

Original article

A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate

Background: Previous research indicates that positive patch tests to nickel (II) sulphate, cobalt (II) chloride and potassium dichromate commonly occur together.

Methods: To further examine the relationship between nickel, cobalt, chromate, and the factors that may potentially be related to concurrent sensitizations to two or all three metal allergens, data from the Information Network of Dermatology Departments (IVDK, <http://www.ivdk.org>) have been investigated.

Results: Women had a higher conditional odds of concurrent nickel–cobalt (OR = 6.80; 95% CI: 5.65–8.19) and nickel–chromate (OR = 2.13; 95% CI: 1.67–2.72) reactions than men. Construction workers had a significantly higher odds of cobalt–chromate reactions (OR = 13.89; 95% CI: 10.36–18.64), while the odds of isolated cobalt allergy was only 0.92 (95% CI: 0.48–1.74). Patients with underlying atopic eczema/dermatitis syndrome had a 40–90% higher chance of any positive outcome, which involved chromate. Polysensitization, defined as the number of positive reactions to standard series substances other than nickel, cobalt, and chromate, was also significantly associated with the concurrent reactions; moreover, steady and significant effect gradients were noted.

Conclusions: This research confirms the occupational nature of cobalt–chromate concurrent reactions, in particular, in construction workers. Polysensitization, which is considered to represent susceptibility to delayed-hypersensitivity in general, is also associated with the concurrent reactions to the metals. Hence, not only coupled exposure, but also individual susceptibility may be responsible for concurrent reactions to metals in man.

**J. Hegewald¹, W. Uter¹,
A. Pfahlberg¹, J. Geier², A. Schnuch²,
for the IVDK***

¹Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, Erlangen; ²Information Network of Department of Dermatology (IVDK), University of Göttingen, Göttingen, Germany

*Centres of the IVDK contributing data are given in Appendix.

Key words: allergic contact dermatitis; chromate; clinical epidemiology; cobalt; nickel.

Janice Hegewald
Department of Medical Informatics, Biometry and Epidemiology
Friedrich-Alexander-University Erlangen-Nürnberg
Waldstrasse 6
91054 Erlangen
Germany

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For decades the metal ions nickel and (VI) chromate have been acknowledged as important contact allergens (1). In the general population, 2.4–5.5% are sensitized to nickel, 0.6–1.5% to potassium dichromate (2), and almost 13% and 5% of patients attending for contact dermatitis investigation were shown to be sensitized to these two metals, respectively (3). Nickel sensitization is more frequent in women, mostly because of cheap jewelry, whereas dichromate sensitization affects men more often (3). In contrast, most of the sensitization to cobalt, although frequent in patients of both sexes, is considered of unclear relevance, and solitary reactions to cobalt are rare (4). Rather, contact allergy to cobalt is often accompanied by sensitization to nickel, chromate or even completely unrelated allergens-like rubber additives (4). These additional sensitizations and other pre-existing dermatoses-like atopic dermatitis were considered necessary predisposing factors (4). However, while nickel-specific T-cell clones do cross to some transition metals, such as copper and lead, they do not

cross to cobalt and chromate (5), and cobalt sensitizations are most likely not because of immunological cross-reactivity, but rather due to co-exposure to other metals, namely to nickel-containing alloys and chromate-containing materials (6). As (i) far from every individual exposed to nickel will be sensitized, e.g. up to 90% of young females have their ears pierced, but about 20% of the young female population are really sensitized to nickel (7), as (ii) only a few patients react to very low nickel concentrations (8), and as (iii) the frequency of co-sensitization between nickel and cobalt seem to be related to the strength of the reaction to nickel (9), sensitization to these metals may partly depend on general susceptibility factors, multiple sensitizations being one clinical indicator (10).

The aims of this evaluation of data from a large multicentre study (11) are:

- To investigate the relation of sensitization between all three metals and eventually further allergens.

- To analyse and identify (demographic or exposure) factors associated with these relations.

