

Cobalt allergy: suitable test concentration, and concomitant reactivity to nickel and chromium

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Summary

Background. Cobalt allergy is frequent, but knowledge about exposure is limited. The patch test concentration and relevance of positive reactions are sometimes questioned.

Objectives. To assess the suitability of cobalt 1% versus 0.5% for patch testing, and to analyse the co-occurrence of allergy to cobalt, chromium, and nickel.

Materials and methods. Consecutive dermatitis patients (n = 656) were patch tested with cobalt chloride 0.5% and 1%, potassium dichromate 0.5%, and nickel sulfate 5%, all in petrolatum. Reactions were assessed on day (D)3, and on D6 or D7, and the reactivity and development of reactions were analysed.

Results. Allergy to any metal was shown in 31% of patients, allergy to cobalt in 14%, allergy to chromium in 7%, and allergy to nickel in 20%. A significant proportion (37%) of cobalt allergy cases were missed by cobalt 0.5% versus 1%, whereas the reactivity profiles were similar. Cobalt allergy was solitary, without concomitant allergy to chromium or nickel, in 50% of patients.

Conclusions. Cobalt chloride 1% pet. is more suitable for patch testing than 0.5%. Solitary cobalt allergy is as frequent as concomitant allergy to cobalt and nickel or chromium. Sources of skin exposure to metals need to be identified for prevention of contact allergy. This is, owing to large knowledge gaps, particularly demanding for cobalt.

Key words: allergic contact dermatitis; cross-reactions; metals; patch test.

Contact allergy to cobalt is common in dermatitis patients (1, 2). Cobalt is also among the most frequent skin sensitizers in adolescents of the general population in Nordic countries (3–5). Surprisingly little is known about the major sources of exposure to cobalt in consumers, whereas some occupational exposures are well known (2, 6–9). The frequent co-occurrence of allergy to cobalt and nickel is often emphasized. The role of concomitant versus solitary exposure and possible cross-reactivity

has been addressed. Animal studies have suggested that concomitant reactivity in patients is attributable to multiple sensitization rather than cross-reactivity (10, 11). It has also been suggested that nickel acts as an adjuvant in cobalt sensitization (12).

The lack of data on skin exposure to cobalt is a missing link and major obstacle when the clinical relevance of patch test reactions is assessed (2, 7, 8, 13, 14). Sources of exposure to metals are present all around in daily life. This is most evident for nickel in metallic items. The amount of metal deposited onto the skin from metallic surfaces is not directly related to the bulk composition of the material, but rather to what is available on the surface. The skin dose is thus largely dependent on the composition of the metal oxide on the surface, and on the frequency and duration of contact (15, 16).

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Some recent trends should be mentioned. Electronic devices such as mobile phones, computer laptops and tablets are increasingly being used, and they have been reported to cause nickel dermatitis and to release nickel (17–19). Such items may also release cobalt, used as a surface coating (17). The increasing frequency of chromium allergy in females has been attributed to chromium-tanned leather (20, 21). Leather products may also contain cobalt as a pigment (22). Cobalt exposure is traditionally described as occurring in hard metal, glass and pottery workers, whereas general knowledge about other sources of cobalt exposure is limited. Cobalt, without nickel, is used in a wide range of metallic and non-metallic products and materials to which consumers are also exposed. Examples are dental alloys, electronic devices, jewellery, magnetic materials, orthopaedic implants, pigments in cosmetics and leather, putty, siccative in paints, and tools (2, 6–8).

The clinical relevance of positive patch test reactions to cobalt has sometimes been questioned (2, 14, 23, 24). It has been suggested that the generally used patch test concentration might be too high, causing many irritant reactions or false-positive reactions. It has also been speculated whether patch test reactions to cobalt may reflect some mechanism other than contact allergy. The cobalt preparation in the European baseline series is cobalt(II) chloride hexahydrate 1% in petrolatum (in the following called cobalt 1%). The Swedish baseline series is, to the best of our knowledge, the only national baseline series with cobalt 0.5%. Cobalt 0.5% was introduced in Sweden around 1985, after it had been suggested that 1% caused false-positive reactions (23). In 2011, cobalt 1% was added to the baseline series of the Unit of Occupational and Environmental Dermatology, Centre for Occupational and Environmental Medicine in Stockholm for comparison.

