

Aalto-Korte Kristiina (Orcid ID: 0000-0002-5595-5512)
Pesonen Maria (Orcid ID: 0000-0003-0356-7064)

**Patterns of positive patch test reactions to formaldehyde and formaldehyde releasers at the
Finnish Institute of Occupational Health from 2007 to 2020**

Kristiina Aalto-Korte, Maria Pesonen

Finnish Institute of Occupational Health (FIOH), Occupational health unit, Helsinki, Finland

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Correspondence:

Kristiina Aalto-Korte

Finnish Institute of Occupational Health

Occupational health unit

FI-00032 TYÖTERVEYSLAITOS

Helsinki, Finland

Tel: +358-30-4741

Email: kristiina.aalto-korte@ttl.fi

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Abstract

Background: Formaldehyde is an important contact sensitiser. Formaldehyde releasing substances induce positive reactions in formaldehyde-allergic patients, but there are also reactions independent of formaldehyde allergy. In an earlier study, stronger formaldehyde reactions lead to more positive reactions to quaternium-15.

Objectives: To analyse patterns of positive patch test reactions to formaldehyde and different formaldehyde releasers.

Methods: Patch test files of 1497 patients investigated during a period of November 2007 – August 2020 were retrospectively reviewed for positive reactions to formaldehyde and its releasers. Almost all ($\geq 99.3\%$) patients during the study period were tested with a formaldehyde dilution series and 6 formaldehyde releasers.

Results: 93 patients tested positive to formaldehyde. 80% of these had positive reactions to at least one formaldehyde releaser, most often benzylhemiformal. There were only 9 independent contact allergies to formaldehyde releasers. There were only two reactions to 2-bromo-2-nitropropane-1,3-diol, and they occurred in formaldehyde-negative patients. In patients with extreme (+++) reactions to formaldehyde, concomitant positive reactions to any of the other 11 investigated formaldehyde releasers were more common than in patients with milder formaldehyde reactions.

Conclusions: Strong formaldehyde reactions were associated with positive reactions to formaldehyde releasers.

Key words: benzylhemiformal, 2-bromo-2-nitropropane-1,3-diol, quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine, Bioban CS 1135, Bioban P 1487, Bioban CS 1246

1. Introduction

Formaldehyde is an important sensitiser in occupational dermatology: in a period of 2005–2016, formaldehyde and its releasers (liberators) caused 5.5% of occupational allergic contact dermatitis in Finland according to our national register of occupational disease.¹ Formaldehyde 2% aq. is included in the recommendation of the European baseline patch test series² together with a formaldehyde-releasing agent quaternium-15. Formaldehyde releasing substances induce positive reactions in formaldehyde-allergic patients, but there are also isolated reactions independent of formaldehyde allergy. The relationship between formaldehyde and its releasers can be examined from different perspectives. A recent European study stated that formaldehyde 2% is not an adequate screen for contact allergy to formaldehyde releasers as the percentage of isolated reactions varied between 46.8% and 96.3% for quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol.³ On the other hand, a Dutch study found that stronger reactions to formaldehyde were associated with a higher frequency of positive quaternium-15 patch tests which suggested an important causative role for formaldehyde in quaternium-15 patch test reactions.⁴

At the Finnish Institute of Occupational Health (FIOH), we routinely perform patch tests with four concentrations of formaldehyde and many formaldehyde-releasing agents. We wanted to analyse patterns of positive reactions to formaldehyde and its releasers in our patient material in a period of November 2007 – August 2020 the same way as in the Dutch study⁴.

2. Methods

FIOH has a clinic of occupational dermatology. All our patients have a suspected occupational skin disease. We performed patch tests using Finn Chambers (Smart Practice, Phoenix, AZ, USA), in accordance with the European Society of Contact Dermatitis guidelines⁵. We read the tests 2–3

times: on D2-D3-D4, D2-D3-D6 or D2-D5, depending on the day of application (Monday, Tuesday or Wednesday).

We routinely patch tested all our patients with a concentration dilution series of formaldehyde 2%, 1%, 0.32% and 0.1% aq. (in-house). In addition, formaldehyde 1% aq. (Trolab/Almirall Hermal, Reinbek, Germany) was tested in the baseline series until July 2014. In March 2017, we introduced an in-house formaldehyde 2% aq. into the baseline series. During the interval, the baseline series contained no formaldehyde. There was double testing of formaldehyde 1% aq. between November 2007 and July 2014, and double testing of formaldehyde 2% aq. starting from August 2017. We make new formaldehyde solutions at intervals of 4 weeks (the solution of the 2% concentration is divided into two bottles, one for the baseline series and the other for the dilution series).

