

Occupational contact allergy to formaldehyde and formaldehyde releasers

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Background: Formaldehyde allergy is common and usually derives from formaldehyde-releasing biocides in cosmetic and other products.

Objectives: To analyse patterns of patch test reactions to formaldehyde and formaldehyde-releasing compounds and the sources of sensitization.

Patients/Methods: At the Finnish Institute of Occupational Health, we screened the patch test files for allergic reactions to formaldehyde and 12 formaldehyde-releasing compounds. All patients with contact allergy to any of the substances were included, and their records were reviewed.

Results: Between January 2001 and May 2007, we had patch tested 81 patients with formaldehyde allergy and 18 with independent allergy to some formaldehyde releaser. Of the formaldehyde allergies, 60 were new sensitizations, 25 of which were considered to be occupational. The most common source of occupational sensitization was metalworking fluids followed by creams and related products. Exposure to formaldehyde-releasing preservatives in liquid soaps and other rinse-off products was common in both occupational and non-occupational cases. Reactions to formaldehyde-releasing compounds were seen in 79% of the formaldehyde-allergic patients.

Conclusions: Occupational formaldehyde allergy was common and occurred in metalworkers, hairdressers, masseurs, and workers using protective creams, detergents, and liquid soaps. When compared with studies on general dermatological patients, contact allergy to formaldehyde releasers without formaldehyde allergy was rare.

Key words: 2-bromo-2-nitropropane-1,3-diol; benzyl hemiformal; Bioban; hexahydro-1,3,5-Tris-(hydroxyethyl)triazine; *N,N'*-methylenebismorpholine; *N,N*-methylene-bis(5-methyl)oxazolidine.
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Formaldehyde is a ubiquitous and potent contact sensitizer. The chemical is used as such for example in pathology and in a large variety of chemical processes, including the manufacture of plastics. Formaldehyde-releasing preservatives are widely used in water-containing products, such as metalworking fluids, shampoos, and other cosmetic products, and detergents (1).

Occupational sensitization is common in machinists who handle metalworking fluids; other concerned occupations include health care workers, cleaners, cosmetologists, painters, photographers, technicians, and maintenance and housekeeping personnel (2–4). Patients with allergic patch test reactions to formaldehyde often have con-

comitant reactions to formaldehyde-releasing agents and to formaldehyde resins used as textile finishes (1).

The study aimed to analyse patients with allergic patch reactions to formaldehyde or formaldehyde-releasing agents, the patterns or concomitant reactions, and exposure data at the Clinic of Occupational Dermatology, the Finnish Institute of Occupational Health (FIOH). The present work deals with the occurrence of the patch test reactions to formaldehyde-releasing agents among formaldehyde-allergic patients, independent contact allergies to the releasers, and occupations and sources of sensitization to formaldehyde and its releasers.

Patients and Methods

At FIOH, we reviewed patch test files from 2001 to May 2007 for allergic reactions to formaldehyde (1% in aqua; Trolab, Reinbeck, Germany) and 12 formaldehyde-releasing compounds in the baseline (standard) series, the antimicrobial series, and the series of oils and cutting fluids (Table 1). The patch tests were performed using the Finn Chambers[®] (Epitest, Tuusula, Finland) according to the recommendations of the International Contact Dermatitis Research Group. We read the tests two or three times [on D2, (D3), and D4/5/6] depending on the day of application. All our patients have a suspicion of occupational skin disease, and many have been patch tested elsewhere prior to our investigations. The patients come from all parts of Finland.

With a short concentration dilution series of formaldehyde (1%, 0.32%, 0.1% in aqua; 2001–2003 also 2%), we try to differentiate between irritant and allergic reactions. The dilution series is used a lot, for instance, when a previous patch test has shown some reactivity to formaldehyde or related compounds.

In the present study, we included all patients with allergic reaction (+/++/+++) to formaldehyde or at least one of the 12 formaldehyde-releasing agents. The patients who had not been tested with formaldehyde in the baseline series because of previously known formaldehyde allergy were also included. We analysed their clinical records for symptoms, occupation, exposure [labelling of the products/safety data sheets/the results of the chemical analyses of the products], patch test reactions to formaldehyde and formaldehyde-releasing compounds, and diagnosis.

