Contact allergy to oxidized linalool and oxidized limonene: Patch testing in consecutive patients with dermatitis

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Abstract
Background: Contact allergy to oxidized (ox.) linalool and ox. limonene has been reported to have a high prevalence, raising the question of inclusion into the baseline series. However, several important issues should be clarified and further investigated before inclusion can be warranted.

Objectives: To report the trends of ox. terpenes allergy in patients with dermatitis, features of the patch test reactions, and clinical characteristics of the patients.

Methods: A retrospective analysis of 5773 patients was performed. All patients were patch tested with baseline series, individual ingredients of fragrance mix I and II, ox. linalool, and ox. limonene from 2013 to 2020.

Results: The prevalence rates of contact allergy to ox. linalool and ox. limonene were 7.0% and 5.1%, respectively. Significantly increasing trends of contact allergy were observed. More than 95% of contact allergy cases were identified on Day 3/4. Patients with contact allergy to ox. linalool and ox. limonene were significantly younger than those with contact allergy to other fragrances and were predominantly female. Strong reactions were associated with older age and multiple fragrance allergies.

Conclusions: Contact allergy to ox. linalool and ox. limonene is becoming increasingly important, and findings show intriguing features. More studies concerning the clinical relevance before recommending these substances for screening are required.

Keywords
allergic contact dermatitis, delayed hypersensitivity, fragrance allergy, hydroperoxides, patch test, prevalence, terpenes

1 | INTRODUCTION

Linalool (C10H18O) and limonene (C10H16) are terpenes formed naturally in plants.1,2 These terpenes carry a low sensitization potential and can be oxidized by air into different end products. Contact sensitizers may be formed when the terpenes are oxidized.1,2 Hydroperoxides (HPs) of linalool and limonene are common oxidized forms of the terpenes that are found to have strong sensitizing properties.
The prevalence rates of allergies to unoxidized linalool and limonene are extremely low compared with their oxidized compounds.\textsuperscript{16} The prevalence rates of ox. linalool and ox. limonene allergy in adults from several studies have been varied during the past decade. Allergy to linalool HPs (1.0% in petrolatum) were reported in 5.9% to 11.7% of patch tested patients.\textsuperscript{16-20} By contrast, allergy to limonene HPs (0.3% in petrolatum) was 5.0% to 9.4%.\textsuperscript{16-18,20-22} Although the prevalence rates and clinical characteristics of ox. linalool and ox. limonene allergy have been reported, there have been differences in the study period, geographical location, and days of patch test reading in the previous studies. Therefore, further research is needed to increase our understanding of the clinical implications of contact allergy to ox. terpenes. This study aimed to report the prevalence rates and changing trends of contact allergy to ox. terpenes in patients with dermatitis, to demonstrate the features of patch test reactions and clinical characteristics of patients with ox. terpenes allergy. This is the first study in a project aiming to improve and understand the diagnostics of contact allergy and allergic contact dermatitis from ox. terpenes.

2 \hspace{1cm} MATERIALS AND METHODS

2.1 \hspace{1cm} Study population

Patients referred for patch testing due to dermatitis between 2013 and 2020 at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden, were included. Patients' characteristics, including age, sex, history of atopic dermatitis, and the primary site of skin lesions, were recorded. This retrospective review study was approved by The Swedish Ethical Review Authority (2020–02190).

