













## ORIGINAL ARTICLE

# European patch test results with audit allergens as candidates for inclusion in the European Baseline Series, 2019/20: Joint results of the ESSCA<sup>A</sup> and the EBS<sup>B</sup> working groups of the ESCD, and the GEIDAC<sup>C</sup>

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#### Abstract

**Background:** In 2019, a number of allergens (haptens), henceforth, “the audit allergens,” were considered as potential additions to the European Baseline Series (EBS), namely, sodium metabisulfite, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, imidazolidinyl urea, Compositae mix II (2.5% or 5% pet), linalool hydroperoxides (lin-OOH), limonene hydroperoxides (lim-OOH), benzisothiazolinone (BIT), octylisothiazolinone (OIT), decyl glucoside, and lauryl glucoside; *Evernia furfuracea* (tree moss), was additionally tested by some departments as well.

**Objectives:** To collect further data on patch test reactivity and clinical relevance of the audit allergens in consecutive patients across Europe.

**Methods:** Patch test data covering the audit allergens in 2019 and 2020 were collected by those departments of the European Surveillance System on Contact Allergies testing these, as well as further collaborators from the EBS working group of the European Society of Contact Dermatitis (ESCD), and the Spanish Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea. As patch test outcome, reactions between day (D) 3 and D5 were considered.

**Results:** Altogether  $n = 12\,403$  patients were tested with any of the audit allergen. Positive reactions were most common to lin-OOH 1% pet. (8.74% [95%CI: 8.14–9.37%]), followed by lin-OOH 0.5% pet., and lim-OOH 0.3% pet (5.41% [95% CI: 4.95–5.89%]). Beyond these terpene hydroperoxides, BIT 0.1% pet. was the second most common allergen with 4.72% (95% CI: 4.2–5.28%), followed by sodium metabisulfite 1% pet. (3.75% [95%CI: 3.32–4.23%]) and Compositae mix 5% pet. (2.31% [95% CI: 1.84–2.87%]). For some allergens, clinical relevance was frequently difficult to ascertain.

**Conclusions:** Despite many positive patch test reactions, it remains controversial whether lin- and lim-OOH should be tested routinely, while at least the two preservatives BIT and sodium metabisulfite appear suitable. The present results are a basis for further discussion and ultimately decision on their implementation into routine testing among the ESCD members.

#### KEYWORDS

baseline series, benzisothiazolinone, clinical epidemiology, contact allergy, decyl glucoside, patch testing, RRID:SCR\_001905, sodium metabisulfite, surveillance

## 1 | INTRODUCTION

The last revision of the European Baseline Series (EBS) was in 2019.<sup>1</sup> Since then, the ESB working group of the European Society of Contact Dermatitis (ESCD) evaluated a group of 11 allergens (haptens) as possible candidates to add to the EBS, because information was yet lacking to definitely include or exclude them according to the contemporaneous criteria.<sup>2</sup> The following substances are considered “audit allergens” not (yet) part of the regular baseline series, which had been

selected for evaluation, that is, auditing of their value for routine patch testing: sodium metabisulfite, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, imidazolidinyl urea, Compositae mix II (2.5% or 5% pet), linalool hydroperoxides (lin-OOH), limonene hydroperoxides (lim-OOH), benzisothiazolinone (BIT), octylisothiazolinone, decyl glucoside, and lauryl glucoside. Moreover, Compositae mix, originally suggested to be tested 2.5% pet., was also considered at 5% pet., and *Evernia furfuracea* (tree moss) was additionally included in the set of audit allergens by some departments. This selection of recommended

additions to the EBS for further study had been presented and discussed in Wilkinson et al.<sup>1</sup> A retrospective analysis has since examined the suitability of formaldehyde-releasing preservatives for inclusion in the EBS.<sup>3</sup> Since then, the criteria for inclusion in the EBS have been updated.<sup>4</sup> Specifically, where allergens may cross or co-react it was considered that the lower 95% confidence interval (CI) of the frequency of reactions additional to any existing allergen in the EBS should be above the 0.5% threshold of reactions to be included in the EBS. In addition, as in the case of DMDM hydantoin, where exposure to an allergen is limited and predictable, that allergen may be better placed in a specialized, for example, cosmetic series. For instance, the frequency of reactions to DMDM hydantoin was 3-fold greater than in the baseline series when tested in a cosmetic/facial series. Where results remain equivocal and the 95%CI crosses the 0.5% threshold, it was considered that an allergen should remain as a recommended addition to the EBS for individual countries/departments to consider adding to their local baseline series.

