

Formaldehyde

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Formaldehyde is the American Contact Dermatitis Society Contact Allergen of the Year for 2015. The exposure is widespread, and contact allergy might be difficult to suspect in the individual dermatitis patient. The relevance of contact allergy to formaldehyde might also be difficult to evaluate. Recently, however, several studies have been performed aimed at enhancing the patch test technique and evaluating the clinical relevance of contact allergy to formaldehyde. The patch test concentration of formaldehyde has been recommended by the European Environmental Contact Dermatitis Research Group to be 2.0%, that is, the dose of 0.60 mg/cm² (wt/vol) instead of 1.0%, which is the concentration previously used for the baseline series in most countries. Without causing any more irritant reactions, the patch test concentration of 2.0% detects twice as many contact allergies and enables the diagnosis of formaldehyde-allergic patients who otherwise would have been missed. The studies that underpin the decision were performed in Europe and partly in the United States. The Finn Chamber patch test system was used. The allergen dose per area was kept uniform with a micropipette. This report describes the background for routinely using formaldehyde 2.0% instead of 1.0% and for using a micropipette when applying the test solution.

BACKGROUND

Formaldehyde is a reactive chemical that can even cause chemical burns at high concentrations. It acts as a preservative and is used as an antimicrobial agent in both skin care products and within industry, where it is a raw material for production at certain work places. The individual exposure to formaldehyde is difficult to determine because it is a very common contact allergen that, besides being present in skin care products, can be found in many other products in contact with the skin, such as metal-working fluids, household products, plastics, textiles, and protective gloves. Thus, formaldehyde is also an important occupational contact allergen.^{1–5} For any contact allergen, it is a basic fact that if you do not test it or test it in too low a concentration, that is, a dose which is too low per unit area of the skin, you will miss the diagnosis. It has been suspected that formaldehyde may have been patch tested in too low a concentration so that clinically relevant contact allergies might have been missed. Because formaldehyde is known to cause chemical burns, it can produce irritant reactions when tested in too high a concentration. Generally, when irritant reactions are suspected and investigated, the exact dose per area of the allergen is crucial for determining an optimized patch test concentration.

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Formaldehyde is a gas in room temperature. It is the simplest aldehyde, and compared with many other contact allergens, it has a very low molecular weight (30.03). The chemical formula is C-H₂-O. It is seldom added as such to skin care products and products used in occupational settings such as metal-working fluids. Instead, formaldehyde-releasing preservatives of different kinds are added. Among formaldehyde releasers, those frequently used for patch testing are quaternium-15, imidazolidinyl urea, diazolidinyl urea, and DMDM hydantoin. Formaldehyde might also be emitted from other sources such as resins for which formaldehyde is used as a raw material and by auto-oxidation of ethoxylated alcohols used in many types of cleaners, laundry products, and toiletries.^{6–8} When results from patch testing in the United States and Europe are compared, it is found that contact allergy to formaldehyde has been more common in the United States, that is, around 8% to 9% versus 2% to 3% in Europe.³ Recently, however, the positive reaction rate for formaldehyde in the United States was lower than previously.⁹

Because formaldehyde has a low molecular weight, the patch test dose of formaldehyde is comparatively high when the number of molecules applied per area is considered. Still, the range of test doses that are appropriate might be narrow. This means that it is likely that the number of found reactions will differ if the applied amount (volume) of the test preparation varies between tested individuals. The effect will be missed diagnosis of contact allergy or false-positive/irritant reactions, and thereby poor results including in studies when doses and patch techniques are compared and changes for the baseline series are suggested. Therefore thorough preparatory studies are necessary when changes are made. In the case of changing the patch test dose of formaldehyde, these studies comprise (1) parallel patch testing with both 2.0% mg/cm² (wt/vol) and 1.0% mg/cm² (wt/vol) while making sure that the dose per area is held constant for each concentration, (2) confirmation of the results in a multicenter study, (3) an investigation of the possible clinical relevance of contact

TABLE 1. Dermatitis Contact Allergens of the Year

2014 (Volume 25, Number 1)

Benzophenones

Ashley Heurung

Srihari Raju

Erin Warshaw

2013 (Volume 24, Number 1)

Methylisothiazolinone

Mari Paz Castaneda-Tardana

Kathryn Zug

2012 (Volume 23, Number 1)

Acrylates

Denis Sasseville

2011 (Volume 22, Number 1)

Dimethyl Fumarate

Magnus Bruze

Erik Zimerson

2010 (Volume 21, Number 1)

Neomycin

Denis Sasseville

2009 (Volume 20, Number 1)

Mixed Dialkyl Thioureas

Bryan E. Anderson

2008 (Volume 19, Number 1)

Nickel

Rachel Komik

Kathryn Zug

2007 (Volume 18, Number 1)

Fragrance

Frances J. Storrs

2006 (Volume 17, Number 2)

P-Phenylenediamine

Vince DeLeo

2005 (Volume 16, Number 1)

Corticosteroids

Marlene Isaksson

Magnus Bruze

2004 (Volume 15, Number 1)

Cocamidopropyl Betaine

Joseph Fowler

2003 (Volume 14, Number 1)

Bacitracin

Apra Sood

James Taylor

2002 (Volume 13, Number 1)

Thimerosal

Donald Belsito

2001 (Volume 12, Number 1)

Gold

Joseph Fowler

2000 (Volume 11, Number 1)

Disperse Blue Dyes

Frances Storrs

allergy to formaldehyde discovered with 2.0% but not with 1.0%, and finally, (4) it would also be advised to determine a dose that is prone to give irritant reactions and therefore cannot be used.

