Formaldehyde 2% is not a useful means of detecting allergy to formaldehyde releasers— results of the ESSCA network, 2015-2018

Heather Whitehouse[1] | Wolfgang Uter[2] | Johannes Geier[3] | Barbara Ballmer-Weber[4,5] | Andrea Bauer[6] | Susan Cooper[7] | Magdalena Czarnecka-Operacz[8] | Simon Dagmar[9] | Heinrich Dickel[10] | Anna Belloni Fortina[11] | Rosella Gallo[12] | Ana M. Giménez-Arnau[13] | Graham A. Johnston[14] | Francesca Laresse Filon[15] | Vera Mahler[16,17] | Maria Pesonen[18] | Thomas Rustemeyer[19] | Marie L. A. Schuttelaar[20] | Skaidra Valiukevičienė[21] | Elke Weisshaar[22] | Thomas Werfel[23] | Mark Wilkinson[1]

[1]Department of Dermatology, Chapel Allerton Hospital, Leeds, UK

[2]Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany

[3]Information Network of Departments of Dermatology (IVDK), Institute at the University Medical Center Göttingen, Göttingen, Germany

[4]Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[5]Allergy Unit, Department of Dermatology, University Hospital Zürich, Zürich, Switzerland

[6]Department of Dermatology, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany

[7]Dermatology Department, Oxford University Hospitals NHS Trust, Oxford, UK

[8]Dermatology Department, University of Medical Sciences, Poznań, Poland

[9]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[10]Department of Dermatology, Venereology and Allergology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany

[11]Pediatric Dermatology Unit, Department of Medicine DIMED, University of Padova, Padova, Italy

[12]Clinica Dermatologica, Department of Health Sciences, University of Genoa, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[13]Department of Dermatology, Hospital del Mar, Universitat Autónoma, Barcelona, Spain

[14]Department of Dermatology, Leicester Royal Infirmary, Leicester, UK

[15]Unit of Occupational Medicine, Department of Medical Sciences, University of Trieste, Trieste, Italy

[16]Department of Dermatology, University Hospital Erlangen, Medical Faculty Friedrich-Alexander University, Erlangen-Nuremberg, Germany

[17]Paul-Ehrlich-Institut, Langen, Germany

[18]Finnish Institute of Occupational Health, Helsinki, Finland

[19]Department of Dermatology, Free University of Amsterdam, Amsterdam, The Netherlands

[20]Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[21]Department of Skin and Venereal Diseases, Lithuanian University of Health Sciences, Kaunas, Lithuania

[22]Department of Dermatology, Occupational Dermatology, University Hospital Heidelberg, Heidelberg, Germany

[23]Department of Immunodermatology and Experimental Allergy, Medizinische Hochschule Hannover, Hannover, Germany

Correspondence
Dr Heather Whitehouse, Department of Dermatology, Chapel Allerton Hospital, Leeds,

Abstract

Background: Studies suggest that patch testing with formaldehyde releasers (FRs) gives significant additional information to formaldehyde 1% aq. and should be

UK.
Email: heatherwhitehouse@doctors.org.uk

considered for addition to the European baseline series (EBS). It is not known if this is also true for formaldehyde 2% aq.

Objectives: To determine the frequency of sensitization to formaldehyde 2% aq. and co-reactivity with FRs. To establish whether there is justification for including FRs in the EBS.

Materials and Methods: A 4-year, multi-center retrospective analysis of patients with positive patch test reactions to formaldehyde 2% aq. and five FRs.

Results: A maximum of 15 067 patients were tested to formaldehyde 2% aq. and at least one FR. The percentage of isolated reactions to FR, without co-reactivity to, formaldehyde 2% aq. for each FR were: 46.8% for quarternium-15 1% pet.; 67.4% imidazolidinyl urea 2% pet.; 64% diazolidinyl urea 2% pet.; 83.3% 1,3-dimethylol-5, 5-dimethyl hydantoin (DMDM) hydantoin 2% pet. and 96.3% 2-bromo-2-nitropropane-1,3-diol 0.5% pet. This demonstrates that co-reactivity varies between FRs and formaldehyde, from being virtually non-existent in 2-bromo-2-nitropropane-1,3-diol 0.5% pet. (Cohen's kappa: 0, 95% confidence interval [CI] −0.02 to 0.02)], to only weak concordance for quaternium-15 [Cohen's kappa: 0.22, 95%CI 0.16 to 0.28)], where Cohen's kappa value of 1 would indicate full concordance.