The present article reports descriptive results offering a broad geographical coverage concerning the above-mentioned scope of audit allergens; results concerning allergens presently included in the EBS will be presented separately.<sup>5</sup> Although the EBS results include the full scope of contributors, data in the present analysis have been contributed by a subset of departments that have patch tested the audit allergens in consecutive patients.

## 2 | METHODS

### 2.1 | ESSCA working group of the ESCD

The European Surveillance System on Contact Allergies (ESSCA) is a working group of the ESCD (<https://www.escd.org>). Its objective is the clinical surveillance of contact allergy.<sup>6,7</sup> To this end, contributing departments (see list of authors and collaborators) submit to the data center in Erlangen either all patch test results, or just patch test results obtained with the EBS (or national or local adaptations thereof), obtained following ESCD standards.<sup>8</sup> This is accompanied by important demographic and clinical information, ranging from “MOAHLFA” characteristics (see Table 1) to a wider range of information according to the ESSCA “minimal data set” definition.<sup>6,7,9</sup> Data from contributing departments are delivered in an anonymous format, or partly, following national network standards, in a pseudonymized format, where the pseudonym cannot be related to actual personal data except in the contributing department itself. This difference is of importance, because only with pseudonymized data can re-investigations of patients be identified and eliminated, to avoid duplication of entries. However, in view of the short study period ranging from, effectively, 1.25 to 2 years, and the special scope of audit allergens considered, the effect of re-consultations appeared negligible. Data were quality checked, providing an “internal report” for each contributing department for scrutiny and approval before pooling of the respective data.<sup>7</sup> Data management and analysis were performed with the R software package (<[www.r-project.org](http://www.r-project.org)>; RRID:

SCR\_001905), version 4.0.3. For the calculation of 95%CIs to zero proportions an approximation to an exact CI was used.<sup>10</sup> With the objective of presenting a descriptive overview of the morbidity in the patch-tested population, we refrained from employing standardization and adjustment techniques usually necessary in risk-factor and time-trend analyses, respectively.

### 2.2 | EBS working group of the ESCD

Started in June 2017, the EBS working group's aim is to review and make recommendations for the ESCD baseline patch test series. For the current data cycle, providing an evidence base for deciding on inclusion of “audit allergens” into a new version of the EBS, additional data beyond those contributed by ESSCA (see above) and GEIDAC (see below), were contributed by working group members not yet having joined ESSCA; these individual data are treated together with ESSCA data, as their structure follows ESSCA definitions. To enable contribution of individual, anonymized data also for those not opting for using the classical WinAlldat/ESSCA software,<sup>9</sup> an online documentation was set up in 2018 based on a local academic implementation of a SoSci server (<https://www.socisurvey.de/>), used by Antwerp/Belgium and Coimbra/Portugal. In addition to the regular 2019 data, Budapest/Hungary contributed aggregated results on 342 patients consecutively patch tested with three of the audit allergens in 2018, which were also included, as an exceptional backward extension of the study period.

### 2.3 | GEIDAC

In Spain, all the participating centers are members of the Spanish Contact Dermatitis and Skin Allergy Research Group (Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea [GEIDAC]). Data were collected prospectively in the Spanish Contact Dermatitis Registry (Registro Español de Dermatitis de Contacto [REIDAC]). This is an online-based multicenter registry that uses the OpenClinica platform (OpenClinica and collaborators). Data are anonymized at source and the registry complies with all ethical standards in terms of informed consent and data-protection legislation. Clinical data match exactly with those set out in the minimal data set of the ESSCA, which allows them to be exported to other databases with identical categories. Ideally, the centers systematically upload clinical data and the results of patch tests on the day of the last reading, thus providing epidemiologic centralized data in real time. The database has a modular structure that can be used for prospective studies over a definite period of time. For the present study, a specific data form with the “candidate allergens” was added to the original structure of the registry for a 2-year period.