During the study period (January 2001 to May 2007), a total of 1166 patients were tested with the baseline series. In all, 71 (6.1%) had an allergic (+/++/+++) reaction to 1% formaldehyde. Nine patients were not tested at FIOH because of previously known occupational formaldehyde allergy (they had been tested at local hospitals, not at FIOH). One patient had an allergic reaction to 2% formaldehyde in the dilution series. In all, 81 cases of formaldehyde allergy were identified, constituting 6.9% of all patients patch tested during the study period.

In 21 cases, the formaldehyde allergy had been diagnosed many years earlier, long before the symptoms that led to the investigations at FIOH (the old cases). In 60 cases, the allergy was detected at FIOH or at local hospitals some months prior to our investigations (the new cases).

A diagnosis of occupational contact allergy at FIOH first requires demonstration of sufficient occupational skin exposure capable of inducing contact allergy. Next, the location and timing of the symptoms must be consistent with the occupational skin exposure. We must be able to conclude that the sensitization has probably occurred at work and not at leisure time. Although the initial cause of the allergy is considered to be non-occupational, the patient may still be eligible for compensation if occupational exposure to the allergen has led to exacerbation of the dermatitis. Assessment of formaldehyde exposure usually involves inquiries made to manufacturers and sales representatives by a chemist; chemical analyses are also used. In the present material, the patients' products were analysed for formaldehyde

Table 1. Formaldehyde-releasing patch test substances, their concentrations, vehicles, suppliers, and patch test results in a group of 81 formaldehyde-allergic patients^a

Test substance	Concentration, vehicle and supplier	Number of formaldehyde-allergic patients tested	Number of allergic reactions among the formaldehyde-allergic patients tested, <i>n</i> (%)
Quaternium 15	1 % pet., T	73	15 (21)
Imidazolidinyl urea	2 % pet., T	74	4 (5)
Diazolidinyl urea	2% pet., C	76	8 (11)
2-Bromo-2-nitropropane-1,3-diol	0.25% pet., C	79	3 (4)
Hexamethylenetetramine	2% pet., C	78	9 (12)
Benzyl hemiformal	1% pet., T	78	53 (68)
Bioban CS 1135	1% pet., C	78	41 (53)
Bioban CS 1246	1% pet., C	24	5 (21)
Bioban P 1487	0.5% pet., C	24	1 (4)
Hexahydro-1,3,5-Tris-(hydroxyethyl)triazine	1% aq., C	77	24 (31)
<i>N,N'</i> -methylenebismorpholine	1% pet., O	8	5 (63)
<i>N,N</i> -methylene-bis(5-methyl)oxazolidine	1% pet., O	7	6 (86)

Bioban CS 1135, mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethyloxazolidine; Bioban CS 1246, 7-ethylbicyclooxazolidine; Bioban P 1487, mixture of 4-(2-nitrobutyl)morpholine and 4,49-(2-ethyl-nitrotrimethylene)dimorpholine; T, Trolab; C, Chemotechnique; O, in-house preparation; pet., petrolatum; aq., aqua.

^aThe first two substances were tested in the baseline series, the next five in the antimicrobial series, and the last five in the series of oils and cutting fluids.

in 23 cases (28%). The formaldehyde content of the products was determined by extracting the product with water, allowing the water-soluble formaldehyde compounds to react with dinitrophenylhydrazine (DNPH), and finally analysing the DNPH-formaldehyde derivative with liquid chromatography and ultraviolet detector. Free formaldehyde was detected from the products (or their water extracts) by allowing the evaporable formaldehyde to react with DNPH in the gas phase (5).

Results

Occupational allergic contact dermatitis was diagnosed in 25 of 60 patients with a new formaldehyde allergy. Exposure data and patch test reactions to formaldehyde-releasing compounds of these 25 occupational cases are presented in Table 2.

In 35 patients, the new formaldehyde allergy was considered non-occupational. Three of them were possibly sensitized from diazolidinyl urea- or dimethylol-dimethyl (DMDM) hydantoin-containing *Aloe vera* gels. In eight cases, shampoos or liquid soaps were labelled with DMDM hydantoin, diazolidinyl urea, or 2-bromo-2-nitropropane-1,3-diol. One of the non-occupational cases had used several cosmetic creams that contained 2-bromo-2-nitropropane-1,3-diol or diazolidinyl urea.

Nine of the 21 patients with old formaldehyde allergy had previously received compensation for occupational formaldehyde dermatitis. In such cases, we usually refrained from testing with formaldehyde, and only assessed present exposure.