Conclusions: Formaldehyde 2% aq. is an inadequate screen for contact allergy to the formaldehyde releasers, which should be considered for inclusion in any series dependant on the frequency of reactions to and relevance of each individual allergen.

KEYWORDS

2-bromo-2-nitropropane-1,3-diol, contact allergy, cosmetics, formaldehyde formaldehyde releasers, diazolidinyl urea, DMDM hydantoin, imidazolidinyl urea, quaternium-15

1 | INTRODUCTION

The European baseline series (EBS) of haptens (contact allergens) is the cornerstone of patch testing, used throughout Europe as a diagnostic screening tool in cases of suspected contact dermatitis. The EBS is periodically updated to capture shifts in exposures to environmental haptens, and incorporate newly detected haptens, ensuring that the EBS stays contemporaneous. The incidence of sensitization to formaldehyde in Europe is between 1% and 3% of all patients undergoing patch testing.[1]The current EBS 2019 includes formaldehyde 2% aq. and the formaldehyde releaser (FR) quaternium-15 1% pet.

Current opinion is unclear about whether testing with additional FRs; 2-bromo-2-nitropropane-1,3-diol 0.5% pet., diazolidinyl urea 2% pet., imidazolidinyl urea 2% pet. and DMDM hydantoin 2% pet., provide additional relevant reactions to warrant inclusion in the EBS. Multiple studies have compared formaldehyde 1% aq. with the formaldehyde releasers, with the following notable findings:

For 2-bromo-2-nitropropane-1,3-diol 0.5% pet, one study found that less than 25% (range 2%-25%, median 17%) of patients who are sensitive to 2-bromo-2-nitropropane-1,3-diol 0.5% pet. co-react to formaldehyde 1% aq.,[2] suggesting that sensitivity to this is distinct to sensitivity to formaldehyde. Another study found that 50% of patients who are sensitive to 2-bromo-2-nitropropane-1,3-diol 0.5% pet co-reacting to formaldehyde 1% aq., suggestive of a stronger correlation, but with a notable small sample size.[3] When looking at the converse situation, fewer patients sensitized to formaldehyde 1% aq. co-react to 2-bromo-2-nitropropane-1,3-diol 0.5% pet., with reports ranging from 0.74% to 10% across different studies.[2,3] This suggests that formaldehyde 1% aq. is a poor marker of sensitivity to 2-bromo-2-nitropropane-1,3-diol 0.5% pet.

Diazolidinyl urea 2% pet. demonstrates a similar trend, with a higher percentage of patients sensitized to this co-reacting to formaldehyde 1% aq. than in the reverse situation.[2] Sensitized patients co-react with formaldehyde in 69%-81% (United States) and 12%-55% (Europe) of the time. Conversely, patients who are sensitized to formaldehyde co-react with diazolidinyl urea 2% pet.: between 24.5% (United States) and 4%-30% (Europe) of cases.[2] Similarly, patients who are allergic to imidazolidinyl urea 2% pet. co-react to formaldehyde 1% aq.: between 46%-63% (United States) and 11%-53% (Europe).[2] Patients reacting to formaldehyde 1% aq. co-react to imidazolidinyl urea 2% pet. less often, in 10%-17% (United States) and 4%-23% (Europe)[2] of cases.

These results suggest that patch testing with the formaldehyde releasers 2-bromo-2-nitropropane-1,3-diol 0.5% pet., diazolidinyl urea 2% pet., and imidazolidinyl urea 2% pet., gives significant additional

information in comparison to formaldehyde 1% aq. The aim of this study was to compare the diagnostic value of patch testing with FRs to formaldehyde 2% aq. that is in the current EBS.

