## **INVESTIGATIVE REPORT**

# Routine Diagnostic Patch-testing with Formaldehyde 2.0% (0.60 mg/cm<sup>2</sup>) may be an Advantage Compared to 1.0%

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Our clinical experience has suggested that the presently recommended patch-test concentration (1.0%) for formaldehyde in the baseline series might be too low. Therefore, consecutively patch-tested dermatitis patients were tested simultaneously with formaldehyde 1.0% and 2.0% (w/v) in aqua. Formaldehyde 1.0% and 2.0% were applied with a micro-pipette (15 µl) to filter paper discs in Finn Chambers (0.30 mg/cm<sup>2</sup> and 0.60 mg/cm<sup>2</sup>, respectively). A total of 1397 patients with dermatitis were patchtested. In all, 68 (4.9%) patients reacted positively to formaldehyde; 37 reacted only to 2.0%, 29 reacted to both concentrations, and 2 reacted only to 1.0%. Significantly more patients were thus diagnosed with contact allergy to formaldehyde 2.0% compared with 1.0% (p < 0.001). We detected 0.1%, 0.4%, and 29.6% irritant reactions to 1.0%, 2.0%, and 3.0% formaldehyde, respectively. We conclude that, with an optimized patch-test technique, doubling the dose per area detects significantly more contact allergies to formaldehyde, but an even higher test concentration causes too many irritant reactions to be usable. Key words: contact allergy; dose mg/cm<sup>2</sup>; formaldehyde; micropipette; patch-test; preservative.

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Preservatives are used to prevent the growth of bacteria, algae and fungi. They are biologically reactive substances and many of them have allergic potential. Formaldehyde is one of the oldest and most widely used preservatives. It is a common contact allergen and has been included in the standard series since the 1930s (1). Based on the patient's history, it is difficult to diagnose contact allergy to formaldehyde because so many products contain it. It is also difficult to completely cure allergic contact dermatitis caused by formaldehyde, as it is almost impossible totally to avoid exposure to formaldehyde-containing products. Studies in Denmark and Sweden in the 1990s showed that formaldehyde or formaldehyde-releasing preservatives are widely used in up to one-third of cosmetic products, in household products such as cleaning agents, and in industrial products (2, 3). In order to optimize preven-

tion of allergic contact dermatitis, the confirmation of contact allergy to formaldehyde by a thoroughly evaluated patch-test technique is important. Formaldehyde has been regarded as a problematic patch-test substance with poor reproducibility of allergic reactions (4). It has been judged to cause irritant reactions, which have been interpreted as positive reactions (5). The recommended patch-test concentration in the baseline series has been reduced gradually, from 4% to the present 1% (1). At our department patch-testing with formaldehyde 2.0% has been used in patients with doubtful reactions to formaldehyde 1.0% and when there has been a strong suspicion of contact allergy to formaldehyde. For more than 25 years, defined micro-pipetted volumes have been used routinely at our department for patch-testing liquid solutions (6). According to our findings, 15 µl is optimal for the Finn Chamber technique (7).

The aim of the present study was to investigate the outcome of simultaneous testing with 15 µl formal-dehyde 1.0% and 2.0% in consecutively patch-tested dermatitis patients. The frequency of positive reactions to formaldehyde compared with formaldehyde-related allergens in our baseline series (i.e. formaldehyde releasers and the resins or plastics in which formaldehyde is used as a raw material) were also examined.

## MATERIALS AND METHODS

Test subjects

A total of 1397 dermatitis patients, 519 males (37.2%, mean age 44.9 years, range 14–84 years) and 878 females (62.8%, mean age 43.9 years, range 12–94 years), were consecutively patch-tested due to suspected allergic contact dermatitis. The patients were tested at the Department of Occupational and Environmental Dermatology during the period 1 January 2006 to 31 December 2007. The distribution of this population according to the MOAHLFA index was as follows: M = 37%, O = 50%, A = 39%, H = 55%, L = 20%, F = 22%, A = 21%.

