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*Published in:*  
Acta Dermato-Venereologica

*DOI:*  
[10.2340/00015555-1748](https://doi.org/10.2340/00015555-1748)

2014

[Link to publication](#)

### *Citation for published version (APA):*

Isaksson, M., Bråred-Christensson, J., Engfeldt, M., Lindberg, M., Matura, M., Möller, H., Morgardt-Ryberg, K., Stenberg, B., Svedman, C., & Bruze, M. (2014). Patch Testing with Formaldehyde 2.0% in Parallel with 1.0% by the Swedish Contact Dermatitis Research Group. *Acta Dermato-Venereologica*, 94(4), 408-410.  
<https://doi.org/10.2340/00015555-1748>

*Total number of authors:*  
10

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## CLINICAL REPORT

# Patch Testing with Formaldehyde 2.0% in Parallel with 1.0% by the Swedish Contact Dermatitis Research Group

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**In a multicentre study consecutively patch-tested dermatitis patients were tested simultaneously with 1.0% and 2.0% (w/v) formaldehyde in aqua applied with a micropipette (15 µl) to the filter paper disc in Finn Chambers (0.30 mg/cm<sup>2</sup> and 0.60 mg/cm<sup>2</sup>, respectively). A total of 2,122 dermatitis patients were patch-tested. In all, 77 (3.6%) patients reacted positively to formaldehyde; 37 reacted only to 2.0%, 35 reacted to both concentrations and 5 patients reacted only to 1.0%. Significantly more patients were thus diagnosed with contact allergy to formaldehyde with 2.0% compared to 1.0% ( $p < 0.001$ ) without causing more irritant reactions. The detected number of isolated allergic reactions to the 2 formaldehyde-releasers in the Swedish baseline series and not to formaldehyde itself raises the question whether quaternium-15 1.0% and diazolidinyl urea 2.0% should be present in the Swedish baseline series. *Key words: formaldehyde; simultaneous contact allergy; baseline series; micropipette; patch test; dose mg/cm<sup>2</sup>; preservative, formaldehyde releasers.***

Accepted Aug 26, 2013; Epub ahead of print Dec 12, 2013

Acta Derm Venereol

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It was recently shown in 2 studies that patch testing with 15 µl formaldehyde 2.0% aqua (w/v) in Finn Chambers (Ø 8 mm) using a micropipette detected significantly more contact allergies in dermatitis patients compared to 1.0% aqua (1, 2). To see whether this had any clinical relevance a repeated open application test with formaldehyde-containing creams was conducted, in which significantly more patients who reacted to 2.0% formaldehyde but not to 1.0% developed dermatitis compared to the controls, who were dermatitis patients without contact allergy to formaldehyde (3). To evaluate the aforementioned patch test results, the present Swedish multicentre study was initiated, testing formaldehyde

2.0% aqua (w/v) and formaldehyde 1.0% aqua (w/v) in parallel in the baseline series. The relationship between positive reactions to formaldehyde and likewise positive reactions to the formaldehyde-releasers quaternium-15 and diazolidinyl urea, which are part of the Swedish baseline series, were also investigated.

## MATERIALS AND METHODS

Seven dermatology clinics (Malmö, Lund, Gothenburg, Uddevalla, Örebro, Stockholm, Umeå) took part in the study in which the majority of members of the Swedish Contact Dermatitis Research Group participated. A total of 2,122 dermatitis patients were tested during the time period January 1–December 31, 2011. There were 1,424 women, mean age 44.3 years (range 10–94 years) and 698 men, mean age 44.7 (range 12–86 years). In all departments except Lund the baseline series was purchased from Chemotechnique Diagnostics (Vellinge, Sweden). In Lund the baseline series was from Mekostest (Vitaflor Scandinavia AB, Gothenburg, Sweden). During the entire study, the baseline series thus included formaldehyde 2.0% (w/v) and 1.0% (w/v) aqua (0.60 mg/cm<sup>2</sup> and 0.30 mg/cm<sup>2</sup>, respectively).

Formaldehyde 37% (w/w) aqua was bought from Acros Organics (Morris Plains, NJ, USA) and used for preparing the formaldehyde patch test solutions. All formaldehyde patch test solutions were made up at the Department of Occupational and Environmental Dermatology in Malmö, Sweden and sent out to participating departments every 2 months. The solutions were kept in glass containers (13 ml) with Teflon caps and kept in the refrigerator when not used for patch testing. The following formaldehyde-releasing preservatives were included in the baseline series: diazolidinyl urea 2.0% (w/v) aqua in all departments except Lund, which tested this preservative in petrolatum (pet.), and quaternium-15 1.0% (w/w) pet. in all departments except Lund, which tested this as part of the Mekostest.