2.2 \hspace{1cm} Patch testing

The patients were patch tested with the Swedish baseline series (30 allergens) and the Malmö extended baseline series. Allergens in the baseline series categorized as markers of fragrance allergy were fragrance mix I (8% w/w petrolatum, containing 1% amyl cinnamal, 1% cinnamyl alcohol, 1% eugenol, 1% hydroxycitronellal, 1% isoeugenol, 1% cinnamal, 1% geraniol, 1% \textit{E. prunastri} extract, and 5% sorbitan sesquioleate); fragrance mix II (14% w/w petrolatum, containing 1% citral, 2.5% coumarin, 2.5% farnesol, 0.5% citronellol, 5% hexyl cinnamic aldehyde, and 2.5% hydroxyisohexyl 3-cyclohexene carboxaldehyde [HICC]), and \textit{Myroxylon pereirae} resin (balsam of Peru; 25% in petrolatum). Colophony was included in the baseline series but was not defined as a fragrance marker in the statistical analysis for the fragrance allergy patient group. The extended baseline series contains a varying number of common allergens added/changed on an annual basis, based on the exposure evaluation (analysis of present exposure data) and scientific literature and present research. The individual 16 fragrance materials were included during the study period: the 14 individual fragrance mix I and II ingredients as well as linalool HPs (1.0% in petrolatum) and limonene HPs (0.3% in petrolatum). The patch test concentrations of the constituents of the fragrance mixes are listed as follows: 2% amyl cinnamal, 1% cinnamal, 2% cinnamyl alcohol, 2% eugenol, 2% \textit{E. prunastri} extract, 2% geraniol, 2% hydroxycitronellal isoeugenol, 20% sorbitan sesquioleate, 2% citral, 1% citronellol, 5% coumarin, 5% farnesol, 10% hexyl cinnamal, and 5% HICC. All allergens
were purchased from Chemotechnique MB Diagnostics AB; Vellinge, Sweden.

The patch testing was performed and interpreted in accordance with the ICDRG guidelines. The allergens were applied (20 mg of petrolatum preparations24 and 15 μL of aqueous solutions25) in 8-mm aluminium Finn Chambers or 8-mm Finn Chambers AQUA (SmartPractice, Phoenix, AZ, USA) to test in most of the patients (94.0%) from the year 2013 to 2017 or from 2018 to 2020, respectively. IQ Ultra or IQ Ultimate chambers 8 × 8 mm (Chemotechnique MB Diagnostics AB) were used in 6.0% of patients throughout the study period. For these chambers, 25 mg of petrolatum preparations (39.06 mg/cm²) and 20 μL of aqueous solutions (31.25 μL/cm²) were used to ensure similar doses of applied allergens between two test chambers systems. A preliminary statistical analysis found no significant differences in the prevalence rates of positive reactions between patients using IQ chambers and Finn Chamber AQUA to the ox. terpenes. The fragrances were applied on the upper back immediately after the patch test chambers preparation. They were left on the back for 2 days after the placement on Day (D) 0. Skin reactions were evaluated on D3 or 4 (D3/4) and D7.

The intensities of reactions were further grouped into positive or negative reactions as follows: The strongest reaction on D3/4 or D7 decided the patient reactivity. Irritant and doubtful reactions were grouped as negative in subsequent analysis. In the analysis, weak (1 +), strong (2 +), and extreme (3 +) reactions were grouped as positive. Fragrance allergy patients were those who reacted to at least one of fragrance allergens in the baseline series, constituents of fragrance mix I and II, linalool HPs, or limonene HPs. Patients with at least one positive patch-test reaction to linalool HPs and/or limonene HPs were counted as ox. terpenes allergy patients. These patients were divided into the following subgroups: exclusively positive to ox. linalool, which indicates those who reacted to only the linalool HPs but not to other fragrance allergy markers, and patients with an exclusively positive to ox. limonene, which describes those who had positive reactions to the limonene HPs without any other fragrances.

2.3 | Statistical analysis

The clinical data and percentage of positive allergens were analysed using descriptive methods. In order to investigate associations between the proportion of (a) patients with positive reactions to ox. linalool and ox. limonene with negative reactions, (b) patients with exclusive positive reactions to ox. linalool and ox. limonene with other patients with fragrance allergy, (c) patients within the ox. terpenes allergy group who had “weak” positive reactions compared with “strong to extreme” positive reactions, and trends of reactions, we used the Pearson chi-square test or Fisher exact test. Univariable logistic regression analysis was utilized to estimate the crude odds ratio (OR). The factors found to be associated with a P-value of less than .2 were further subjected to multivariable logistic analysis. Spearman correlation was used to investigate associations between the intensity of reactions to ox. linalool and ox. limonene. A P-value of less than .05 was deemed statistically significant. IBM SPSS Statistics for Windows (version 27.0; IBM Inc., New York, NY) was used for statistical analysis.

3 | RESULTS

In all, 5773 patients were patch tested with all fragrance allergens and allergens in the Swedish baseline series between 2013 and 2020. There were 3924 (68.0%) females and 1849 (32.0%) males. The mean age was 44.6 ± 17.0 years (44.4 ± 16.4 years for males and 44.7 ± 17.2 years for females; P = .67). Atopic dermatitis was reported in 24.2% of patients. The main sites of lesions were hands and fingers (30.3%), face (18.0%), arms and armpits (8.6%), trunk (4.7%), and in 3.4%, the dermatitis was defined as generalized.

