

Contact Allergy to 3-Methylol Phenol, 2,4-Dimethylol Phenol and 2,6-Dimethylol Phenol

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Bruze M, Zimerson E. Contact allergy to 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol. *Acta Derm Venereol (Stockh)* 1985; 65: 548-551.

Thirteen patients with contact allergy to phenol-formaldehyde resins (P-F-R) were patch tested with 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol. Nine patients reacted to at least 1 compound, all giving positive test responses to 2,4-dimethylol phenol. Seven patients reacted simultaneously to 2,6-dimethylol phenol while only 1 patient reacted to 3-methylol phenol. Negative test responses were noted in 20 controls. Chemical investigation by high pressure liquid chromatography indicated that the compounds tested were pure and separable. The 3 reported sensitizers may, theoretically, be generated during the manufacture of P-F-R. 2,4-Dimethylol phenol and 2,6-dimethylol phenol have been demonstrated and there has been chromatographic evidence of 3-methylol phenol in the P-F-R used in the routine test series at the department. *Key words:* Allergic contact dermatitis; Delayed hypersensitivity; High pressure liquid chromatography; Phenol-formaldehyde resins. (Received May 15, 1985.)

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Allergic contact dermatitis caused by phenol-formaldehyde resin, based on phenol and formaldehyde (P-F-R), is not uncommon. During the production of P-F-R a great many and mainly unknown substances are formed. There are presumably many sensitizers in P-F-R and so far 3 compounds have been identified, viz. 2-methylol phenol, 4-methylol phenol and 2,4,6-trimethylol phenol (1-5). In this paper, 3 more sensitizers of P-F-R are reported.

MATERIAL AND METHODS

Patch testing

Three different phenol-formaldehyde resins are included in the standard test series at our department (5). Two of these resins are based on phenol and formaldehyde (P-F-R-1 and P-F-R-2) and both were manufactured in an alkaline environment and are thus of the resol type (5).

Thirteen patients reacting to these P-F-R, all with hand dermatitis, 8 with occupational exposure and 5 with unknown exposure to P-F-R, were patch tested (AI-test, Astra Agency, Sweden) with 3-methylol phenol (Janssen Chimica, Belgium) 2,4-dimethylol phenol and 2,6-dimethylol phenol. The dimethylol phenols were synthesized at the department and identified by mass-spectrometry and nuclear magnetic resonance spectrometry. All three methylol phenols were dissolved in ethanol (99.5%) at equimolar concentrations; 1.00% w/v ($0.081 \text{ mole} \times 10^{-1}$) for 3-methylol phenol and 1.24% w/v ($0.081 \text{ mole} \times 10^{-1}$) for each of 2,4-dimethylol phenol and 2,6-dimethylol phenol. These stock solutions were patch tested as such and also tested when diluted to 0.1%, 0.01%, 0.001% w/v and 0.124%, 0.0124%, 0.00124% w/v respectively. The structural formulae are shown in Fig. 1.

High Pressure Liquid Chromatography (HPLC)

The three methylol phenols in this study were analyzed by HPLC on a bonded octadecylsilylphase using acetonitrile (Merck, Lichrosolv)/water as the mobile phase and detected by a UV-detector. All analyses were performed using a column (20 cm, 3 mm i.d.) packed with Nucleosil C₁₈ (5 μ , Macherey-Nagel and Co., Düren, West Germany). The samples were dissolved in the mobile phase. The flow rate was 1 ml/min and the eluate monitored at 280 nm by using an LDC-spectroMonitor D, variable wavelength detector.

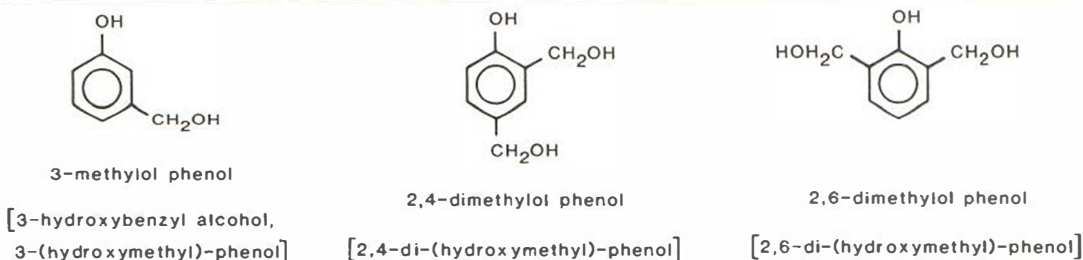


Fig. 1. The structural formulae of 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol.

RESULTS

The results of patch testing with 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol are given in Table I for the 9 patients (out of 13) who reacted to at least one of the compounds tested. All 9 patients reported here reacted to 2,4-dimethylol phenol. Seven patients reacted simultaneously to 2,6-dimethylol phenol, while only one patient reacted to 3-methylol phenol. The strength of the contact allergy seems to be of the same degree for the two dimethylol phenols tested. There were no differences in pattern and strength of reactivity between the patients with occupational exposure to P-F-R and those without.