## 3 | RESULTS

In total, 21 633 patients were patch tested with the EBS or the TRUE Test baseline series from January 2019 to December 2020 in the participating departments. Because a varying scope of audit allergens has

**TABLE 1** Demographic and clinical characteristics according to the MOAHLFA index<sup>11</sup> with “P-measure,”<sup>12</sup> see note below table

Country	M	O	A	H	L	F	A <sup>(2)</sup>	P
AT (Austria)	26.6	15.6	28.9	23.1	6.4	19.7	59.0	78.0
BE (Belgium)	32.3	13.0	38.4	19.7	10.9	20.6	58.4	66.1
CH (Switzerland)	39.9	11.7	22.8	24.8	6.1	20.7	71.1	64.0
DE (Germany)	39.4	36.0	31.5	50.1	4.7	9.3	72.9	56.4
ES (Spain)	33.9	8.5	17.3	22.8	6.0	15.6	70.5	47.5
FI (Finland)	49.5	76.3	23.7	80.4	1.0	9.3	44.3	49.5
HU (Hungary)	24.1	0.8	13.0	35.4	7.4	17.0	69.7	34.8
IT (Italy)	26.0	5.5	14.7	22.6	4.1	21.2	65.4	41.8
LT (Lithuania)	24.6	27.5	5.2	33.1	9.8	25.7	60.7	47.9
NL (The Netherlands)	33.5	16.9	38.3	14.4	1.0	4.9	59.6	72.6
PT (Portugal)	29.4	32.8	18.0	43.3	7.1	14.2	57.0	51.7
UK (United Kingdom)	30.4	5.5	46.0	24.6	2.6	34.1	54.2	41.0

Note: M, % male patients; O, % patients with occupational dermatitis; A, % patients with atopic dermatitis; H, % patients with hand dermatitis; L, % patients with leg dermatitis; F, % patients with face dermatitis; A<sup>(2)</sup>, % patients age 40 and above; P, share of patients with at least one positive reaction to a baseline series allergen.

been tested by some of these departments, and in some countries none of these, the individual contribution is lower. Population characteristics according to the MOAHLFA index,<sup>11</sup> extended by the “P-measure” (the proportion of patients positive to at least one allergen from the baseline series<sup>12</sup>) are illustrated in Table 1 regarding the subset of patients who were patch tested with at least one audit allergen, which is the focus of the present analysis. Results of the GEIDAC obtained with the audit (“candidate”) allergens have already been published separately.<sup>13</sup>

The audit allergens<sup>1</sup> were tested along with the EBS, that is, in consecutive patients. However, as mentioned, most departments or national groups did not include all audit allergens, and partly not for the entire study period. Hence, the total numbers of single audit allergens tested is markedly smaller and variable, as shown in Table 2. A supplemental analysis stratified for the contributing countries can be found online in Table S1.

Regarding reactivity to Compositae mix II, which was one of the candidate allergens, compared to sesquiterpene lactone (SL) mix, 4005 patients were tested both with SL mix and Compositae mix II 2.5% pet. (SL mix and Compositae mix 5% had not been tested in parallel, thus not permitting a comparison with SL mix). Among these 4005 patients, 19 reacted positive to both, 18 only to Compositae mix II 2.5%, that is, 0.45 (95% CI: 0.27–0.71%), and 18 only to SL mix.

Coupled reactions between decyl and lauryl glucoside were common. In the 4730 patients who were tested with both agents, 37 were positive to both, 45, that is, 0.95 (95% CI: 0.69–1.27%), only to decyl glucoside but not lauryl glucoside, and 14, that is, 0.3 (95% CI: 0.16–0.5%) only to lauryl glucoside.

The coupled reactivity between benzisothiazolinone (BIT) and octylisothiazolinone (OIT) on the one hand, and methylisothiazolinone (MI) and methylchloroisothiazolinone(MCI)/MI on the other hand was of interest. Altogether 3728 patients were tested with both BIT and OIT. Among these, 23 (0.62%) reacted to both allergens, 42 (1.13%) only to OIT, and 192 (5.15%) only to BIT, which represents a highly

significant asymmetry (McNemar test:  $p < .00001$ ). Results comparing OIT and BIT, respectively, with MI and MCI/MI, respectively, are shown in Table 3. The two rightmost columns of this table compare OIT and BIT reactions with positive reactions to either MI or MCI/MI or both vs a negative reaction to both MI and MCI/MI. The degree of co-reactivity was stronger between OIT and MI or MCI/MI, with an odds ratio (OR) of 14.6 (95% CI: 8.8–24.3), than in the case of BIT, with an OR of 4.4 (95% CI: 3.1–6.3). In the subset of patients who were not positive to MI or to MCI/MI ( $n = 3118$ ), 11 were positive to both BIT and OIT, 134 only to BIT, and 21 only to OIT (McNemar test:  $p < .00001$ ).