The test technique for the 4 test preparations described here used Finn Chambers (diameter 8 mm) (Epitest Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) in all centres except Uddevalla, which used IQ Ultra chambers on a high quality hypoallergenic surgical tape (Chemotechnique Diagnostics). The patch testing personnel placed 20 mg of each petrolatum test preparation into each Finn Chamber when using these (4). In all centres a micropipette was used when testing liquid test solutions of formaldehyde, which enables exact dosage (15 µl in each Finn Chamber (5) and 20 µl in IQ Ultra chambers). Patch tests were removed after 2 days and read after an additional day or 2 according to ICDRG criteria (6). A 2<sup>nd</sup> reading was done 7 days after application of patches. A dermatologist read all patch tests in all centres except Umeå on

both days, while in Umeå a trained nurse did the 1<sup>st</sup> reading and a dermatologist the 2<sup>nd</sup> one. The minimal criterion for an allergic reaction is erythema and infiltration covering the whole tested area. Additionally, there may be papules and/or vesicles. Reactions consistent with an allergic nature but where the minimal criterion was not present (e.g. erythema only) were judged as doubtful. Reactions that lacked the morphology consistent with an allergic nature and had a different morphology (e.g. cigarette paper-like shiny surface) were judged as irritant.

The formaldehyde content was analysed in the test preparations by means of the 2,4-dinitrophenylhydrazine method (7). The detection limit was 0.00005% formaldehyde.

### Statistics

The McNemar test (2-tailed) was used to compare the number of positive reactions to formaldehyde 2.0% and 1.0%. Fisher's exact 2-tailed test was used to compare the contact allergy rate in males and females. The differences were considered significant when  $p < 0.05$ .

## RESULTS

A summary of patch test reactions to formaldehyde is given in Table I. Of 2,122 patients (67.1% females) 77 (3.6%) reacted to either 1.0% or 2.0% formaldehyde or both. Seventy-two out of 2,122 (3.4%) were diagnosed with contact allergy to formaldehyde by patch testing with 2.0% and 40 (1.9%) were diagnosed with contact allergy to formaldehyde by patch testing with 1.0% ( $p < 0.001$ ). Only 5 patients (0.2%) reacted positively to 1.0% without reacting to 2.0%. Between participating clinics the proportions of cases reacting to formaldehyde varied. For formaldehyde 1.0%, the lowest proportion was 0.6% and the highest 4.1%. For formaldehyde 2.0%, the range was 0–9.7%. The ratios between cases found when patch testing with 2.0% and 1.0% ranged from 3–0.

Of those allergic to 2.0%, 81.9% were females and of those reacting positively to 1.0%, 72.5% were females. For 2.0%, the difference between females and males was statistically significant ( $p < 0.01$ ), whereas for 1.0% it was not ( $p > 0.3$ ).

In the 7 clinics the relative proportions of formaldehyde-positive males and females varied (Table I).

The number of irritant and doubtful reactions to the 2 formaldehyde test preparations was low. Only 4 reactions in total were judged as irritant when 2.0%

formaldehyde was tested and for 1.0% the number was 3. Of all patients that were tested with 1.0% formaldehyde and read both on early and late readings only 8 had patch test reactions to 1.0% that were doubtful. In these 8 patients the test reactions to 2.0% formaldehyde turned out positive in 4 cases and negative in 4.

Of the 40 patients positive to 1.0%, 6 (15%) were only positive on D7 and not on D3. Of the 72 that reacted positively to 2.0%, 5 (7%) were only positive on D7 and not on D3.

Eighteen cases of contact allergy to quaternium-15 and 10 cases of contact allergy to diazolidinyl urea were reported. Only 5/18 and 6/18 cases as well as 4/10 and 3/10 cases, respectively, had contact allergy to quaternium-15 and diazolidinyl urea without reacting positively to formaldehyde (Table SI<sup>1</sup>).

The formaldehyde content in the patch test solution 2.0% was found to be 1.9% whereas the formaldehyde content in the test solution 1.0% was found to be 0.9%.

## DISCUSSION

A few previous studies have compared simultaneous testing with 1.0% and 2.0% formaldehyde (1, 2, 8). In one of them (8) neither the amount of test preparation nor the technique used for applying the solutions are explicitly stated. However, in 2 recent studies, in which exact amounts of test preparations were used, i.e. the same dose/area each time by means of a micropipette, it was found that consecutive patch testing with formaldehyde 2.0% aqua detects significantly more reacting individuals compared to 1.0% aqua ( $p < 0.001$ ) (1, 2). These results are supported by the present study.

