant interaction between nickel sensitization and year of patch testing. The fact that the hands are evidently associated with cobalt sensitization is difficult to interpret, as this may be attributable to occupational exposures (e.g. in construction workers) or to non-occupational exposures (e.g. jewellery). Focusing on the different occupations, aggregated basically according to previous similar analyses (10, 28), shows some variation in adjusted cobalt sensitization risk.

A number of clearly identifiable high-risk occupations are apparent (see also Table 4):

- Construction workers have a well-known high risk of chromium sensitization; cobalt contact sensitization is known to often accompany chromium-induced allergic contact dermatitis (29, 30). It is as yet unclear whether the recent, significant decline in cement-related chromium dermatitis in the building trade will additionally contribute to a decline in isolated cobalt sensitization in this field.
- Metal surface treaters, for example galvanizers, may be exposed if cobalt-containing electrolyte solutions are involved, for instance in the 'Achrolyte' process available since the 1970s, an electroplating procedure with 80% tin and 20% cobalt, yielding a shiny and resistant metal surface. It is furthermore possible that such coated objects are available on the consumer market from certain sources, including costume jewellery (K. Leydendecker, pers. comm. 2014), but it is not known to what extent these coated objects liberate cobalt.
- Exposure of cashiers, almost exclusively female, to metals (coins) is traditionally considered to be insufficient for elicitation of allergic contact dermatitis caused by these metals. Short, repetitive exposure to metal objects such as coins on skin is not reflected by standard methods for determining metal release, such as EN 1811:2012 for nickel, aimed at detecting release after prolonged contact with the skin. However, as the previous 'Deutsche Mark', the former GDR coins, the current euro coins (also Swiss francs and rappen and the previous Austrian schilling) are known not to contain

Table 4. Important characteristics of patients working in occupations with an above-average crude prevalence of sensitization (third and fourth columns) to cobalt in terms of the MOAHLFA index (19) and additional information, stratified for cobalt-positive and cobalt-negative patients

