

ORIGINAL ARTICLE

Contact allergy to oxidized geraniol among Swedish dermatitis patients—A multicentre study by the Swedish Contact Dermatitis Research Group

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Background: Geraniol is a widely used fragrance terpene, and is included in fragrance mix I. Geraniol is prone to autoxidation, forming the skin sensitizers geranial, neral, and geraniol-7-hydroperoxide. Oxidized geraniol has previously been patch tested in 1 clinic, giving 1% to 4.6% positive reactions in consecutive patients when tested at 2% to 11%.

Aim: To compare test reactions to pure and oxidized geraniol, to compare 2 different test concentrations of oxidized geraniol and to investigate the pattern of concomitant reactions to fragrance markers of the baseline series in a multicentre setting.

Methods: One thousand four hundred and seventy-six consecutive patients referred for patch testing were patch tested with geraniol 6% pet. and oxidized geraniol 6% and 11% pet.

Results: Pure geraniol 6% pet., oxidized geraniol 6% pet. and oxidized geraniol 11% pet. gave 1%, 3% and 8% positive patch test reactions and 0.7%, 3% and 5% doubtful reactions, respectively. Approximately 50% of the patients with doubtful reactions to oxidized geraniol 6% pet. had positive reactions to oxidized geraniol 11% pet.

Conclusions: Oxidized geraniol 11% pet. provides better detection than oxidized geraniol 6% pet. As most patients reacted only to oxidized geraniol, it is important to explore further whether oxidized geraniol should be included in a baseline patch test series.

KEYWORDS

allergic contact dermatitis, autoxidation, fragrance contact allergy, fragrance mix I, geraniol, patch testing, terpenes

1 | INTRODUCTION

Geraniol is a widely used fragrance terpene with a fresh flowery odour. It is found naturally in several natural oils, including citronella oil, rose oil, and palmarosa oil, and is also synthesized industrially. Geraniol is present in perfumes and fine fragrances, and in common household and hygiene products, and has been found on labels or detected by analysis in approximately 40% to 60% of such products.^{1–3} On calculation of consumer exposure based on concentrations of fragrance compounds in 10 types of cosmetic products, it

was found that geraniol was among the fragrances with the highest accumulated dermal exposure for high-end users of such products.⁴

Geraniol, at a concentration of 1%, is a component of fragrance mix I (FM I), which is included in the European baseline series for patch testing dermatitis patients. The frequency of positive reactions to FM I was found to be 6.6% in a large screening study.⁵ On patch testing with constituents of the mix, 4.7% of these positive reactions were found to be attributable to geraniol.

Geraniol, like several other common fragrance terpenes, has been shown to autoxidize when in contact with air, thus acting as a

prehapten forming the skin-sensitizing oxidation products geraniol-7-hydroperoxide, geranial, and neral.⁶ Geraniol has also been shown to be a substrate for metabolic activity, thus making it a prohapten, as the sensitizers geranial and neral, as well as geraniol epoxide, were detected when geraniol was incubated with a cocktail of cytochrome P450 enzymes simulating metabolism in the skin (Figure 1).⁷

In an earlier study at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden, geraniol and autoxidized geraniol were patch tested concomitantly to investigate whether oxidized geraniol would detect more cases of fragrance contact allergy related to geraniol than pure geraniol. Pure and oxidized geraniol were tested 2.0% pet. in 2200 patients, and gave positive patch test reactions in 0.13% and 0.55% of the patients, respectively.⁸ The irritancy of pure and oxidized geraniol was investigated in dermatitis patients with concentrations ranging from 2.5% to 20.0% pet., but very little irritation was recorded even at the highest concentrations.⁹ Subsequently, a dose-response patch test study was performed in order to investigate the outcome of patch testing with increasing test concentrations of pure and oxidized geraniol, that is, 4.0%, 6.0% and 11.0% pet. Pure geraniol gave positive reactions in 0.15%, 0.46% and 1.1% of the patients, respectively, and oxidized geraniol gave positive reactions in 0.9%, 2.3% and 4.6% of the patients, respectively.⁹

The aims of the present study were to compare patch test reactions to pure and oxidized geraniol, to compare 2 different test concentrations of oxidized geraniol, and to investigate the pattern of concomitant reactions to fragrance markers of the baseline series in a

multicentre setting at 5 Swedish dermatology clinics of the Swedish Contact Dermatitis Research Group. The results were compared with the results of previous clinical studies on oxidized geraniol.^{8,9}

2 | PATIENTS AND METHODS

2.1 | Chemicals, analysis, and synthesis

Geraniol (98% purity) was from Sigma Aldrich (St Louis, Missouri). Geranial (98% purity), neral (>99% purity) and citral (neral 34% and geranial 66%) were from Bedoukian Research (Danbury, Connecticut). All chemicals were distilled prior to use.