Materials and methods

Information collected by the multicentre Information Network of Dermatology Departments (IVDK), which has been conducting the surveillance of contact allergies in Germany and Austria for over 10-years, was used to examine the nickel–cobalt–chromate relationships. The IVDK and its surveillance methods have been described previously in detail (11). All centres of the IVDK network are members of the German Contact Dermatitis Research Group (DKG). The patch-test population examined consisted of consecutive patch-test patients visiting any one of the IVDK dermatological clinics between January 1995 and December 2002. Most patients were tested with the DKG standard series, and a standard set of anamnestic data was collected for each patient. Patch tests are performed in accordance with the guidelines of the DKG (12) and current international recommendations (13). The analysis was limited to the 57 341 patients

that were patch-tested with nickel (II) sulphate (5% in pet.), cobalt (II) chloride (1% in pet.), potassium dichromate (0.5% in pet.), and at least 10 additional standard series substances. All allergens were supplied by Hermal/Trolab of Reinbek, Germany. The maximum content of nickel in the cobalt patch-test preparation was 0.5 ppm, according to the manufacturer. The MOA-HLFA index indicates that the patient sample is similar to many other patch-test patient populations, in that a majority of the patch-test patients were female ($N = 35\,862$; 62.54%) and the patch-test patients tended to be over 40 years of age ($N = 35\,154$; 61.31%) (Table 1) (3).

For the purposes of the analysis, patch-test reactions to nickel (II) sulphate, cobalt (II) chloride, and potassium dichromate were considered either positive or negative. Positive reactions comprised weak-positive (+) and strong-positive (++/+++ reactions recorded on the third day after application of tests (D3), and negative reactions comprised questionable and irritative reactions, as well as negative readings. Additional patient characteristics and potential risk factors were obtained from the patient history (Table 2). Dermatitis was considered occupational by the attending doctor if the patients' medical history, occupational exposure, and the pattern and course of dermatitis made occupational causation probable or certain. Employment in the construction industry was considered a potential risk factor because of the well-known relationship between cement and concurrent sensitizations to cobalt and chromate (14). 'Polysensitization' was also considered a potential risk factor, and a variable was derived from the standard series patch-test results to explore the possibility that persons with multiple sensitizations might be more likely to develop concurrent sensitizations to the metals. This polysensitization variable was derived by counting the number of positive reactions (+, ++, +++) to standard series substances (other than the three metals of interest) on D3. Logistic regression was used to examine the relationships between the patient characteristics and concomitant patch-test results to the metals. All analyses were performed with

Table 1. Population characteristics distributed according to the MOAHLFA index (3)

	<i>N</i> (%)
Male (M)	21 479 (37.5)
Occupational (O)	8514 (14.8)
Atopic eczema/dermatitis syndrome (AEDS) (A)	11 644 (20.3)
Hand dermatitis (H)	16 467 (28.7)
Leg dermatitis (L)	6223 (10.9)
Face dermatitis (F)	8827 (15.4)
Age (>40 years) (A)	35 154 (61.3)