## Patch-test technique

All 1397 patients were tested with our baseline series, which is based on the European baseline series (8) and supplemented with sensitizers such as metals, preservatives, plastics, and textile dyes. A 15  $\mu$ l volume of each of the test preparations in aqueous solution was applied with a micro-pipette to the filter paper discs in the test chambers. For the test preparations in petrolatum (pet), 20 mg was applied as recommended by the European Society of Contact Dermatitis (ESCD) (9). Finn

Chambers 8 mm diameter (Epitest OY, Tuusula, Finland) on Scanpor tape (Norgeplaster AS, Vennesla, Norway) were used to apply the allergens to the upper back. The patches were removed by the patient after 48 h and read on day (D) 3 or D4 and D7. Readings were performed according to the guidelines of the International Contact Dermatitis Research Group (10). The reactions were judged as doubtful when the morphological features of the reaction were consistent with an allergic nature, but where the minimal criteria for an allergic reaction, i.e. erythema and infiltration were not present on the whole test area. The reactions were judged as irritant when they lacked the morphology consistent with a reaction of allergic nature.

During the whole period of the study, the baseline series of our department thus included formaldehyde 2.0% (w/v) and 1.0% (w/v) aqua (aq) (0.60 mg/cm<sup>2</sup> and 0.30 mg/cm<sup>2</sup>, respectively). Formaldehyde 0.32% (w/v) aq and 0.10% (w/v) aq were included in the baseline series from 1 January 2007 (738 patients were tested, 264 males and 474 females). All formaldehyde patch-test solutions were made at our department. The following formaldehyde-releasing preservatives were included in our baseline series: imidazolidinyl urea 2.0% (w/v) aq, diazolidinyl urea 2.0% (w/v) aq and quaternium-15 1.0% (w/w) pet. The simultaneously tested formaldehyde-based resins were 4-tert-butylphenol-formaldehyde resin (1.0% (w/w) pet), phenol-formaldehyde resin, a resol resin based on phenol and formaldehyde (1.0% (w/w) pet) (6), and tosylamide/formaldehyde resin (10.0% (w/w) pet). To find the threshold for irritant reactions, 27 consecutive patients were tested with formaldehyde 3.0% (w/v) aq in addition to formaldehyde 2.0%, 1.0%, 0.32% and 0.10%. All patch-test preparations in the baseline series except formaldehyde were bought from Chemotechnique Diagnostics AB (Vellinge, Sweden). Formaldehyde 37% (w/w) aq was bought from Acros Organics (New Jersey, USA) and used for preparing the formaldehyde patch-test solutions at our department.

## Data recording

Daluk, a data-based registration system, in which age, gender, and contact allergies are recorded, was used (11).

## Statistics

The McNemar test 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, as well as the association between formaldehyde and: (i) the separate formaldehyde-releasing preservatives; and (ii) the separate formaldehyde-based resins. The differences were considered significant when p < 0.05.

#### Ethics

The study was approved by the regional ethical review board in Lund, Sweden.

# **RESULTS**

A summary of patch-test reactions to formaldehyde is given in Tables I and II.

Thirty-seven patients reacted positively to formal-dehyde 2.0% but negatively to formaldehyde 1.0%, 29 patients reacted to both concentrations, and 2 patients reacted positively to formaldehyde 1.0% but negatively to 2.0%. Significantly more patients reacted to 2.0% compared with 1.0% (p < 0.001). Thus, in all, 68

Table I. Patch-test reactions to 15  $\mu$ l formaldehyde with different concentrations (w/v %)

Formaldehyde	Contact allergy reactions					Oth	Total			
(% w/v)	+++a	++	+	Tota	1 %b	?c	% <sup>b</sup>	IR	% <sup>b</sup>	tested
3.0										-
All	2	0	0	2	7.4	1	3.7	8	29.6	27
Mend	0	0	0	0	0					0
Women	2	0	0	2	7.4					27
2.0										
All	11	22	33	66	4.7	48	3.4	5	0.4	1397
Men	2	5	7	14	2.7					519
Women	9	17	26	52	5.9					878
1.0										
All	3	18	10	31e	2.2	$21^{\rm f}$	1.5	1	0.1	1397
Men	0	5	2	7	1.3					519
Women	3	13	8	24	2.7					878
0.32										
All	1	4	6	11	1.5	2	0.3	0	0	738
Men	0	0	2	2	0.8					264
Women	1	4	4	9	1.9					474
0.10										
All	1	2	1	4	0.5	1	0.1	0	0	738
Men	0	0	0	0	0					264
Women	1	2	1	4	0.8					474
0.032										
All	0	1	0	1	0.1	0	0	0	0	738
Men	0	0	0	0	0					264
Women	0	1	0	1	0.2					474

<sup>&</sup>lt;sup>a</sup>The strongest recorded reaction day (D) 3/4 and D7 is given.

patients (4.9%), 53 women (53/878, 6.0%) and 15 men (15/519, 2.9%), were found to have contact allergy to formaldehyde. The gender difference was statistically significant (p<0.01). The proportion of women and men, mean age and range of the groups reacting to 2.0% only and to both concentrations were similar. Eleven (1.5%) reacted positively to formaldehyde 0.32% and 4 of them (0.5%) to 0.10%. One of them reacted positively to formaldehyde 0.032%.