2 | METHODS

The European Surveillance System on Contact Allergies (ESSCA; www.essca-dc.org) is a working group of the European Society of Contact Dermatitis (ESCD; www.escd.org) dedicated to the clinical surveillance of contact allergy.[4] ESSCA participants contribute results with the baseline series, along with pertinent demographic and clinical data, in accordance with the initial objective of ESSCA. Some ESSCA participants (1) extend their baseline series to temporarily include audit allergens and/or (2) collect the full scope of their patch test results, including a cosmetic series. These departments use a patch test software capable of flexibly recording (evolving versions) of various test series, such as the WinAlldat/IVDK software used by the IVDK network, the multilingual WinAlldat/ESSCA sister version of that software,[5] or, in case of the British Society of Cutaneous Allergy (BSCA), a differently structured, MS Access–based relational data management system (contribution listed in Table S1).

Data delivered in an anonymous format or partly, following national network standards, in a pseudonymised format, where the pseudonym cannot be related to actual personal data except in the contributing department itself. This difference is of importance, as only with pseudonymized data can re-consultations of patients be identified, and eliminated, to avoid duplicate counts of results. Data were collected from January 2015 to December 2018. In the present analysis, the most current consultation of a patient has been selected. Data were quality checked, providing an "internal report" for each contributing department for scrutiny and approval before pooling of the respective data.[1] Data management and analysis were performed with the R software package (www.r-project.org; RRID:SCR_001905), version 3.6. For the calculation of 95% confidence intervals (or CIs) to zero proportions, the recently suggested approximation to an exact CI was used.[6]

It is recommended to patch test formaldehyde 2% aq., and not rely on 1% aq., in order not to miss relevant contact allergy.[7] However, a number of departments still test with formaldehyde 1% aq.; their corresponding results are presented separately in a supplemental table. In addition to cross-tabulations of coupled reactivity between formaldehyde and the single releasers, the degree of "chance corrected concordance" was quantified with Cohen's kappa coefficient, supplemented with 95%CIs.

3 | RESULTS

The univariate frequency of positive, doubtful, and irritant reactions to formaldehyde 2% and 1% aq., and the formaldehyde releasers considered in this analysis are shown in Table 1. As can be seen, the context of testing the allergens in the baseline vs a special series was not related to the relative frequency of positive reactions ($P > .15$) in simple cross-tabulations. As, however, the *prior* likelihood may vary between departments, a further (logistic regression) analysis was performed with the testing department included as adjustment factor. This, too, yielded no evidence of a notable impact, except for DMDM hydantoin, where the "department adjusted" likelihood of a positive patch test was about one third if tested in the baseline series, compared to a special series (odds ratio [OR] 0.31, 95%CI 0.11-0.87). Therefore, the analysis of cross-reactivity with formaldehyde (both concentrations) was stratified for test context for DMDM hydantoin.

The degree of cross-reactivity varies substantially between the FRs, from virtually nonexistent in case of 2-bromo-2-nitropropane-1,-3-diol 0.5% pet. to a weak concordance observed for diazolidinyl urea and quaternium-15 (Table 2). The corresponding results for formaldehyde 1% aq. are shown in Table S2, showing very similar, almost identical results regarding concordance. Table 3 shows concomitant reactivity between imidazolidinyl (IU) and diazolidinyl urea (DU), both 2% pet. both with and without the presence of formaldehyde allergy.

4 | DISCUSSION

As a rule, products that contain water require preservation. Formaldehyde and FRs are ubiquitous preservatives, and the potential sources of exposure are broad, being both occupational and non-occupational including cosmetics, toiletries, household products such as washing and cleaning agents, and in a great number of industrial applications including adhesives, paints, lacquers, and metalworking fluids.[2,7]

Formaldehyde has been reported to be used in disinfectants in the food sector and as a disinfectant and preservative in both medical and technical sectors. It is a raw material for plastics and synthetic resins and is used in paints/lacquers, printing inks, cleaning agents, adhesives, fillers, flooring materials, hardeners, impregnating agents, and building materials.[8,9] Less common exposures, that may be insufficient to elicit dermatitis, include in wood-based materials, floor coverings, furniture, and insulation materials (eg, urea-formaldehyde in situ foams). Tobacco smoke contains comparatively large amounts of formaldehyde, and even burning candles can be a source of formaldehyde in indoor air.[10]