We tested quaternium-15 1% and imidazolidinyl urea 2% (both in pet.) in our modified Finnish baseline series during the whole study period.

For formaldehyde releasers, we have mainly used Trolab's (when possible) and Chemotechnique's (Chemotechnique Diagnostics, Vellinge, Sweden) test substances. We tested other formaldehyde releasers in the antimicrobial series and in the oil and cutting fluid series. Diazolidinyl urea (2% pet.), 2-bromo-2-nitropropane-1,3-diol (Bronopol; 0.25% pet.), methenamine (hexamethylenetetramine; 2% pet.), and benzylhemiformal (1% pet.) were tested in the antimicrobial series during the whole study period. DMDM hydantoin (2% aq.) was introduced into this series in March 2009. Hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine (1% aq.) and Bioban CS 1135 (1% pet.) were first tested in the antimicrobial series but moved to the oil and cutting fluid series in August 2012. Bioban CS 1246 (1% pet.), N,N'-methylenebismorpholine (1% pet.; CAS no. 5625-90-1; in-house test substance), and N,N-methylene-bis(5-methyl)oxazolidine (1% pet.; CAS no. 66204-44-2; in-house test substance; Biocide OX) have been tested in the oil and cutting fluid series during the whole study period. Bioban P 1487 0.5% pet. was first tested in this series but omitted in August 2012.

We screened our test files (19.11.2007–31.8.2020) for patients with positive reactions to formaldehyde and formaldehyde releasers. Of these patients, we included individuals who were tested with formaldehyde and the above-mentioned formaldehyde releasers in the baseline series, and the antimicrobial series. A subgroup was additionally tested with the oil and cutting fluid series. We analysed concomitant reactions to different formaldehyde test substances and formaldehyde releasers. The strongest reactions to individual formaldehyde test substances were used for analyses. Single positive reactions in the dilution series were also interpreted positive as long as they met the morphological criteria of a positive reaction.

3. Results

During the study period a total of 1497 patients were tested with the baseline series, 1486 (99.3%) with the formaldehyde dilution series, 1494 (99.8%) patients with the antimicrobial series, and 366 (24.4%) with the oil and cooling fluid series. We identified a total of 105 patients with a positive reaction (+/++/+++) to at least one of the formaldehyde test substances or a formaldehyde releaser. One formaldehyde-positive case was excluded because not all formaldehyde releasers in the antimicrobial series were tested due to previous positivity (this patient had a + reaction to formaldehyde 1%). Of the remaining 104 patients, 103 (99.0%) were tested with the formaldehyde dilution series and 37 (35.6%) were tested with the oil and cooling fluid series.

3.1. Reactions to formaldehyde

A total of 94 (6.2%) patients had positive reactions to formaldehyde. One of these was excluded (see above) from further analyses leaving 93 formaldehyde-positive patients. Of these, in 22 (24%) patients the strongest reaction was extreme (+++), in 52 (56%) patients strong (++) and in 19 (20%) patients mild (+).

Of the 93 formaldehyde-positive patients, 19 didn't have co-reactions to any of the tested formaldehyde releasers (20%). This group comprised 3 patients with +++ reactions, 10 with ++ reactions and 6 with + reactions.

Double testing with two formaldehyde 1% tests was performed in 857 patients: 51 patients tested positive, of whom 15 (29.4%) were discordant (one of the 2 tests was not positive). Double testing with two formaldehyde 2% test substances was performed in 328 patients: 13 patients tested positive, of whom one (7.7%) was discordant.

3.2. Reactions to formaldehyde releasers

We present the numbers of positive reactions to the formaldehyde releasers in Table 1.

Benzylhemiformal was the most commonly positive formaldehyde releaser with 69 allergic reactions. Imidazolidinyl urea in the baseline series provoked 10 positive reactions while diazolidinyl urea in the antimicrobial series was positive in 16 patients. Bioban P 1487 didn't induce positive reactions in any of the 152 patients tested.

Nine patients had positive reactions to one formaldehyde releaser or two cross-reacting formaldehyde releasers but no positive reactions to formaldehyde or other formaldehyde releasers i.e. these were independent formaldehyde releaser reactions without formaldehyde allergy. Two patients reacted to 2-bromo-2-nitropropane-1,3-diol and one to benzylhemiformal. Three patients reacted to both quaternium-15 and methenamine, compounds that cross react with each other.⁶ The same is true for imidazolidinyl urea and diazolidinyl urea. Two patients reacted to both of them, and one patient to imidazolidinyl urea only.