Job title	Cobalt- positive													Cobalt- negative												
	n (test)	% positive	95% CI	n (positive)	M	O	A	H	L	F	A	Median age (years)	% Ni- positive	n (negative)	M	O	A	H	L	F	A	Median age (years)	% Ni- positive			
Cashier	434	10.14	7.46–13.37	44	0	36.4	22.7	59.1	4.5	11.4	50.0	40	72.7	390	3.1	16.2	22.1	41.3	4.9	17.4	59.2	45	21.8			
Metal surface treater	234	7.69	4.62–11.88	18	66.7	77.8	27.8	55.6	5.6	5.6	72.2	44.5	55.6	216	72.7	47.7	18.1	56.9	4.6	7.9	50.0	40	18.1			
Cosmetician	653	7.66	5.74–9.97	50	2.0	44.0	30.0	58.0	2.0	10.0	36.0	36	68.0	603	2.2	46.4	26.7	54.2	1.2	16.6	48.6	39	23.7			
Leather worker	249	7.63	4.66–11.66	19	21.1	26.3	42.1	47.4	0	10.5	57.9	45	57.9	230	39.1	27.8	18.3	42.6	3.9	16.5	58.3	43.5	12.6			
Construction worker	2413	7.63	6.60–8.76	184	93.5	75.0	15.8	76.6	1.1	4.3	54.9	41	17.9	2229	95.1	44.9	15.8	52.7	6.7	9.4	55.7	42	4.5			
Healthcare worker	9176	7.57	7.04–8.13	695	5.2	44.6	29.5	57.7	2.0	10.2	37.8	36	67.8	8481	12.4	39.6	29.1	50.9	2.1	14.3	45.3	37	20.8			
Guest service worker	1521	7.43	6.16–8.86	113	14.2	16.8	19.5	42.5	5.3	10.6	37.2	35	66.4	1408	32.5	18.0	20.7	38.9	7.7	14.9	49.4	39	18.0			
Florist	1377	7.33	6.01–8.84	101	20.8	41.6	20.8	51.5	4.0	8.9	38.6	37	63.4	1276	32.6	34.6	23.9	45.8	5.9	13.4	51.4	40	17.4			
Sales personnel	3099	7.16	6.28–8.13	222	8.1	18.0	28.8	42.3	2.3	18.5	49.5	39	63.1	2877	25.0	10.8	22.2	27.6	6.0	20	60.0	44	18.8			
Textile worker	938	7.14	5.58–8.98	67	4.5	17.9	23.9	40.3	3.0	19.4	55.2	43	68.7	871	16.1	16.1	22.3	30.7	4.9	24	63.7	46	18.6			
Cook	2413	6.88	5.90–7.96	166	27.1	41.6	25.3	62.0	2.4	5.4	38.6	37	63.3	2247	45.2	41.4	23.5	58.0	4.7	8.3	47.5	38	15.4			
Cleaner	3661	6.88	6.08–7.75	252	10.7	46.4	19.4	59.1	2.8	6.3	59.5	43	69.0	3409	15.5	39.9	15.1	50.9	3.7	11.4	69.0	45	20.1			
Mail clerk	630	6.83	4.98–9.08	43	7.0	27.9	23.3	37.2	4.7	20.9	51.2	41	69.8	587	33.9	8.7	23.5	29.6	4.4	15.8	63.7	45	16.5			
Hairdresser	2760	6.74	5.83–7.74	186	3.2	67.7	23.1	73.1	0.5	6.5	27.4	28	66.1	2574	8.5	67.5	28.6	71.9	1.1	8.3	27.6	26	21.3			
Office worker	23 519	6.61	6.29–6.93	1554	14.7	6.0	26.8	26.5	3.6	22.8	48.5	39	65.0	21 965	32.8	4.2	22.6	21.8	5.4	23.8	60.8	44	16.7			
Photographer	199	6.53	3.52–10.91	13	15.4	15.4	15.4	15.4	0	15.4	53.8	42	76.9	186	36.6	18.3	22.0	31.7	2.2	24.7	53.2	41	16.7			
Animal care	234	6.41	3.63–10.35	15	0	46.7	33.3	46.7	0	6.7	40.0	34	80.0	219	36.1	39.7	19.2	44.3	5.5	13.2	53.9	40	11.0			
Physician or surgeon	2838	6.24	5.37–7.19	177	11.9	53.7	28.8	66.1	0.6	13.6	24.3	31	59.9	2661	31.3	37.9	26.5	47.9	2.9	16.7	44.0	36	14.7			
Printer	482	6.22	4.24–8.77	30	53.3	20.0	46.7	63.3	0	0	43.3	33	30.0	452	74.8	31.4	21.0	46.9	4.4	13.9	57.5	43	10.2			
Medical assistant	1253	6.15	4.88–7.62	77	1.3	27.3	20.8	41.6	3.9	13.0	35.1	36	63.6	1176	7.2	23.7	25.4	39.3	2.6	23.2	48.3	39	21.0			
Precision mechanic	457	5.91	3.93–8.48	27	44.4	66.7	29.6	63.0	3.7	14.8	59.3	41	29.6	430	56.7	30.7	24.7	41.4	4.7	12.3	49.3	39	14.7			
Domestic worker	17 413	5.65	5.31–6.00	983	1.4	6.7	20.7	29.0	8.1	16.8	68.6	48	63.5	16 430	1.7	3.3	16.0	19.4	10.6	20.1	79.3	55	15.2			
Metal bender	177	5.65	2.74–10.14	10	80.0	80.0	30.0	70.0	0	0	40.0	38	50.0	167	83.8	44.9	17.4	54.5	3.6	7.2	59.9	43	5.4			
Meat or fish processor	622	5.31	3.68–7.37	33	27.3	42.4	12.1	48.5	6.1	18.2	51.5	40	54.5	589	51.6	33.3	21.9	46.5	9.8	10.0	50.6	40	12.6			
Teacher	5155	5.28	4.68–5.92	272	5.9	8.5	29.8	28.7	4.8	21.0	52.2	41	59.9	4883	22.2	4.4	22.8	20.1	4.7	24.3	69.3	47	15.2			

CI, confidence interval.

