

Elicitation threshold of cobalt chloride: analysis of patch test dose–response studies

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doi:10.1111/cod.12499

Summary

Background. Cobalt is a strong skin sensitizer (grade 5 of 5 in the guinea-pig maximization test) that is used in various industrial and consumer applications. To prevent sensitization to cobalt and elicitation of allergic cobalt dermatitis, information about the elicitation threshold level of cobalt is important.

Objective. To identify the dermatitis elicitation threshold levels in cobalt-allergic individuals.

Materials and methods. Published patch test dose–response studies were reviewed to determine the elicitation dose (ED) levels in dermatitis patients with a previous positive patch test reaction to cobalt. A logistic dose–response model was applied to data collected from the published literature to estimate ED values. The 95% confidence interval (CI) for the ratio of mean doses that can elicit a reaction in 10% (ED₁₀) of a population was calculated with Fieller's method.

Results. On the basis of five included studies, the ED₁₀ values of aqueous cobalt chloride ranged between 0.0663 and 1.95 µg cobalt/cm², corresponding to 30.8–259 ppm.

Conclusions. Our analysis provides an overview of the doses of cobalt that are required to elicit allergic cobalt contact dermatitis in sensitized individuals, and thereby the basis for future prevention of cobalt allergy.

Key words: cobalt; contact dermatitis; dose–response; elicitation; elicitation dose; patch test; spot test.

Although positive patch test reactions to cobalt are common, the clinical relevance is often difficult to determine, as the sources of cobalt may be difficult to identify (1). Recent epidemiological studies have shown that cobalt

allergy remains frequent, but also that fluctuations and patient characteristics are variable between study populations (2–4). Cobalt exposure and sensitization have been reported to occur following skin contact with a variety of items, including jewellery, makeup, leather, magnets, dyes, clay, glaze, cement, and hard metal alloys (5, 6). A recent market survey from Germany showed that 38 of 87 earrings and items of piercing jewellery contained at least one part releasing cobalt, that 75% of the jewellery items released up to 0.085 µg/cm²/week, and that 22.1% of the earring posts released ≥ 0.2 µg/cm²/week (7). Moreover, leather products appear to constitute a hitherto unrecognized source of cobalt exposure, as shown by a patient who reacted with generalized dermatitis following contact with his leather couch (6). Finally, few studies have

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Funding sources: None.

Conflict of interests: J. P. Thyssen sold the cobalt spot test to Smarthealth, Phoenix, Arizona, USA, and will receive annual royalties depending on net sales.

Accepted for publication 29 September 2015

measured the levels of cobalt deposition on the skin in different occupations and found clinically relevant doses (5, 8, 9).

To limit skin sensitization to cobalt and allergic cobalt dermatitis, identification of the cobalt elicitation threshold level is warranted. Notably, such elicitation threshold levels have previously been calculated for a number of contact allergens (10–12) and used by regulatory institutions in the prevention of allergic contact dermatitis (13–16). The aim of the present study was to review the published cobalt patch test dose–response studies to determine the elicitation dose (ED) levels in patients with cobalt sensitization. The ED₁₀ is the dose (in $\mu\text{g cobalt}/\text{cm}^2$) at which 10% of allergic individuals develop allergic contact dermatitis in the patch test dilution series. This dose appears to be fairly effective in the prevention of skin sensitization to nickel (14, 16).

Materials and Methods

Literature search

The literature was searched for published patch test elicitation studies on cobalt. The search was carried out with PubMed (last accessed June 2015), and the following search terms were used: ‘cobalt’, ‘dilution series’, ‘elicitation’, and ‘patch test’. The literature was manually searched for additional publications. Given that very few studies have been published, the following criteria were used for inclusion: (i) cobalt had to be diluted in water, as it has been reported that there can be problems in obtaining good test material with the cobalt chloride evenly dispersed in petrolatum (17); (ii) use of the Finn Chambers® method or a method similar to the Finn Chambers® method; (iii) use of at least four patch test dilutions of cobalt; (iv) at least 5 participants in each study; (v) it should be possible to calculate the applied dose of cobalt in $\mu\text{g}/\text{cm}^2$; and (vi) there should be sufficient data in the publication to enable calculation of the dose–response relationship for cobalt chloride.

Data selection

To exclude non-allergic individuals, all included individuals needed to have a positive patch test reaction to the highest cobalt dose (concentration) used in the dilution series. An allergic reaction to the lowest patch test concentration in a continuous line of reactions was included in the calculations if the information was available.