We had two patients with doubtful reactions to formaldehyde and positive reactions to 6 and 8 formaldehyde releasers, respectively. Although these patients did not test positive to formaldehyde, we didn't consider their reactions to formaldehyde releasers independent as the probable

explanation for such high numbers of simultaneous positive reactions to releasers is formaldehyde allergy.

3.3. Reactions to formaldehyde releasers in relation to the strength of formaldehyde reaction

Of the 93 patients with positive reactions to formaldehyde, 74 (79.6%) also reacted to at least one formaldehyde releaser. Positive reactions to releasers were more common in patients with strong and extreme reactions to formaldehyde than in those with mild reactions: 19 (86.4%) patients out of the 22 patients with +++ reactions to formaldehyde also tested positive to at least one formaldehyde releaser. Of the 52 patients with a ++ reaction to formaldehyde, 42 (80.8%) tested positive to at least one formaldehyde releaser. The corresponding figure for mild (+) formaldehyde reactors was 13 (68%) out of 19. These groups were not fully comparable as the set of tested releasers varied quite a lot during the study period and not all patients were tested with the oil and cooling fluid series. [The differences were not significant at $p < 0.05$ (Fisher's exact test)]. In Table 2, we present data on formaldehyde releaser positivity ratio in relation to the strength of the formaldehyde reaction. Apart from 2-bromo-2-nitropropane-1,3-diol all the releasers showed the trend described above: Patients with +++ reactions to formaldehyde were more likely to react to individual formaldehyde releasers than patients with ++ or + reactions.

Discussion

Formaldehyde is an important contact allergen in both occupational and general dermatology. Its recommended test concentration has varied over the years. In earlier decades, concentrations of 3–5% were used, but due to irritancy and false positive reactions a concentration of 2% was recommended in the 1960s.⁷ It was later further reduced to 1%, and recently increased back to 2%. In a Danish comparison of 1% and 2% test concentrations from the late 1990s, there was a striking discrepancy of the results: Only 48.8% of the formaldehyde-positive patients had positive reactions to both of the concentrations; 19% only reacted to 1% formaldehyde and 32.2% only reacted to 2%

formaldehyde.⁷ There are other studies demonstrating difficulties in the diagnosis of formaldehyde allergy: In a left-versus-right-sided patch test study by the German Contact Dermatitis Research Group, formaldehyde had the weakest reproducibility of 10 allergens of the baseline series,⁸ and in a study combining meteorological and patch test data of 12 allergens, formaldehyde showed the strongest association between increased irritant, doubtful and mild patch test reactions, and low temperature and low humidity.⁹ Concentration of formaldehyde was 1% in these two studies.

At the FIOH, we have limited possibilities for repeated tests, and that's why we have chosen to perform wide simultaneous tests in one session. In 2007 we started to screen our patients with the formaldehyde dilution series as a supplement of our baseline series. In addition, most of the patients in the present material were tested with formaldehyde 1% or 2% in the baseline series i.e. with a total of 5 formaldehyde test substances. Five tests may increase the likelihood of detecting at least one positive reaction compared to only one test. We also prepare fresh test substances at intervals of 4 weeks which may also increase the positivity ratio to some extent.

As patch test positivity to formaldehyde in the present analysis was based on the strongest result of 4–5 formaldehyde tests, it is no wonder that the fraction of mild reactions was smaller than in studies using only one formaldehyde test: of the 93 included patients 20% had a mild reaction, while in a recent ESSCA study mild reactions were more common than extreme and strong reactions combined.³ It is possible that multiple positive tests lead to stronger individual reactions – close proximity of the reactions might have an enhancing effect.⁸ As 80% of our formaldehyde-positive patients had co-reactions to formaldehyde releasers, we assume that most of our formaldehyde diagnoses were true contact allergies and not false positive results. The latter possibility remained in patients with positive patch test to formaldehyde without positive reactions to formaldehyde releasers, 20% of all. Majority of this group had doubtful reactions to some releasers.

In our data, only a few patients with previously known formaldehyde contact allergy were not tested with the dilution series. Quaternium-15 and imidazolidinyl urea were screened in all patients as a

part of the Finnish baseline series. The antimicrobial series was tested in all but three patients investigated at FIOH during the study period, so the frequencies of positive reactions to diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol, methenamine and benzylhemiformal in this series were quite well comparable with those of the allergens in the baseline series.