In June 2019, European legislation came into force that banned the use of formaldehyde and quaternium-15 in cosmetics.[11] All finished products that release formaldehyde listed in the Annex V of EU cosmetic regulation must be labeled with the warning "contains formaldehyde" if the concentration of formaldehyde in the finished product exceeds 0.05%. However, monitoring authorities of the German federal states have examined several samples of novel hair-straightening agents for their ingredients and found that the agents contain free formaldehyde in higher concentrations of between 1.7% and 1.8%, despite, in the European Union, formaldehyde being not permitted as an active ingredient in hair straightening products.[12]

TABLE 1 Patch test reactions to formaldehyde and formaldehyde releasers, the latter tested either consecutively or in a special series. +ve, positive.

Allergen	n (test)	% +	% ++/+++	% ?+/IR	% +ve	% +ve std	(95% CI)	*P*-value	% extra +ve	(95% CI)
Formaldehyde 2% aq.	15 067	1.01	0.99	0.76	2	1.96	(1.73-2.18)			
Formaldehyde 1% aq.	30 283	1.14	0.94	1.31	2.08	2.01	(1.85-2.17)			
Quaternium-15 1% pet.	25 207	0.37	0.36	0.25	0.74	0.71	(0.6-0.81)	.98	0.29	(0.19-0.41)
2-Bromo-2-nitro-1,3-propanediol 0.5% pet.	8139	0.34	0.15	0.2	0.49	0.49	(0.34-0.65)	.81	0.44	(0.29-0.65)
Diazolidinyl urea 2% pet.	20 722	0.46	0.15	0.3	0.61	0.61	(0.5-0.71)	.97	0.39	(0.30-0.51)
Imidazolidinyl urea 1% pet.	567	0.35	0		0.35	0.34	(0-0.84)			
Imidazolidinyl urea 2% pet.	21 160	0.34	0.08	0.27	0.42	0.42	(0.33-0.51)	>.99	0.22	(0.15-0.32)
DMDM hydantoin 2% pet.	21 160	0.34	0.08	0.27	0.42	0.42	(0.33-0.51)	.03	1.31	(0.43-3.02)

Note: The *P*-value is that of the chi-square test comparing the frequency of positive reactions when testing in the baseline series vs a special series, adjusted for testing department. % extra +ve represents the % of additional positive reactions detected by the FR over and above that detected by formaldehyde 2% aq. when tested in the baseline series. The rightmost column indicates the share of patients positive to the respective FR, but not to formaldehyde 2% aq., thereby extracting information from the cross-tabulations presented in Table 2A–E. Note that these are partly much smaller subsets of the samples used in the overall, univariate analyses presented in the other columns.

According to reports from Germany[13] and Italy,[14] FRs trigger a positive reaction in less than 1% of patch tested patients. This may be due to the relatively low prevalence of these preservatives in cosmetic products.[15] In the United States, for example, the formaldehyde releasers diazolidinyl urea and imidazolidinyl urea are more common in cosmetics and the sensitization prevalences are accordingly higher.[16] Contact allergic reactions to formaldehyde releasers can be directed against the released formaldehyde, against the substance itself, or both.[17-22] Our finding that allergy to formaldehyde 2% aq. occurs at a frequency of 1.96% is consistent with prevalences reported across Europe of between 1% and 3%.[3,23]