The terpene hydroperoxides, lin-OOHs and lim-OOHs, had been tested in two concentrations each because the optimum patch test concentration has hitherto not been identified, and also to support the interpretation of patch test reactions. Univariate results are presented in Table 2 and co-reactivity in Table 4. Taking the two respective concentrations together, coupled reactivity is moderate, with an OR of 32.6 (95% CI: 25.2–42.1). If, instead, co-reactivity between the two respective lower concentrations is considered in a sensitivity analysis, the OR changes marginally to 28.2 (95% CI: 21.2–37.4). Concerning coupled reactivity to any of the four other fragrance allergens of the baseline series (fragrance mix [FM] I, FM II, hydroxyisohexyl 3-cyclohexene carboxaldehyde [HICC], and *Myroxylon pereirae* [balsam of Peru]), the following results were obtained:

- Although many patients for whom individual data were available had been tested with all these four fragrances ( $n = 10\,427$ ), 6651 patients had been tested with one or both of the concentrations of lin-OOHs, and 7142 patients had been tested with one or both concentrations of lim-OOHs (see Table 2).
- Among the 4790 tested with all four fragrances of the EBS and any concentration of lin-OOHs, 126 were positive to both, 386 only to at least one fragrance marker, but not lin-OOHs, and vice versa, 234 only to lin-OOHs but not any fragrance marker, the latter amounting to 4.89% (95% CI: 4.29–5.53%) of patients such tested.

**TABLE 2** Patch test results (day 3 to day 5) with the 2019/20 audit allergens in consecutive patients in the departments of the European Surveillance System on Contact Allergies (ESSCA), additional contributors from the EBS working group, and the contributing GEIDAC members<sup>13</sup>

Allergen	Conc.	Tested	+ / ++ / +++	?+ / IR	% pos. (95%CI)
Sodium metabisulfite	1.0	6819	256	75	3.75 (3.32–4.23)
2-Bromo-2-nitropropane-1,3-diol	0.5	6977	52	28	0.75 (0.56–0.98)
Diazolidinyl urea	2.0	6127	50	21	0.82 (0.61–1.07)
Imidazolidinyl urea	2.0	7538	35	23	0.46 (0.32–0.65)
Compositae mix II <sup>a</sup>	2.5	6271	49	10	0.78 (0.58–1.03)
Compositae mix <sup>b</sup>	5.0	3460	80	33	2.31 (1.84–2.87)
Linalool hydroperoxides	1.0	8264	722	494	8.74 (8.14–9.37)
Linalool hydroperoxides	0.5	5539	363	190	6.55 (5.92–7.24)
Limonene hydroperoxides	0.3	9047	489	371	5.41 (4.95–5.89)
Limonene hydroperoxides	0.2	5495	258	197	4.7 (4.15–5.29)
Benzisothiazolinone	0.1	6210	293	103	4.72 (4.2–5.28)
Octylisothiazolinone	0.1	6003	73	30	1.22 (0.95–1.53)
Decyl glucoside	5.0	7354	105	91	1.43 (1.17–1.73)
Lauryl glucoside	3.0	7350	63	63	0.86 (0.66–1.1)
<i>Evernia furfuracea</i> (tree moss)	1.0	3833	55	14	1.43 (1.08–1.86)

Note: Conc., concentration in %, tested in petrolatum. pos., all positive reactions (+, ++, and +++).

<sup>a</sup>Compositae mix 2.5% pet. contains the following extracts and single compounds, respectively: *Anthemis nobilis* 0.6%, *Chamomilla recutita* 0.6%, *Achillea millefolium* 0.5%, *Tanacetum vulgare* 0.5%, *Arnica montana* 0.25% and parthenolide 0.05%. Compositae mix 5% pet.

<sup>b</sup>Includes the same extracts and compounds at twice the concentration.

