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### **Allergy to oxidized limonene and linalool is frequent throughout the UK**

H. Audrain<sup>1,2</sup>, C. Kenward<sup>1</sup>, C.R. Lovell<sup>1</sup>, C. Green<sup>3</sup>, A.D. Ormerod<sup>4</sup>, J. Sansom<sup>2</sup>, M.M.U. Chowdhury<sup>5</sup>, S.M. Cooper<sup>6</sup>, G.A. Johnston<sup>7</sup>, M. Wilkinson<sup>8</sup>, C. King<sup>9</sup>, N. Stone<sup>10</sup>, H.L. Horne<sup>11</sup>, C.R. Holden<sup>12</sup>, S. Wakelin<sup>13</sup>, D.A. Buckley<sup>1</sup>

<sup>1</sup>Royal United Hospital, Bath, United Kingdom

<sup>2</sup>Bristol Royal Infirmary, Bristol, United Kingdom

<sup>3</sup>Ninewells Hospital, Dundee, United Kingdom

<sup>4</sup>University of Aberdeen, Aberdeen, United Kingdom

<sup>5</sup>University Hospital of Wales, Cardiff, United Kingdom

<sup>6</sup>Oxford University Hospitals, Oxford, United Kingdom

<sup>7</sup>Leicester Royal Infirmary, Leicester, United Kingdom

<sup>8</sup>Leeds General Infirmary, Leeds, United Kingdom

<sup>9</sup>Royal Liverpool Hospitals, Liverpool, United Kingdom

<sup>10</sup>Royal Gwent Hospital, Newport, United Kingdom

<sup>11</sup>The James Cook University Hospital, Middlesbrough, United Kingdom

<sup>12</sup>Royal Hallamshire Hospital, Sheffield, United Kingdom

<sup>13</sup>Imperial College, London, United Kingdom

**Correspondence:** Helen Audrain

**E-mail:** hels2002uk@yahoo.co.uk

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#### **Abstract**

**Background:** The oxidized forms of the fragrance terpenes limonene and linalool are known to cause allergic contact dermatitis. Significant rates of contact allergy to these fragrances have been

reported in European studies and in a recent worldwide study. Patch testing to oxidized terpenes is not routinely carried out either in the UK or in other centres internationally.

**Objective:** To investigate the prevalence of contact allergy to oxidized limonene and linalool in the UK.

**Method:** Between 01.08.2011 and 31.12.2012, 4731 consecutive patients in 13 UK dermatology departments were tested to hydroperoxides of limonene 0.3% pet., hydroperoxides of linalool 1% pet., stabilized limonene 10% pet., and stabilized linalool 10% pet. Doubtful (?+) and equivocal (+/-) reactions were grouped together as irritant reactions.

**Results:** 237 patients (5%) had a positive patch test reaction to hydroperoxides of limonene 0.3% pet. and 281 (5.9%) to hydroperoxides of linalool 1% pet. Irritant reactions to one or both oxidized terpenes were found in 242 patients (7.3%). 11 patients (0.2%) had a positive patch test reaction to the stabilized terpenes alone.

**Conclusion:** This large multicentre UK audit shows a significant rate of allergy to the hydroperoxides of limonene and linalool plus a high rate of irritant reactions. Testing to the oxidized forms alone captures the majority (97%; 411 of 422) of positive reactions; testing to non-oxidized terpenes appears to be less useful. We recommend that the hydroperoxides of limonene and linalool be added to an extended baseline patch test series.

## Introduction

Fragrance allergy may be more frequent than is commonly understood, as many common fragrance chemicals are not routinely tested during patch testing. A number of these fragrances are known to be pre-haptens (substances requiring transformation by heat, light or oxidation to acquire sensitizing potential) or pro-haptens (substances requiring metabolic activation by enzymes in the skin to acquire sensitizing potential). Strongly sensitizing compounds have been identified among the oxidation products or metabolites of such fragrances.