**FIGURE 2** Prevalence of oxidized terpenes allergy in 5773 patients with dermatitis
Of the 5773 patients, 403 (7.0%) reacted positively to ox. linalool (7.8% for females and 5.3% for males; \( P = .001 \)), and 296 (5.1%) had a positive reaction to ox. limonene (6.2% for females and 2.9% for males; \( P < .001 \)), respectively. In total, 543 of 5773 (9.4%) patients were allergic to ox. terpenes. Of these, simultaneous reactions to ox. terpenes were found in 156 (28.7%) patients, 247 (45.5%) reacted to only linalool HPs but not limonene HPs, and 140 (25.8%) reacted to only limonene HPs but not linalool HPs (Figure 2). In 949 patients with fragrance allergy (16.4% of all tested patients), 162 patients reacted “exclusively positive to ox. linalool” and 98 patients reacted “exclusively positive to ox. limonene”.

Figure 3 demonstrates the trends of positive reactions to ox. terpenes. The overall positive (either 1+, 2+, or 3+) and weak positive (only 1+) reactions showed significantly increasing trends in both ox. terpenes (\( P = .004 \) for ox. linalool, and \( <.001 \) for ox. limonene). There were no significantly increasing trends for strong and extreme positive reactions (\( P = .513 \) for ox. linalool, and \( .097 \) for ox. limonene). The intensities of readings are detailed in Tables 1 and 2. About one-fifth of patients with ox. terpenes allergy (84 out of 403, 20.8% for ox. linalool; 59 out of 296, 19.9% for ox. limonene) had strong to extreme positive reactions. Some positive cases were additionally detected on D7 (11 of 403, 2.7% of the overall ox. linalool patients; 11 of 289, 3.8% of the overall ox. limonene patients), which had negative or doubtful reactions on D3/4. In patients with a doubtful reaction to ox. linalool and ox. limonene on the first reading, 1.4% and 1.6% of the patients turned to react positively on D7, respectively. The Spearman correlation of reading intensities between ox. linalool and ox. limonene was 0.468 (\( P < .001 \)). The patients with strong to extreme reactions to either ox. linalool or ox. limonene had a significantly higher risk to react simultaneously to both ox. terpenes and all other fragrances in the baseline series (Table 3).

Table S1 details all patients’ demographic data and the results of univariable and multivariable regression analyses of the patients with
Table 3 Concurrent reactions to other fragrances: Comparison between patients with “weak positive reactions” with “strong and extreme reactions” to oxidized linalool and oxidized limonene

| Other fragrances | Oxidized linalool allergy | Oxidized limonene allergy |
|------------------|---------------------------|--------------------------|
|                  | All positive, n (%)       | Strong and extreme reactions, n (%) | Weak reaction, n (%) | P-value | OR (95%CI)
| Oxidized linalool | 156 (38.7) | 48 (57.1) | 108 (33.9) | <.001 | 2.61 (1.60-4.25) |
| Myroxylon pereirae resin | 95 (23.6) | 33 (39.3) | 62 (19.4) | <.001 | 2.68 (1.60-4.50) |
| Fragrance mix I | 94 (23.3) | 33 (39.3) | 61 (19.1) | <.001 | 2.74 (1.63-4.60) |
| Fragrance mix II | 42 (10.4) | 20 (23.8) | 22 (6.9) | <.001 | 4.22 (2.17-8.19) |
| Oxidized limonene | 156 (38.7) | 48 (57.1) | 108 (33.9) | <.001 | 2.61 (1.60-4.25) |
| M. pereirae resin | 67 (22.6) | 22 (37.3) | 45 (19.0) | .003 | 2.54 (1.37-4.71) |
| Fragrance mix I | 78 (26.4) | 23 (39.0) | 55 (23.2) | .014 | 2.11 (1.16-3.87) |
| Fragrance mix II | 26 (8.7) | 11 (18.6) | 15 (6.3) | .003 | 3.39 (1.47-7.84) |
| Oxidized linalool | 156 (52.7) | 45 (76.3) | 111 (46.8) | <.001 | 3.65 (1.90-7.00) |

Note: P-value <.05 indicates a statistically significant difference. Abbreviations: CI, confidence interval; OR, odds ratio.