Statistical analyses

Each study was analysed with a threshold logistic regression analysis. The dose–response relationship was

estimated, and the results, in terms of EDs, were presented in $\mu\text{g cobalt}/\text{cm}^2$ and in ppm. The ED in each patch test study that gave positive patch test reactions in 50%, 25%, 10%, 5% and 1% of cobalt-sensitized individuals, the ED_{xx}, was calculated, and fitted dose–response curves were constructed. The 95% confidence interval (CI) for the ED_{xx} was calculated with Fieller’s method. This method expresses ratios as linear combinations of random variables, and provides computation of CIs of ratios. The logistic dose–response model has been used previously to describe the dose–response relationship in contact allergy (18, 19).

Results

In total, six studies using cobalt (17, 20–24) and meeting the selected criteria were identified and included in our analyses. The studies were: (A) Hindsen et al. (21), (B) Allenby and Basketter (20), (C) Fischer and Rystedt (17), (D) Wahlberg (24), (E) Julander et al. (22), and (F) Piela and Kiec-Swierczynska (23). Information on the study details in each publication, and in some cases additional information from other sources, is shown in Table 1. The number of patients varied between studies, from study B with only 6 participants, to study F with 72 participants. In study A, data on allergic cobalt reactions from 14 individuals, who all reacted to the highest dose in the dilution series (corresponding to 7.8% cobalt), were included. Study B included 6 individuals, but, as it only provided allergic reactions to cobalt at two test concentrations, it was not used for calculating the ED values. In study C, a total of 32 individuals were included in the calculations. In study D, a total of 60 individuals were included. In study E, we chose to include 17 patients (1 of the tested individuals did not react to any test concentration of cobalt, and 1 had only a doubtful test reaction to the highest concentration). Thus, 2 individuals were excluded. Study F included 72 individuals, and the patch test readings were performed according to standard methods.

On the basis of the allergic responses from five studies (A, C–F) and a total of 195 patients, the calculated ED₁₀ values, were between 0.0663 and 1.95 $\mu\text{g cobalt}/\text{cm}^2$ (Table 2a). The ED₁₀ values for the corresponding concentrations of aqueous cobalt (in ppm) were 30.8–259 (Table 2b). The dose–response curves for the selected studies are shown in Fig. 1a,b. Note that, for study B, only two observed allergic responses are shown, because, in this case, it was impossible to fit a curve. The skin doses of cobalt that will elicit a positive patch test reaction in, respectively, 1%, 5%, 10%, 25% and 50% of cobalt-allergic individuals from each study (except study

Table 1. The study details as presented in the publications and additional information obtained by pers. comm. with D Basketter and Z Pielą 2014, for studies B and F, respectively

	Study	Information on the applied amount	Information on the patch test material and calculated area	Number of individuals included in calculations	Patch test concentrations used (%)	Year of publication
A	Hindsén et al. (21)	15 µl	Diameter: 8 mm Area: 0.5 cm ² Finn Chambers®	14	7.8, 3.12, 1.25, 0.5, 0.2, 0.08, 0.032, 0.013, 0.0052, 0.0021	2005
B	Allenby and Basketter (20)	40 µl	Diameter: 12 mm Area: 1.13 cm ² Large Finn Chambers®	6	1, 0.1, 0.01, 0.001	1989
C	Fischer and Rystedt (17)	15 µl	Diameter: 8 mm Area: 0.5 cm ² Finn Chambers®	32	1, 0.5, 0.25, 0.13, 0.62, 0.031, 0.061, 0.0078, 0.0039, 0.0019	1983
D	Wahlberg (24)	35 µl	Diameter: 10 mm Area: 0.79 cm ² Al-test™ (25)	60	2, 1, 0.5, 0.25, 0.125, 0.0625, 0.0312, 0.0156	1973
E	Julander et al. (22)	15 µl	Diameter: 8 mm Area: 0.5 cm ² Finn Chambers®	17	1.25, 0.5, 0.2, 0.08, 0.032	2009
F	Pielą and Kieć-Swierczyńska (23)	20–30 µl (25 µl was used for the calculation)	Area (square): 81 mm ² IQ Chamber™	72	1, 0.5, 0.2, 0.1, 0.05, 0.02, 0.01, 0.005, 0.002, 0.001, 0.0005	1998