Table 2. Patient characteristics used in the analysis

	Negative [<i>N</i> (%)]	Nickel [<i>N</i> (%)]	Cobalt [<i>N</i> (%)]	Chromate [<i>N</i> (%)]	Nickel–cobalt [<i>N</i> (%)]	Nickel–chromate [<i>N</i> (%)]	Cobalt–chromate [<i>N</i> (%)]	Nickel–cobalt–chromate [<i>N</i> (%)]	Total [<i>N</i> (%)]
Sex									
Male	19 251 (41.30)	820 (12.94)	253 (34.01)	625 (51.82)	127 (9.53)	97 (25.87)	215 (52.96)	91 (28.26)	21 479 (37.46)
Female	27 367 (58.70)	5517 (87.06)	491 (65.99)	581 (48.18)	1206 (90.47)	278 (74.13)	191 (47.04)	231 (71.74)	35 862 (62.54)
Age group (years)									
<40	16 462 (35.31)	3752 (59.21)	310 (41.67)	377 (31.26)	849 (63.69)	147 (39.20)	147 (36.21)	143 (44.41)	22 187 (38.69)
≥40	30 156 (64.69)	2585 (40.79)	434 (58.33)	829 (68.74)	484 (36.31)	228 (60.80)	259 (63.79)	179 (55.59)	35 154 (61.31)
Atopic eczema/dermatitis syndrome (AEDS)									
No	37 700 (80.87)	4734 (74.70)	563 (75.67)	928 (76.95)	990 (74.27)	255 (68.00)	298 (73.40)	229 (71.12)	45 697 (79.69)
Yes	8918 (19.13)	1603 (25.30)	181 (24.33)	278 (23.05)	343 (25.73)	120 (32.00)	108 (26.60)	93 (28.88)	11 644 (20.31)
Occupational dermatitis									
No	40 332 (86.52)	5188 (81.87)	582 (78.23)	861 (71.39)	1043 (78.24)	303 (80.80)	269 (66.26)	249 (77.33)	48 827 (85.15)
Yes	6286 (13.48)	1149 (18.13)	162 (21.77)	345 (28.61)	290 (21.76)	72 (19.20)	137 (33.74)	73 (22.67)	8514 (14.85)
Construction work									
No	45 881 (98.42)	6304 (99.48)	734 (98.66)	1040 (86.24)	1332 (99.92)	362 (96.53)	321 (79.06)	308 (95.65)	56 282 (98.15)
Yes	737 (1.58)	33 (0.52)	10 (1.34)	166 (13.76)	1 (0.08)	13 (3.47)	85 (20.94)	14 (4.35)	1059 (1.85)
Polysensitization*									
0	31 718 (68.04)	4009 (63.26)	314 (42.20)	548 (45.44)	711 (53.34)	158 (42.13)	157 (38.67)	127 (39.44)	37 742 (65.82)
1	8373 (17.96)	1409 (22.23)	203 (27.28)	281 (23.30)	331 (24.83)	98 (26.13)	123 (30.30)	80 (24.84)	10 898 (19.01)
2	3518 (7.55)	533 (8.41)	96 (12.90)	192 (15.92)	154 (11.55)	57 (15.20)	59 (14.53)	65 (20.19)	4674 (8.15)
3 or more	3009 (6.45)	386 (6.09)	131 (17.61)	185 (15.34)	137 (10.28)	62 (16.53)	67 (16.50)	50 (15.53)	4027 (7.02)
4 or more	1417 (3.04)	179 (2.82)	64 (8.60)	95 (7.88)	57 (4.28)	33 (8.80)	34 (8.37)	27 (8.39)	1906 (3.32)
Total	46 618 (81.30)	6337 (11.05)	744 (1.30)	1206 (2.10)	1333 (2.32)	375 (0.65)	406 (0.71)	322 (0.56)	57 341 (100.00)

*Other than nickel (II) sulphate, cobalt (II) chloride, and potassium dichromate.

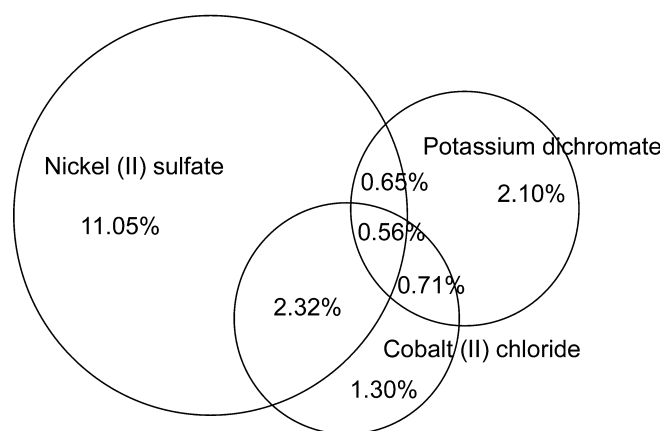


Figure 1. Venn diagram representing the percentage of patients positive to nickel (II) sulphate, potassium dichromate, or cobalt (II) chloride (the size of the circles and the overlapping areas do not accurately represent their corresponding percentages).

the statistical software package SAS (version 8.2, SAS Institute, Cary, NC, USA).