There were 5 patients who reacted only on D7. Among positives to 2.0%, 3 patients reacted only on D7, and among positives to 1.0%, 2 patients reacted only on D7 (Table II).

Forty-eight patients had doubtful reactions to 2.0%, without being positive to any simultaneously tested concentration of formaldehyde. Thirty-eight patients had doubtful reactions to 1.0%, but 17 of these reacted positively to 2.0%. Five irritant reactions (0.4%) were recorded to 2.0% and 1 (0.1%) to 1.0%. Out of 27 patients who were tested with formaldehyde 3.0%, 8 (29.6%) patients had irritant reactions to formaldehyde 3.0% but did not react to 1.0% and 2.0%; 2 patients reacted positively to 3.0% and both of them were positive

<sup>&</sup>lt;sup>b</sup>Proportion (%) among tested patients.

<sup>&</sup>lt;sup>e</sup>Doubtful reaction without positive reaction to any other simultaneously tested formaldehyde patch-test preparations in the baseline series.

<sup>&</sup>lt;sup>d</sup>Gender is given only for allergic reactions.

<sup>&</sup>lt;sup>e</sup>Two patients reacted to 1.0% without reacting to 2.0%.

<sup>&</sup>lt;sup>f</sup>Additionally, 17 patients had doubtful reactions to 1.0%, but reacted positively to 2.0%.

IR: Irritant reaction

Table II. Number of positive reactions to 15 µl formaldehyde 2.0% and 1.0% by reading day (D) and proportions among positives (%)

Concentration (%)	D 3 or 4 only <i>n</i> (%)	D7 only <i>n</i> (%)	D3 or 4 and D7 n (%)	Total n
2.0	28 (42.4)	3 (4.5)	35 (53.0)	66
1.0	11 (35.3)	2 (6.5)	18 (58.1)	31

to formaldehyde 1.0% and 2.0%; 1/27 had a doubtful reaction to formaldehyde 3.0% but was negative to 1.0% and 2.0% in the baseline series (Table I).

In all, 28 positive reactions to the formaldehyde releasers included in our baseline series were found. Among the formaldehyde-allergic patients detected by testing 1.0%, 7/10 patients with contact allergy to quaternium-15, 4/10 patients with contact allergy to diazolidinyl urea, and 2/8 cases with contact allergy to imidazolidinyl urea were found. The corresponding numbers of contact allergies found when testing formaldehyde 2.0% were 9/10, 5/10, and 3/8, respectively (Table III). The association between contact allergy to formaldehyde, independent of patch-test concentration used, and the 3 formaldehyde-releasing preservatives was statistically significant (Table III). On the other hand, there was no significant association between contact allergy to formaldehyde and formaldehyde-based resins (Table III). In all, 16 (1.1%) among all tested patients reacted positively to phenol-formaldehyde resin. Thirteen (0.9%) reacted positively to 4-tertbutylphenol-formaldehyde resin. Two patients (0.1%) reacted positively to tosylamide/formaldehyde resin, and one of these reacted positively with weak reactions both to tosylamide/formaldehyde resin and formaldehyde 2.0%, but negatively to 1.0%.

## **DISCUSSION**

This study found that consecutive patch-testing with  $15 \mu l$  formaldehyde 2.0% aq detects twice as many

reacting individuals compared with 1.0% aq. To the best of our knowledge, the study by Trattner et al. (1) is the only previously published study that compares simultaneous testing with 1.0% and 2.0%. In that study, the Finn Chamber technique was used, i.e. the same patch-test system as in our study, and the tests were read on days 2, 3/4 and 7, but neither the amount of test preparation nor the technique used for applying the solution are explicitly stated. According to our results, significantly more patients reacted to 2.0% compared with 1.0% (p < 0.001), whereas in the study by Trattner et al. no statistically significant difference between these two concentrations was found. We suggest that the difference with regard to the statistical significance between these studies can be explained by the usage of exactly the same amount, i.e. 15 µl in our study, and thereby the same dose/area for the respective concentrations.