Of the old cases, 12 were non-occupational but 5 had experienced exacerbation of dermatitis because of occupational exposure to formaldehyde. Details of the five patients with occupational exacerbation are presented in Table 3.

Allergic reaction to at least 1 of the 12 formaldehyde-releasing test substances were detected in 64 (79%) of the 81 formaldehyde-allergic patients. The numbers of allergic test reactions to each formaldehyde-releasing compound among the 81 formaldehyde-allergic patients are presented in Table 1. The patients reacting to lower concentrations of formaldehyde in the dilution series tended to have allergic reaction to a larger number of releasers: 29 patients negative to 0.1% formaldehyde had a median of one positive releaser in the standard and antimicrobial series, whereas in the group of 5 patients reacting to 0.1% formaldehyde with a strong reaction (++), the median of positive releasers was four.

The total numbers of allergic reactions to different formaldehyde releasers and concurrent

reactions to formaldehyde are presented in Table 4. A total of 18 patients had allergic reactions (+/++/+++) to formaldehyde releasers without clear allergic reactions to formaldehyde. Their patch test reactions and clinical data are presented in Table 5.

Urea formaldehyde [10% in petrolatum (pet.); Chemotechnique, Vellinge, Sweden] and melamine formaldehyde (7% pet.; Chemotechnique) were tested in 29 of the formaldehyde-allergic patients and found positive in 8 (28%) and 10 (34%) patients, respectively. One of the non-occupational cases had allergic reactions to *p*-tertiary butylphenol formaldehyde resin (1% in pet.; Trolab) and tosylamide/formaldehyde resin (10% in pet.; Trolab) and another patient reacted to Novolac phenol formaldehyde resin (5% in pet.; Trolab).

Discussion

Contact allergy to formaldehyde was common (6.9%) among our patients, all of whom had a suspicion of occupational dermatitis. The frequency was two to three times higher than in studies on general dermatological patients in Europe (6, 7). In previous studies, formaldehyde allergy has been associated with hand dermatitis (2, 8), and our series mainly consisted of such patients (93%). The large proportion of occupational cases in our series shows the importance of formaldehyde as an occupational allergen.

The recommended patch test concentration for formaldehyde has been reduced from 4–5% to 2% and is now 1% (in aqua) (9). The concentration has been changed to reduce irritancy and false-positive reactions. Irritant reactions still occur with 1% and 2% concentrations (9). In our material, there is the possibility of both false-positive and false-negative reactions: patient reacting to only formaldehyde and not to any releaser might represent false-positive cases, and patients reacting to releasers without clear formaldehyde allergy (Table 5) might be sensitized to formaldehyde. Especially the reactions of patient 13 in Table 5 are best explained by true formaldehyde allergy [formaldehyde 1% and 0.32% ?+, *N,N'*-methylenebismorpholine +, *N,N*-methylene-bis(5-methyl) oxazolidine +, and melamine formaldehyde resin +] (10).

Reactions to formaldehyde releasers among formaldehyde-allergic patients

In the present series, the great majority (79%) of the formaldehyde-allergic patients reacted to at least one formaldehyde-releasing substance.

Table 2. New cases of occupational formaldehyde contact dermatitis: occupation, patch test reactions to 12 formaldehyde-releasing compounds, and data on exposure to formaldehyde/formaldehyde-releasing compounds