In the present multicentre study the variation between participating clinics regarding the proportion of cases having contact allergy to 2.0% formaldehyde was 10-fold, whereas the variation was 7-fold for 1.0% positives. We have no explanation to these variations, e.g. why there were no allergic individuals found in Umeå and almost 10% allergic patients found in Örebro. All centres were instructed to use the ICDRG criteria when

<sup>1</sup><http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1748>

Table I. Positive reactions to formaldehyde 2.0% vs. 1.0% when tested in parallel in 2,122 patients in 7 dermatology clinics in Sweden

	Total tested <i>n</i>	Females <i>n</i> (%)	2.0% positive			1.0% positive			2.0%/1.0%
			All <i>n</i> (%)	Females <i>n</i> (%)	Males <i>n</i> (%)	All <i>n</i> (%)	Females <i>n</i> (%)	Males <i>n</i> (%)	
Malmö	642	432 (67.3)	16 (2.5)	12 (1.9)	4 (0.6)	8 (1.9)	5 (0.8)	3 (0.5)	2.0
Lund	295	194 (65.8)	7 (2.4)	7 (2.4)	0 (0)	6 (2.0)	5 (1.7)	1 (0.3)	1.2
Gothenburg	475	331 (69.7)	11 (2.3)	8 (1.7)	3 (0.6)	8 (1.7)	5 (1.1)	3 (0.6)	1.2
Uddevalla	165	118 (71.5)	6 (3.6)	6 (3.6)	0 (0)	2 (1.2)	2 (1.2)	0 (0)	3.0
Örebro	145	99 (68.3)	14 (9.7)	10 (6.9)	4 (2.8)	6 (4.1)	4 (2.8)	2 (1.4)	2.3
Norrbacka (Stockholm)	222	137 (61.7)	18 (8.1)	16 (7.2)	2 (0.9)	9 (4.0)	7 (3.2)	2 (0.9)	2.0
Umeå	178	113 (63.5)	0 (0)	0 (0)	0 (0)	1 (0.6)	1 (0.6)	0 (0)	0
Total	2,122	1,424 (67.1)	72 (3.4)	59 (4.1)	13 (1.9)	40 (1.9)	29 (2.0)	11 (1.6)	1.8

reading the patch tests, so differences in reading tests should be minimised. It is possible that the indication for patch testing was different, although this was not scrutinised further. Furthermore, the proportion of additionally found allergic cases with 2.0% when comparing 1.0% and 2.0% showed a 3-fold variation. Despite these variations the overall result demonstrates that significantly more cases are found when patch testing with 2.0% than with 1.0%. Furthermore, as mentioned before, a significant number of patients who react to 2.0% but not to 1.0% have been shown to develop dermatitis when exposed to a formaldehyde-containing moisturiser (3).

It is reported in the literature that formaldehyde contact allergy is more common in women than in men, and formaldehyde is a significant allergen in women with hand eczema (9). The explanation to higher allergy rates in women is said to be associated with the usage of cosmetics and household products (9, 10). In our study, when looking at the difference in detected cases testing 1.0% formaldehyde, no sex difference was seen. However, when looking at the cases detected with 2.0% there is a significant sex difference ( $p=0.0069$ , Fisher's exact test, 2-tailed) and also when looking at the increase in number of detected cases that were negative to 1.0% and positive to 2.0% formaldehyde ( $p<0.001$ , Fisher's exact test, 2-tailed). This is an interesting finding and may reflect different exposures in women and men, as a lower exposure concentration may lead to a weaker contact allergy (11). As women seem to have weaker contact allergies (i.e. requiring higher concentrations of patch test substance for a positive reaction) we may wonder if women are sensitised through cosmetics and toiletries containing lower concentrations of formaldehyde. On the other hand men may have been sensitised through exposure to industrial products such as paints and metal working fluids, which then probably contain higher concentrations of formaldehyde, and hence get stronger contact allergies.

One may argue that formaldehyde should be tested even higher than 2.0%. However, testing 3.0% gave a high yield of irritant reactions despite exact dosage, which makes it impossible to use (1).

In our study, few additional contact allergies to the 2 formaldehyde releasers were detected, i.e.  $<0.5\%$  for each of the 2 (Table SI<sup>1</sup>). This raises the question whether quaternium-15 and diazolidinyl urea should be present in the Swedish baseline series.

In earlier studies (1, 2) it was demonstrated that positive test reactions to formaldehyde can appear later than on day 3 or 4 after test application, why a late reading is important in order not to miss this important contact allergy. Our study confirms earlier results, showing that a 2<sup>nd</sup> late reading is important when patch testing with formaldehyde, as is also the case for many other allergens (12–15).

Recently, a recommendation to include formaldehyde 2.0% aqua in the European baseline patch test series was published (16). Results from that study are much the

same as ours. Formaldehyde is a ubiquitous allergen and it is therefore of utmost importance to detect contact allergy to this preservative. We therefore aim at removing 1.0% formaldehyde from the Swedish baseline series and adding 2.0% aqua to it instead. It should also be emphasised that irritant reactions are virtually not seen when using a micropipette for the appropriate dosing to a specific chamber.

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