The main aim of this study was to compare the patch test responses to two different cobalt concentrations, in order to assess their suitability for diagnostic patch testing. Another aim was to analyse the co-occurrence of patch test reactivity to cobalt, chromium, and nickel.

Patients, Materials, and Methods

Consecutive dermatitis patients who had been referred to our outpatient clinic were included in the study. They had been patch tested concomitantly with cobalt(II) chloride hexahydrate (cobalt) 0.5% and 1%, potassium dichromate (chromium) 0.5%, and nickel(II) sulfate hexahydrate (nickel) 5%, all in pet. (Chemotechnique Diagnostics, Vellinge, Sweden), during the period August 2011 to January 2015, as part of testing with the

Swedish baseline series and additional substances. Finn Chambers® (8 mm) on Scanpor® tape (SmartPractice®, Phoenix, AZ, USA) were used. Testing, including morphological criteria for the assessments, was performed according to international recommendations corresponding to the current European Society of Contact Dermatitis guideline (25). The application time was 2 days, and readings were performed on day 3 (D3) and D6 or D7 (D6–D7). Readings were performed by dermatologists experienced in patch testing. Positive reactions (+, ++, and +++), doubtful reactions (?+) and irritant reactions (IR) were recorded. Taken together, these are here called visible reactions. Tests with no visible reaction are called negative. The inclusion criteria were concomitant testing with cobalt 0.5%, cobalt 1%, chromium, and nickel, and participation in both readings (D3 and D6–D7). All patients had given consent for scientific compilation and publication of unidentified patch test data.

Statistical analysis

Results are visualized as area-proportional diagrams using ellipses (Euler diagrams, often called Venn diagrams, by EULERAPE v3; available at <http://www.eulerdiagrams.org/eulerAPE/>) and pie charts. Differences between groups were calculated with the proportion test between groups by use of STATA STATISTICAL SOFTWARE Release 13 (StataCorp, College Station, TX, USA). Differences were considered to be statistically significant at $p < 0.05$.

Results

In total, 656 dermatitis patients (426 females and 230 males; born 1924–2005) were included in the study. The patch test results are shown in Figs. 1 and 2, in Tables 1 and 2, and in Table 3.

Contact allergy to any of the metals was shown in 200 patients (30.5% of all tested), allergy to cobalt in 92 (14.0%) (87 by cobalt 1%, and 5 by cobalt 0.5% only), allergy to chromium in 43 (6.6%), and allergy to nickel in 129 (19.7%) (Table 1). Concomitant and solitary allergy to cobalt, chromium and/or nickel is shown in Fig. 1a. Solitary allergy to cobalt was shown in 46 patients (50.0% of the cobalt-positive patients). Thirty-four of the 92 (37.0%) patients with cobalt allergy were missed by cobalt 0.5%, and 5 were missed by cobalt 1% (Fig. 1b). Likewise, considering only the stronger (++ and +++) patch test reactions to cobalt, 18 of 71 (25.4%) patients were missed by cobalt 0.5% and 5 by cobalt 1% (not shown). Comparison of reactions to