Patch test reactions													Exposure to f. at work, data from SDSs, product declarations and chemical analyses	
Patient number	Occupation	Imidazolidinyl urea	Quaternium-15	Hexamethyl- enetetramine	Hexamethyl- Diazolidinyl urea	Bromonitro- propanediol	Benzyl hemiformal	Bioban CS 1135	Hexahydro- Tri- s- hydroxyethyltriazine	Bioban CS 1246	Bioban P 1487	<i>N,N'</i> -methylene bis-morpholine		<i>N,N</i> -methylene- bis(5-methyl) oxazolidine
1	Machinist	?+	++	++	++	++	++	++	++	++	–	NT	NT	Cutting fluid: <i>N,N</i> -methylene- bis-(5-methyl)oxazolidine <3% ^a ; cutting fluid disinfectant: hexahydro- triazine compound 70% ^a
2	CNC machinist	–	–	–	–	–	+	–	–	–	–	NT	NT	Cutting fluid: triazine derivative 1–5% ^a ; cutting fluid disinfectant: triazine derivative 5–15% CAS 4719-04-4 ^a ; the present compositions of the two products: <i>N</i> -formal ^b , SDSs had old information
3	Machinist	–	+	–	–	–	+	+	–	–	–	NT	NT	Cutting fluid: methylene-bis-oxazine 1–5% CAS 5625-90-1 ^a , f. 0.58% ^c
4	Machinist student	++	++	?	++	–	++	++	++	++	++	++	NT	Cutting fluid: <i>N</i> -formal 1-5% CAS 34375-28-5 ^a
5	Machinist	–	–	–	–	–	–	+	–	–	–	+	+	Cutting fluid: methylene- bis-oxazine 1-5% CAS 5625-90-1 ^a
6	Machinist	–	–	–	–	–	+	+	–	–	–	NT	NT	Cutting fluid A: <i>N,N</i> -methylene- bis-methyl-oxazolidine 2.7% ^c , t.f. 1.3% ^c , (oxazolidine 2.4% ^a); cutting fluid B: <i>N,N</i> -methylene- bismethyl-oxazolidine 1.5% ^c and t.f. 0.71% ^c (oxazolidine 2.4% ^{a,b})
7	Plate maker	?+	+	–	–	–	+	–	?	–	–	–	–	Cutting fluid: 0.272% f. ^c , no mention in SDS, hand- washing agent: 239 p.p.m. f. ^c
8	AAR driller	+	–	–	–	–	–	–	–	+	–	–	++	Cutting fluid: <i>N</i> -formal 1–5% ^a CAS 34375-28-5; cutting fluid disinfectant: <i>N,N'</i> -methylenebis- (5-methyl)oxazolidine ^b CAS 66204-44-2; earlier <i>N</i> -formal 5–15% ^{a,b}
9	Assembler	–	–	–	–	–	++	++	–	?	–	+	+	Cutting fluid: <i>N,N'</i> -methylene- bis-(5-methyl) oxazolidine < 3% ^a
10	Driller	–	–	–	–	–	–	–	+	–	–	NT	NT	Cutting fluid A: hexahydrotria- zine derivative CAS 4719-04-4 1.6% ^a ; 0.54% f. ^c ; cutting fluid B: 0.11% f. ^c ; cutting fluid C: 0.77% f. ^c

(Continued)

Table 2. Continued

Patient number	Occupation	Patch test reactions										Exposure to f. at work, data from SDSs, product declarations and chemical analyses	
		Imidazolidinyl urea	Quaternium-15	Hexamethyl-ene-tetramine	Diazolidinyl urea	Bromonitropropanediol	Benzyl hemiformal	Bioban CS 1135	Hexahydro-Tris-hydroxyethyltriazine	Bioban CS 1246	<i>N,N'</i> -methylene bis-morpholine	<i>N,N</i> -methylene bis(5-methyl)oxazolidine	
11	Masseur	–	–	–	–	–	?+	–	–	NT	NT	NT	Massage cream: diazolidinyl urea ^a , t.f. 540 p.p.m. ^c , free f. 100 p.p.m. ^c
12	Masseur	+	+	++	–	–	+	+	–	NT	NT	NT	Massage oil and cold cream: diazolidinyl urea ^d
13	Hairdresser	–	–	–	–	–	+	–	–	NT	NT	NT	Quaternium-15, DMDM hydantoin, and diazolidinyl urea in many products ^d
14	Hairdresser	–	–	?+	–	–	–	?+	–	NT	NT	NT	DMDM hydantoin and diazolidinyl urea in many products ^d
15	Hairdresser	–	?+	–	–	–	+	+	–	NT	NT	NT	Shampoo: DMDM hydantoin ^d
16	Assistant nurse	–	+	–	–	–	–	–	–	NT	NT	NT	Liquid soap: Bromonitropropanediol ^d
17	Assistant nurse	–	–	–	–	–	+	?+	–	NT	NT	NT	Liquid detergent: Preventol D2 (= benzyl hemiformal) ^b
18	Waiter	–	–	–	–	–	–	–	–	NT	NT	NT	Dishwashing liquid: 31 p.p.m. f. ^c ; liquid soap: 14 p.p.m. f. ^c
19	Plastic worker	–	–	–	–	+	+	+	–	NT	NT	NT	Hand-washing agent: dimethylloxazolidine ^a ; liquid soap: bromonitropropanediol ^b
20	Home aid	–	–	–	+	–	–	–	–	NT	NT	NT	Shampoo: DMDM hydantoin ^d ; conditioner liquid: bromonitropropanediol ^d
21	Sweet worker	NT	NT	–	–	–	+++	+	–	NT	NT	NT	Dishwashing liquid: Preventol D2 (= benzyl hemiformal) ^b
22	Painter/carpenter	–	+	+	+	–	++	+	+	NT	NT	NT	Liquid soap: 2-bromo-2-nitropropane-1,3-diol ^a ; sawing of chipboard
23	Fibreglass worker	NT	NT	–	–	–	++	–	–	NT	NT	NT	Protective cream: a formaldehyde releaser (not specified)
24	Gardener	–	++	+	+	–	+++	–	–	NT	NT	NT	Pesticide: polymerization product of f. that contains free f. ^b
25	Maintenance man	–	?+	+	–	–	–	?+	–	–	++	++	Protective cream: Quaternium-15 ^b