We compared our results with three other studies: a multicentre study from Spain by Latorre et al.,¹⁰ a study from Denmark by Lundov et al.,¹¹ and an ESSCA network study by Whitehouse et al.,³ all presenting patterns of concomitant reactions to formaldehyde and the five releasers quaternium-15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol. Frequencies of positive reactions to formaldehyde and quaternium-15 in these studies were lower than ours (formaldehyde positivity varied between 1.7% and 3.1%, and that of quaternium-15 between 0.74% and 1.0%). When frequencies of positive reactions to other releasers were compared, our figures were mainly in line with the figures in these three previous studies. Also, our frequencies of positive reactions to the five formaldehyde releasers in formaldehyde-positive patients were within the range of the corresponding figures of the three other studies.

We had only two positive reactions to 2-bromo-2-nitropropane-1,3-diol, and they occurred in patients who tested negative to formaldehyde and all other formaldehyde releasers. We can't draw any conclusions from these two cases, but the finding was in line with the previous literature: 2-bromo-2-nitropropane-1,3-diol reactions are mostly independent i.e. not related to formaldehyde contact allergy.¹² The reverse was true for other formaldehyde releasers analysed in this study: co-reactions to formaldehyde were more common in patients with positive reactions to quaternium-15, imidazolidinyl urea, diazolidinyl urea and DMDM hydantoin in our material than in the other 3 studies (quaternium-15: 85% v. 50–74%; diazolidinyl urea: 81% v. 19–54%; imidazolidinyl urea 70% v. 26–34%; DMDM hydantoin 100% v. 17–79%). Positive reactions to methenamine occurred with formaldehyde allergy as often as positive reactions to cross-reacting quaternium-15 (85%).⁶

Reactions to other formaldehyde releasers benzylhemiformal, hexahydro-1,3,5-tris-(2-

hydroxyethyl)triazine, Bioban CS 1135, Bioban CS 1246, N,N'-methylenebismorpholine, and N,N-methylene-bis(5-methyl)oxazolidine were even more closely related to formaldehyde reactions (91–94% of co-reactivity).

In 2010, a Dutch study found that individuals with stronger reactions to formaldehyde were more likely to have positive reactions to quaternium-15 which was considered as favouring an important causative role for formaldehyde in quaternium-15 patch test reactions.⁴ We analysed more formaldehyde releasers in the same way and found that with the exception of 2-bromo-2-nitropropane-1,3-diol, all the releasers showed the same trend: patients with +++ reactions to formaldehyde had relatively more often reactions to individual releasers than patients with ++ or + reactions (Table 2).

In our material, solitary reactions to formaldehyde releasers were rare. It is possible that solitary reactions to releasers are truly more common in general dermatology patients. The releasers with the relatively low association with formaldehyde allergy, diazolidinyl urea, imidazolidinyl urea and quaternium-15, have almost uniquely been used in cosmetics,¹¹ and at the FIOH clinic for occupational dermatology, we lack patients who present with consumers' problems from cosmetics. It is also possible that we diagnose formaldehyde contact allergy more accurately by using many test substances.

Although our patients were tested with formaldehyde at concentrations of 2%, 1%, 0.32% and 0.1% in one session, we still had two patients with multiple positive reactions to 6 and 8 formaldehyde releasers but only doubtful reactions to formaldehyde. Geier et al. 2008¹³ described a machinist exposed to metal-working fluids with positive reactions to 3 formaldehyde releasers but negative to formaldehyde in the first patch test session. Later, the patient tested positive with 1% formaldehyde in a large Finn Chamber. In case of positive reactions to 6-8 formaldehyde releasers, we diagnose probable formaldehyde contact allergy without repeating any test. These patients are not extremely

rare: in our preceding report from the FIOH covering January 2001–May 2007, there was one patient with positive reactions to three releasers.¹⁴

Schubert et al. recently noted that Bioban CS 1135 and Bioban P 1487 were outdated allergens as they are no longer used in the EU.¹⁵ We have stopped testing Bioban P 1487 because it was so rarely positive. There were no independent reactions to Bioban CS 1135 in the present material, and in our earlier material (January 2001–May 2007) there were two positive cases without formaldehyde-positivity, a farmer and a cleaner, in whom we could not show exposure to Bioban CS 1135.¹⁴ This test substance is, however, a rather good indicator of formaldehyde allergy, and for this reason we will probably continue testing it.

Formaldehyde is a difficult test substance that gives rather inconsistent results on patch testing. Presumably, there are false positive reactions and also a few false negative results, both depending on the test concentration. It is true that formaldehyde is not an adequate tool for diagnosing all contact allergies to releasers, but this partly relates to the relatively poor performance of the test substance in diagnosing contact allergy to itself.