A multinomial logistic regression analysis was conducted with the dependent variable consisting of a categorical variable representing all eight possible combinations of metal allergy outcomes. The eight outcome combinations included positive reactions to (i) nickel only, (ii) cobalt only, (iii) chromate only, (iv) nickel and cobalt, (v) nickel and chromate, (vi) cobalt and chromate, (vii) nickel, cobalt, and chromate, and (viii) no positive reactions to any of the three metals (Fig. 1). Conditional odds ratios were calculated from the multinomial logistic regression model with negative reactions to all three metals serving as the reference category. The explanatory (independent) variables considered in the analyses were the patients' sex, a suspected occupational dermatitis, age over 40 years, past or current atopic eczema/dermatitis syndrome (AEDS), current or previous employment in the construction field, and the number of positive reactions to other (unrelated) patch tests (polysensitization). Lastly, linear trends in the proportion of positive reactions to the metal combinations over the (four) levels of the polysensitization variable were tested within the multinomial logistic regression model by entering the polysensitization variable into the model as an ordinal variable and examining the Wald chi-squared *P*-values corresponding to the ordinal polysensitization variable.

Results

About 18.70% (*N* = 10 723) of the eligible patient population tested positive to at least one of the metals (Table 2), with about 4.25% of the patients testing positive to two or more. The number of patients testing positive to nickel and chromate or cobalt and chromate both consisted of <1% of the sample, at 0.65% (*N* = 375) and 0.71% (*N* = 406), respectively. A larger proportion of the patients tested positive to both nickel and cobalt (2.32%, *N* = 1333), while only 0.56% (*N* = 322) patients tested positive to all three of the metals (Fig. 1).

Nickel

Gender had a very strong association with positive reactions to nickel alone, with odds of a positive reaction to nickel alone being almost five times greater for women than for men (OR = 4.95; 95% CI: 4.58–5.35). Patients positive to nickel alone tended to be younger with the OR for patients above 40 being significantly below unity (OR = 0.36; 95% CI: 0.34–0.38). Suspected occupational dermatitis was also significant, although, the association between reactions to nickel and occupational dermatitis was not as strong as those between gender and age. Positive reactions to other standard series substance were also significant factors. However, unlike the other metals and metal combinations, the odds decreased with an increasing number of positive reactions to other substances with a significant linear trend (*P* < 0.0001) (Table 3).

Cobalt

Similar to nickel, females and younger patients had significantly higher odds of having a positive reaction to cobalt alone. However, unlike reactions to nickel alone, the strength of association between gender and age and reactions to cobalt alone were not as considerable. Suspected occupational dermatitis and AEDS was also significantly associated with reactions to cobalt, although atopic dermatitis was only barely significant. Unlike reactions to nickel, the odds of a reaction to cobalt increased with increasing number of positive reactions to other standard series substances, with three or more positive reactions to other standard series substances having the strongest association with positive reactions to cobalt alone (OR = 4.76; 95% CI: 3.85–5.88).

Chromate

All of the factors considered in the model were significantly associated with reactions to cobalt alone. However, unlike nickel and cobalt, men and patients over 40 years of age were more likely to test positive to chromate. A strong association was observed between construction work and reactions to chromate (OR = 7.93; 95% CI: 6.49–9.69), and the odds of reactions to chromate alone increased with increasing number of positive reactions to other substances.

Nickel–cobalt

Female patch-test patients were highly overrepresented among patients positive to both nickel and cobalt (OR = 6.80; 95% CI: 5.65–8.19), while older patients over 40 years of age were severely underrepresented (OR = 0.27; 95% CI: 0.24–0.31). Atopic dermatitis and construction work were not significantly associated with reactions to both nickel and cobalt, however, the fact that only one patient in the nickel–cobalt category reported

Table 3. Multinomial logistic regression results (odds ratio, 95% confidence intervals) for various factors and the outcome of positive patch test reactions (+, ++, +++) to only one metal, a combination of two metals, or to all three metals vs nonpositive reactions to all three metals (i.e. including questionable and irritative reactions)