*Univariable logistic regression analysis.

and without an ox. linalool allergy, and with and without an ox. limonene allergy. Females were predominant in both ox. linalool and ox. limonene allergy. The lower age group and having primary lesion on the trunk were found to be significant factors related to the overall ox. limonene allergy compared with other patients with dermatitis.

Within the group of patients with fragrance allergy, comparisons of “exclusively positive ox. linalool” patients with others (excluded patients with ox. limonene allergy) and of “exclusively positive ox. limonene” patients with others (excluded patients with ox. linalool allergy) were performed (Tables S2 and S3). Patients who were exclusively positive to ox. linalool and ox. limonene were significantly younger than other patients with fragrance allergy. The mean age differences are illustrated in Figure 4. The younger age group was the only significant associated factor for exclusive ox. linalool allergy (P = .009) with the OR and 95% confidence interval (CI) of |.63 (1.13-2.35) (Table S2). For exclusive ox. limonene allergy, younger age group, female sex, and having primary skin lesions on head and neck were significantly associated factors with the P-values, ORs (95% CI) of <.001, 2.44 (1.55-3.83); .001, 2.82 (1.50-5.30); and .028, 4.64 (1.18-18.26), respectively (Table S3).

The characteristics of patients with ox. terpenes allergy were further compared between weak and strong to extreme positive reactions groups (Tables S4 and S5). Patients with older age (more than 40 years) were significantly associated with having strong to extreme patch test reactions to both ox. linalool (P = .001) and ox. limonene allergy (P = .001).

4 Discussion

4.1 Prevalence rates and trends of ox. Terpenes allergy

Comparing the overall prevalence rates with the previous reports, our study found similar numbers of positive reactions to ox. terpenes. Concurrent reaction to ox. terpenes was previously found in 25.3% to 28.1% of patients, which were also comparable to the result in this study. The prevalence of positive reactions to linalool HPs was higher than to limonene HPs. It might result from the difference in the tendency of the molecules to be oxidized, mode and amount of exposure, mechanism of absorption, and pathway of hypersensitive reactions in the skin.

Interestingly, the trends of positive reactions to both HPs showed no significantly increase in this study. When comparing two previous studies conducted in 2010 and from 2015 to 2017, the prevalence rates of ox. terpenes allergies were higher in the later years. However, the settings of the population in those studies were different. Our study, however, confirms that the trends seem increasing. There may be at least three explanations for the increasing trends, with one that may actually be caused by the effect of a patch test technique “error.” First, it has been shown in a recent study that doubtful and positive reactions were reported to have higher prevalence rates for some selected test allergens in Finn Chamber AQUA, including ox. linalool. The test preparations were supplied from the same manufacturer during our study. However, the test chambers were changed in January 2018 from Finn Chamber to Finn Chamber AQUA. In this study, as compared with the quoted, more patients were included; thus, the difference in detecting positive reactions between two test systems might be enhanced, especially for peroxides, which might react with the aluminum in the chamber material and give rise to a false-positive reaction. A better occlusion from using...
Finn Chamber AQUA might be another possible explanation. Further research focusing on the flaws of the respective patch testing procedures may help elucidate the possible impact on this factor for the found increasing trend.

Second, there has been increased exposure to the terpenes in products, leading to an “automatic” increase in exposure to the ox. terpenes. Third, there has been no increase in exposure to the terpenes, but products containing the terpenes contain more HPs. However, there is still a lack of strong evidence about sufficient concentrations of ox. terpenes in products that could induce dermatitis.

Of positive patients, 95.7% (6.7 out of 7.0%) of ox. linalool and 96.1% (4.9 out of 5.1%) of ox. limonene allergies were detected on D3/4. Among patients who did not react at the first reading, the risk of having a positive reaction at D7 was low. With regard to factors influencing the patch test reading technique, it might be accurate to take into consideration the fact that earlier reading on D2 might not be efficient because the crescendo reaction has also been reported. This could imply that most allergy cases should be read and diagnosed on D3/4. Regarding the concern of active sensitization to ox. terpenes in patch testing, there was no sign of delayed reaction or active sensitization in this study.