Patch-testing with formaldehyde began in 1929 and the concentrations used were 1-5% ag (mostly 4% ag) (1). At the end of the 1950s, the test concentration was revised to 2.0% aq due to many recognized false-positive and irritant reactions. The standard concentration in the 1980s was 2.0%. When the patch-test system at many clinics was changed from the Al-test to the Finn Chamber system, the International Contact Dermatitis Research Group (ICDRG) anticipated an increased risk of irritant reactions from formaldehyde 2.0% and therefore lowered the recommended patch-test concentration to 1.0% (1). Contact allergy to formaldehyde 1.0% was found in around 2.5% of patients tested with the European baseline series 1991–2000 (12). In 1983 to 1984, the prevalence of sensitization to formaldehyde 2.0% ag tested with the Finn Chamber technique in a Swedish study of hand eczema was 1.6% (13). Formaldehyde allergy is more common in women than in men, and formaldehyde is a significant allergen in women with hand eczema (14). Among our tested patients, there was also a statistically significant difference between women

Table III. Positive reactions to 15 µl formaldehyde 2.0% and 1.0% among patients with contact allergy to formaldehyde releasers and formaldehyde-based resins in 1397 patients

	Total number of positive reactions		2.0%			1.0%		
	$n^{a}$	% b	n°	% <sup>d</sup>	<i>p</i> -value	$n^{c}$	% <sup>d</sup>	<i>p</i> -value
Formaldehyde releasers		·						
Quaternium-15	10	0.7	9	90	< 0.001	7	70	< 0.001
Diazolidinyl urea	10	0.7	5	50	< 0.001	4	40	< 0.001
Imidazolidinyl urea	8	0.6	3	38	0.005	2	25	0.013
Formaldehyde-based resins								
4- <i>tert</i> -butylphenol-formaldehyde resin	13	0.9	0	0	1	0	0	1
Phenol-formaldehyde resin	16	1.1	0	0	1	0	0	1
Tosylamide/formaldehyde resin	2	0.1	1	50	0.094	0	0	1

<sup>&</sup>lt;sup>a</sup>Total number of positive reactions.

<sup>&</sup>lt;sup>b</sup>Proportion (%) of positive reactions among all tested.

<sup>&</sup>lt;sup>c</sup>Number of simultaneous positive reactions to a formaldehyde releaser or a formaldehyde-based resin.

<sup>&</sup>lt;sup>d</sup>Proportion (%) of formaldehyde-allergic patients among positives to a formaldehyde releaser or a formaldehyde-based resin.

and men. This may be explained by the fact that contact allergy to formaldehyde is most often associated with the usage of cosmetics and household products (14, 15). Formaldehyde is a ubiquitous allergen that might be very difficult to avoid.

Among our patients irritant reactions to formaldehyde 2.0% and 1.0% were noted in 0.3% and 0.1% of the patients, respectively (Table I). This is a small amount compared with the study by Trattner et al. (1), who noted 3.9% irritant reactions to formaldehyde 2% and 2.1% to formaldehyde 1%. We found 29.6% irritant reactions among the patients tested with 3.0% (Table I). Our explanation for the lower number of irritant reactions to 2.0% and 1.0% in the present study is, again, the usage of micropipettes, which enables exact dosage. According to our results, there is a large increase in irritant reactions between 2.0% (0.60 mg/cm<sup>2</sup>) and 3.0% (0.90 mg/cm<sup>2</sup>). There is, thus, a narrow range of concentrations with which formaldehyde can be tested and by which the detection of contact allergy can be established without either missing contact allergies or causing irritant reactions. Such a narrow range makes an exact test dose per area even more important. A recent study at our department (18) showed that with the commonly used drop technique, by which the solution is applied by squeezing the plastic bottle containing the solution, the amount applied might vary between approximately 11 and 44 mg. Since the dose of allergen is dependent on the amount of solution applied, this may cause varying results with regard to allergic reactions, and more frequent irritant reactions.