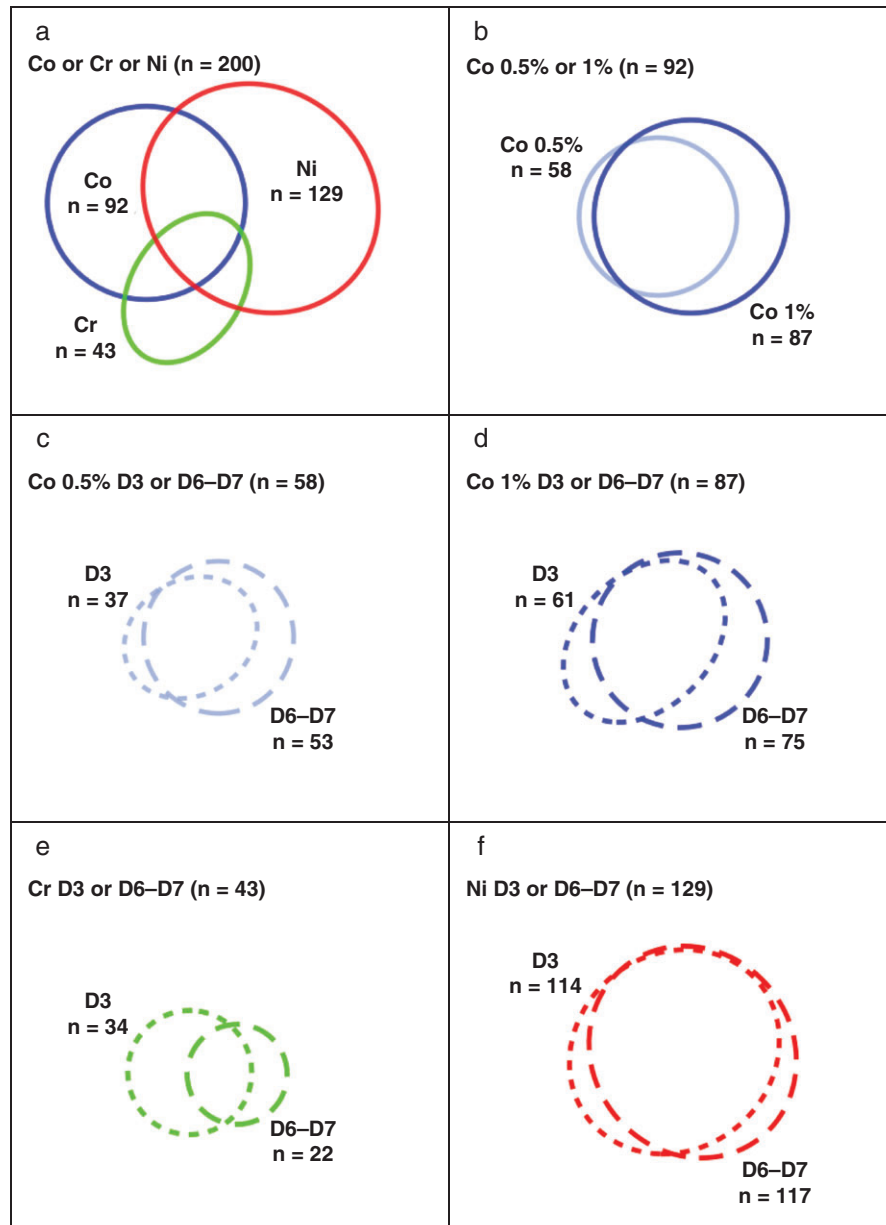


Fig. 1. Proportions of positive patch test reactions to Co, Cr and Ni in dermatitis patients ($n = 656$), shown as area-proportional Euler diagrams. (a) Concomitant and solitary reactions to Co, Cr or Ni on either D3 or D6–D7. (b) Overlap of reactions to Co 0.5% and Co 1% on either D3 or D6–D7, showing the proportion missed by testing with Co 0.5%. (c–f) Overlap on D3 and D6–D7 of reactions to Co 0.5%, Co 1%, Cr, and Ni, respectively, showing the proportions missed by single readings. The number of individuals (n) in each diagram is given. Detailed numbers are shown in Table 3.

cobalt 1% on D3 and D6–D7 showed that 26 of 87 (29.9%) of all cobalt-allergic patients would have been missed by reading on D3 only (Fig. 1d). The proportion of chromium-allergic patients who would have been missed by only D3 readings would have been 9 of 43 (20.9%), and the proportion of nickel-allergic patients who would have been missed would have been 15 of 129 (11.6%) (Fig. 1e, f).

The patch test reactivities on D3 and D6–D7 are shown in Fig. 2, and detailed results are shown in Table 2. Figure 2 shows the patch test reactivity as pie charts of the relative proportions of visible reactions (positive

versus doubtful or irritant). To facilitate visual comparison, the positives are in one category, and the doubtful and irritant reactions are in another, as is generally performed in the clinic. The appearance on D6–D7 of D3 results is also shown. The reason for showing the results as pie charts was primarily to facilitate comparison of the reactivity pattern for cobalt 0.5% with that for cobalt 1%. The overall reactivity pattern was similar for cobalt 0.5% and 1% (Fig. 2a–j; Tables 1 and 2), whereas the relative proportion of doubtful or irritant reactions was substantially larger for chromium (Fig. 2k–m) than for cobalt and nickel (Fig. 2a–c, f–h, and p–r).