APPLYING SOLUTIONS OF PATCH TEST SUBSTANCES

When 3 different techniques for applying a solution were compared, it was found that the micropipette technique has the lowest intraindividual and interindividual variation compared with the drop technique and the drop-and-wipe technique.¹⁰ The drop technique in the study involved squeezing the plastic bottle in which the test solution is purchased from Chemotechnique and applying a drop of the solution onto the filter paper in the Finn Chamber with the diameter of 8 mm. The drop-and-wipe technique used the same bottle, but the excess solution was gently wiped off the filter paper. The drop technique showed the largest variation both intraindividually and interindividually. Concerning formaldehyde, it was found that for 1 of the technicians enrolled in the study for 10 consecutive applications, the lowest and highest dose differed by a factor 4. From these results, it can be understood that when the drop technique is used, the dose of an allergen might differ within the very range under investigation, for example, the comparison of formaldehyde 2.0% versus 1.0%. There is also a risk of irritant reactions because formaldehyde has a comparatively narrow dose response curve between negative and irritant reactions. The optimized amount of solution for Finn Chambers is 15 μL .¹¹ This amount corresponds to a volume per area of 30 $\mu\text{L}/\text{cm}^2$. In Malmö, at the Department of Occupational and Environmental Dermatology, the micropipette technique has been used for decades.

PARALLEL PATCH TESTING WITH DIFFERENT DOSES

Adequate comparisons between different patch test doses of sensitizers is meaningful only when the technique for applying the test solution is established and thereby a standardized dose/area. In 1 study, patch test results from the Department of Occupational and Environmental Dermatology in Malmö for different patch test concentrations of formaldehyde were compared.¹² One thousand three hundred ninety-seven 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 because of suspected allergic contact dermatitis. Fifteen microliters of each of the 2 test preparations with 2.0% and 1.0% in aqueous solution was applied with a micropipette to the filter paper discs in the test chambers. Besides 2.0% and 1.0% formaldehyde, 27 patients were tested with formaldehyde 3.0%. Statistically significantly more patients reacted to 2.0% compared with 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%. Of the 27 patients who

were tested with formaldehyde 3.0%, 8 patients (29.6%) had irritant reactions but did not react to either 1.0% or 2.0%. Among these 1397 patients, irritant reactions to formaldehyde 2.0% and 1.0% were noted in 0.3% and 0.1% of the patients, respectively, which are significantly lower proportions than for 3.0%.¹²

The results from Malmö, Sweden, were confirmed in a multicenter study performed in 11 European dermatology clinics and 1 in the United States.¹³ In that study, 3591 patients were routinely patch tested simultaneously with 2.0% and 1.0% formaldehyde. Micropipettes were used for delivering the exact dosage of the allergen, that is, 15 μ L for Finn Chambers and 20 μ L for Van der Bend Chambers.¹⁰

Statistically significantly more patients reacted to 2.0% formaldehyde than to 1.0% (3.4% vs 1.8%, $P < 0.001$). Overall, there were no differences between those reacting positively to 2.0% and 1.0% regarding sex. The proportions of cases reacting to formaldehyde 2.0% varied between 1.3% and 11.9% among the participating clinics with the clinic in the United States having the lowest proportion. The ratios between cases found when patch testing with 2.0% compared with 1.0% ranged from 5 to 1. Based on the data from the participating clinics, it was difficult to evaluate the disadvantages of 2.0% as compared with 1.0% with respect to irritant reactions because they varied greatly between the participating clinics. Whether the variation depended on differences in evaluation of the morphology of a test reaction or possibly other reasons is not yet known. Regardless of these variations, the conclusion was that the overall result shows that significantly more cases were found when patch testing with 2.0%.¹³

REPEATED OPEN APPLICATION TEST

Even if more contact allergies to an allergen are detected by a certain dose of the allergen in question, it is still important to try to establish the clinical relevance of these further cases found by the optimized test dose. To achieve this, a repeated open application test (ROAT) can be performed. The ROAT simulates the everyday use of a skin care product such as a moisturizer. In a study performed at the Department of Occupational and Environmental Dermatology in Malmö, 17 patients (mean age, 44.1 years; range, 23-64; 4 men and 14 women), who reacted positively to 2.0% but were negative to 1.0% when tested simultaneously with both concentrations, participated in an ROAT study.¹⁴ In addition, 19 matched controls were enrolled. The participants were instructed to apply 1 of 2 moisturizers on 1 of their arms and the other on the other arm twice a day. One of the moisturizers contained the highest allowed concentration of formaldehyde according to the European Cosmetics Regulation (2000 ppm = 0.2% w/w and the other moisturizer without formaldehyde served as a control). The moisturizers were applied on 5 $\times$ 5 cm areas on each of their arms. The study was double-blind and randomized. Within the group of formaldehyde-positive patients, 9 of 17 reacted to the formaldehyde-containing moisturizer versus none of 17 to the moisturizer without formaldehyde ($P < 0.001$,