Bioban CS 1135, mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethylloxazolidine; Bioban CS 1246, 7-ethylbicyclooxazolidine; Bioban P 1487, mixture of 4-(2-nitrobutyl)morpholine and 4,49-(2-ethyl-nitrotrimethylene)dimorpholine; f., formaldehyde; NT, not tested; SDSs, safety data sheets; t.f., total formaldehyde; [CAS 5625-90-1 = *N,N*-methylenebismorpholine; CAS 4719-04-4 = Hexahydro-1,3,5-Tris(hydroxyethyltriazine)].

^aMentioned in the safety data sheet of subject's own products.

^bInformation from the manufacturer or sales representative.

^cDetected in the chemical analysis of subject's own products.

^dMentioned in the labelling of the product.

Table 3. Patients with exacerbations of previously diagnosed non-occupational allergic formaldehyde dermatitis because of occupational exposure

Patient number	Occupation	Location of dermatitis	Exposure to formaldehyde at work
1	Farmer	Forearms	Shower soap, liquid soap, and hand cream: DMDM hydantoin
2	Assistant nurse	Hands	Liquid soap: bromonitropropanediol
3	Machinist	Hands	Cutting fluid: total formaldehyde 50 p.p.m., free formaldehyde 5 p.p.m.; SDS: 1,2-ethanedithiolbis (oxy)oxybismethanol < 5% (weak formaldehyde releaser)
4	Production worker	Hands (earlier axillae and eyelids)	Hand cream: imidazolidinyl urea; two liquid soaps: 2-bromo-2-nitropropane-1,3-diol
5	Hairdresser	Hands and eyelids	Styling products: DMDM hydantoin; shampoos: imidazolidinyl urea

SDSs, safety data sheets.

The proportion of releaser-positive cases depends on the releasers that are tested. In earlier studies, about half of formaldehyde-allergic patients have had concomitant reactions to releasers, when quaternium-15, imidazolidinyl urea, diazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol have been tested (7, 8), but the proportion of releaser-positive cases has increased to 92% when Biobans CS 1135 (mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethyloxazolidine), CS 1246 (7-ethylbicyclooxazolidine), and P 1487 [mixture of 4-(2-nitrobutyl)morpholine and 4,49-(2-ethyl-nitrotrimethylene)dimorpholine] were also tested (2). The high number of formaldehyde-allergic patients reacting to releasers in the present series is largely explained by the three Biobans.

Benzyl hemiformal

Reactions to benzyl hemiformal were also strongly associated with formaldehyde allergy (93%; Table 4), and conversely, benzyl hemiformal was the most commonly positive releaser among our formaldehyde-allergic patients. In this respect, our results are in accordance with an earlier study from Denmark, where 76% of benzyl hemiformal-positive cases also had formaldehyde allergy (11).

Exposure to benzyl hemiformal was not found in any of the Danish patients, but our series included two patients with solitary reactions to benzyl hemiformal, both of whom had used a moisturizer containing the chemical at work (patients 3 and 4 in Table 5). In addition, patient 21 (Table 2) had a +++ reaction to benzyl hemiformal and had used a dishwashing liquid that contained the same chemical. Specific sensitization to benzyl hemiformal was possible in these three cases. We have not found descriptions of similar patients in the literature.