The oxidized forms of the fragrance terpenes limonene and linalool are known to cause allergic contact dermatitis. Significant rates of allergy to these fragrances have been reported in a small study from one UK centre; in Europe; and in a recent worldwide multicentre study.<sup>1-3</sup> Patch testing to the oxidized terpenes is not routinely carried out in the UK. Previously available preparations for patch testing to terpenes differ in concentration and not all are oxidized. A retrospective multicentre audit was performed throughout the UK to investigate the prevalence of allergy to the hydroperoxides of limonene and linalool.

## Method

Between 01.08.2011 and 31.12.2012, 13 UK dermatology departments, (Aberdeen, Bath, Bristol, Cardiff, Dundee, Leeds, Leicester, Liverpool, London, Middlesbrough, Newport, Oxford, Sheffield) had patch tested 4731 consecutive patients to an extended baseline series including hydroperoxides of limonene 0.3% pet. (H-032), hydroperoxides of linalool 1% pet. (H-031), stabilized limonene 10% pet. and stabilized linalool 10% pet. All allergens were from Chemotechnique Diagnostics, Vellinge, Sweden and allergens were applied to patients' backs in Finn Chambers® (Epitest Oy, Tuusula, Finland), on Scanpor® tape (Norgesplaster A/S, Vennsela, Norway). Readings were carried out by a dermatologist experienced in interpreting patch test results on Day 2 and Day 4 according to the International Contact Dermatitis Research Group criteria. Allergic patch test reactions were scored in terms of intensity using an accepted grading scale from 1+ to 3+ shown in Table 1.<sup>4</sup> Irritant reactions were characterised as well defined inflammation limited to the exposure area composed of papules with a lack of infiltrate and with a decrescendo effect between Day 2 and Day 4. Doubtful (?+) and equivocal (+/-) reactions were grouped together with irritant reactions for the purposes of analysis.

A retrospective audit was carried out, looking at the frequency of reactions and the clinical characteristics of patients with positive reactions to these fragrances.

## Results

Of the 4731 patients tested, 411 (8.7%) patients had positive patch test reactions to one or both terpene hydroperoxides: 237 (5%) to hydroperoxides of limonene; and 281 (5.9%) to hydroperoxides of linalool. In the 9 of 13 centres who recorded irritant reactions (n= 3297), there were 242 irritant reactions to one or both limonene and linalool hydroperoxides (7.3%): 129 (3.9%) to hydroperoxides of limonene and 196 (5.9%) to hydroperoxides of linalool. There were 15 (0.5%) irritant reactions to the stabilized terpenes. The percentage of positive and irritant reactions by centre is shown in Table 2. There was a wide range in the frequency of positive reactions between the 13 centres, from 2.1% to 15.9%. Similarly, the frequency of irritant reactions ranged from 2.1 to 27%. There were 38 reactions to stabilized linalool 10% pet and limonene 10% pet; 15 irritant reactions (12 to limonene and 3 to linalool) and 23 allergic reactions. There were 11 (0.2% of the 4731 patients tested) allergic reactions to stabilized limonene and 12 (0.3%) to stabilized linalool. 12 (52%) patients with allergic reactions to the stabilized forms also reacted to the hydroperoxides of limonene and linalool; 6 reacted to hydroperoxides of limonene, 6 to linalool, and none to all. 11 (0.2% of all tested patients) reacted only to the stabilized forms of limonene and linalool (Fig. 1).

The distribution of the strength of positive reactions to hydroperoxides of limonene and linalool is shown in Tables 3 and 4. 210 of the 237 (89%) patients with positive reactions to hydroperoxides of limonene had a + reaction and 27 (11%) had ++ or +++ reactions. 250 of the 281 (89%) patients with positive reactions to hydroperoxides of linalool had + reactions and 31 (11%) had ++ or +++ reactions.

The mean age of the 237 patients (155 F: 82 M) allergic to hydroperoxides of limonene was 46 years (range 3-90). The mean duration of the dermatitis was 3.5 years (range 1 week to 20 years). The most common sites affected were the face (n=59) and hands (n=57) (Fig. 2). The most common patient groups affected were the retired (n=39), office workers (n=32) and healthcare workers (n=26) (Fig. 3).

The mean age of the 281 patients (188 F: 87 M) allergic to hydroperoxides of linalool was 47 years (range 4-90). The mean duration of the dermatitis was 3.4 years and the most common sites affected were the face (n=69) and whole body (n=51) (Fig. 2). The most common groups affected were the retired (n=60), office workers (n=34) and healthcare workers (n=24) (Fig. 3).