McNemar's test). The difference between the formaldehyde-allergic patients and the controls was statistically significant ($P < 0.001$, Fisher's exact test). The mean number of applications before a recorded positive ROAT was 37 (range, 9-56). Thus, for some participants, it could take up to 3 to 4 weeks before the allergic contact dermatitis appeared. Furthermore, the study showed that patch testing with the product "as is" might fail to elicit a reaction. The calculated dose per area of formaldehyde would have been 0.06 mg/cm² for the moisturizer with formaldehyde making it less probable that the formaldehyde-allergic participants would have reacted.¹⁴

CONTACT ALLERGIES TO FORMALDEHYDE RELEASERS AND FORMALDEHYDE

Usually, patients with contact allergy to formaldehyde are advised to avoid products declared to contain formaldehyde releasers. It has been found that atopic individuals were significantly more likely to show cutaneous delayed-type hypersensitivity to quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol but not to formaldehyde or diazolidinyl urea.¹⁵ The vehicle used for patch testing formaldehyde releasers is also important. According to 1 study, significantly more patients reacted to imidazolidinylurea, diazolidinylurea, and DMDM hydantoin when diluted in petrolatum than in water.¹⁶ Quaternium-15 is the only formaldehyde releaser present in the baseline series in Europe, and the prevalence of contact allergy varies between different countries with the highest number in United Kingdom. Around half of the patients reacting to quaternium-15 also react to formaldehyde 1%. It has been argued that quaternium-15 would appear not to qualify for continued inclusion in the European baseline series because the number of additional cases found among patients negative to formaldehyde is too small.¹⁷ Furthermore, patients with stronger reactivity to formaldehyde are more likely to simultaneously react to quaternium-15.¹⁸ However, contrarily, it has also been shown that the severity of the formaldehyde reaction does not predict reactivity to quaternium-15 and that despite coreactivity with formaldehyde, quaternium-15 may not be a significant formaldehyde releaser.¹⁹ When analyzed, most aqueous solutions of formaldehyde releasers contain free formaldehyde, whereas petrolatum-based patch test preparations with formaldehyde releasers do not contain free formaldehyde. It is, however, assumed that formaldehyde is released when the patch test preparations are in contact with the humidity of the skin.²⁰ The main reason to test specific formaldehyde releasers routinely would be that a significant number of additional cases without contact allergy to formaldehyde were found. Based on the recommendation that patch testing with formaldehyde 2.0% should be used in the baseline series, the coreactivity between different formaldehyde releasers might have to be revised, and the studies should then be done in comparison with formaldehyde 2.0% and with the correct dose/area for formaldehyde. There are also no firmly established results regarding test dose and vehicle concerning the formaldehyde releasers.

COMPARISONS BETWEEN PATCH TEST SYSTEMS

When the frequencies of found contact allergies are compared, the patch test system used for the comparisons ideally should be the same. This might, however, be difficult to accomplish. Formaldehyde has been judged to show a good concordance of positive results (76.9%) when IQ Chamber and TRUE test were compared. Among the 207 patients tested simultaneously with both test systems, 10 patients (4.8%) reacted simultaneously to formaldehyde in both systems. Six more patients (16/207, 7.7%) reacted to formaldehyde in the IQ Chamber, and none more to formaldehyde in the TRUE test system.²¹ However, an earlier study concluded that when only the TRUE test methodology is used, it is necessary to be aware that relevant reactions to formaldehyde may be missed with this system.²² The dose per area of formaldehyde, which is chosen for the TRUE test, is 0.18 mg/cm².²³ It is around a third of the dose now recommended for the European baseline series based on investigations performed with the Finn Chamber system (2.0% = 0.6 mg/cm²). However, because the vehicle is different in the TRUE test, the dose per area might be difficult to compare.

FORMALDEHYDE ANALYSIS OF PRODUCTS

According to the European Cosmetics Regulation, skin care products must be declared, including all added preservatives.²⁴ In the United States, all marketed cosmetics, whether manufactured here or imported from abroad, must be in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act; the Fair Packaging and Labeling Act; and the regulations published under the authority of these laws. In regards to labeling, all additives, including but not limited to preservatives, must be labeled in accordance with Title 21, Code of Federal Regulations (21 CFR 700 to 740).²⁵ However, low concentrations of formaldehyde might be present in a product either due to undeclared presence of a preservative or formaldehyde emanating from other components of the products. Products that have been used frequently by formaldehyde-allergic patients should therefore preferably be analyzed with respect to the presence of formaldehyde, especially when they are not declared to contain any formaldehyde releaser. There are comparatively simple spot tests, which can be used.^{26,27}

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