Biobans CS 1135, CS 1246, and P 1487

Positive reactions to Biobans CS 1135 and CS 1246 were also often concurrent with formaldehyde allergy (95% and 100% respectively; Table 4). We did not find any specific exposure to the three Biobans (CS 1135, CS 1246, and P 1487) in patients with allergic reactions to them. Contact allergy to the Biobans in metalworkers has been studied in Germany (12–14): positive reactions to Bioban CS 1135 were common in these studies, too, but in contrast to our results, many of the reactions were seen in formaldehyde-negative patients (13). Similarly to one of the German studies (14), the majority

Table 4. Allergic reactions to various formaldehyde-releasing agents and concomitant reactions to formaldehyde

	Total number of allergic reactions	Concomitant allergic reactions to formaldehyde, <i>n</i> (%)
Quaternium 15	18	15 (83)
Imidazolidinyl urea	6	4 (67)
Diazolidinyl urea	9	8 (89)
2-Bromo-2-nitropropane-1,3-diol	5	3 (60)
Hexamethylenetetramine	15	9 (60)
Benzyl hemiformal	57	53 (93)
Bioban CS 1135	43	41 (95)
Bioban CS 1246	5	5 (100)
Bioban P 1487	2	1 (50)
Hexahydro-1,3,5-Tris-(hydroxyethyl)triazine	24	24 (100)
<i>N,N'</i> -methylenebismorpholine	6	5 (83)
<i>N,N</i> -methylene-bis(5-methyl)oxazolidine	7	6 (86)

Bioban CS 1135, mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethyloxazolidine; Bioban CS 1246, 7-ethylbicyclooxazolidine; Bioban P 1487, mixture of 4-(2-nitrobutyl)morpholine and 4,49-(2-ethyl-nitrotrimethylene)dimorpholine.

Table 5. New cases of contact allergy to formaldehyde-releasing compounds without clear formaldehyde allergy: occupation, patch test results to formaldehyde and formaldehyde-releasing compounds, and data on occupational exposure to formaldehyde-releasing compounds^a

Patch test reactions													
Patient number	Occupation	Formaldehyde 1%	Imidazolidinyl urea	Quaternium-15	Hexamethylene-tetramine	Diazolidinyl urea	Bromonitropropanediol	Benzylhemiformal	Bioban CS 1135	Bioban P 1487	N,N'-methylene bis-morpholine	N,N'-methylene-bis(5-methyl)oxazolidine	Exposure to formaldehyde-releasing compounds at work
1	Physiotherapist	–	–	–	–	–	+	–	–	NT	NT	NT	Massage liniment: 2-Bromo-2-nitropropane-1,3-diol ^b
2	Masseuse	–	–	–	–	–	++	–	–	NT	NT	NT	Massage emulsion: 2-Bromo-2-nitropropane-1,3-diol ^c
3	Cook	–	–	–	–	–	–	+	–	NT	NT	NT	Moisturizing cream: Preventol D2 (= benzyl hemiformal) ^c
4	Dental nurse	–	–	–	–	–	–	++	–	NT	NT	NT	Moisturizing cream: Preventol D2 (= benzyl hemiformal) ^c
5	Psychiatric nurse	– (2% ?+)	–	–	–	–	–	++	?+	NT	NT	NT	
6	Dental nurse	?+	–	–	–	–	–	+	–	NT	NT	NT	
7	Car mechanic	–	?+	–	–	–	–	IR	–	–	NT	NT	
8	Biochemist	–	–	?+	++	–	–	–	–	NT	NT	NT	
9	Cook	?+	–	++	++	–	–	–	–	NT	NT	NT	
10	Cosmetician	–	–	++	++	–	–	–	–	NT	NT	NT	
11	CNC machinist	–	–	–	++	–	–	–	–	NT	NT	NT	
12	Veterinarian	?+	–	–	++	?+	–	?+	?+	NT	NT	NT	
13	Carpenter	?+	–	–	++	–	–	–	?+	–	+	+	
14	Assembler	–	+	–	–	–	–	–	–	NT	NT	NT	
15	Assembler	–	+	–	–	++	–	–	–	–	NT	NT	
16	Cleaner	–	–	–	–	++	–	–	–	–	NT	NT	
17	Farm worker	–	–	–	–	–	–	–	+	NT	NT	NT	
18	Assembler	–	–	–	–	–	–	–	–	+	NT	NT	

Bioban CS 1135, mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethyloxazolidine; Bioban CS 1246, 7-ethylbicyclooxazolidine; Bioban P 1487, mixture of 4-(2-nitrobutyl)morpholine and 4,49-(2-ethyl-nitrotrimethylene)dimorpholine; IR, irritant reaction; NT, not tested.