**TABLE 3** Coupled reactivity between octylisothiazolinone (OIT) and benzisothiazolinone (BIT), resp., and methylisothiazolinone (MI), methylchloroisothiazolinone (MCI)/MI 3:1, and either MI or MCI/MI

		MI		MCI/MI		MI and/or MCI/MI	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
OIT	Pos.	28	37	21	39	32	32 (0.95%, 95%CI: 0.65–1.34%)
	Neg.	153	3510	134	3613	211	3087
BIT	Pos.	34	197	26	172	43	159 (3.89%, 95%CI: 3.32–4.52%)
	Neg.	170	4062	143	3724	225	3664

Note: Note that for the latter cross-tabulation, all three allergen preparations had to be tested in the same patient, whereas in the former two, only the two allergens involved. Patch test results (day 3 to day 5) 2019–2020. OIT and BIT tested in pet.; MI (0.2 and 0.05% pooled) and MCI/MI (0.02 and 0.01% pooled) in aq.

**TABLE 4** Coupled reactivity between linalool hydroperoxides (lin-OOH) and limonene hydroperoxides (lim-OOH) in the two concentrations tested

		Lim-OOH 0.3%		Lim-OOH 0.2%		Lim-OOH	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Lin-OOH 1.0%	Pos.	207	377	141	185	230	162
	Neg.	166	5572	138	3133	203	3108
Lin-OOH 0.5%	Pos.	151	180	162	169	184	147
	Neg.	118	3447	117	3448	145	3420
Lin-OOH	Pos.	231	429	173	229	268	200
	Neg.	103	3093	106	3090	126	3070

Note: In the two rightmost columns and the two bottom rows, resp., results with both concentrations were aggregated, that is, patients positive to one or both concentrations were regarded as positive, and those not reacting to any concentration as negative.

**TABLE 5** Clinical relevance of positive reactions; this has been regularly documented in 13 134 patients

Allergen	Current NEC	Current occ.	Current non-occ.	Past NEC	Past occ.	Past non-occ.	Unknown
Sodium metabisulfite	23.5	3.7	18.9	3.7	0.5	2.3	47.5
2-Bromo-2-nitropropane-1,3-diol	18.3	3.7	18.3	1.2	0.0	2.4	56.1
Diazolidinyl urea	15.9	1.6	31.7	0.0	0.0	3.2	47.6
Imidazolidinyl urea	5.8	1.9	25.0	0.0	0.0	5.8	61.5
Compositae mix	24.4	2.4	11.4	2.4	1.6	0.0	57.7
Linalool hydroperoxides	19.2	2.1	33.2	1.2	0.1	1.5	42.7
Limonene hydroperoxides	17.0	3.8	42.3	1.1	0.0	1.3	34.5
Benzisothiazolinone	21.3	7.7	18.4	1.0	1.4	1.0	49.3
Octylisothiazolinone	17.1	10.0	14.3	0.0	1.4	1.4	55.7
Decyl glucoside	9.7	1.1	20.0	2.3	0.0	1.7	65.1
Lauryl glucoside	24.6	1.6	41.0	1.6	0.0	4.9	26.2
<i>Evernia furfuracea</i> (tree moss) NEC, not elsewhere classified; unknown, relevance information lacking or classified as “unknown.”	32.1	2.6	25.6	2.6	1.3	1.3	34.6

- Among the 5264 tested with all four fragrances of the EBS and any concentration of lim-OOHs, 65 were positive to both, 478 only to at least one fragrance marker but not lim-OOHs, and, vice versa, 119 only to lim-OOHs but not any fragrance marker, the latter amounting to 2.48% (95% CI: 2.06-2.97%) patients with such isolated positive reactions.

In addition, concomitant reactivity between *E. furfuracea* (tree moss) and colophonium as well as fragrance mix FM I was assessed based on data from those departments which also included this additional allergen. Among the 3212 patients tested with *E. furfuracea*, all were tested with colophonium, and all but 2 with FM I, too. Concerning co-reactivity between *E. furfuracea* and colophonium, positive reactions to both allergen preparations were seen in 27 (0.84%), whereas in 66 (2.05%) only to colophonium and 17 (0.53% [95% CI: 0.31-0.85%]) only to *E. furfuracea* (OR = 74.6 [95%CI: 38.8-143.5],  $p < .0001$ ). Regarding concomitant reactivity between *E. furfuracea* and FM I (specifically, to the *E. prunastri* extract included in FM I), positive reactions to both allergen preparations were seen in 17 (0.53%), whereas in 198 (6.17%) only to FM I and 26 (0.81% [95% CI: 0.53-1.18%]) only to *E. furfuracea* (OR = 9.8 [95% CI: 5.2-18.4],  $p < .0001$ ).