Table 5a. Non-occupational risk factors: results of a Poisson regression analysis with (i) a +, (ii) a ++ or +++ and (iii) a + to +++ patch test reaction to cobalt chloride (1% pet.) as outcome. Risk is quantified by the prevalence ratio (PR) with accompanying 95% confidence interval (CI). The second column shows the prevalence of the risk factor (%). 'Other' and missing anatomical sites were included in the model, but the results are not shown

		+		++/+++		+ to +++	
Risk factor	%	PR	95% CI	PR	(95% CI)	PR	95% CI
Year of test							
1992	3.3	1.00	Reference	1.00	Reference	1.00	Reference
1993	4.3	1.13	0.90–1.41	1.15	0.88–1.50	1.13	0.95–1.35
1994	4.9	1.28	1.03–1.59	0.97	0.74–1.27	1.15	0.97–1.36
1995	4.5	1.17	0.94–1.45	1.03	0.78–1.34	1.10	0.93–1.31
1996	4.3	0.99	0.79–1.25	0.99	0.75–1.30	0.99	0.83–1.18
1997	4.5	1.08	0.86–1.36	1.22	0.94–1.59	1.13	0.95–1.34
1998	4.5	1.33	1.07–1.65	0.84	0.63–1.11	1.13	0.95–1.34
1999	4.5	1.90	1.55–2.34	1.35	1.04–1.76	1.66	1.41–1.95
2000	4.2	1.46	1.18–1.82	0.90	0.68–1.20	1.23	1.03–1.46
2001	4.1	1.64	1.33–2.04	1.12	0.85–1.49	1.42	1.20–1.68
2002	3.7	2.04	1.65–2.52	1.23	0.93–1.63	1.69	1.43–2.00
2003	4.4	2.22	1.81–2.72	1.83	1.42–2.35	2.01	1.72–2.35
2004	4.7	1.73	1.40–2.13	1.46	1.13–1.89	1.59	1.36–1.87
2005	4.3	1.75	1.42–2.16	1.22	0.93–1.61	1.52	1.28–1.79
2006	4.8	1.94	1.58–2.39	1.57	1.21–2.02	1.76	1.50–2.06
2007	5.5	1.99	1.63–2.43	1.73	1.35–2.22	1.84	1.58–2.16
2008	5.5	1.89	1.55–2.32	1.48	1.15–1.90	1.69	1.45–1.98
2009	5.9	1.41	1.14–1.73	1.05	0.81–1.37	1.26	1.07–1.48
2010	6.1	1.20	0.97–1.48	0.89	0.68–1.16	1.07	0.91–1.26
2011	6.1	1.49	1.22–1.83	0.90	0.68–1.17	1.25	1.06–1.47
2012	5.6	1.57	1.28–1.94	1.03	0.79–1.35	1.35	1.14–1.58
Female sex	62.9	1.75	1.63–1.87	2.85	2.56–3.16	1.99	1.88–2.11
Age (years)							
1–17	2.8	1.00	Reference	1.00	Reference	1.00	Reference
18–30	17.5	1.03	0.88–1.20	1.13	0.89–1.43	1.05	0.93–1.20
31–44	21.7	1.00	0.86–1.17	1.38	1.09–1.74	1.11	0.97–1.26
45–99	57.6	0.69	0.59–0.80	0.75	0.59–0.94	0.71	0.63–0.80
Atopic eczema	14.6	1.22	1.15–1.31	1.14	1.04–1.25	1.19	1.13–1.26
Site							
Trunk	15.5	1.00	Reference	1.00	Reference	1.00	Reference
Hand	28.5	1.41	1.30–1.53	1.90	1.68–2.15	1.53	1.43–1.64
Arm	3.9	1.07	0.93–1.24	1.39	1.13–1.71	1.16	1.03–1.30
Feet/leg	14.3	1.01	0.91–1.11	1.11	0.94–1.30	1.03	0.95–1.12
Face	15.5	0.87	0.79–0.96	1.08	0.94–1.25	0.93	0.86–1.01
Head/neck	4.3	1.08	0.95–1.24	1.30	1.07–1.58	1.14	1.02–1.27