Table 2. ED_{XX} patch test values from each of the five selected cobalt dose–response patch test studies – (A) Hindsén et al (21), (C) Fischer and Rystedt (17), (D) Wahlberg (24), (E) Julander et al. (22), and (F) Pielą and Kieć-Swierczyńska (23) – with enough responses to obtain a curve and the 95% confidence intervals (CIs). Data are presented as µg cobalt/cm² (a), and as ppm cobalt (b)

	Study A	Study C	Study D	Study E	Study F
(a)					
ED ₁ (µg/cm ²)	0.0796	0.0224	0.0487	0.00229	0.184
95%CI	0.0022–0.35	0.0016–0.10	0.0092–0.14	1.6 × 10 ⁻⁷ to 0.036	0.052–0.44
ED ₅ (µg/cm ²)	0.337	0.174	0.265	0.0232	0.935
95%CI	0.029–0.98	0.027–0.53	0.084–0.65	3.3 × 10 ⁻⁵ to 0.17	0.38–1.8
ED₁₀ (µg/cm²)	0.647	0.441	0.571	0.0663	1.95
95%CI	0.091–1.6	0.096–1.2	0.22–1.1	3.5 × 10 ⁻⁴ to 0.35	0.93–3.4
ED ₂₅ (µg/cm ²)	1.69	1.73	1.76	0.31	5.77
95%CI	0.44–3.8	0.57–3.8	0.92–2.9	0.011–1.2	3.3–9
ED ₅₀ (µg/cm ²)	4.41	6.76	5.45	1.45	17
95%CI	1.8–11	3.0–15	3.4–8.7	0.22–5.4	11–25
(b)					
ED ₁ (ppm)	10.7	3.03	4.44	1.96	24.4
95%CI	0.30–45	0.22–14	0.84–1.3	7.7 × 10 ⁻⁴ to 19	7–58
ED ₅ (ppm)	45.2	23.6	24.2	13.1	124
95%CI	3.9–130	3.7–72	7.6–51	0.06–67	51–240
ED₁₀ (ppm)	86.9	59.6	52	30.8	259
95%CI	12–220	13–160	20–97	0.42–120	120–450
ED ₂₅ (ppm)	227	233	161	109	763
95%CI	60–510	78–520	84–260	6.8–320	440–1200
ED ₅₀ (ppm)	593	914	496	383	2250
95%CI	238–1400	400–2000	310–790	83–1100	150–3400

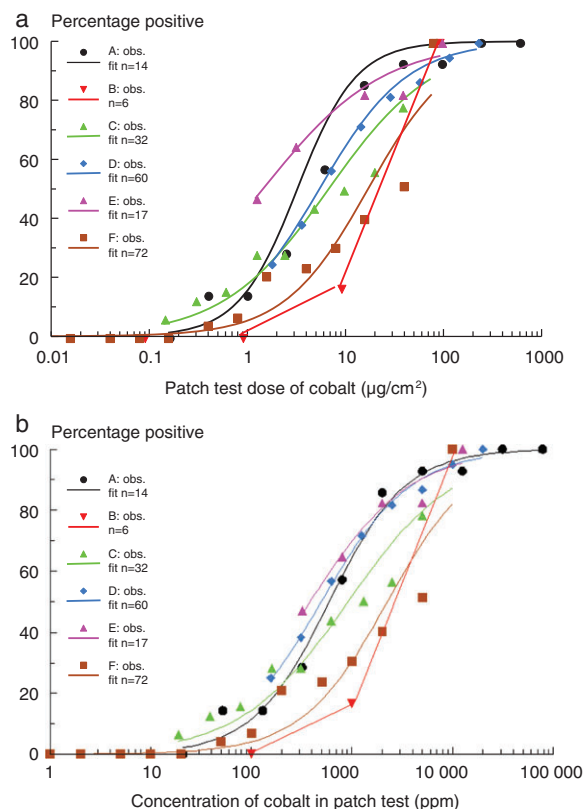


Fig. 1. The dose–response relationship. The curves are: (A) Hindsén et al. (21), (B) Allenby and Basketter (20), (C) Fischer and Rystedt (17), (D) Wahlberg (24), (E) Julander et al. (22), and (F) Piela and Kieć-Swierczyńska (23). The observed reactions in each study are indicated by a coloured dot, triangle, square, or diamond. The elicitation doses that will elicit reactions in 50%, 25%, 10%, 5% and 1% of allergic individuals, the ED_{xx} values, were calculated, and a fitted dose–response curve was drawn with a coloured line for each study (fit). The number of individuals in each study is shown by ($n = x$). For study B, it was not possible to make a curve, so there is no fitted line, because there were positive responses to two test concentrations only. Data are presented as $\mu\text{g cobalt}/\text{cm}^2$ (a), and as in ppm cobalt (b).

