

ORIGINAL ARTICLE

Allergic reactions to lower concentrations of nickel sulfate and formaldehyde often appear later than reactions to higher concentrations

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Background: A late-appearing patch test reaction may be a sign of active sensitization or represent a delayed elicitation reaction.

Objectives: To retrospectively study the effect of concentration on the time course of allergic reactions to routine concentration dilution series of formaldehyde and nickel sulfate.

Methods: We tested concentration dilution series of 2%, 1%, 0.32% and 0.1% formaldehyde and 5%, 1.6%, 0.5% and 0.16% nickel sulfate, respectively. The last readings were performed on day 4 to day 6. We included patients with allergic reactions to either of the two lowest concentrations in each dilution series and whose tests had been read three times.

Results: Forty-two nickel-allergic and 23 formaldehyde-allergic patients fulfilled the inclusion criteria. In 26 (62%) of the nickel-sensitive patients, reactions to lower concentrations appeared later than reactions to the highest concentration. Of the formaldehyde-sensitive patients, 17 (74%) developed one or two allergic reactions to lower concentrations later than reactions to the highest concentration, and one (4%) patient developed allergic reactions to lower concentrations sooner than a reaction to the highest concentration. The remaining patients showed all allergic reactions at the same reading.

Conclusions: In these selected, relatively strongly sensitized patients, allergic reactions to lower concentrations quite regularly appeared later than reactions to higher concentrations.

KEYWORDS

active sensitization, late reaction, patch test, time course

1 | INTRODUCTION

Most patch test reactions appear within 3 to 4 days, but at least some allergens require an additional reading between day (D) 5 and D10. Reactions appearing after 2 weeks can constitute a sign of active sensitization. However, it may be difficult to differentiate patch test-induced sensitization from a delayed elicitation reaction.¹ An aspect that has not been much discussed is the effect of patch test concentration on the time course of an allergic patch test reaction.

At the Finnish Institute of Occupational Health (FIOH), we read most patch tests three times, and we have the impression that, in concentration dilution series, allergic reactions to the highest concentration usually appear first, and it takes more time for allergic reactions

to the lower concentrations to develop. We test all our patients with a concentration dilution series of formaldehyde, and a nickel concentration dilution series is often applied on day (D)0, providing two or three consecutive readings for different concentrations. We wanted to test our clinical impression by analysing our routine patch test results for nickel sulfate and formaldehyde.

2 | METHODS

The FIOH has a clinic of occupational dermatology. All of our patients have a suspected occupational skin disease, and they come from all parts of Finland. We performed the patch tests with Finn Chambers (8-mm inner diameter; SmartPractice, Phoenix, Arizona), in accordance

TABLE 1 Patch test results obtained with the nickel sulfate concentration dilution series in 42 patients who had been tested with all four test concentrations, reacted to either of the two lowest concentrations, and whose tests had been read three times

Concentration (%)	Case no. 7				Case no. 13				Case no. 19				Case no. 25				Case no. 31				Case no. 37			
	D2	D3	D4	Reading	D2	D3	D4	Reading	D2	D3	D4	Reading	D2	D3	D4	Reading	D2	D3	D4	Reading	D2	D3	D4	Reading
5	++	+++	+++	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
1.6	++	+++	+++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.5	+	++	+++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	+	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	++	+++	+++	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
1.6	+	++	+++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.5	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	++	++	+++	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
1.6	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.5	+	+	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	+	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
1.6	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
0.5	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
1.6	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
0.5	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
1.6	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
0.5	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
1.6	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
0.5	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
1.6	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
0.5	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
0.16	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++

Sequential appearances of allergic reactions are highlighted in grey (26 patients). All of these patients developed at least one allergic reaction to a lower concentration later than to the highest 5% concentration.

with the ESCD guidelines.¹ For petrolatum-diluted test substances, we use a dose of 20 mg, and for aqueous test substances we use a volume of 15 µL. A micropipette has not been routinely used. We read the tests two or three times: on D2, D3, and D4, on D2, D3, and D6, or on D2 and D5, depending on the day of application (Monday, Tuesday, or Wednesday). We also ask the patients to inform us if they noticed new reactions after the final reading.