cobalt [in contrast to nickel, to which a high prevalence of (co-)sensitization was observed; Table 4], the finding of an increased risk of cobalt contact allergy in cashiers is hard to explain, considering the fact that this analysis was age-adjusted and sex-adjusted. It may be speculated that dyes or resins used in the production of bank notes may contain cobalt. Interestingly, a previous, similarly adjusted multifactorial analysis of nickel allergy showed a moderately elevated risk of sensitization in cashiers (10).

- Printers may be exposed by using cobalt-containing inks (4); other potential sources of exposure need to be investigated.

Shifts in the ranking of job titles associated with cobalt sensitization between the crude analysis (Table 4) and the adjusted analysis (Table 5b) point to some confounding, for example by age and sex. The finding of an average risk of cobalt sensitization in metal workers (Table 5b), despite the observation that hard-metal workers are not infrequently found to be sensitized to cobalt (31), and that hard metals release potentially eliciting cobalt levels (32),

Table 5b. Occupational risk factors: results of a Poisson regression analysis with (i) a +, (ii) a ++ or +++ and (iii) a + to +++ patch test reaction to cobalt chloride (1% pet.) as outcome. For further explanation see legend to Table 5a. A subgroup with 'undetermined exposure' ($n = 66\ 868$, mainly old-age pensioners and students) is not considered in this table