High-performance liquid chromatography (HPLC) analyses were conducted on an Agilent 1260 HPLC system with a 1260 DAD VL+ detector. An Eclipse Plus C8 column (3.5 μ m, 4.6 $\times$ 150 mm; Agilent Technologies, Santa Clara, California) was used. Analysis of pure and oxidized geraniol was conducted with external standards as previously described.⁸ Analysis of the patch test preparations was performed with solid-phase extraction to determine the stability of the hydroperoxide, according to previous experience.¹⁰

Geraniol-7-hydroperoxide and geraniol-6-hydroperoxide (7-hydroperoxy-3,7-dimethyl-octa-2,5-dien-1-ol and 6-hydroperoxy-3,7-dimethyl-octa-2,7-dien-1-ol, respectively) were synthesized as previously described⁶ and used as reference compounds in the analysis of oxidized geraniol.

2.2 | Air exposure procedure

A distilled sample of geraniol (>98%) was air-exposed in an Erlenmeyer flask, and covered with aluminium foil to prevent contamination. It was stirred with magnetic stirrer at room temperature for 1 hour, 4 times daily, and exposed to light for 12 hours daily by use of a daylight fluorescent lamp (Philips, Eindhoven, the Netherlands; 18 W), as previously described.^{6,11} Samples were taken on a regular basis, and stored at -20°C under nitrogen until being analysed with HPLC with ultraviolet detection to determine the concentrations of geraniol and its major oxidation products. The oxidation was interrupted after 10 weeks, when the concentrations in the oxidation mixture were in accordance with those in previous studies, and the oxidation mixture was stored at -20°C under nitrogen.

2.3 | Patch test preparations

All chemicals were analysed before the patch test preparations were made. The oxidation mixture of geraniol contained geraniol 59% (wt/wt), geranial 4.6%, neral 1.2%, and geraniol-7-hydroperoxide 3.7%. No oxidation products could be detected in the purified geraniol with the method used. In accordance with previous experience, non-stabilized petrolatum (Prolabo, Chester, Pennsylvania) was used as the vehicle in the patch test preparations.¹² Patch test preparations of pure geraniol 6.0% pet., oxidized geraniol 6.0% pet. and oxidized geraniol 11% pet. were prepared at the Department of Dermatology, Gothenburg, according to previous experience.⁹ In the present study, test concentrations were selected to enable comparison between the tested compounds. The patch test preparation of oxidized geraniol

