

Recommendation to include formaldehyde 2.0% aqua in the European baseline patch test series

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Summary

Background. The currently used patch test concentration of formaldehyde (1.0% aqua; 0.30 mg/cm²) has been shown to fail to detect ~ 50% of contact allergies to formaldehyde.

Objectives. To justify the inclusion of formaldehyde 2.0% aqua (0.60 mg/cm²) in the European baseline patch test series.

Methods. A survey of the reported frequencies of contact allergy to formaldehyde found with formaldehyde 2.0% aqua as compared with 1.0% aqua was performed. Studies that describe a standardized patch test technique for obtaining a correct dose per unit area were included. Experimental provocation tests in patients with contact allergy to formaldehyde detected only with 2.0% aqua were also surveyed.

Results. In a multicentre study performed in 12 dermatology clinics among 3591 individuals, 3.4% reacted to 2.0%, and 1.8% reacted to 1.0% ($p < 0.001$). A randomized double-blind repeated open application test performed in individuals reacting only to 2.0% but not to 1.0% showed that 9 of 17 formaldehyde-allergic individuals reacted to a moisturizer that contained formaldehyde ($p < 0.001$).

Conclusions. It is recommended that formaldehyde 2.0% aqua (0.60 mg/cm²) should replace formaldehyde 1.0% in the European baseline series from 2014. With the Finn Chambers[®] technique, a standardized amount of 15 µl of the solution obtained by using a micropipette should be used.

Key words: allergic contact dermatitis; baseline series; contact allergy; cosmetics; dose; EU legislation; formaldehyde; micropipette; patch test; preservatives.

Background

The European baseline patch test series consists of the minimum recommended test set that should be used during routine diagnostic patch test investigations and that will ordinarily be supplemented by additional

series and other allergens as appropriate to adequately investigate the clinical problem. Any baseline patch test series must be regularly re-evaluated for the need for changes in composition. Inclusion of new allergens, as well as exclusion of old substances, may be considered. Furthermore, changes in patch test concentration may be warranted (1). For the European baseline patch test series (baseline series), the major responsibility for this process has been delegated to the European Environmental Contact Dermatitis Research Group (EECDRG) by the European Society of Contact Dermatitis. The latest revision recommended by EECDRG was the inclusion of methylisothiazolinone in 2013 (2).

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Contact Allergy to Formaldehyde 2.0% aqua

Formaldehyde is a ubiquitous contact allergen, and is present both in consumer products and in occupational settings. The frequency of contact allergy to formaldehyde among patients investigated with the baseline series because of suspected allergic contact dermatitis varies among dermatology clinics in Europe, but is often reported to be ~2% (3–5). In order to optimize prevention of allergic contact dermatitis, the confirmation of contact allergy to formaldehyde with a thoroughly evaluated patch test technique is important. Formaldehyde has been regarded as a problematic patch test substance with poor reproducibility of allergic reactions. It has been judged to cause irritant reactions, which have been interpreted as positive reactions. The recommended patch test concentration in the baseline series has been gradually reduced from 4% to the present 1% aqua. However, there has also been a suspicion that relevant contact allergies might be missed when patch testing is performed with 1% aqua. At the Department of Occupational and Environmental Dermatology in Malmö, Sweden, 2.0% formaldehyde has, for decades, been patch tested in patients with doubtful reactions to 1.0%. These circumstances led to a study with parallel patch testing with formaldehyde at concentrations of 1.0% and 2.0% aqua (6). The results showed that significantly more patients reacted to 2.0% than to 1.0% ($p < 0.001$). In all, 68 patients (4.9%), 53 women (53/878, 6.0%) and 15 men (15/519, 2.9%), were found to have contact allergy to formaldehyde. Thirty-eight patients had doubtful reactions to 1.0%, but 17 of these reacted positively to 2.0%. Among 27 patients tested with 3.0% (0.90 mg/cm²) formaldehyde, 29.6% reacted with an irritant reaction (6). To obtain identical correct doses (1.0% = 0.30 mg/cm² and 2.0% = 0.60 mg/cm²) for each patient, a micropipette was used to apply 15 µl to the Finn Chambers[®] (7). To investigate whether the results concerning the 1.0% and 2.0% patch test doses could be repeated, 12 dermatology clinics, 11 in Europe and one in the United States, participated in a multicentre study. All 3591 patients were patch tested simultaneously with formaldehyde 1.0% and 2.0%. Micropipettes were

used in all clinics to obtain the correct dose per area. Significantly more patients reacted to 2.0% than to 1.0% (3.4% versus 1.8%, $p < 0.001$) (8). In Malmö, 4540 patients were tested in 2006–2012 simultaneously with 1.0% and 2.0% formaldehyde, and 0.6% of these patients had irritant reactions to 2.0% formaldehyde (M Bruze, pers. comm. 2013). We are not aware of any active sensitization to formaldehyde during this time.

Clinical Relevance

The possible clinical relevance might be difficult to establish for the individual allergic patients. To study whether application with a formaldehyde-containing moisturizer would elicit allergic contact dermatitis in patients in which the allergy was diagnosed by 2.0% but not by 1.0%, an experimental exposure study was performed (9). In a randomized double-blind repeated open application test (ROAT), which continued for 4 weeks, it was found that a moisturizer containing 0.2% formaldehyde (the maximum concentration allowed in Europe) elicited allergic contact dermatitis in 9 of 17 formaldehyde-allergic patients, but in none of the controls ($p < 0.001$) (9). The finding that applications twice daily for ≥ 3 weeks were needed to give a positive ROAT result in 5 of 9 patients is important. It means that an even longer exposure may be needed to elicit the dermatitis. Furthermore, the ROAT was performed on healthy skin, whereas moisturizers are, presumably, very often used on damaged skin, where a lower concentration of formaldehyde might elicit allergic dermatitis.

Conclusion

On the basis of the results of the multicentre study and of the ROAT, it is recommended that formaldehyde 2.0% aqua (0.60 mg/cm²) should replace formaldehyde 1.0% in the European baseline series. To minimize undesired reactions, including irritant reactions (false-positive reactions), it is strongly recommended that a micropipette be used to apply the solution. In the Finn Chambers[®] patch test system, 15 µl should be applied (7).

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