Risk factor (job title)	%	+		++/+++		+ to +++	
		PR	95% CI	PR	95% CI	PR	95% CI
Construction worker	1.3	1.64	1.29–2.07	3.57	2.52–5.04	2.03	1.67–2.47
Metal surface treater	0.1	0.97	0.48–1.97	3.72	1.91–7.23	1.63	1.01–2.62
Cashier	0.2	1.40	0.94–2.09	2.05	1.19–3.53	1.54	1.12–2.12
Printer	0.3	1.54	1.00–2.35	1.34	0.58–3.08	1.49	1.02–2.17
Leather worker	0.1	1.08	0.57–2.03	2.31	1.11–4.80	1.38	0.86–2.23
Driver or petrol station attendant	0.8	1.02	0.73–1.41	2.64	1.73–4.04	1.37	1.06–1.78
Photographer	0.1	1.25	0.64–2.44	1.48	0.54–4.06	1.30	0.75–2.28
Metal bender	0.1	1.46	0.72–2.97	0.65	0.09–4.66	1.30	0.67–2.54
Sales personnel	1.7	1.10	0.88–1.37	1.89	1.37–2.59	1.29	1.08–1.54
Office worker	12.7	1.13	0.97–1.32	1.73	1.35–2.22	1.28	1.12–1.45
Textile worker	0.5	1.16	0.84–1.62	1.60	0.99–2.59	1.27	0.97–1.66
Guest service worker	0.8	1.20	0.93–1.56	1.50	0.99–2.26	1.27	1.02–1.59
Mail clerk	0.3	1.07	0.71–1.61	1.84	1.07–3.16	1.25	0.90–1.73
Florist	0.7	0.98	0.73–1.31	1.83	1.24–2.71	1.20	0.95–1.51
Precision mechanic	0.2	0.89	0.53–1.50	2.19	1.18–4.04	1.20	0.81–1.79
Cook	1.3	0.91	0.71–1.17	2.03	1.46–2.83	1.19	0.98–1.45
Security service worker	0.9	0.8	0.57–1.12	2.47	1.64–3.70	1.17	0.91–1.51
Metal furnace operator	0.1	1.23	0.65–2.32	0.90	0.22–3.68	1.16	0.65–2.08
Painter	0.6	1.00	0.70–1.44	1.53	0.87–2.69	1.13	0.83–1.53
Logistics personnel	0.8	1.01	0.74–1.38	1.49	0.92–2.40	1.13	0.87–1.46
Animal care	0.1	0.73	0.34–1.55	2.24	1.07–4.65	1.12	0.67–1.89
Cleaner	2.0	0.99	0.80–1.22	1.43	1.04–1.96	1.10	0.93–1.31
Healthcare worker	5.0	0.92	0.78–1.09	1.55	1.19–2.02	1.09	0.94–1.25
Domestic worker	9.4	0.94	0.81–1.11	1.35	1.04–1.75	1.05	0.92–1.20
Civil engineer	2.2	0.9	0.71–1.14	1.52	1.06–2.18	1.05	0.86–1.28
Artist	0.4	0.92	0.58–1.44	1.45	0.77–2.75	1.05	0.73–1.51
Glass maker or potter	0.1	0.54	0.17–1.68	2.50	1.01–6.21	1.03	0.51–2.09
Metal worker	0.9	1.00	0.74–1.35	1.06	0.61–1.83	1.03	0.79–1.34
Cosmetician	0.4	0.90	0.61–1.31	1.42	0.86–2.37	1.03	0.76–1.40
Mechanic	2.7	0.90	0.73–1.12	1.35	0.95–1.91	1.02	0.85–1.22
Meat or fish processor	0.3	0.79	0.49–1.26	1.71	0.96–3.04	1.02	0.71–1.47
Teacher	2.8	1.00	Reference	1.00	Reference	1.00	Reference
Physician or surgeon	1.5	0.86	0.68–1.09	1.42	1.01–1.99	1.00	0.83–1.21
Chemical worker	0.7	0.80	0.56–1.13	1.42	0.88–2.27	0.96	0.72–1.26
Paper maker	0.1	0.68	0.32–1.45	1.67	0.72–3.84	0.94	0.54–1.64
'Other' occupation	36.1	0.85	0.74–0.99	1.16	0.90–1.48	0.94	0.82–1.06
Medical assistant	0.7	0.77	0.56–1.07	1.31	0.85–2.01	0.92	0.71–1.19
Plastics manufacturer	0.6	0.92	0.65–1.29	0.77	0.42–1.43	0.89	0.66–1.19
Pharmacist	0.2	0.78	0.43–1.44	1.19	0.51–2.73	0.89	0.55–1.45
Hairdresser	1.5	0.72	0.57–0.91	1.17	0.84–1.64	0.85	0.70–1.02
Electrician	0.8	0.68	0.46–0.99	1.35	0.79–2.30	0.84	0.62–1.14
Baker or confectioner	0.6	0.72	0.51–1.01	1.19	0.73–1.92	0.84	0.64–1.11
Miner	0.1	0.59	0.22–1.58	1.61	0.51–5.14	0.82	0.39–1.74
Carpenter	0.6	0.71	0.46–1.09	0.54	0.22–1.35	0.69	0.47–1.02
Forestry worker	0.1	0.39	0.06–2.82	1.49	0.21–10.74	0.64	0.16–2.56
Rubber manufacturer	0.1	0.54	0.13–2.18	0.86	0.12–6.18	0.63	0.20–1.96
Locksmith	1.0	0.54	0.37–0.79	0.81	0.43–1.50	0.61	0.44–0.85
Agricultural worker	0.5	0.42	0.24–0.74	0.89	0.44–1.78	0.55	0.36–0.85
Metal joiner, including solderer	0.2	0.31	0.10–0.97	1.10	0.35–3.50	0.50	0.22–1.12

may be attributable to a dilution of the risk in this particular subgroup through a majority of metal workers having no contact with hard metals. A previous, more detailed analysis found 7.6% of positive reactions to cobalt in male metal workers exposed to water-based cutting fluids, as compared with 3.8% in male metal workers not exposed to water-based cutting fluids (33). The role of occupationally used materials is limited to the relatively small share of persons working in these fields; nevertheless, there is a need to improve prevention in these areas.