The number of formaldehyde-releasing substances is large. Avoiding formaldehyde exposure is difficult even for the most motivated patients, and their symptoms tend to continue or recur. They need thorough counselling. On the other hand, patients with possibly false positive reactions should not be unnecessarily advised to avoid all formaldehyde releasers. We have found our approach to diagnose formaldehyde allergy quite useful – if all formaldehyde test substances and all releasers are negative, we think we can reliably exclude formaldehyde allergy. Problems remain with the isolated reactions to formaldehyde without co-reactions to formaldehyde releasers – are they true allergies or false positive results? In these cases, repeated tests and/or follow-up might give the answer. If the patient stays in remission, the threshold for elicitation is probably not very low and very strict avoidance possibly not necessary. In every recurrence, however, sources of formaldehyde exposure

should be searched for as the first measure. For retesting, we suggest inclusion of all formaldehyde releasing test substances available in the clinic.

4. Conclusions

In this retrospective clinical material of 93 formaldehyde-positive patients, as many as 80% had co-reactions to at least one formaldehyde releaser. The high percentage probably resulted from regular testing of a formaldehyde dilution series and a large number of formaldehyde releasers. Positive reactions to 2-bromo-2-nitropropane-1,3-diol were few and not related to formaldehyde allergy. In patients with extreme (+++) formaldehyde reactions, concomitant positive reactions to any of the other 11 investigated formaldehyde releasers were more common than in patients with milder formaldehyde reactions. This favours an important causative role for formaldehyde in positive reactions to these releasers.

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Table 1 Positive reactions to formaldehyde releasers and their relation to formaldehyde reactions

Formaldehyde releaser	Patch test concentration and vehicle	Number of patients tested during the study period	Total number of positive reactions	Formaldehyde patch test positive
Quaternium-15	1% pet.	1497	26 (1.7%)	22 (85%)
Imidazolidine urea	2% pet.	1497	10 (0.67%)	7 (70%)
Diazolidinyl urea	2% pet.	1495	16 (1.1%)	13 (81%)
2-Bromo-2-nitropropane-1,3-diol	0.25% pet.	1494	2 (0.13%)	0
Hexamethylene tetramine	2% pet.	1495	26 (1.7%)	22 (85%)
Benzylhemiformal	1% pet.	1495	69 (4.6%)	66 (96%)
DMDM hydantoin	2% aq.	1304	11 (0.84%)	11 (100%)
Hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine	1% aq.	817	26 (3.2%)	24 (92%)
Bioban CS 1135	1% pet.	816	31 (3.8%)	29 (94%)
Bioban CS 1246	1% pet.	367	12 (3.3%)	11 (92%)
N,N'-methylenebismorpholine	1% pet.	369	22 (6.0%)	20 (91%)
N,N-methylene-bis(5-methyl)oxazolidine	1% pet.	369	24 (6.5%)	22 (92%)

Table 2 Formaldehyde releaser positivity ratio in relation to the strength of the formaldehyde reaction

Formaldehyde releaser	Patch test concentration and vehicle	Formaldehyde +++ (N=22)		Formaldehyde ++ (N=52)		Formaldehyde + (N=19)		Formaldehyde +++/++/+ (N=93)	
		N	%	N	%	N	%	N	%
Quaternium 15	1% pet.	11/22	50	10/52	19	1/19	5	22/93	24
Imidazolidine urea	2% pet.	7/22	32	0/52	0	0/19	0	7/93	8
Diazolidinyl urea	2% pet.	8/22	36	5/52	10	0/19	0	13/93	14
2-Bromo-2-nitropropane-1,3-diol	0.25% pet.	0/22	0	0/52	0	0/19	0	0/93	0
Hexamethylene tetramine	2% pet.	10/22	45	7/52	13	5/19	26	22/93	24
Benzylhemiformal	1% pet.	19/22	86	40/52	77	7/19	37	66/93	71
DMDM hydantoin	2% aq.	8/19	42	2/41	5	1/17	6	11/77	14
Hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine	1% aq.	12/16	75	12/34	35	0/7	0	24/57	42
Bioban CS 1135	1% pet.	14/16	88	15/33	45	0/7	0	29/56	52
Bioban CS 1246	1% pet.	6/8	75	5/20	25	0/5	0	11/33	33
N,N'-methylenebismorpholine	1% pet.	6/8	75	14/20	70	0/5	0	20/33	61
N,N-methylene-bis(5-methyl)oxazolidine	1% pet.	6/8	75	14/20	70	2/5	40	22/33	67