B) with 95% CIs are shown in Table 2a (in $\mu\text{g}/\text{cm}^2$). The corresponding concentrations (in ppm) are compiled in Table 2b. In study C and study F, the observed responses did not correspond well with the fitted logistic curves.

Discussion

Here, we provide an overview of the patch test dose–response relationship for cobalt chloride in water, based on literature data from six previously published studies. Such dose–response data are of great value in risk assessment and risk management for the prevention of allergic contact dermatitis caused by cobalt. In general,

the patch test concentrations in ppm (or percentage) were provided in the included studies, but the dose in terms of $\mu\text{g cobalt}/\text{cm}^2$ is a more accurate and useful estimate for correlating dose–response data with real-life skin exposure. We therefore identified the EDs for cobalt chloride in water expressed as a dose per unit area ($\mu\text{g cobalt}/\text{cm}^2$).

Variation in ED values is expected when studies from different geographical areas and time periods are compared. Also, factors such as sex, age, patch test materials, patch test reading and amount of daily exposure may affect the outcome of testing. We are also aware that skin reactivity in a patch test varies within each individual over time. The fact that the observed responses did not correspond well with the fitted logistic curve could be attributable to increased or decreased reactivity in some of the test individuals at a given time. Furthermore, study E was not designed to determine the elicitation threshold; hence, no low dose to which none of the participants responded was included. The characteristics of the included patients in each study, the reading scale and the criteria for a positive patch test reaction could also influence the results, and account for some of the variability between the different studies. We acknowledge that the number of included studies is low, and that patch testing cannot work as a perfect model for real-life exposures. This is supported by the observation that higher concentrations are needed to produce a skin reaction by patch testing than by the repeated open application test (26). Furthermore, skin absorption of cobalt may vary by test site, condition of the skin, and possibly genetic factors.

On the basis of five of six included studies, the ED_{10} values in $\mu\text{g cobalt}/\text{cm}^2$ varied from 0.0663 to 1.95, and the corresponding concentrations of aqueous cobalt chloride varied from 30.8 to 259 ppm. In a recent study (27), in which 5 participants handled two types of hard metal disc (Co 6%, and Co 15%/Cr 0.6%) for 30 min, the average cobalt skin doses deposited on three fingers of all participants were, respectively, $1.1 \mu\text{g}/\text{cm}^2$ [standard deviation (SD) $\pm 0.4 \mu\text{g}/\text{cm}^2$; range 0.5–1.7 $\mu\text{g}/\text{cm}^2$] and $0.7 \mu\text{g}/\text{cm}^2$ (SD $\pm 0.5 \mu\text{g}/\text{cm}^2$; range 0.3–1.6 $\mu\text{g}/\text{cm}^2$), suggesting that such skin contact may indeed cause allergic cobalt dermatitis. Moreover, when skin deposition was studied in 24 workers in the metal industry, up to $4.5 \mu\text{g cobalt}/\text{cm}^2$ was found on the fingers (8). However, when such data are interpreted, it is important to note that penetration of the metal ions into the viable layers of the epidermis needs to be studied and accounted for. A cobalt spot test was recently marketed, and can be used to screen for cobalt release from metallic items. The cobalt spot test reagent is a clear yellow solution that changes colour from yellow to bright orange–red when cobalt ions are present at a concentration of > 8 ppm.

Lower concentrations of cobalt may also be detected with the spot test, but the colour change is then more difficult to assess. A recent study showed that the cobalt spot test became positive at a skin dose of 0.125 µg cobalt/cm² (5 ppm) under controlled test conditions (50 µl of cobalt spot test reagent on 2 cm² of skin surface) (28). In a clinical context, this test can therefore be useful when inform-

ing patients that they can reduce the burden of cobalt on their skin by avoiding contact with cobalt test-positive items.

In conclusion, our analysis provides an overview of the doses of cobalt that are required to elicit allergic contact dermatitis, and thereby the basis for better prevention of cobalt allergy in the future.

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