In addition to this, broad exposure to cobalt via various consumer items (34–38) should be considered. The association found between 'leather' and 'shoes' as culprit contact materials, and that between the job title 'leather worker' and cobalt allergy, may point to a role of cobalt in dyes used in 'pre-metallized dyeing' of leather products (36). Beyond results from surveys using the cobalt spot test (39) cited above, analytical measurements have shown cobalt in amounts over 5 ppm in 5 of 52 samples of 'toy make-up' (40). However, the approximately average risk in cosmetologists (Table 5b) does not seem to point to cosmetics being a broadly relevant source of cobalt. Recently, published routine surveillance data on earrings and piercing jewellery in Germany have shown that exposure via these everyday contacts is considerable (41): 38 of 87 earrings and piercing jewellery items had at least one part releasing cobalt in measurable amounts. The median cobalt release was estimated to be $0.013 \mu\text{g}/\text{cm}^2/\text{week}$, 75% of the parts released up to $0.085 \mu\text{g}/\text{cm}^2/\text{week}$, and 22.1% of posts released $\geq 0.2 \mu\text{g}/\text{cm}^2/\text{week}$. In the special work environment of dental technicians, both tools ($n = 21$) and dental alloys ($n = 5$) released cobalt amounts between 0.0047–820 and 0.0010 – $17 \mu\text{g}/\text{cm}^2/\text{week}$, respectively, after immersion in artificial sweat (42).

Even though the cobalt spot test (39) improves the chances of detecting relevant sources of cobalt exposure in the individual environment of a patient, it has become available only recently. Hence, information on clinical relevance (as in the present IVDK data) will usually build on similar considerations as in the case of nickel (except in the particular occupational context mentioned earlier), and will thus be difficult to rely on. A Danish study found that only 25% of cobalt reactions were clinically relevant – at the same time stating that 'there is a need for further studies to determine sources of cobalt exposure' (35).

As in previous analyses, pronounced coupled reactivity between cobalt and nickel was observed, with the typical 'asymmetry' of the estimates of relative risk (in contrast to an odds ratio that is invariate), because more patients are sensitized to nickel than to cobalt (Table 1). In some subgroups, for example the high-risk occupations

analysed in more depth, huge differences in coupled reactivity were apparent (Table 4), most likely because of coupled exposure rather than immunological cross-reactivity (which would be expected not to vary with surrogate markers of exposure, but probably with the intensity of sensitization to the respective metal). The fact that at least some subgroups, namely the youngest males and females, may recently have benefited from nickel regulation to some extent (15, 21) may explain the significant heterogeneity of the nickel–cobalt coupling across the years; an effect of this regulation on cobalt sensitization prevalence rates is not apparent, and would also not have been expected. On the contrary, it has been suggested that cobalt may have partly replaced nickel in costume jewellery (43). On comparison with a similar analysis with nickel allergy as outcome (10), some similarities in terms of risk factors can be observed: (i) female sex is a risk factor, albeit a less strong one; (ii) young age is associated with cobalt sensitization, as it is with nickel sensitization, although not nearly as strongly; and (iii) there is limited overlap in terms of high-risk occupations (e.g. concerning metal surface treaters and cashiers). In contrast, construction workers have an approximately average risk of nickel sensitization, whereas cobalt sensitization is quite common (29, 30). Although other cobalt-specific industrial exposures, for example to cobalt pigments or resins, may contribute to a partly diverging sensitization pattern, the similarities noted above point to similar exposures in a non-occupational context, namely metal objects of various sorts (34–38).

In conclusion, clinical data indicate a persisting problem, and the as yet limited exposure data point to potential sources of exposure. Further studies need to address dose–elicitation relationships to identify levels of exposure regarded as tolerable for the prevention of sensitization (and for the prevention of elicitation, at least for the vast majority of sensitized individuals). These data can then be used as an evidence base for future regulation of cobalt release, similar to the regulation of nickel under REACH (2).