When interpreting the frequency of sensitization to the different allergens, it is important to consider that although formaldehyde is tested in all baseline series, and quaternium-15 in the European baseline series (but not, for example, in Austria, Germany, and Switzerland), the other formaldehyde releasers are normally tested in a special series, such as a cosmetics series or a more general preservatives series, as these circumstances may affect sensitisation prevalence—with lower prevalence expected when tested routinely in the baseline series. We have compared the sensitization prevalence obtained with an FR tested in the baseline series and the same FR when tested in a special series, adjusted for the testing department. Generally the context had no impact, which suggests that the allergens are widely distributed in the patient's environment and that exposure is not specifically limited to, for example, cosmetics, and may not be predicted by the type of presentation. The exception to this was DMDM hydantoin, which had a slight, but statistically significant, lower number of co-reactions when tested in the baseline series compared to a special series. This may reflect the route of exposure and different potential co-reacting substances applied when comparing patients with facial/cosmetic dermatitis to patients with other types/localizations of dermatitis. A second consideration when interpreting these results is that + positive reactions to formaldehyde and FRs were included in the positive reaction analysis, along with ++ and +++ reactions. Formaldehyde is known to cause irritant reactions and the possibility that some of the + positives could have been irritant needs to be borne in mind.

The formaldehyde releasers with the highest sensitization prevalences were quaternium-15 1% pet. 0.71%, diazolidinyl urea 2% pet. 0.61%, 2-bromo-2-nitropropane-1,3-diol 0.5% pet. 0.49%, imidazolidinyl urea 2% pet. 0.42%, and DMDM hydantoin 2% pet. 0.42%. In their multicenter study, Latorre et al found imidazolidinyl urea and diazolidinyl urea to be the most frequent sensitizers, as has Faith et al.[3,23] They comment that it is unsurprising that both of these formaldehyde releasers have been added to the baseline series of the contact societies of North America and some, but not all, European countries, such as the UK. However, the prevalence of sensitization to FRs in the United States is significantly higher than in Europe, with quaternium-15 reaching 9.5% and decreasing only in recent years.[24-26]

The percentage of isolated reactions to FR, without co-reactivity to formaldehyde 2% aq. for each FR, varied between 46.8% for quaternium-15 1% pet. and 96.3% 2-bromo-2-nitropropane-1,3-diol 0.5% pet. This demonstrates that the degree of co-reactivity is virtually nonexistent in 2-bromo-2-nitropropane-1,3-diol 0.5% pet. (Cohen's kappa: 0, 95%CI −0.02 to 0.02), to only a weak concordance for quaternium-15 (Cohen's kappa: 0.22, 95%CI 0.16 to 0.28), the formaldehyde releaser showing the most co-reactivity with formaldehyde 2% aq. (a Cohen's kappa value of 1 would indicate full concordance). These findings are consistent with de Groot et al, who reported that less than 10% of patients allergic to formaldehyde react to 2-bromo-1,3,diol and that between 18% and 52% of patients positive to quaternium-15 also have an allergy to formaldehyde.[2] Similar data have been reported showing low co-reactivity (0.74%) for 2-bromo-2-nitropropane-1,3-diol.[3] Of note, a 2008 study by Aalto-Korte et al analyzed patterns of patch test reactions to formaldehyde 1% aq., and dilution series, plus FRs. Of their formaldehyde allergic patients, 79% were allergic to one or more FRs.[27] Of interest, unlike in the data presented here, FR allergy without formaldehyde allergy varied between each FR but was rare. This may be explained

TABLE 2 Co-reactivity between formaldehyde 2% aq. (in rows) and different formaldehyde releasers (in columns); in parentheses: Cohen's kappa (95% confidence interval)