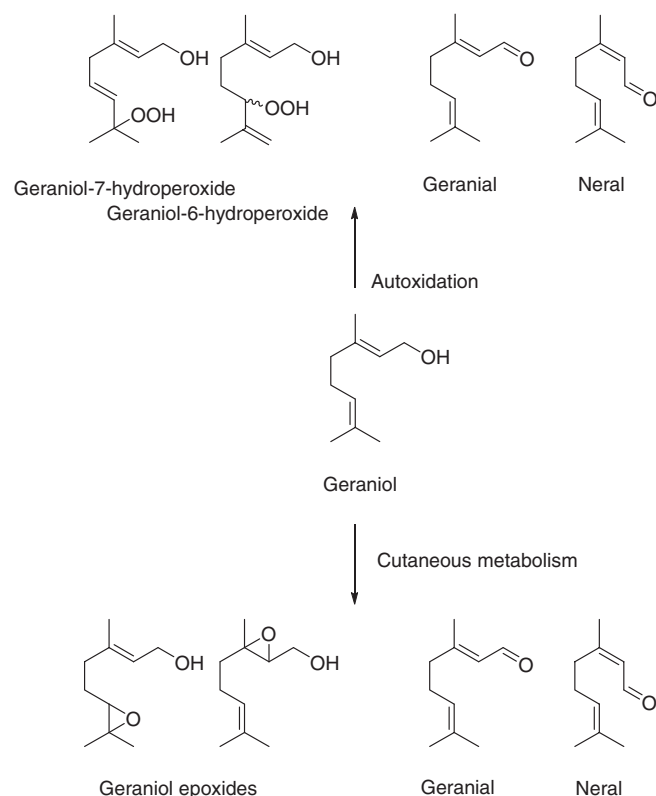


FIGURE 1 Schematic overview of the activation of geraniol to skin-sensitizing oxidation products. In the oxidation mixture, geranial, neral and geraniol-7-hydroperoxide (7-hydroperoxy-3,7-dimethyl-octa-2,5-dien-1-ol) have been detected⁶

6.0% pet. contained geraniol 3.5%, geraniol 0.3%, neral 0.07%, and geraniol-7-hydroperoxide 0.2%. The patch test preparation of oxidized geraniol 11% pet. contained geraniol 6.5%, geraniol 0.5%, neral 0.1%, and geraniol-7-hydroperoxide 0.4%. Pure geraniol was patch tested concomitantly 6.0% pet.

Patch test preparations were prepared directly before the start of the study, and stored in a refrigerator between use. New preparations were prepared and distributed after 6 months, and analysis of the oxidation mixture and pure geraniol was performed before the preparation of new patch test preparations. Analysis of a 6-month-old preparation of oxidized geraniol 6.0% with solid-phase extraction showed that the degradation of geraniol hydroperoxide was <20%, which has been considered to be the acceptable limit of variation of concentration in patch test preparations. The patch test materials were therefore replaced after 6 months.

2.4 | Test centres and patients

This study included 5 dermatology clinics in Sweden: Gothenburg, Malmö, Uddevalla, Umeå, and Örebro. The participants in the study were patients who were referred for patch testing because of suspected allergic contact dermatitis during 2012. A total of 1476 patients, 984 (67%) women and 492 (33%) men, were patch tested.

In addition to the usual patch tests used in each centre, the 3 test substances were applied to the upper part of the back. Approximately 20 mg of each test material was applied in small Finn Chambers (Epitest, Tuusula, Finland), with an inner area of 0.5 cm² and a diameter of 8 mm, and the tape used was Scanpor (Norgeplaster, Vennsela, Norway). After 48 hours of occlusion, the patches were removed and discarded by the patients. Readings were performed on 2 occasions, on day (D) 3 or D4 and on D7, according to ESCD recommendations.^{13,14}

2.5 | Statistical analysis

Analyses were performed with R version 3.0.3 (R foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and $P < .05$ was considered to be statistically significant. The exact binomial test was used to test for differences in positive reactions between the test materials. Fisher's exact test was used to evaluate differences in concomitant reactions to fragrance markers of the baseline series and differences in reaction patterns between centres. Confidence intervals of frequencies of contact allergy were calculated with the Mid-P exact test and OPENEPI (<http://openepi.com>). Venn diagrams were created with EULERAPE.¹⁵

3 | RESULTS

The overall test results are shown in Table 1. Pure geraniol gave the lowest frequency of positive patch test reactions (1.0%) of the investigated substances, and oxidized geraniol 11.0% pet. gave the highest frequency of positive reactions (8.2%). The frequency of positive reactions to pure geraniol was significantly lower than the frequency of positive reactions to oxidized geraniol both 6.0% and 11.0% pet. ($P < .0001$). The frequency of positive reactions to oxidized geraniol 6.0% pet. was significantly lower than the frequency of positive reactions to oxidized geraniol 11.0% pet. ($P < .0001$). Table 2 shows the positive reactions to geraniol and oxidized geraniol stratified for gender. In particular, for oxidized geraniol more positive patch test reactions were seen in women than in men (97/984 vs 24/492 for oxidized geraniol at 11.0% pet.; $P = .0008$, Fisher's exact test, 2-sided). The distributions of the strengths of the positive reactions to the 3 test materials are shown in Table 3.

Doubtful reactions to pure and oxidized geraniol are shown in Table 4. Few patients (0.7%) showed doubtful reactions to pure geraniol, whereas 3.5% of the patients showed doubtful reactions to oxidized geraniol 6.0% pet., and 4.9% of the patients showed doubtful reactions to oxidized geraniol 11% pet. Few irritant reactions were detected in the 5 clinics. Six of 1489 patients (0.4%) showed ≥ 1 irritant reactions to pure or oxidized geraniol. In all, 4 irritant reactions to oxidized geraniol 11% pet., 1 irritant reaction to oxidized geraniol 6.0% pet. and 1 irritant reaction to pure geraniol were recorded.