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References

- Anonymous. COMMISSION REGULATION (EC) No. 552/2009 of 22 June 2009 amending Regulation (EC) No. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XVII. *Off J L* 2009; **L 164**: 7–31.
- Anonymous. COMMISSION REGULATION (EU) No. 301/2014 of 25 March 2014 amending Annex XVII to Regulation (EC) No. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards chromium VI compounds. *Off J L* 2014; **L 90**: 1–3.
- Wahlberg J E, Boman A. Sensitization and testing of guinea pigs with cobalt chloride. *Contact Dermatitis* 1978; **4**: 128–132.
- Lidén C, Julander A. Cobalt. In: *Kanerva's Occupational Dermatology*, Rustemeyer T, Elsner P, John S, Maibach H (eds): Heidelberg, Springer, 2012: pp. 505–510.
- Thyssen J P. Cobalt sensitization and dermatitis: considerations for the clinician. *Dermatitis* 2012; **23**: 203–209.
- Basketter D A, Angelini G, Ingber A, Kern P S, Menné T. Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis* 2003; **49**: 1–7.
- Wahlberg J E, Lidén C. Cross-reactivity patterns of cobalt and nickel studied with repeated open applications (ROATS) to the skin of guinea pigs. *Am J Contact Dermatitis* 2000; **11**: 42–48.
- Hindsén M, Spirén A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis* 2005; **53**: 2–8.
- Rachmawati D, Bontkes H J, Verstege M I, Muris J, von Blomberg B M, Scheper R J, van Hoogstraten I M. Transition metal sensing by Toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators. *Contact Dermatitis* 2013; **68**: 331–338.
- Uter W, Pfahlberg A, Gefeller O, Geier J, Schnuch A. Risk factors for contact allergy to nickel – results of a multifactorial analysis. *Contact Dermatitis* 2003; **48**: 33–38.
- Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy* 2012; **67**: 847–857.
- Lindberg M, Matura M. Patch testing. In: *Contact Dermatitis*, Johansen J, Frosch P J, Lepoittevin J-P (eds): Heidelberg, Springer, 2011: pp. 439–464.
- Schnuch A, Aberer W, Agathos M et al. Performing patch testing with contact allergens. *J Dtsch Dermatol Ges* 2008; **6**: 770–775.
- Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes 'Informationsverbund Dermatologischer Kliniken' (IVDK). *Derm Beruf Umwelt* 2005; **53**: 107–114.
- 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**: 142–150.
- R Core Team. *R: A Language and Environment for Statistical Computing*, 2014. Vienna, Austria, R Foundation for Statistical Computing.
- Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47–56.
- Hausen B, Schubert B. False reading of skin tests from cobalt chloride. *Akt Dermatol* 2002; **28**: 410–414.
- 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.
- Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013; **69**: 231–238.
- Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. *Contact Dermatitis* 2013; **69**: 253–256.
- Thyssen J P, Ross-Hansen K, Menné T, Johansen J D. Patch test reactivity to metal allergens following regulatory interventions: a 33-year retrospective study. *Contact Dermatitis* 2010; **63**: 102–106.
- Rui F, Bovenzi M, Prodi A, Belloni Fortina A, Romano I, Corradin M T, Larese Filon