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On D3/4, overall doubtful reactions were found in about 10% and 8% for ox. linalool and ox. limonene, respectively. Most of these patients turned to be negative, whereas 1.5% of patients had positive reactions on D7. Management of patients with doubtful reactions remains challenging. Doubtful reactions were previously reported in
2.4% to 12.1% of the patch tested patients for either ox. linalool or ox. limonene. As the day of readings was different according to the test centres, and the studies were conducted in different years, the prevalence rates could be varying. The most important factor is, of course, if the test doses and patch test chambers were standardized. One hypothesis is that the doubtful reaction could be a sign of irritation not fulfilling the criteria of an irritant reaction. By contrast, the doubtful reactions might be a mild or early response of allergic reaction, which might have a tendency to become stronger later or with a higher dose. It could be possible that the test concentrations might not be optimal. A higher rate of positive reactions had been shown to be detected by a higher concentration of ox. linalool in a previous study, which might be useful to perform as a supplementary test in doubtful cases.

Although there was evidence that the ox. terpenes can cause irritation, this study found extremely low irritation rates. The prevalence rates of irritation reactions might also differ among test centres, which might result from the differences in patch test methods, materials, reading traditions of reactions that might not qualify to be classified as allergic reactions, and physician’s experience. Therefore, the patch test reactions of ox. terpenes remain problematic even though the test preparations were standardized. Use test or repeated open application test (ROAT) with personal products containing linalool or limonene might be helpful to give advice to the patients on whether the products should be avoided. However, the clinical relevance of positive patch test reactions cannot be proven because the amount and concentrations of ox. terpenes in the products are unknown.

Patients with strong to extreme patch test reactions to ox. linalool and ox. limonene had a tendency to have simultaneous reactions to the other ox. fragrance terpene and other fragrances in the baseline series. The finding supports that the patients had a true allergy to fragrances, and patient education about scented products avoidance should be highly encouraged in this patient group because they were much more predisposed to be sensitized by multiple common fragrance allergens.

Simultaneous reactions to ox. linalool and ox. limonene were common, and the intensities of reactions of the ox. terpenes had a significant, moderately positive correlation demonstrated by Spearman correlation analysis in this study. Concerning the two test materials, they are, however, quite different structurally (Figure 1). The differences in chemical structures, amount, and minor structural alterations of the HPs were found to affect the responses of dendritic cells in the skin sensitization process; thus, contact allergy to ox. linalool and ox. limonene should occur independently. Moreover, cross-reactivity between HPs could not be established. One possible explanation for our findings would be co-sensitization because both limonene and linalool were common ingredients used simultaneously in personal products. With regard to published data, however, chemical analysis of products in a market survey found very low concentrations of the ox. terpenes compared with those concentrations that have been used for local lymph node assay and patch testing, which could not explain the prevalence rates of contact sensitization in humans. Therefore, further studies regarding patients with contact allergy, personal products chemical analysis, and use tests will help uncover the causes of induction of sensitization in the population.

### 4.2 Clinical characteristics of patients with ox. terpenes allergy

When analysing the different age groups, certain interesting features were found. There were no statistically significant differences between ages comparing patients who had positive and negative reactions to the ox. terpenes. Surprisingly, we found that the patients who had exclusively positive reactions to either ox. linalool or ox. limonene had a significantly lower age than other fragrance allergy patients. The most recent study reported dissimilar results, which showed that a group of patients with positive reactions to ox. limonene had a significantly older age than the group with other fragrances allergy. This difference might be a result of different inclusion criteria of comparing groups. The patients with ox. terpenes allergy and other fragrances allergy were definitely divided without overlap in our study. The prevalence of positive reactions in children seemed to be higher in adults; 13.0% and 17.9% of tested paediatric patients in the United States from 2007 to 2019 had positive reactions to ox. limonene and ox. linalool, respectively. In general, contact sensitization is uncommon in children or young adults, and the prevalence rates of positive reactions were found to be lower in children for most of the allergens in the baseline series. Early and prolonged exposure to allergens could be an explanation for diagnosing contact sensitization cases in the lower age groups of patients. Limonene and linalool were also found in nearly 30% of baby care products, while other common allergens in fragrance mix I and II were rarely found. Regardless of contact sensitization to cosmetic products, all products in close contact for a prolonged time, particularly under occlusion that contain sensitizing fragrances in a sufficient dose, will pose a possible risk of sensitization.