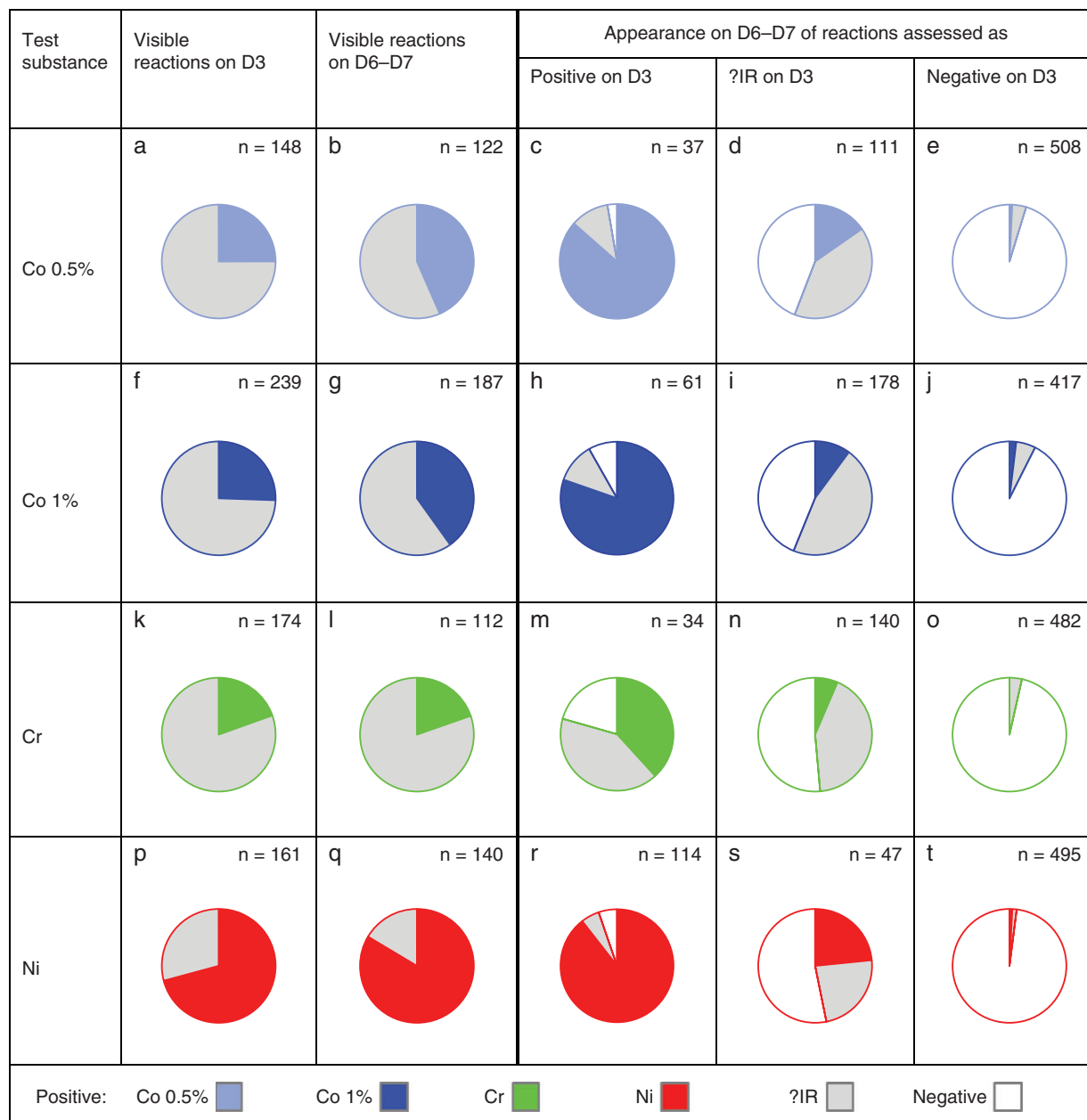


Fig. 2. Patch test reactions to Co 0.5%, Co 1%, Cr 0.5% and Ni 5% in pet. are summarized as pie charts (a–t) for visual comparison of the reactivity patterns. Consecutive dermatitis patients ($n = 656$) were concomitantly tested with the test substances, and readings were performed on D3 and D6–D7. The proportion of visible reactions (positive, doubtful or irritant) on D3 and D6–D7, and the appearance on D6–D7 of reactions on D3 (positive, doubtful or irritant, and negative), are shown. The total number of reactions shown in each pie chart ($n = x$) is given to the right above the chart. Detailed numerical values and morphological criteria are shown in Table 2. ?IR, doubtful or irritant reaction.

Comparison of positive reactions between the sexes and age groups is shown in Table 1. Female patients had larger proportions of positive reactions to cobalt 1% (17.1%), chromium (7.8%) and nickel (25.4%) than males (6.1%, 4.3%, and 9.1%, respectively). The difference between the

sexes was statistically significant for cobalt 1% and nickel (both $p < 0.001$), but not for chromium ($p = 0.093$). Female patients had larger proportions of solitary positive reactions to cobalt 1% (8.7%) and nickel (18.5%) than males (3.0% and 6.5%, respectively); the differences

Table 1. Results of concomitant patch testing of dermatitis patients (n = 656) with cobalt (0.5% and 1%), chromium, and nickel, and two readings

Test substance	Positive reactions on D3 and/or D6–D7, number (%)						
	All (n = 656)	Sex			Age		
		Female (n = 426)	Male (n = 230)	<i>p</i>	Younger half (n = 328)	Older half (n = 328)	<i>p</i>