- F. Nickel, chromium and cobalt sensitization in a patch test population in north-eastern Italy (1996–2010). *Contact Dermatitis* 2013; **68**: 23–31.
- 24 Carøe C, Andersen KE, Mortz C G. Fluctuations in the prevalence of nickel and cobalt allergy in eczema patients patch tested after implementation of the nickel regulation in Denmark. *Contact Dermatitis* 2011; **64**: 126–131.
 - 25 Fischer T, Rystedt I. False-positive, follicular and irritant patch test reactions to metal salts. *Contact Dermatitis* 1985; **12**: 93–98.
 - 26 Storrs F J, White C Jr. False-positive 'poral' cobalt patch test reactions reside in the eccrine acrosyringium. *Cutis* 2000; **65**: 49–53.
 - 27 Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. *Allergy* 2005; **60**: 372–378.
 - 28 Uter W, Gefeller O, Geier J, Lessmann H, Pfahlberg A, Schnuch A. *Epidemiologische Untersuchungen zur Abhängigkeit der Kontaktsensibilisierungen gegen wichtige 'ubiquitäre' Allergene von arbeitsbedingten sowie individuellen Faktoren – Bericht zum Forschungsvorhaben F 5156 der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Berlin: Bremerhaven, Wirtschaftsverband NW, 2002.*
 - 29 Geier J, Krautheim A, Uter W, Lessmann H, Schnuch A. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health* 2011; **84**: 403–411.
 - 30 Geier J, Lessmann H, Skudlik C, Ballmer-Weber B, Weisshaar E, Uter W, Schnuch A. Berufsbedingte Kontaktallergie bei Maurern, Fliesenlegern und Angehörigen verwandter Berufe. Aktuelles Sensibilisierungsspektrum und Entwicklungen der letzten Jahre. *Dermatol Beruf Umwelt* 2012; **60**: 136–150.
 - 31 Fischer T, Rystedt I. Cobalt allergy in hard metal workers. *Contact Dermatitis* 1983; **9**: 115–121.
 - 32 Midander K, Julander A, Skare L, Lidén C. Cobalt skin dose resulting from short and repetitive contact with hard metals. *Contact Dermatitis* 2014; **70**: 361–368.
 - 33 Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids: results of the research project 'FaSt'. *Int Arch Occup Environ Health* 2004; **77**: 543–551.
 - 34 Hamann D, Hamann C, Li L F, Xiang H, Hamann K, Maibach H, Taylor J S, Thyssen J P. The Sino-American belt study: nickel and cobalt exposure, epidemiology, and clinical considerations. *Dermatitis* 2012; **23**: 117–123.
 - 35 Thyssen J P, Menné T, Lidén C et al. Cobalt release from implants and consumer items and characteristics of cobalt sensitized patients with dermatitis. *Contact Dermatitis* 2012; **66**: 113–122.
 - 36 Thyssen J P, Johansen J D, Jellesen M S, Möller P, Sloth J J, Zachariae C, Menné T. Consumer leather exposure: an unrecognized cause of cobalt sensitization. *Contact Dermatitis* 2013; **69**: 276–279.
 - 37 Aquino M, Mucci T, Chong M, Lorton M D, Fonacier L. Mobile phones: potential sources of nickel and cobalt exposure for metal allergic patients. *Pediatr Allergy Immunol Pulmonol* 2013; **26**: 181–186.
 - 38 Cheong S H, Choi Y W, Choi H Y, Byun J Y. Nickel and cobalt release from jewellery and metal clothing items in Korea. *Contact Dermatitis* 2014; **70**: 11–18.
 - 39 Thyssen J P, Menné T, Johansen J D, Lidén C, Julander A, Möller P, Jellesen M S. A spot test for detection of cobalt release – early experience and findings. *Contact Dermatitis* 2010; **63**: 63–69.
 - 40 Corazza M, Baldo F, Pagnoni A, Miscioscia R, Virgili A. Measurement of nickel, cobalt and chromium in toy make-up by atomic absorption spectroscopy. *Acta Derm Venereol* 2009; **89**: 130–133.
 - 41 Uter W, Schmid M, Schmidt O, Bock C, Wolter J. Cobalt release from earrings and piercing jewellery – analytical results of a German survey. *Contact Dermatitis* 2014; **70**: 369–375.
 - 42 Kettelarij J, Lidén C, Axén E, Julander A. Cobalt, nickel and chromium release from dental tools and alloys. *Contact Dermatitis* 2014; **70**: 3–10.
 - 43 Thyssen J P, Jellesen M S, Menné T, Lidén C, Julander A, Möller P, Johansen J D. Cobalt release from inexpensive jewellery: has the use of cobalt replaced nickel following regulatory intervention? *Contact Dermatitis* 2010; **63**: 70–76.