At the FIOH, we use a concentration dilution series of 5%, 1.6%, 0.5% and 0.16% nickel sulfate pet. (lower concentrations are diluted from Chemotechnique's test substance; Vellinge, Sweden) to help confirm a diagnosis of contact allergy. We also use an in-house formaldehyde dilution series of 2%, 1%, 0.32% and 0.1% aq. in all of our patients. We searched our test files of 2008 to 2017 for patients with allergic reactions (+/++/+++) to these two concentration dilution series. We only included patients who had three consecutive patch test readings, and who had at least one allergic reaction to either of the two lowest concentrations of each dilution series (i.e. 0.5% nickel sulfate,

0.16% nickel sulfate, 0.32% formaldehyde, or 0.1% formaldehyde). In practice, all included patients had allergic reactions to three or four different concentrations of the same allergen. Patients not tested with all four concentrations were excluded. We analysed patch test reactions to the two concentration dilution series in this selected patient population. As we audited the results of our routine patch tests, ethical approval was not needed.

3 | RESULTS

Among a total of 491 patients tested with the nickel sulfate dilution series, we found 42 patients who had allergic reactions to 0.5% and/or 0.16% nickel sulfate and whose nickel dilution series had been read three times during the same session. In 26 (62%) of these patients, at least one allergic reaction to a lower concentration appeared later than an allergic reaction to a higher concentration

TABLE 2 Patch test results obtained with the formaldehyde concentration dilution series in 23 patients who had been tested with all four test concentrations, reacted to either of the two lowest concentrations, and whose tests had been read three times. A "?" symbol denotes slight skin changes in the test area not qualifying for a "?+" reaction

Concentration (%)	Case no.	Reading			Case no.	Reading			Case no.	Reading			Case no.	Reading		
		D2	D3	D4		D2	D3	D4		D2	D3	D6		D2	D3	D6
2	1	+	+	++	7	+	++	++	13	+	++	++	19	?+	?+	++
1		?+	+	+		?+	++	++		+	++	++		?+	+	++
0.32		?+	?+	+		?	+	++		?+	+	+		?+	+	++
0.10		–	?	?+		–	?+	?+		–	+	+		–	?+	?+
2	2	+	++	+++	8	+	++	++	14	+	+++	++	20	?+	+	++
1		+	++	++		+	+	++		+	+++	++		–	+	++
0.32		?+	+	++		?+	?+	+		–	+	?+		–	?+	+
0.10		–	–	–		–	–	?		–	–	–		–	?	?+
2	3	+	+++	+++	9	+	++	++	15	+	++	+++	21	?+	++	++
1		+	++	++		?+	+	+		+	++	++		?+	++	++
0.32		?	+	+		?+	+	+		?	++	++		?	+	+
0.10		–	–	–		–	–	–		–	+	+		–	?	?+
2	4	+	+++	+++	10	+	+	+	16	+	+++	++	22	?+	++	+++
1		+	++	++		+	+	+		+	++	++		?	++	++
0.32		–	+	+		?+	+	+		–	+	+		?	+	+
0.10		–	?+	?+		–	?+	?+		–	?+	–		–	–	?+
2	5	+	++	++	11	?	++	+++	17	+	++	++	23	+	++	+++
1		+	++	++		?+	++	++		?+	++	+		+	+	++
0.32		+	+	++		–	+	+		–	+	?+		+	+	+
0.10		?+	?+	+		–	?+	?+		–	–	–		?	?+	?+
2	6	++	++	+++	12	+	++	++	18	?+	++	++		+	++	+++
1		–	?+	+		+	++	++		–	+	++		–	+	++
0.32		–	?+	+		+	+	++		–	?+	+		–	+	++
0.10		–	–	–		+	+	++		–	–	?+		–	–	?+

Sequential appearances of allergic reactions are highlighted in grey. Among the highlighted patients, no. 19 was the only one who did not develop any allergic reaction to lower concentrations later than a reaction to the highest 2% concentration.

(Table 1). In 16 (38%) patients, all allergic reactions were seen at the same reading. Of these, 11 patients already had allergic reactions to all four concentrations at the first reading on D2.

A total of 1240 patients were tested with the formaldehyde dilution series. Of these, 23 patients had allergic reactions to concentrations of 0.32% and/or 0.1%, and the tests with the dilution series had been read three times (Table 2). In this group, 17 (74%) patients developed at least one allergic reaction later than an allergic reaction to a higher concentration, one patient (4%; no. 19 in Table 2) developed allergic reactions to concentrations of 1% and 0.32% before a reaction to the highest concentration of 2%, and five (22%) patients showed all allergic reactions to different concentrations at the same reading.