Our study also found stronger patch test reactions in the older patient group (Figure 4 and Tables S4 and S5). A possible explanation could be that the exposure and sensitization to these allergens seem to start since young and induce stronger hypersensitization activity over time. Repeated skin contact to fragrances at higher doses and more products containing the sensitizers might also result in cumulative exposure in older patients.

Female sex was predominant in patients with positive reactions to ox. linalool and ox. limonene. However, when compared with other patients with fragrance allergy, there was no significant difference between sexes in patients with only ox. linalool allergy. Interestingly, exclusive allergic reactions to ox. limonene were significantly more common in females than those found in patients with other fragrance allergies. Being a female showed a 2.82 times higher risk of getting ox. limonene allergy than other fragrances. One of the reasons that could explain this is that the scent of limonene might not be popular among men.

Among cosmetics categories, shampoo demonstrated the highest number of fragrance allergens in products. Limonene and linalool remained the two most common fragrance ingredients found in
almost all kinds of cosmetics.\textsuperscript{10} The area of skin exposure to the fragrances, especially the ox. terpenes, could be widespread. Thus, when comparing the main sites of lesions between patients with positive and negative reactions to ox. linalool and ox. limonene (Table S1), the lesions in patients with ox. linalool and ox. limonene allergy were mostly similarly distributed as patients with other dermatitis. Patients who had an exclusive ox. linalool allergy showed a similar distribution of skin lesions as patients with other fragrance allergy. However, the patients who had an exclusively positive reaction to ox. limonene were found to have primary lesions on the head and neck more than patients with other fragrance allergy (Table S3). Exposure to allergens in different kinds of products might be a cause. Limonene might be preferred in haircare or facial products. Performing market surveys of product labelling together with chemical analysis of the products used on different parts of the body might give further understanding.

4.3 Limitation

Although there are limitations in a retrospective study, mainly that some data might be missing, most of the important information was recorded and available for analysis. The evaluation of the clinical relevance of the positive reactions to ox. linalool and ox. limonene was extremely problematic and could be a limitation of this study because we could not truly explain the sources of exposure to the HPs. Neither could the clinical symptoms at patch testing by necessity be found associated with the allergy found. Even though plenty of personal products were declared to contain linalool or limonene, we are not sure if they contained ox. linalool and ox. limonene, neither qualitatively nor quantitatively with levels of HPs that could help explain sensitization and elicitation of clinical dermatitis. So far, we have not been able to ascribe contact allergy to personal products labelled to contain linalool and/or limonene even though the patients sometimes had positive patch test reactions to such products frequently tested, mainly because it was unknown whether these products contained the sensitizing HPs and partly because the products contained other sensitizers including many fragrance materials as well as preservatives. Although ROATs could be helpful to determine the clinical relevance in patients with positive reactions,\textsuperscript{40,41} further ROATs study with precise concentrations of ox. linalool and ox. limonene should be performed.

5 Conclusions

In conclusion, this study found increasing contact allergy trends to ox. linalool and ox. limonene. The vast majority of allergic reactions to ox. terpenes was registered on the first patch test reading on D3/4. Young females should be aware of the risk of getting sensitized to the ox. terpenes, and younger individuals may be continuously elicited and develop stronger skin reactions over time. Patients with strong to extreme reactions to ox. linalool and ox. limonene should be recommended to avoid using scented products because the results indicate that these patients would risk having allergies to multiple fragrances compared with patients with weak reactions. Future research aiming at explaining the complexity between patch test reactions and exposure to the ox. terpenes rather than the non-oxidized ones to provide strong evidence of clinical relevance due to the high exposure to these fragrances is absolutely needed. Ox. linalool and ox. limonene should be tested in baseline series for experts, not for every dermatologist, to allow better knowledge about exposure and relevance. Improved knowledge is also needed on the qualitative and quantitative presence of the sensitizing HPs in consumer products labelled to contain limonene and linalool. Randomized trials and controlled ROATs with high, realistic concentrations of the ox. terpenes must be undertaken to provide scientific evidence of the clinical relevance before recommending these substances for screening.

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AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST
M.B. is a member of the Expert Panel for Fragrance Safety - http://fragrancesafetypanel.org/. The other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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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