Results on clinical relevance of the audit allergens are shown in Table 5 and in more detail concerning product categories involved, online in Table S2. With considerable differences between the allergens, which are difficult to interpret, the share of unknown relevance (summarizing both “not reported” and “unknown relevance”) is partly high. The aggregated REIDAC data used, except for Barcelona/Hospital del Mar contributing via WinAlldat/ESSCA, did not include relevance information; the respective positive cases are not included in the denominator for the two relevance tables. In a few instances relevance information had been documented but could not be related to the product categories used (“not classified”; see Table S2). Because ingredient labeling is mandatory only in cosmetics and

household products in the EU, disclosure of allergens used in such products is evidently over-represented. Of note, both OIT and BIT had each been identified as causes of ACD in cosmetic products in five and nine patients, respectively. As both are not permitted in the EU as cosmetic preservatives (not listed in Annex V of the Cosmetics Regulation [EU 1223/2009]), the culprit cosmetics have presumably been bought outside the EU.

## 4 | DISCUSSION

This article presents an audit of testing with the recommended additions to the EBS<sup>1</sup> to enable a further revision. With respect to the 0.5% threshold for inclusion,<sup>4</sup> specifically the lower 95% confidence limit to the prevalence estimate, the univariate results in Table 2 are a first approach. Concerning the additional yield beyond a “related” marker/allergen, the calculations added in the text of the results are considered.

### 4.1 | Preservative allergy

With the restrictions on the use of MI it is unsurprising that departments have seen a rapid fall in allergy to both MI and MCI/MI<sup>14,15</sup> back to pre-epidemic levels, or not quite so.<sup>16</sup> Although not permitted in cosmetics, both OIT and BIT were recommended for more routine testing<sup>1</sup> and a statistically significant rise in the prevalence of allergy to BIT, in particular, has been found.<sup>15,17</sup> It seemed probable that this increased prevalence had occurred as a consequence of exposure in domestic cleaning products, detergents, and paints. Notwithstanding co-sensitizations to MI, BIT, and OIT, cross-reactivity might also occur between MI and BIT, and to a greater extent between MI and OIT,<sup>18</sup> the latter also found as a leather-treating agent.<sup>19</sup> Our data confirm

this association but despite this, the additional yield of testing BIT was 3.89% (95%CI: 3.32-4.52%) and OIT 0.95% (95% CI: 0.65-1.34%)—see Table 3. Both are above the threshold for inclusion in the EBS, although with a share of current or rarely past relevance of 44.2%, OIT (Table 5) is at the borderline for inclusion. In the few cases where cosmetic exposure had been found relevant for OIT and BIT, respectively, these had presumably been bought outside the EU and brought home by patients. Alternatively, these “cosmetics” (such as hand creams) had been marketed within the EU as, for example, medical devices, for instance, as barrier creams used in hospitals. It is unfortunate that for medical devices restrictions for BIT or OIT do not exist, and labeling is not mandatory (but of course possible).<sup>20</sup> Moreover, a standard nomenclature, such as the International Nomenclature of Cosmetic ingredients (INCI; <https://ec.europa.eu/growth/tools-databases/cosing/>) in the realm of cosmetics is required, to unify labeling terminology and to avoid mis-labelling.<sup>21</sup> Generally, improved ingredient information for medical devices has been called for by the major European scientific societies in the field.<sup>22</sup>

Following the withdrawal of MI in leave-on cosmetics, other preservatives must be taking their place, likely including the so-called formaldehyde releasers. These recommended additions to the EBS<sup>1</sup> have been the subject of a separate article and will not be further discussed here.<sup>3,4</sup> However, a nonsignificant upward trend in allergy to sodium metabisulfite has been seen.<sup>17</sup> In 2019, it was felt that there was limited geographic data for this allergen and that relevance was not always apparent.<sup>1</sup> Rubber gloves have in the meantime, by the use of an experimental spot test, been identified as a likely source of sulfites; however, chemical-analytical confirmation is still necessary.<sup>23</sup> In conclusion, with a prevalence of presently 3.0% (95% CI: 2.58-3.51%) and current relevance of 58%, it seems clear that this fairly widespread preservative allergen meets the criteria for inclusion.