	Nickel	Cobalt	Chromate	Nickel–cobalt	Nickel–chromate	Cobalt–chromate	Nickel–cobalt–chromate
Female	4.95 (4.58–5.35)	1.36 (1.16–1.59)	0.84 (0.74–0.95)	6.80 (5.65–8.19)	2.13 (1.67–2.72)	0.96 (0.77–1.20)	1.97 (1.52–2.55)
Age >40 years	0.36 (0.34–0.38)	0.70 (0.60–0.82)	1.27 (1.12–1.46)	0.27 (0.24–0.31)	0.84 (0.67–1.06)	1.05 (0.84–1.30)	0.64 (0.50–0.81)
Atopic eczema/dermatitis syndrome (AEDS)	0.99 (0.92–1.05)	1.21 (1.02–1.45)	1.42 (1.23–1.64)	0.93 (0.82–1.06)	1.89 (1.50–2.37)	1.68 (1.33–2.12)	1.49 (1.16–1.92)
Occupational dermatitis	1.26 (1.17–1.36)	1.62 (1.35–1.95)	1.98 (1.73–2.28)	1.50 (1.31–1.72)	1.37 (1.04–1.79)	2.12 (1.69–2.66)	1.57 (1.19–2.07)
Construction worker	0.85 (0.59–1.21)	0.92 (0.48–1.74)	7.93 (6.49–9.69)	0.15 (0.02–1.05)	3.70 (2.05–6.68)	13.89 (10.36–18.64)	4.10 (2.30–7.31)
Polysensitization*							
1 vs 0	1.39 (1.30–1.49)	2.47 (2.07–2.96)	1.89 (1.63–2.19)	1.86 (1.63–2.13)	2.35 (1.82–3.03)	2.94 (2.31–3.75)	2.43 (1.83–3.22)
2 vs 0	1.33 (1.20–1.47)	2.85 (2.25–3.59)	3.13 (2.64–3.72)	2.22 (1.85–2.66)	3.28 (2.41–4.46)	3.52 (2.59–4.79)	4.84 (3.57–6.56)
3 or more vs 0	1.24 (1.11–1.39)	4.76 (3.85–5.88)	3.56 (2.99–4.25)	2.62 (2.16–3.18)	4.34 (3.21–5.86)	4.81 (3.58–6.48)	4.62 (3.31–6.46)
Trend test (<i>P</i> -value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Number of positive (+, ++, +++) reactions to standard series substances other than nickel (II) sulphate, cobalt (II) chloride, and potassium dichromate.

working in the construction industry (Table 2) makes it difficult to interpret the construction work estimate. Conversely, occupational dermatitis was a significant factor within the range of the risk estimates for the two solitary contact allergies. While additional sensitizations to unrelated substances were also significantly associated with the odds of reactions to both nickel and cobalt, this relationship was the weakest of all positive associations of this kind.

Nickel–chromate

Simultaneous reactions to nickel and chromate were observed less frequently than the other two metal salt pairs (Fig. 1). Unlike most of the other combinations of metal allergies, age did not have a significant association with concurrent allergic reactions to nickel and chromate. Conversely, women, patients with AEDS or occupational dermatitis, construction workers, and patients with an increasing level of polysensitization had significantly increased odds of concurrent positive reactions.

Cobalt–chromate

All of the factors except age and gender had significantly increased odds of positive reactions to cobalt and chromate. Like positive reactions to cobalt alone, the largest OR estimate was that of construction workers (OR = 13.89; 95% CI: 10.36–18.64). The second most influential parameter regarding reactions to cobalt and chromate were positive reactions to unrelated substances. Persons testing positive to three or more standard series substances had almost a five times greater odds of testing positive to cobalt and chromate than the reference group.

Nickel–cobalt–chromate

Females, younger patients under 40 years of age, patients with AEDS, patients with a suspected occupational dermatitis, construction workers, and persons with multiple sensitizations had an increased odds of a

three-way concurrent reaction. The odds of positive reactions to all three metals were most drastically increased for patients with positive reactions to other unrelated allergens. Construction work and three or more positive reactions to other substances had the greatest conditional ORs for concurrent reactions to all three metal allergens at 4.10 (95% CI: 2.30–7.31) and 4.62 (95% CI: 3.31–6.46), respectively.