^aPatients 1–4 were occupational cases.

^bLabelling of the product.

^cInformation from the manufacturer.

(60%) of Bioban CS 1135 reactions in the present study were weak. Thus, our reactions to the three Biobans were mainly in connection with formaldehyde allergy and without any specific relevance beyond formaldehyde allergy.

Quaternium-15, imidazolidinyl urea, diazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol

Regarding quaternium 15, imidazolidinyl urea, diazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol, most of our reactions were in connection with formaldehyde allergy, and the share of formaldehyde-negative patients for each substance (Table 4) was much lower than in many other studies on the subject (2, 8, 15). Our patients suffered mainly from hand dermatitis, and contact allergies to the four preservatives have been associated with facial dermatitis (8). Thus, the differences probably derive from dissimilar exposure.

Formaldehyde-releasing biocides in metalworking fluids

Metalworkers were the most widely represented occupation constituting 40% of the new occupational sensitizations to formaldehyde. Moreover, there were several hairdressers and health care workers, and two masseurs, but the rest of the patients represented diverse occupational fields.

Formaldehyde in metalworking fluids usually derives from formaldehyde-releasing biocides. The metalworkers in the present series were exposed to metalworking fluids that most often contained *N,N'*-methylenebismorpholine, *N,N*-methylene-bis(5-methyl)oxazolidine, hexahydro-1,3,5-Tris-(hydroxyethyl)triazine, and *N*-formal (the CAS numbers are in Table 6). *N,N'*-methylenebismorpholine has been studied in a metalworking fluid

series in Germany, and it was positive in 4.9% of the patients, but the presence of the biocide could not be confirmed in any of the patients (12). In our series, however, there was one (patient 5 in Table 2) formaldehyde-allergic metalworker who reacted to *N,N'*-methylenebismorpholine and was exposed to a metalworking fluid that contained the same chemical. *N,N*-methylene-bis(5-methyl)oxazolidine has also been studied in UK: it was positive in 4.7% of the patch-tested patients, and exposure to the chemical could be established in 47% of the cases (16). We have tested *N,N'*-methylenebismorpholine and *N,N*-methylene-bis(5-methyl)oxazolidine since 2003, and allergic reactions to these chemicals often occur simultaneously, but usually concurrently with formaldehyde allergy. Two patients reacted to *N,N*-methylene-bis(5-methyl)oxazolidine and were exposed to it (patients 8 and 9 in Table 2), and similarly two metalworkers reacted and were exposed to hexahydro-1,3,5-Tris-(hydroxyethyl)triazine (patients 1 and 10 in Table 2). Based on the present and the related studies, specific sensitization to *N,N'*-methylenebismorpholine, *N,N*-methylene-bis(5-methyl)oxazolidine, and hexahydro-1,3,5-Tris-(hydroxyethyl)triazine is possible, but all the present patients were also allergic to formaldehyde.

Creams and related products

Various creams and related products were an important source of sensitization in the present series: in addition to the above mentioned, two occupational sensitizations to benzyl hemiformal from a moisturizing cream, formaldehyde releasers in protective creams caused two sensitizations (patients 23 and 25 in Table 2), and formaldehyde releasers in massage products four. Two masseurs were sensitized to 2-bromo-2-nitropropane-1,