Fifty-two patients had doubtful test reactions when patch tested with oxidized geraniol 6.0% pet., and, of these, 27 had positive patch test reactions to oxidized geraniol 11.0% pet. (Figure 2). There were no significant differences between the clinics in the proportions of patients with doubtful reactions using 6.0% pet. and positive reactions with 11.0% pet. (Fisher's exact test, 2-sided).

The pattern of concomitant reactions to oxidized geraniol 11.0% pet. and 6.0% pet. and pure geraniol is presented as a Venn diagram in Figure 3. The majority of the patients reacting to oxidized geraniol 11.0% pet., showed a large overlap with reactions to oxidized geraniol 6.0% pet. Of the patients with positive reactions to oxidized geraniol 6.0% pet., 83% also reacted to oxidized geraniol 11.0% pet. Most of the patients reacting to pure geraniol showed positive reactions to all 3 test preparations.

Concomitant reactions to the 5 fragrance markers of the Swedish baseline series in patients reacting to pure and oxidized geraniol are shown in Table 5. Concomitant reactions to FM I in patients reacting to pure geraniol were common (67%), whereas the frequency of

TABLE 1 The number of positive patch test reactions (+, ++, and +++) in 1476 patients tested with pure and oxidized geraniol in the 5 dermatology clinics

	Positive reactions												95%CI
	Gothenburg		Malmö		Uddevalla		Umeå		Örebro		Total		
	N = 388		N = 672		N = 182		N = 134		N = 100		1476		
	n	%	n	%	n	%	n	%	n	%	n	%	
Oxidized geraniol 11.0% pet.	39	10.0	43	6.4	24	13.2	6	4.5	10	10	122	8.2	6.9-9.8
Oxidized geraniol 6.0% pet.	13	3.3	14	2.1	7	3.8	3	2.2	5	5	42	2.8	2.0-3.8
Geraniol 6.0% pet.	5	1.3	2	0.3	5	2.7	1	0.7	2	2	15	1.0	0.6-1.6

TABLE 2 Positive reactions to geraniol and oxidized geraniol stratified for gender

	Tested men (N)	Positive men, n (%)	95%CI	Tested women (N)	Positive women, n (%)	95%CI
Oxidized geraniol 11.0% pet.	492	24 (4.9)	3.2-7.1	984	97 (9.9)	8.0-12
Oxidized geraniol 6.0% pet.	492	5 (1.0)	0.37-2.3	984	37 (3.8)	2.7-5.1
Geraniol 6.0% pet.	492	4 (0.81)	0.3-2.0	984	11 (1.1)	0.59-1.9

One patient reacting to oxidized geraniol 11.0% pet. was excluded from the analysis, as gender was not specified.

TABLE 3 Distribution of strength of positive reactions to oxidized geraniol and geraniol

	Oxidized geraniol 11.0% pet.		Oxidized geraniol 6.0% pet.		Geraniol 6.0% pet.	
	+	++/+++	+	++/+++	+	++/+++
Gothenburg	29	10	12	1	4	1
Malmö	35	8	9	5	1	1
Uddevalla	21	3	5	2	4	1
Umeå	4	2	3	0	1	0
Örebro	5	5	1	4	2	0
Total	94 (77%)	28 (33%)	30 (71%)	12 (39%)	12 (80%)	3 (20%)

TABLE 4 Doubtful reactions to pure and oxidized geraniol

	Gothenburg N = 388		Malmö N = 672		Uddevalla N = 182		Umeå N = 134		Örebro N = 100		Total 1476		95%CI
	n	%	n	%	n	%	n	%	n	%	n	%	
Oxidized geraniol 11% pet.	13	3.3	44	6.5	6	3.3	8	6.0	1	1	72	4.9	3.8-6.1
Oxidized geraniol 6.0% pet.	9	2.3	28	4.2	6	3.3	3	2.2	6	6	52	3.5	2.6-4.6
Geraniol 6.0% pet.	0	0.0	10	1.5	1	0.5	0	0.0	0	0	11	0.7	0.4-1.3

concomitant reactions between oxidized geraniol and FM I was, at most, 40%. Patients with positive reactions to oxidized geraniol at 6.0% pet. had a significantly higher share of concomitant reactions to ≥ 1 fragrance markers of the baseline series than patients reacting to oxidized geraniol at 11.0% pet. only, but the statistical significance of this difference was weak ($P = .038$). No significant difference in concomitant reactions was found when only FM I and oxidized geraniol were compared at the 2 test concentrations.