Discussion

Delayed type hypersensitivity reactions to nickel, cobalt, and chromate have been observed to be related to one another, however, the extent of this relationship and the external factors that may influence these relationships have not yet been fully investigated. This analysis of patch-test data has attempted to describe these relationships in more detail, with an emphasis placed on the identification of potential predictors of concurrent reactions. Lisi et al. recently reported on a contamination of cobalt patch-test material with significant amounts of nickel (15). However, such a contamination has probably not distorted our analysis, because the maximum concentration of 0.5 ppm nickel in our patch-test material is insufficient to elicit a positive patch-test reaction to nickel even in exquisitely nickel-sensitive patients, according to a previous nickel threshold testing study (8).

Concerning the interpretation of concomitant reactions in general it should be mentioned that in observational studies of humans such as ours it is impossible to know if the concomitant reactions to any of the metals analysed (i) represent concomitant sensitizations because of coupled exposure, (ii) if the sensitizations were the result of separate unrelated exposures or (iii) are due to structural similarity of the haptens (16), (iv) are due to a specific increased susceptibility to metals [metal haptens may be differently processed by antigen-presenting cells (APC) compared with organic haptens (17), and nickel contact sensitivity is also associated with a different human leucocyte antigen (HLA) pattern (18, 19) allowing for a

direct interaction of nickel with peptides in the antigen-presenting groove of the HLA-molecule (20)], or (v) are due to a general increased susceptibility (see below).

Age and sex

The results of the analysis indicate that females and younger members of the patient sample were often more likely to be sensitized to a majority of the metal combinations. Given that young women are often sensitized to nickel (typically due to jewelry exposures) (21), levels of the dependent variable including positive reactions to nickel may reflect, at least in part, this characteristic nickel exposure pattern in the OR estimates of gender and age. Since cobalt sensitization is also more common among women and younger persons, the odds of concurrent positive patch-test reactions to nickel and cobalt were naturally greater for women and patients under 40. The reason for this increased risk is most likely skin contact with jewelry containing both metals. Another possibility could be the use of consumer or cosmetic products containing traces of both metals. For example, some eye shadows have been shown to contain both nickel and cobalt (22). However, metal sensitizations because of consumer products have generally been considered unlikely (23).

The strong influence of nickel was obvious in the analysis of nickel and chromate, where women had an increased odds of a concurrent reaction, although men tended to test positive to dichromate alone more often than women. Age, however, did not appear to have an association with concomitant reactions to nickel and chromate.

Atopic eczema/dermatitis syndrome

The association between AEDS and the different outcomes considered is generally weaker than the associations observed with other explanatory factors. In fact, no association at all was observed between AEDS and reactions to nickel, which is largely in accordance with a previous analysis of IVDK data focusing on nickel allergy alone (21). In contrast, positive reactions to chromate, either isolated, or in particular, if combined with positive patch-test reactions to other metal salts, were weakly but consistently associated with AEDS. In view of the marginally irritating properties of the chromate patch-test preparation on one hand, and the susceptibility of the skin of AEDS patients to irritation on the other hand, the apparent association may be due to a certain proportion of false-positive chromate test reactions (24) in this particular subgroup of patients. Concerning cobalt, a certain proportion of weak positive reactions may have been false-positive reactions caused by test samples in use for several months, albeit not expired: the formation of tiny jagged crystals in these older or improperly stored test preparations of cobalt in petrolatum has been shown to cause petechia mimicking weak-positive reactions (25),

particularly in patients susceptible to irritation, such as patients with AEDS.

Occupational exposures

Occupational exposure has been included in our model both on a general level ('occupational dermatitis') and on a specific level ('work in the construction trade'). The pattern of association observed with the first factor shows little overall variation, indicative of the moderate importance of these metals, in particular chromate, as occupational allergens. However, because of the retrospective study-design, causal chains implicating occupational exposures as the cause of the metal sensitizations cannot be established. In other words, while patients with positive reactions to the metal allergens may have been sensitized by workplace exposures to the metals, it is also possible that an increased susceptibility to sensitization among the metal-sensitized caused these patients to be at higher risk of occupational dermatitis (involving other workplace irritants or allergens). In contrast, the specific exposure to wet cement in construction work, namely, to chromate and cobalt as a contaminants, and the associated risk of cobalt and, in particular, chromate allergy (14, 26) is well illustrated by our results: while isolated cobalt allergy is uncommon, compared with patients not working in the construction trade, the risk of chromate allergy, and in particular, of coupled chromate-cobalt allergy is exceedingly high.