Doubtful reactions are problematic in the diagnostics of contact allergy. These reactions may be the expression of both irritant reactions and weak contact allergies (16). Patch-testing with any sensitizer can result in a doubtful reaction, but it varies among different allergens (16). Reactions to formaldehyde belong to patch-test reactions that are considered to be difficult to evaluate. In our study there were relatively more doubtful reactions to 1.0% compared with 2.0% (38/31 and 48/66, respectively). However, 17/38 (45%) of the doubtful reactions to 1.0% turned out to be positive to 2.0% and were thus confirmed contact allergies (Fig. 1). This means that the theoretical "price" in the form of doubtful reactions that are not contact allergies could be the same regardless of patch-test concentration, but also that, by testing with 2.0%, a considerable proportion of doubtful reactions to 1.0% are diagnosed as formaldehyde allergy.

Of the three investigated formaldehyde releasers, quaternium-15 is currently the only formaldehyde releaser included in the European baseline series. Under the assumption that patients with contact allergy to formaldehyde are advised to avoid products that contain formaldehyde releasers, our results imply that there are very few additional cases found by routinely testing quaternium-15 compared with imidazolidinyl urea and diazolidinyl urea when 2.0% is used. When 1.0% for-

maldehyde is tested, 3 additional patients with contact allergy to quaternium-15 are found, corresponding to 0.2% among all tested. When 2.0% formaldehyde is routinely tested only one (0.07%) more quaternium-15-allergic patient is found. These numbers are too low to qualify quaternium-15 to be included in the baseline series according to published recommendations (16). Ouaternium-15 was tested in pet, while the other two formaldehyde releasers were tested in aq. A study, which has shown that patch-testing with the formaldehyde releasers imidazolidinyl urea and diazolidinyl urea in pet detects more reacting individuals compared with aq has been published (17). However, when comparisons between vehicles are performed, it is important that the dose per area is standardized. Formaldehyde is one of the contact allergens with the lowest molecular weight (MW 30) and therefore the number of molecules/area in a patch-test is comparatively large. When 15 ul formaldehyde is tested at 1.0%, the dose per area is 10 µmol/ cm<sup>2</sup>. This can be compared with quaternium-15 1.0%, for which the corresponding dose is approximately ten times lower, i.e. 1.2 µmol/cm<sup>2</sup>. On the other hand, each molecule of quaternium-15 may theoretically, based on its chemical structure, release six molecules of formaldehyde. Approximately 5% of our formaldehydeallergic patients had positive patch-tests only on D7. This means that at our department, the number of contact allergies to formaldehyde 2.0% that would have been missed if no reading on D7 was performed is higher than the number of missed contact allergies to, for example, quaternium-15, were it omitted from the baseline series. The described circumstances imply that the inclusion of any formaldehyde releaser in the baseline series should

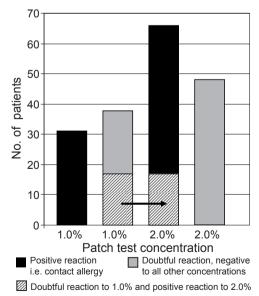


Fig. 1. The number of doubtful and contact allergy reactions found in 1397 patients when testing formaldehyde 1.0% (0.30 mg/cm<sup>2</sup>) and 2.0% (0.60 mg/cm<sup>2</sup>). In all, 38 patients had a doubtful reaction to 1.0%, but 17 of them reacted positively to 2.0%, as indicated by the arrow.

be based on the results of parallel routine testing with formaldehyde and the formaldehyde releaser in question with optimized patch-test doses obtained with standardized patch-test techniques.

There was no association between patients reacting to formaldehyde and the resins or plastics in which formaldehyde is used as a raw material, a phenomenon commented on in an earlier study (6).

## Conclusion

The present study shows that patch-testing with 15 µl formaldehyde 2.0% ag (w/v) while using a micropipette detects twice as many reacting individuals compared with 1.0% ag. Patch-testing with 15 ul formaldehyde 2.0% ag does not lead to a high frequency of irritant reactions when micropipettes are used. Thus, for the Finn Chamber technique, this concentration, and consequently the dose, is suited to use in consecutive patch-testing. However, before 2.0% formaldehyde is suggested to be included in the baseline series internationally, a patch-test technique that is standardized with respect to the dose per area has to be implemented and our results confirmed. On the whole, the clinical relevance is difficult to assess in formaldehyde-allergic patients. Even so, whether the reactivity in a patient reacting to formaldehyde 2.0% but not to 1.0% is clinically relevant or not should be investigated. Thus, experimental studies, which investigate the clinical relevance in patients reacting to 2.0% but not to 1.0%, are needed. With regard to quaternium-15, its presence in the baseline series needs to be evaluated further.

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