4 | DISCUSSION

The results of this study support earlier findings that oxidized geraniol is a more important test material than pure geraniol for the diagnosis of contact allergy in dermatitis patients. It is likely that contact allergy is most commonly induced by contact with the sensitizers in air-exposed geraniol. In this study, 2 concentrations of oxidized geraniol were used in a multicentre setting. The highest test concentration of oxidized geraniol detected more positive reactions, indicating that this concentration of the haptens is more optimal for detecting contact allergy. This test concentration also gave more doubtful reactions than the lower concentration; however, the increase in doubtful reactions was lower than the increase in the positive reactions (Tables 1–2 and 4).

The majority of patients with positive reactions to either oxidized geraniol at 6.0% pet. or pure geraniol at 6.0% pet. also reacted to

oxidized geraniol 11.0% pet. There was no statistically significant difference in concomitant reactions to pure geraniol between the 2 concentrations of oxidized geraniol. Furthermore, the majority of patients with positive reactions to oxidized geraniol 11.0% pet. did not react to either oxidized geraniol 6.0% pet. or pure geraniol, indicating that the 11% concentration detects cases that are not detected by the other test preparations. A large proportion of the patients with doubtful reactions to oxidized geraniol 6.0% pet. showed positive reactions to the 11.0% concentration, implying that the 6.0% concentration was too low to yield a positive patch test reaction (Figure 2). When a patch test concentration is selected, it is important for the culprit haptens to be tested at the highest possible concentration that does not cause irritation or sensitization.¹⁶ Few irritant reactions and no active sensitization to the test materials were reported, including at the highest patch test concentration. This would support using oxidized geraniol 11.0% pet. as a tool for diagnosing contact allergy to this oxidized fragrance.

In the test materials used, the preparation of oxidized geraniol 11.0% pet. contained 0.35% geraniol-7-hydroperoxide and 6.5% geraniol. The concentration of geraniol is thus basically the same as in the preparation of pure geraniol 6.0% pet. Ten of 15 patients reacting to pure geraniol also reacted to oxidized geraniol 11.0% pet. Patch testing with oxidized geraniol 11.0% pet. thus detected as many cases of contact allergy to pure geraniol as patch testing with FM I (Table 5). Thus, patch testing with oxidized geraniol 11.0% pet. detects contact allergy to geraniol at the same level as FM I while also detecting