Polysensitization

Polysensitization was associated with all of the metal reaction combinations. Multiple sensitizations have been regarded as a clinical sign of heightened susceptibility (10), which could be partly due to genetic polymorphisms of relevant cytokines (27, 28). While it is possible that some of the patients categorized as having three or more sensitizations to other standard series substances may have in fact have exhibited signs of 'angry back', only a small proportion (3.32%) of the patients had four or more sensitizations (Table 2), suggesting that the results were probably not greatly influenced by the manifestation of 'angry back'. Our results strongly suggest that some people are more susceptible to contact sensitizations in general, and these people are also more likely to test positive to nickel, cobalt, and chromate. Ancillary support of a relationship between polysensitization and concurrent reactions is the 'dose-response' relationship of the number of reactions and the odds of concurrent reactions. Interestingly, such a relationship was observed for all of the reaction categories, except for reactions to nickel alone. Consequently, individual susceptibility may be responsible for concurrent reactions to metals in man. The fact that reactions to nickel alone did not exhibit a similar dose-response pattern of susceptibility fits well with a previous observation finding nickel a relatively 'solitary'

allergen (29). This may be due to certain exposure conditions favouring isolated nickel contact allergy.

In conclusion, these analyses have demonstrated the associations of various factors with concurrent reactions to nickel, cobalt, and chromate. It has also been shown that the factors associated with reactions to chromate only and cobalt–chromate reactions differ from the factors associated with the other reaction categories,

and supports the existence of a link between cobalt–chromate and construction work. In addition, our results indicate that persons with other sensitizations are more likely to have concurrent sensitizations to the three metals. However, further research is needed to fully understand the implications of vulnerability to delayed-hypersensitivity and these concurrent sensitizations.

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Appendix

Aachen (H. Dickel, S. Erdmann), Augsburg (A. Ludwig), Berlin B.-Frank (B. Tebbe, R. Treudler), Berlin BWK (A. Köhler), Berlin Charité (B. Laubstein, T. Zuberbier, M. Worm), Bochum (Ch. Szliska, M. Straube, M. Freitag), Dortmund (P. J. Frosch, B. Pilz, C. Pirker, R. Herbst), Dresden (G. Richter, R. Aschoff), Duisburg (J. Schaller), Erlangen (K.-P. Peters, T. L. Diepgen, M. Fartasch, M. Hertl, V. Mahler), Essen (H.-M. Ockenfels, U. Hillen), Freudenberg (Ch. Szliska), Gera (J. Meyer), Göttingen (Th. Fuchs, J. Geier), Graz (W. Aberer, B. Kränke), Halle (G. Gaber, D. Lübke), Hamburg (M. Kiehn, D. Vieluf, R. Weißbecher), Heidelberg (A. Schulze-Dirks, U. Jappe, M. Hartmann),

Heidelberg AKS (H. Dickel, T. L. Diepgen, E. Weisshaar), Homburg/Saar (P. Koch), Jena (M. Gebhardt, A. Bauer, W. Wigger-Alberti, M. Kaatz, S. Schliemann-Willers), Kiel (J. Brasch), Krefeld (M. Lilie, A. Wallerand, S. Wassilew), Lübeck (J. Kreusch, J. Grabbe), Mainz (D. Becker), Mannheim (Ch. Bayerl), Marburg (I. Effendy, H. Löffler), München Schwabing (M. Agathos), München TU (J. Rakoski), Nürnberg (I. Müller), Osnabrück (W. Uter, S. M. John, H. J. Schwanitz, N. Schürer), Rostock (H. Heise), Tübingen (Lischka), Ulm BKW/Univ. (H. Gall, P. Gottlöber, G. Staib, R. Hinrichs, H. Pillekamp), Wuppertal (O. Mainusch, J. Raguz, B. Dierbach), Würzburg (J. Arnold, A. Trautmann).