	Formaldehyde releaser		
	Positive	**Negative**	**Total**
(**A**) Quaternium-15; Cohen's kappa: 0.22, 95% CI 0.16to 0.28			
Formaldehyde positive	33	196	229
Row %	14.4%	85.6%	
Col. %	53.2%	1.9%	
Formaldehyde negative	29	9909	9938
Row %	0.3%	99.7%	
Col. %	46.8%	98.1%	
Formaldehyde releaser total	62	10 105	10 167
(**B**) 2-Bromo-2-nitro-1,3-propanediol (Bronopol); Cohen's kappa: 0, 95%CI −0.02 to 0.02)			
Formaldehyde positive	1	154	155
Row %	0.6%	99.4%	
Col. %	3.7%	2.6%	
Formaldehyde negative	26	5679	5705
Row %	0.5%	99.5%	
Col. %	96.3%	97.4%	
Formaldehyde releaser total	27	5833	5860
(**C**) Diazolidinyl urea; Cohen's kappa: 0.14, 95%CI, 0.09 to 0.18			
Formaldehyde positive	31	306	337
Row %	9.2%	90.8%	
Col. %	36%	2.2%	
Formaldehyde negative	55	13 606	13 661
Row %	0.4%	99.6%	
Col. %	64%	97.8%	
Formaldehyde releaser total	86	13 912	13 998
(**D**) Imidazolidinyl urea (2%); Cohen's kappa: 0.07, 95%CI 0.03 to 0.1			
Formaldehyde positive	15	341	356
Row %	4.2%	95.8%	
Col. %	32.6%	2.5%	
Formaldehyde negative	31	13 488	13 519
Row %	0.2%	99.8%	
Col. %	67.4%	97.5%	
Formaldehyde releaser total	46	13 829	13 875
(**E**) DMDM hydantoin (baseline series); Cohen's kappa: 0.05, 95%CI −0.08 to 0.18			
Formaldehyde positive	1	21	22
Row %	4.5%	95.5%	
Col. %	16.7%	5.6%	
Formaldehyde negative	5	356	361
Row %	1.4%	98.6%	
Col. %	83.3%	94.4%	
Formaldehyde releaser total	6	377	383

in the potential difference between the selected patient material in small occupational clinics vs large clinics with more unselected patients.

Multiple variables can affect the amount of formaldehyde released including its concentration, pH, temperature, composition, and age (upon storage increased levels of formaldehyde will be released). Heat and alkaline conditions hasten the rate of formaldehyde release.[28,29] The findings of this study can be explained in that quaternium-15 releases the greatest amount of formaldehyde, whereas 2-bromo-2-nitropropane-1,3-diol releases negligible formaldehyde under physiological conditions.[30]

TABLE 3 (**A**), Concomitant reactivity to imidazolidinyl (IU) and diazolidinyl urea (DU) (2% pet.) in patients positive to formaldehyde 2% aq. (Cohen's kappa: 0.41, 95%CI 0.24 to 0.59). (**B**), Concomitant reactivity to imidazolidinyl (IU) and diazolidinyl urea (DU) (2% pet.) in patients negative to formaldehyde 2% aq. (Cohen's kappa: 0.47, 95% CI 0.37 to 0.58)

	DU		
	Positive	Negative	IU total
(**A**)			
IU positive	11	5	16
Row %	68.8%	31.2%	
Col. %	32.4%	1.1%	
IU negative	23	463	486
Row %	4.7%	95.3%	
Col. %	67.6%	98.9%	
DU total	34	468	502
(**B**)			
IU positive	15 531	57	15 588
Row %	99.6%	0.4%	
Col. %	99.9%	63.3%	
IU negative	16	33	49
Row %	32.7%	67.3%	
Col. %	0.1%	36.7%	
DU total	15 547	90	15 637

Table 1 shows the percentage of additional positive reactions detected by FRs above the use of formaldehyde 2%. These ranged from 0.22% for imidazolidinyl urea 2% pet to 0.44% for 2-bromo-2-nitro-1,3-propanediol 0.5% pet. Sensitization prevalence to formaldehyde and FRs varies across the participating centres, with highest proportions observed in the centers from Finland and Poland, most likely reflecting the occupational nature of the referrals.[30] As a rule, an allergen should have at least a 0.5% prevalence to be considered for inclusion in the EBS. Many of these allergens detect additional reactions close to this rate and do not seem to be predicted by the history. It is interesting to note that although none of 2-bromo-2-nitro-1,3-propanediol 0.5% pet, diazolidinyl urea 2% pet., and DMDM hydantoin 2% pet. reach the 0.5% sensitisation prevalence threshold, they detect a higher number of additional allergic reactions compared to quaternium-15 1% pet., which has already been included in the EBS.