Table 6. CAS numbers of formaldehyde and releasers

Test substance; chemical composition [synonym]	CAS number
Formaldehyde	50-00-0
Quaternium 15	4080-31-1
Imidazolidinyl urea [Germall 115]	39236-46-9
Diazolidinyl urea [Germall II]	78491-02-8
2-Bromo-2-nitropropane-1,3-diol [Bronopol]	52-51-7
Hexamethylenetetramine [Methenamine]	100-97-0
Benzyl hemiformal [Preventol D2]	14548-60-8
Bioban CS 1135; mixture of 3,4,4-trimethyl-oxazolidine and 4,4-dimethyloxazolidine	81099-36-7
Bioban CS 1246; 7-ethylbicyclooxazolidine	7747-35-5
Bioban P 1487; mixture of 4-(2-nitrobutyl)morpholine and 4,4'-(2-ethyl-nitrotrimethylene)dimorpholine	37304-88-4; mixture of 2224-44-4 and 1854-23-5
Hexahydro-1,3,5-Tris-(hydroxyethyl)triazine [Grotan BK]	4719-04-4
<i>N,N'</i> -methylenebismorpholine [methylene-bis-oxazine]	5625-90-1
<i>N,N</i> -methylene-bis(5-methyl)oxazolidine [Grotan OX]	66204-44-2
<i>N</i> -formal [2-hydroxy-methylaminoethanol]	34375-28-5

3-diol (patients 1 and 2 in Table 5) and two to formaldehyde liberated by diazolidinyl urea (patients 11 and 12 in Table 2).

Liquid soaps and other detergents

After metalworking fluids and creams and related products, various rinse-off products, liquid soaps, hand-washing agents, shampoos, dishwashing liquids, and other detergents formed the next largest source of occupational formaldehyde allergy (patients 15–21 in Table 2). Exposure to liquid soaps and shampoos containing formaldehyde releasers was also common in the group of non-occupational cases. It should also be considered that the sensitization to formaldehyde may not have been the primary event, but that the patient may first have had irritant contact dermatitis or other hand dermatitis, and sensitization to preservatives in rinse-off products has followed only after the skin barrier has been broken. Hand dermatitis is common in the general population (17), and formaldehyde releasers in rinse-off cosmetic products might be a substantial risk for this subgroup. Protective creams, moisturizers, hand creams, detergents, and hand-washing agents are used in a great variety of occupations. Together, these products form an important source of formaldehyde allergy that must be considered in every patient investigated for occupational contact dermatitis.

Formaldehyde-allergic patients often have difficulty avoiding products containing formaldehyde releasers as preservatives (18, 19). Eight of our 21 patients with a previously known formaldehyde allergy were using shampoos, liquid soaps, or creams containing formaldehyde releasers, all products that have suitable alternatives. The large number of patients with a previously known formaldehyde allergy requesting a new evaluation probably also reflected the difficulties in avoiding formaldehyde and formaldehyde releasers.

Formaldehyde and textiles

We analysed the textiles of protective clothing in four cases and other textiles in one case: in three cases, the analysis of was negative (<10 p.p.m.), one sample of protective clothing contained 18 p.p.m. formaldehyde, and the formaldehyde content of a sample of mattress textiles was 19–21 p.p.m. These concentrations were probably too low to cause sensitization to formaldehyde or elicitation in previously sensitized patients. (20) The latter case has been described in detail elsewhere (21). Our experience is in accordance with the conception that formaldehyde allergy from textiles is rare today because the manufacturers have

improved their method of fabric finish treatment and reduced the amount of formaldehyde residues in new clothing (1).

Reactions to amino plastics – urea formaldehyde and melamine formaldehyde resins – were common among our formaldehyde-allergic patients, but they probably also represented cross-allergy to formaldehyde because in these cases textile finishes were not the cause of dermatitis and the subjects were not exposed to amino plastics elsewhere. In the present series, there were no cases of formaldehyde allergy from occupational exposure to phenol formaldehyde resins, which is in line with earlier findings that formaldehyde is not a main sensitizer in these resins (22).

Conclusions

Formaldehyde allergy was common among patients investigated for occupational contact dermatitis. About half of the cases had occupational relevance. The most common source of occupational sensitization was metalworking fluids, and creams and related products formed the next largest group. Exposure to formaldehyde-releasing preservatives in liquid soaps, shampoos, and other rinse-off products was common in both occupational and non-occupational cases. People with hand dermatitis, about 10% of the general population, might risk sensitization to formaldehyde through their use of these cosmetic products. Reactions to formaldehyde-releasing substances were seen in about 80% of the formaldehyde-allergic patients, and independent reactions to the releasers were rare. We assume that allergic reactions to various formaldehyde-releasing compounds usually represent sensitization to formaldehyde and take them as factors supporting the allergic nature of the concurrent formaldehyde reaction. There were, however, some cases where specific sensitizations to formaldehyde releasers seemed to have a role. Our series included three cases of possible specific sensitization to benzyl hemiformal, which, to our knowledge, has not previously been described.

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