## 4.2 | Fragrance allergy

It is recognised that the current fragrance markers in the baseline series are a limited screen to detect contact allergy to fragrance ingredients. One strategy to improve the diagnostic yield has been to test to individual fragrance allergens from the 26 individual fragrance substances for which cosmetic ingredient labeling is mandatory within the European Union.<sup>24,25</sup>

*Evernia furfuracea* (tree moss) has been reported to be potentially of added value beyond the baseline series markers.<sup>24</sup> Extending the actual set of “audit allergens,” some departments have consecutively tested with this natural mixture, enabling an assessment of the added value. Although the additional yield from testing *E. furfuracea* was 0.80% (95% CI: 0.53-1.18%) when compared to FM I, this fell to 0.53% (95%CI: 0.31-0.85%) when compared with colophonium. It seems that this may, therefore, be more a marker of allergy to resin acids as found in colophonium and not warrant further consideration. Specifically, during production, tree moss is scraped from pine tree bark, leading to contamination and a substantial share of *E. furfuracea* contact allergy being related to colophonium sensitization.<sup>26</sup> In

accordance, 75% of patients who are positive to *E. furfuracea* in a Danish study have had relevant contact allergy to colophonium.<sup>27</sup>

Two other allergens identified as audit allergens were the hydroperoxides of linalool and limonene (lin-OOH and lim-OOH, respectively).<sup>24,25</sup> Although exposure to these seems difficult to confirm in products,<sup>28</sup> clinical studies suggest relevance<sup>29</sup> with positive repeated open application test (ROAT) in those with definite patch test reactions and a smaller proportion (15%) of those even with doubtful patch test reactions.<sup>30</sup> This has led to suggestions that they be included in various national baseline series.<sup>31,32</sup> Our data show an additional yield above the current baseline fragrance markers of 4.89% (95%CI: 4.29-5.53%) for lin-OOH and 2.48% (95%CI: 2.06-2.97%) for lim-OOH, suggesting that both should be included in the EBS despite a degree of co-reactivity between the two (odds ratio 32.6, 95%CI: 25.2-42.1 at the higher concentration of both). Concern has been expressed, however, about the irritancy of the patch test preparations, with irritant/doubtful reactions in 6.0% of those tested to lin-OOH and 4.1% to lim-OOH seen in the present results, diminishing only to some extent with the lower tested concentration. This potentially leads to a risk of over-interpretation of irritant reactions as allergic, and the patient given wrong advice if the tests are being undertaken in untrained hands. Although verification by ROAT generally is a useful tool to confirm or rule out contact allergy, the practicalities of such a ROAT have—beyond the very few systematic ROAT studies—not been established firmly enough to ensure valid guidance for routine clinical use. Moreover, purification of the patch test preparation to reduce the irritant potential of non- or less-sensitizing oxidation by-products would not be a financially viable proposition (personal communication, Bo Niklasson, April 2021). There currently remains a dilemma, and a discussion also among the authors of this article, as to whether to include these allergens in the EBS or, as at present, keep them as a recommended addition until a less-irritant alternative is developed.

## 4.3 | Compositae allergy

It has long been recognized that the sesquiterpene lactone (SL) mix is an inadequate screen to diagnose Compositae allergy<sup>33</sup> and that supplementation with a Compositae mix may be of value. More recently, similar results have been found with the Compositae mix (CM) II 2.5% pet.,<sup>34</sup> in which feverfew extract has been substituted by parthenolide 0.05%. In 53 newly diagnosed patients, SL mix elicited positive reactions most frequently (53% positive), followed by CM II 2.5 (47% positive), and parthenolide 0.1% pet. (45% positive). Sixteen patients (28%) were not detected by any of the three screening agents. In our data, the additional yield of testing CM II 2.5% pet. above SL mix was 0.45% (95%CI: 0.27-0.71%), which is below the threshold for inclusion in the EBS. Of note, members of the IDVK who test CM II at 5% pet.<sup>35</sup> had an overall share of positive reactions of 2.31% (95%CI: 1.84-2.87%) compared to 0.75% (95%CI: 0.55-1.0%) in centers testing the 2.5% CM II. Active sensitization that had been a concern with the previous CM I 5% pet. had not been reported in this study; however,