Any metal	200 (30.5)	164 (38.5)	36 (15.7)	<0.001	90 (27.4)	110 (33.5)	0.090
Co 0.5% (all) ^a	58 (8.8)	50 (11.7)	8 (3.5)	<0.001	25 (7.6)	33 (10.1)	0.27
Co 1% (all) ^a	87 (13.3)	73 (17.1)	14 (6.1)	<0.001	43 (13.1)	44 (13.4)	0.91
Cr (all)	43 (6.6)	33 (7.8)	10 (4.3)	0.093	16 (4.9)	27 (8.2)	0.083
Ni (all)	129 (19.7)	108 (25.4)	21 (9.1)	<0.001	55 (16.8)	74 (22.6)	0.062
Co 0.5% (solitary)	27 (4.1)	24 (5.6)	3 (1.3)	0.008	11 (3.4)	16 (4.9)	0.33
Co 1% (solitary)	44 (6.7)	37 (8.7)	7 (3.0)	0.006	23 (7.0)	21 (6.4)	0.75
Cr (solitary)	19 (2.9)	13 (3.1)	6 (2.6)	0.75	9 (2.7)	10 (3.0)	0.82
Ni (solitary)	85 (13.0)	79 (18.5)	15 (6.5)	<0.001	36 (11.0)	49 (14.9)	0.13

Proportion of reactions	Difference in proportion of patch test reactions					
	D3			D6–D7		
	Co 0.5%	Co 1%	<i>p</i>	Co 0.5%	Co 1%	<i>p</i>
Positive/doubtful or irritant	37/111	61/178	0.87	53/69	75/112	0.16

Comparisons of frequency of positive reactions and solitary reactions, and by sex and age, are shown. Testing was performed from August 2011 to January 2015. Patch test reactivity is shown in Figs. 1 and 2, and shown in detail in Table 2.

Co, cobalt(II) chloride hexahydrate; Cr, potassium dichromate; Ni, nickel(II) sulfate hexahydrate.

Younger half born in 1972–2005; older half born in 1924–1971.

^aThe total number of positive reactions to Co (1% and/or 0.5%) was 92 (14.0% of all patients); the corresponding number of solitary reactions to Co was 46 (50.0% of the Co-positive patients).

were statistically significant ($p = 0.006$ and $p < 0.001$). The frequency of solitary positive reactions did not differ significantly between the younger and older half of the patients (Table 1).