None of 20 control patients reacted to any of the compounds tested (3-methylol phenol 1.00% w/v, 2,4-dimethylol phenol and 2,6-dimethylol phenol 1.24% w/v).

Each methylol phenol was investigated by HPLC for the presence of the 2 other methylol phenols. The highest possible concentrations of contaminating 3-methylol phenol in 2,4-dimethylol phenol and 2,6-dimethylol phenol were 0.006% and 0.160% w/w respectively. The figures for 2,4-dimethylol phenol in 3-methylol phenol and 2,6-dimethylol phenol were 0.004% and 0.238% w/w. The corresponding figures for 2,6-dimethylol phenol in 3-methylol phenol and 2,4-dimethylol phenol were 0.143% and 0.011% w/w respectively. These values for the highest possible concentrations of contaminating methylol phenols were similar for 2-methylol phenol, 4-methylol phenol and 2,4,6-trimethylol phenol in 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol respectively.

Table I. Results of patch testing with 3-methylol phenol, 2,4-dimethylol phenol and 2,6-dimethylol phenol in 9 patients reacting to at least 1 of these compounds

Substance/ethanol	% w/v	Patient								
		1	2	3	4	5	6	7	8	9
3-methylol phenol	1	-	-	-	-	+	-	-	-	-
	0.1					-				
2,4-dimethylol phenol	1.24	+	+	+	+	+	+	+	+	+
	0.124	+	+	+	+	-	+	+	+	+
	0.0124	-	-	-	-		-	+	-	-
	0.00124							-		
2,6-dimethylol phenol	1.24	+	+	+	+	-	-	+	+	+
	0.124	+	-	+	+		+	-	+	
	0.0124	-		+	-			+		-
	0.00124			-				-		

DISCUSSION

Besides formaldehyde 3 other sensitizers have previously been identified in P-F-R. 2-Methylol phenol, described as a sensitizer in iodobismutol (6), was demonstrated to be a sensitizer in P-F-R in the forties (1). This compound was rediscovered 30 years later when a worker in the phenol-formaldehyde industry reacted to 2-methylol phenol and to a lesser degree, to 2,4,6-trimethylol phenol, but not to 4-methylol phenol (2). Recently a patient reacting to this latter substance was reported (3). Other patients with contact allergy to these three methylol phenols (2-methylol phenol, 4-methylol phenol, 2,4,6-trimethylol phenol) have been described in the last year (4, 5).

At present we are trying to identify sensitizers in P-F-R. Since contact allergens are usually small molecules and three methylol phenols which are low molecular weight substances, have already been demonstrated to be sensitizers, it seemed reasonable to suspect that other equal-sized methylol phenols were sensitizers as well.

The base-catalysed reaction of phenol with formaldehyde results in the formation of five main methylol phenols, viz. 2-methylol phenol, 4-methylol phenol, 2,4-dimethylol phenol, 2,6-dimethylol phenol and 2,4,6-trimethylol phenol (7). The two dimethylol phenols mentioned were not commercially available, so they were synthesized. The first step in the methylation of phenol is the formation of monomethylol phenols. This reaction favours substitution at the ortho-position (giving 2-methylol phenol) and para-position (giving 4-methylol phenol) of the phenol, but from a theoretical point of view methylation at the meta-position (giving 3-methylol phenol) cannot be excluded (8). 2,4-Dimethylol phenol and 2,6-dimethylol phenol have been demonstrated and there has been chromatographic evidence of 3-methylol phenol in the P-F-R used in the routine test series of the department (9).

The contact allergies to 2,4-dimethylol phenol and 2,6-dimethylol phenol are presumably genuine since the control patients did not react to 1.24% w/v while most patients reacted to more diluted solutions and the HPLC investigation indicated that these compounds and 3-methylol phenol were pure. The only patient positive to 3-methylol phenol reacted only to 1.00% w/v. In spite of this weak reactivity, such sensitivity is presumably genuine since 20 control patients did not react to the same concentration and the patient showed strong reactions to P-F-R-1 and P-F-R-2. The reaction to 3-methylol phenol, however, and the reactions to 2,4-dimethylol phenol and 2,6-dimethylol phenol, may be expressions of cross-reactivity to other main sensitizers. This point may be elucidated by predictive patch testing of guinea pigs.

With the results of this study, three more methylol phenols are added to the number of known sensitizers in P-F-R. However, these sensitizers are not the only ones; other contact allergens will be reported later.

ACKNOWLEDGEMENTS

The authors are indebted to Kerstin Hjorth and Lena Persson for valuable technical assistance. This investigation was supported by a grant from The Swedish Work Environment Fund (ASF 84-0914).

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