Imidazolidinyl urea and diazolidinyl urea are structurally similar, and it is therefore unsurprising that they demonstrate a degree of concordance in their co-reactivity (Table 3). Patients who were positive to imidazolidinyl urea 2% pet. were also positive to diazolidinyl urea 2% pet. in 54.4% (49/90) of cases. Conversely, patients who were positive to diazolidinyl urea 2% were also positive to imidazolidinyl urea 2% pet. in 37.4% of cases (49/131). This would suggest that if only one of these FRs were to be chosen for inclusion in the EBS, diazolidinyl urea 2% would be the most sensitive of the two. Experimental studies had already shown that diazolidinyl urea is the stronger sensitizer compared to imidazolidinyl urea.[31] When patients show contact allergy to formaldehyde plus one or more of the FRs, it is often assumed to be due to formaldehyde present in the FR. Often more than one FR elicits positive reactions, even when the FRs are not structurally similar, making cross-reactions unlikely. However, studies have demonstrated that sensitivity to an FR can exist independently of a formaldehyde contact allergy.[32] This suggests that components of the formaldehyde releasers other than the formaldehyde can induce sensitization. Indeed, it has been found that DMDM hydantoin, methenamine, and 2-bromo-2-nitropopane-1, 3-diol can degrade to intermediaries distinct from formaldehyde, which are able to form a hapten-protein antigen complex, a key step in the pathway of developing sensitization.[33] This has also been described for imidazolidinyl urea —and diazolidinyl urea.[34,35] This would be another supportive argument for considering testing of each individual FR allergen within the EBS, rather than screening with formaldehyde 2% aq.

Exposure to environmental allergens is continuously changing, and it is recognized that the EBS needs to be adapted to reflect these changes. Quaternium-15 1% pet. is included in the EBS currently. According to the latest publication from the European Commission database for information on cosmetic substances and ingredients (CosIng), updated in January 2020, it is no longer listed as a permitted preservative in cosmetics in the EU.[11] It is important to consider therefore, that other FRs, which currently are in use in cosmetics, should be included in the EBS to reflect this change.

In conclusion, the high percentage of isolated reactions to FR show that co-reactivity to formaldehyde 2% aq. is virtually non-existent for 2-bromo-2-nitropropane-1,3-diol 0.5% pet. (Cohen's kappa: 0, 95%CI −0.02 to 0.02), whereas a weak concordance for quaternium-15 was detected (Cohen's kappa: 0.22, 95%CI 0.16 to 0.28). Our results suggest that patch testing with formaldehyde 2% aq. is an inadequate screen to identify independent contact sensitization to FRs. Therefore, inclusion of FRs in the baseline series based on the frequency of reactions to, and relevance of each individual allergen, should be reviewed.

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AUTHOR CONTRIBUTIONS

Heather Whitehouse: Conceptualization; investigation; methodology; project administration; validation; visualization; writing-original draft; writing-review and editing. **Wolfgang Uter:** Conceptualization; data curation; formal analysis; methodology; project administration; resources; software; visualization; writing-original draft; writing-review and editing. **Johannes Geier:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Barbara Ballmer-Weber:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Andrea Bauer:** Conceptualization; data curation;

investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Susan Cooper:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Magdalena Czarnecka-Operacz:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Dagmar Simon:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Heinrich Dickel:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Anna Belloni Fortina:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Rosella Gallo:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Ana Giménez-Arnau:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Graham Johnston:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Francesca Larese Filon:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Vera Mahler:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Maria Pesonen:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Thomas Rustemeyer:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Marie Schuttelaar:** Conceptualization; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Skaidra Valiukeviciene:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Elke Weisshaar:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Thomas Werfel:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Stephen Wilkinson:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing-original draft; writing-review and editing.

CONFLICT OF INTERESTS

The IVDK, maintained by the IVDK e.V., of which J. Geier is an employee, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. MLS received travel reimbursement from cosmetic/fragrance industry associations to attend meetings organized by those associations. WU has accepted honoraria for presentations or travel reimbursement from cosmetic industry associations and has received lecture fees from dermatology-related sponsors for educational lectures on contact allergy. SMW has received travel reimbursement to attend meetings with the cosmetic industry. The other authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data not available due to privacy/ethical restrictions.

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