this particular aspect has not been investigated systematically, and hence evidence in this regard is weak. In a subset of patients in that Information Network of Departments of Dermatology (IVDK) study also tested with the “plant series” ( $n = 9098$ ), and thus with SL mix, 0.98% had reacted only to SL mix, 2.7% to both SL and CM II mixes, and 3.1% only to CM II.<sup>35</sup> However, these results obtained with aimed testing are not directly transferable to screening with the baseline series. Hence, it would appear that for the future, a comparison of SL mix with CM II 5% pet. results in consecutively tested patients should be undertaken.

#### 4.4 | Glucosides

In 2017, the North American Contact Dermatitis Group had noticed a steadily increasing frequency of reactions to above 1% of those tested.<sup>36</sup> At the time of the last update of the EBS<sup>1</sup> there were few data from Europe, and hence lauryl and decyl glucoside were included as recommended additions. With a share of positive reactions of 1.73% (95% CI 1.38-2.15%) decyl glucoside appears to be the more frequently reactive of the two. Although the relatively low current relevance of 30.9% is of some concern, this still potentially warrants inclusion in the EBS. Conversely the additional yield from testing lauryl glucoside in addition to decyl glucoside was only 0.30% (95%CI 0.16-0.5%), suggesting it may be better placed in a cosmetic/facial series despite a current relevance of 67.3%. The low additional yield reflects the high frequency of cross-reactions between the different glucoside chemicals.<sup>37</sup>

In conclusion, we present the results of an audit testing with “recommended additions” to the baseline series<sup>1</sup> with suggestions for updating the EBS (i.e., adding sodium metabisulfite, benzisothiazolinone, and decyl glucoside) and identifying where further work is required (e.g., concerning Compositae mix, and lin- and lim-OOHs).

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## CONFLICT OF INTERESTS

W.U. has accepted travel reimbursement and research funds from the cosmetic industry association International Fragrance Research Association. S.M.W. has received travel reimbursement to attend meetings with the cosmetic industry. O.A. is investigator for Leo Pharma. T.B. has been a speaker/investigator/advisor during the last 5 years for Abbvie, ALK, Amgen, AstraZeneca, Bencard, Eli Lilly & Co, Galderma, Janssen, Kiniska Pharmaceuticals, LEO Pharma, Philips, Novartis, and Sanofi-Genzyme. A.A.N. declares being a consultant and advisor and/or receiving speaking fees and/or grants and/or served as an investigator in clinical trials for AbbVie, Ammirall, Amgen, Biomed, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Glaxo Smith Kline, LEO Pharma, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre Pharma, Regeneron, Sandoz, Sanofi, and UCB Pharma. The Information Network of Departments of Dermatology (IVDK), maintained by the IVDK e.V., of which S. Schubert is an employee, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. S.S. declares to have been an advisor and/or speaker and/or investigator for AbbVie, Bayer Pharma, Celgene, LEO Pharma, Lilly Pharma, Novartis Pharma, Pierre Fabre, and Sanofi-Genzyme. M.-L.A.S. is an advisor, consultant, speaker, and/or investigator for Abbvie, Pfizer, LEO Pharma, Regeneron, Sanofi-Genzyme, Eli Lilly, and Galderma, and has received research grants from Regeneron, Sanofi-Genzyme, Novartis, and Pfizer. N.W. received lecture and advisory board honoraria from Novartis, ALK-Abellò, Abbvie, Galderma, and Takeda, and a research grant from Novartis, and participated in clinical trials with Novartis, Sanofi, and Blueprint. M. G. has received honoraria for advisory boards and lectures from Novartis, Abbvie, Leo, Lilly, Pfizer, Sanofi, and Takeda. The other authors have no pertinent conflict of interests to declare.

## DATA AVAILABILITY STATEMENT

As no consent for publication of raw data had been obtained from patients, the original data are not available owing to GDPR privacy constraints.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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## APPENDIX

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