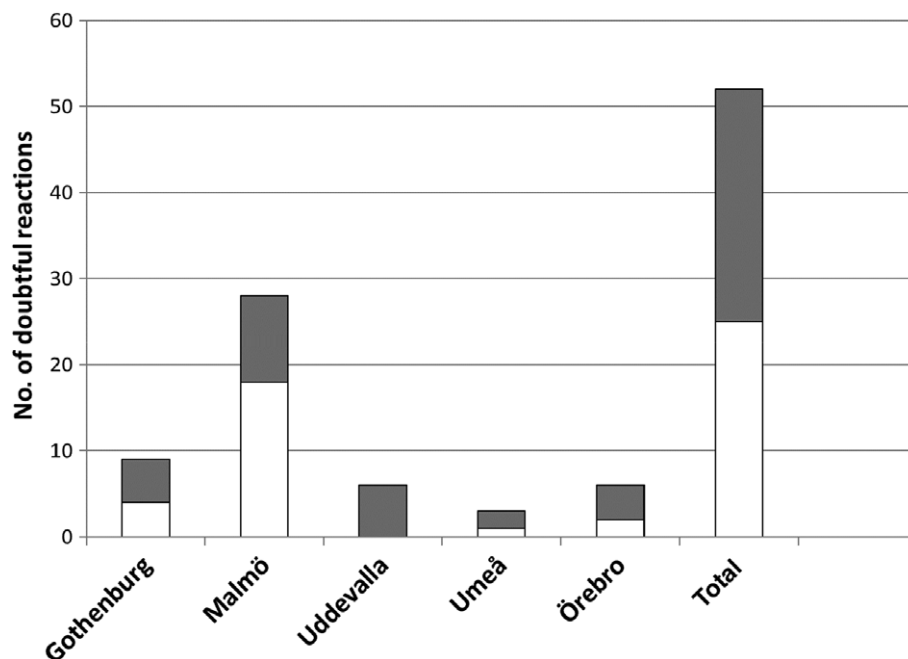


FIGURE 2 Patients with doubtful patch test reactions to oxidized geraniol 6.0% pet. are indicated by white. The subgroup that also showed positive patch test reactions to oxidized geraniol 11.0% pet. is indicated by grey. Of 52 patients with doubtful reactions to oxidized geraniol 6.0% pet., 27 showed positive reactions at the higher test concentration

contact allergy to oxidation products of geraniol. Of the sensitizers detected in oxidized geraniol, geraniol-7-hydroperoxide is considered to be the most important, followed by geranial and neral. Other hydroperoxides may theoretically be produced by autoxidation of geraniol (Figure 1),¹⁷ but have not been detected in the oxidation mixture. As the aldehydes are formed as secondary oxidation products from an unstable hydroperoxide, lower levels of hydroperoxides are formed in geraniol than in related fragrance terpenes such as linalool.¹⁸

Concomitant reactions to other fragrance markers among patients with positive patch test reactions to oxidized geraniol at any concentration were more common in the present study (Table 5) than in the earlier Gothenburg study, in which 25% of patients with contact allergy to oxidized geraniol showed concomitant reactions to fragrance markers present in the baseline series.⁹ The levels of concomitant reactions to fragrance markers were, however, in line with the levels of concomitant reactions to fragrance markers among patients with positive reactions to other oxidized fragrance terpenes.^{19–21} This indicates that the hydroperoxide in the oxidation mixture is an important fragrance allergen.

Concomitant reactions to FM I were seen more often among patients with positive reactions to pure geraniol than among patients with positive reactions to oxidized geraniol (Table 5). Previous results have indicated that geraniol can act as a prohaptens and be activated enzymatically to sensitizing aldehydes and geraniol epoxide.⁷ Pure geraniol and geraniol in FM I are thus considered to be prohaptens, in that the reactions could be caused by aldehydes or epoxides detected in the cutaneous metabolism of geraniol. Concomitant reactions between geraniol, geranial and neral will be discussed in a subsequent article.

A higher frequency of positive patch test reactions to oxidized geraniol 11% pet. was recorded than in the earlier study on oxidized geraniol (8.2% and 4.6%, respectively).⁹ Higher frequencies than previously found were seen in all test centres except for 1 (4.5% in Umeå; Table 1). For pure geraniol 6.0% pet., the frequency of positive reactions was also slightly higher than in earlier studies. With the concentration of 2.0% pet., frequencies of 0.4% to 0.6% were observed among dermatitis patients in Europe.^{22,23} However, in a recent study performed with dermatitis patients in Thailand, geraniol tested at 2% gave positive reactions in 2.6% of the tested patients.²⁴

The high frequencies of reactions to oxidized fragrance compounds in clinical testing have turned the focus to potential haptens

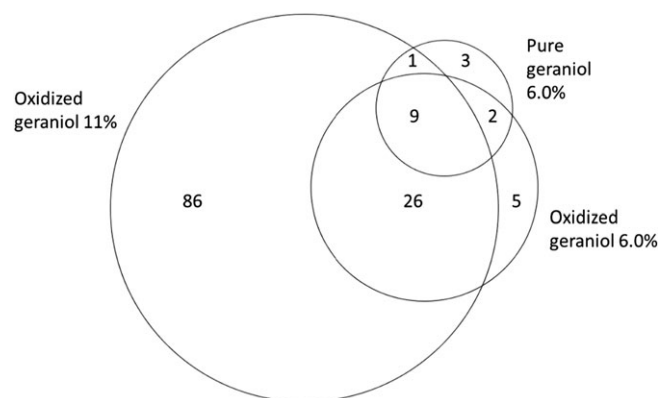


FIGURE 3 Pattern of concomitant reactions to oxidized geraniol 11.0% pet., oxidized geraniol 6.0% pet., and pure geraniol 6.0% pet. Figures represent the number of individuals with a certain reaction pattern