Discussion

We conclude that cobalt 1% in pet., the generally used patch test preparation, is more suitable than cobalt 0.5%. Our study shows that a significant proportion of cobalt allergy cases are missed by testing with cobalt 0.5% as compared with 1%. The proportion of doubtful or irritant reactions, in relation to positive reactions, is of equal magnitude for cobalt 1% and 0.5%.

This study shows that solitary allergy to cobalt, without concomitant allergy to nickel or chromium, is frequent (50%) in cobalt-allergic dermatitis patients, corresponding to previous findings in Germany (41% and 42%), and in cobalt-allergic adolescents of the general population in Sweden (62%) (2, 4, 26). This is, however, often expressed in reverse: that cobalt allergy is often seen together with nickel allergy. We suggest that studies of solitary cobalt allergy cases would contribute significantly to an understanding of exposure and sensitization, and to prevention.

There are attempts to harmonize reading routines (27, 28). According to our experience, there is large variability in the recording of doubtful and irritant reactions, which can make it difficult to compare the frequency of such reactions between clinics. In our clinic, we record all doubtful and irritant reactions, irrespective of test substance. Our results show that chromium causes relatively more doubtful and irritant reactions in relation to positive reactions than cobalt does. We consider it likely that dermatologists, who are well informed about the major sources of exposure to chromium, may be less concerned about doubtful or irritant reactions to chromium than those to cobalt. We believe that relatively scarce knowledge about sources of exposure to cobalt contributes to questioning the clinical relevance of reactions and the adequacy of the patch test preparation. Today, it is generally well known that two readings (D3–D4 and around D7) are recommended for diagnostic patch testing in patients (25). Our results underscore this, as a relatively large proportion of positive reactions, particularly to chromium and cobalt, were missed by a single reading.

Exposure assessments and dose–response studies, including elimination and provocation tests, would elucidate the issue of true versus false-positive cobalt reactions. It should be recalled that the elicitation threshold (ED10 value) in cobalt-allergic individuals is comparable with

Table 2. Morphology of patch test reactions [reading criteria shown below, corresponding to (25)]

Test substance	Reaction	No. of reactions		Appearance on D6–D7 of D3 reactions assessed as			
		D3	D6–D7	Positive	?+	IR	Negative
Co 0.5%	+	17	31	15	12	2	2
	++	16	18	14	1	1	2
	+++	4	4	3	1	0	0
	+ /+++ /+++	37	53	32	14	3	4
	?+	48	32	4	12	4	12
	IR	63	37	0	2	27	8
	Negative	508	534	1	20	29	484
	All	656	656	37	48	63	508
Co 1%	+	35	37	22	8	2	5
	++	20	31	22	6	1	2
	+++	6	7	5	0	1	1
	+ /+++ /+++	61	75	49	14	4	8
	?+	65	28	4	10	7	7
	IR	113	84	3	10	55	16
	Negative	417	469	5	31	47	386
	All	656	656	61	65	113	417
Cr	+	29	10	6	4	0	0
	++	1	6	4	1	1	0
	+++	4	6	3	3	0	0
	+ /+++ /+++	34	22	13	8	1	0
	?+	80	32	7	17	1	7
	IR	60	58	7	16	25	10
	Negative	482	544	7	39	33	465
	All	656	656	34	80	60	482
Ni	+	43	40	27	9	0	4
	++	52	60	58	2	0	0
	+++	19	17	17	0	0	0
	+ /+++ /+++	114	117	102	11	0	4
	?+	45	21	6	11	0	4
	IR	2	2	0	0	0	2
	Negative	495	516	6	23	2	485
	All	656	656	114	45	2	495

Dermatitis patients (n = 656) were tested simultaneously with Co 0.5%, Co 1%, Cr 0.5% and Ni 5% in pet. Assessments on D3 and D6–D7, and the appearance on D6–D7 of reactions on D3, are shown. Results are shown as diagrams in Fig. 2.

Co, cobalt(II) chloride hexahydrate; Cr, potassium dichromate; Ni, nickel(II) sulfate hexahydrate.

+, weak positive (erythema, infiltration, and possibly papules); ++, strong positive (erythema, infiltration, papules, and vesicles); +++, extreme positive (intense erythema, infiltrate, and coalescing vesicles); ?+, doubtful (faint erythema only); + /+++ /+++ , summary of all positive reactions; IR, irritant reaction (various morphologies, e.g. soap effect, bulla, and necrosis); negative (no reaction).

the ED10 values for nickel, chromium, and several other allergens (29, 30).