4 | DISCUSSION

In Sweden, reactions to concentration dilution series of gold sodium thiosulfate,² 2-hydroxyethyl methacrylate (2-HEMA) and ethyleneglycol dimethacrylate (EGDMA)³ and various diphenylmethane diisocyanate (MDI)-related test substances⁴ were followed over a long period of time (up to 24–56 days). Of 11 patients tested with two to four concentrations of 2-HEMA and EGDMA, four showed allergic reactions to lower concentrations later than reactions to higher concentrations.³ Of 12 patients tested with several concentrations of 4,4-MDI and 4,4'-diamonidiphenylmethane, five patients reacted in the same way.⁴ Regarding gold sodium thiosulfate, five of 10 patients tested with a concentration dilution series developed allergic reactions to higher concentrations first and reactions to lower concentrations later.² All of these Swedish investigations were performed in patients with previously diagnosed contact allergy to the allergen(s) in question.

For the present study, we intentionally chose relatively strongly sensitized patients whose nickel sulfate and formaldehyde reactions occurred down to the two lowest concentrations of each of our concentration dilution series. In these subgroups of nickel-sensitized and formaldehyde-sensitized patients, lower patch test concentrations quite regularly induced allergic reactions more slowly than higher concentrations. Some patients developed allergic reactions sequentially at three time points, and always to higher concentrations sooner than to lower concentrations. Moreover, the great majority of the nickel-allergic patients who did not show sequential allergic reactions already had allergic reactions to all four concentrations at the first reading on D2, so it was impossible to detect any new allergic reactions later.

Our follow-up was limited to 4 or 6 days, and the dilution series were relatively short and did not show individual threshold concentrations in all of the patients. Longer follow-up with longer dilution series would possibly have shown the phenomenon even more clearly. Regarding nickel sulfate, a reading on D1 might have shown more early reactions to the higher concentrations. The above-cited literature shows that similar findings have been made not only for nickel sulfate and formaldehyde, but also for several other allergens. In the Swedish studies, some of the reactions appeared on D14 or later, and the majority of these were to lower concentrations than the usual test concentrations. Such a reaction can easily be interpreted as active sensitization, if it is separately tested in a patient without previously diagnosed contact allergy. If we test a substance at a suboptimal

concentration, it may induce a late reaction that does not represent patch test sensitization, but is a late-appearing elicitation reaction. Sometimes, the right approach might be to increase the test concentration instead of lowering it as active sensitization would require.

However, we by no means claim that all late patch test reactions are attributable to excessively low test concentrations. Instead, we want to draw attention to this rather neglected aspect, which should be considered among many others when the relevance of a late reaction is being evaluated.^{1,5–7}

5 | CONCLUSIONS

In the present study, we analysed the results of routine patch tests read up to 6 days with concentration dilution series of nickel sulfate and formaldehyde. In selected, relatively strongly sensitized patients with allergic reactions to three or four different concentrations, allergic reactions to lower concentrations quite regularly appeared later than reactions to higher concentrations.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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REFERENCES

1. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis*. 2015;73:195–221.
2. Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. *Contact Dermatitis*. 1995;33:386–391.
3. Isaksson M, Lindberg M, Sundberg K, Hallander A, Bruze M. The development and course of patch-test reactions to 2-hydroxyethyl methacrylate and ethyleneglycol dimethacrylate. *Contact Dermatitis*. 2005;53:292–297.
4. Frick-Engfeldt M, Isaksson M, Zimerson E, Bruze M. How to optimize patch testing with diphenylmethane diisocyanate. *Contact Dermatitis*. 2007;57:138–151.
5. Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Late reactions in patch tests: a 4-year review from a clinic of occupational dermatology. *Contact Dermatitis*. 2007;56:81–86.
6. Jensen CD, Paulsen E, Andersen KE. Retrospective evaluation of the consequence of alleged patch test sensitization. *Contact Dermatitis*. 2006;55:30–35.
7. Hindsén M, Bruze M, Christensen OB. Individual variation in nickel patch test reactivity. *Am J Contact Dermat*. 1999;10:62–67.

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