TABLE 5 Concomitant reactions to the fragrance markers of the Swedish baseline series in patients reacting to the study materials

	Clinics	N	FM I		FM II		HICC		Myroxylon pereiarae		Colophonium		≥1	
			n	%	n	%	n	%	n	%	n	%	n	%
Patients reacting to oxidized geraniol 11.0% pet.	Gothenburg	39	17	44	8	21	2	5	3	8	4	10	17	44
	Malmö	43	12	28	10	23	3	7	8	19	3	7	19	44
	Uddevalla	24	5	21	3	13	1	4	3	13	-	-	6	25
	Umeå	6	2	33	3	50	1	17	1	17	2	33	4	67
	Örebro	10	2	20	1	10	1	10	2	20	1	10	4	40
	Total	122	38	31	25	20	8	7	17	14	10	8	50	41
Patients reacting to oxidized geraniol 6.0% pet.	Gothenburg	13	8	62	4	31	-	-	2	15	1	8	8	62
	Malmö	14	4	29	4	29	-	-	3	21	5	36	10	71
	Uddevalla	7	3	43	2	29	-	-	-	-	1	14	4	57
	Umeå	3	1	33	1	33	1	33	-	-	-	-	1	33
	Örebro	5	1	20	1	20	1	20	-	-	-	-	2	40
	Total	42	17	40	12	29	2	5	5	12	7	17	25	60
Patients reacting to geraniol 6.0% pet.	Gothenburg	5	5	100	4	80	-	-	1	20	-	-	5	100
	Malmö	2	1	50	1	50	-	-	-	-	-	-	1	50
	Uddevalla	5	3	60	1	20	-	-	-	-	-	-	3	60
	Umeå	1	-	-	-	-	-	-	-	-	-	-	-	-
	Örebro	2	1	50	1	50	1	50	1	50	1	50	2	100
	Total	15	10	67	7	47	1	7	2	13	1	7	11	73

FM I, fragrance mix I; FM II, fragrance mix II; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

that are formed by air oxidation from far less sensitizing materials. The clinical relevance of these reactions has been discussed, and it has been shown that the patients, if questioned, will, in many cases, be using a product containing the mother compound on the dermatitis areas.^{8,10,19,25} For many individuals, the dermatitis will clear when such exposure is terminated.^{8,26} Interestingly, in all of the studies on oxidized fragrance terpenes, there is a strong female dominance among the allergic patients.^{9,19–21,27,28} In the present study, there is also a female dominance, with 2–3 times higher frequencies of positive patch test reactions to oxidized geraniol among women (Table 2). If the reactions were false positive, no such sex difference would be expected.

Although high frequencies of positive patch test reactions to oxidized fragrance compounds have been recorded, exposure to the exact hapten of the oxidation mixture for the individual consumer has not yet been generally shown. The identification and quantification of labile hydroperoxides in complex products are rarely available, for technical reasons. A case report described a girl with solitary contact allergy to oxidized linalool.²⁶ Her dermatitis cleared when the use of a scented shampoo was discontinued. The shampoo was analysed and found to contain minute amounts of linalool hydroperoxides.

Criteria for the performance of high-quality multicentre studies have been put forward.²⁹ The test materials should be well defined, the test centres should be well informed, and the reading criteria should be standardized. The current study was performed in accordance with these criteria, and can be regarded as being of high quality according to the grading system presented along with these criteria.

5 | CONCLUSIONS

The present study, in a multicentre setting, confirms the importance of patch testing with oxidized geraniol. Oxidized geraniol 11.0% pet. was found to be more useful in detecting contact allergy than oxidized geraniol 6.0% pet. as well as FM I with regard to both geraniol and its oxidation products. Concomitant reactions to other fragrance markers in the baseline series were common, supporting the connection with fragrance exposure. It is important to consider whether oxidized geraniol should be made commercially available for routine testing in accordance with using oxidized limonene and oxidized linalool for patch testing in dermatitis patients. Further assessment of exposure and the performance of usage tests are needed.

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Conflict of interest

Magnus Bruze is a member of an expert panel for fragrance safety ([www.http://fragrancesafetypanel.org/](http://fragrancesafetypanel.org/)). The other authors declare no potential conflict of interests.

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