The manufacture, composition, stability and other features of cobalt patch test preparations may differ between brands and over time. Formation of crystals in the syringe has been described, but we do not know how relevant this is for today's preparations (31). It is sometimes suggested that follicular, petechial and 'poral' patch test reactions to cobalt are relatively frequent, and that they may be false positives. However, we are aware of only a few publications with original descriptions of the morphology or histopathology of such irregular cobalt reactions, the most recent being (24). The patch test readers in our study

did not recall seeing such reactions to cobalt, which may indicate that the problem has declined.

Obvious strengths of our study are that it was relatively large, and that it generated comparable patch test results with concomitant testing and two readings. The readings were performed by experienced dermatologists, 'calibrated' by continuous tuning of assessments. The study generates new knowledge concerning cobalt reactivity, concomitant versus solitary reactions, and the dynamics of patch test reactions. A limitation is that assessment of exposure and clinical relevance (current, previous, or unknown) of patch test reactions was outside the aim of the study. Serial dilution testing and

Table 3. Proportions of positive patch test reactions to Co, Cr and Ni in dermatitis patients (n = 656) are shown as proportional Euler diagrams in Fig. 1a–f

Region for diagram	No. positive	Region for diagram	No. positive
(a) Co Cr Ni (n = 200)		(b) Co 0.5% versus 1% (n = 92)	
Co	46	Co 0.5%	5
Cr	18	Co 1%	34
Ni	84	Co 0.5% and 1%	53
CoCr	7		
CoNi	27		
CrNi	6		
CoCrNi	12		
(c) Co 0.5% D3 versus D6–D7 (n = 58)		(d) Co 1% D3 versus D6–D7 (n = 87)	
D3	5	D3	5
D6–D7	21	D6–D7	34
D3 and D6–D7	32	D3 and D6–D7	53
(e) Cr D3 versus D6–D7 (n = 43)		(f) Ni D3 versus D6–D7 (n = 129)	
D3	21	D3	12
D6–D7	9	D6–D7	15
D3 and D6–D7	13	D3 and D6–D7	102

The number of individuals (n) in each diagram, and the number of positive reactions in each region, are shown in the same order as in Fig. 1, to facilitate comparison.

retesting were performed on single occasions only. There is some selection of patients in our clinic, and thus also in this study, as compared with general dermatology. The majority of the patients are referred because of suspected work-related skin disease, severe dermatitis affecting ability to work, or complicated contact allergy. We do not know how this may have affected the outcome. It would have been of interest to compare patch test reactivity to cobalt 0.5% and 1% in patients with and without atopic dermatitis. Owing to limitations in our patient database at the time, however, this was not possible.

We suggest that assessment of skin exposure to cobalt, and also to chromium and nickel, should be mandatory in patch test clinics. Simple screening with the cobalt spot test, the dimethylglyoxime test for nickel, and the diphenylcarbazide test for Cr(VI) provides valuable qualitative or semiquantitative information (20, 32, 33). Ingredient information is currently available only for cosmetic products. Use tests, serial dilution patch tests, requests to manufacturers, acid wipe sampling, metal release in artificial sweat and X-ray fluorescence spectroscopy are additional tools for contact dermatitis clinics and research. This would increase the knowledge base on exposure, and promote understanding of multiple

sensitization versus cross-reactivity and prevention, particularly concerning cobalt. Relevant information on how to avoid exposure to cobalt would be of great benefit to cobalt-allergic patients.

Conclusions

- Cobalt 1% pet. is a more suitable patch test preparation than cobalt 0.5%. A relatively large proportion of cobalt allergy cases are missed by 0.5% as compared with 1%, whereas the reactivity profiles are similar.
- Solitary cobalt allergy is relatively frequent, whereas knowledge about cobalt exposure is scarce.
- It is time for all patch testers to track the sources of skin exposure to cobalt, as well as to chromium and nickel. This is very important for diagnosis, information to patients, medico-legal purposes, and prevention.
- Our results do not support the use of cobalt 0.5%, as has been the practice since the 1980s in Sweden.

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