11 of 13 centres recorded the presence of atopy of any type (n=4421). Of the 368 patients in these centres with allergic reactions to one or both terpene hydroperoxides, 176 (48%) patients were atopic. 94 (43%) of 219 patients with allergic reactions to hydroperoxides of limonene and 111 (45%) of 249 patients with allergic reactions to hydroperoxides of linalool were atopic. 7 of 13 centres recorded both the presence of irritant reactions and the presence of atopy (n=2987). Of the 163 patients in those centres with irritant reactions to one or both terpene hydroperoxides, 83 (51%) patients were atopic. There were 83 irritant reactions to hydroperoxides of limonene of which 40 (48%) patients were atopic and 107 irritant reactions to hydroperoxides of linalool of which 50 (47%) patients were atopic.

In 152 (37%) of the 411 patients, dermatitis was associated with the use of a product labelled to contain the terpene which had elicited a positive patch test. In 237 (58%), the relevance of a positive patch test was not recorded and in 22 (5%) it was unknown. Products containing limonene and/or linalool of probable clinical relevance to the allergic reactions were fine fragrances (n=37), moisturizing creams (n=29), detergents (n=19), hair products (n=17), essential oils (n=16), soaps (n=12), cosmetics (n=10), wet wipes (n=10), toothpaste (n=9), antiperspirant (n=8) and sunscreen (n=8) (Fig. 4).

## Discussion

Limonene and linalool are common fragrance chemicals of the terpene class present in the vast majority of cosmetics and detergents sold in the UK.<sup>5</sup> In their non-oxidized forms, they are weak allergens. However, when exposed to air, they auto-oxidize to form a variety of oxidation products, including hydroperoxides, which are highly allergenic.<sup>6</sup> Previously, relevant patch test materials for these allergens have not been commercially available.

Limonene has a strong fresh odour of lemon. It is the main constituent of peel oil from citrus fruits and is also found in several plant oils. It is a major by-product of the citrus juice industry and is labelled as an ingredient in 98% of women's fragrances and more than half of household cleaning products and detergents.<sup>5</sup> Linalool has a fresh flowery aroma. It is present in a variety of plants and is the main constituent of many essential oils including lavender, rosewood, sage, bergamot, jasmine and geranium. It is also synthetically produced and widely used as a fragrance chemical and may be present in up to 95% of fine fragrances.<sup>5</sup> Assessment of daily consumer exposure to linalool suggests that contact with it is the highest among all fragrance terpenes, as it is so commonly found in ordinary products.<sup>7</sup> Both limonene and linalool are among the 26 fragrances which require labelling on cosmetic and detergent products in the European Union if they are added in their pure form.<sup>8</sup> However, if they are added as part of an essential (plant) oil, they do not have to be labelled specifically and consumers may be unaware of their presence.<sup>9</sup> Although limonene and linalool are present in a significant number of personal care products, in the majority of patients, reactions will only occur if these chemicals have already been air-oxidised. It has been shown that commercially available fine fragrances have quantifiable levels of limonene and linalool hydroperoxides present due to auto-oxidation.<sup>10</sup>

This large multicentre UK audit shows a significant rate of allergy - 5% of patients tested had a positive patch test to hydroperoxides of limonene 0.3% pet and 5.9% to hydroperoxides of linalool 1% pet. The rates of allergy are similar to those in multicentre European studies where 5.2% of patients tested had a positive reaction to oxidized limonene 3% pet. (containing 0.33% limonene hydroperoxides) and 6.9% positive to oxidized linalool 6% pet. (containing 1% linalool hydroperoxides) respectively.<sup>2,3</sup> There was a large difference in the rate of allergy according to centre with 2.1% recorded in Bristol and 15.9% in Leeds. The variation in the rate of allergy between test centres was similar to those in multicentre European studies where positive reactions ranged from 2.3% to 12.1% for oxidised limonene 3% pet. (containing 0.33% limonene hydroperoxides) and 3.3% to 14.3% to oxidised linalool 6% pet. (containing 1% linalool hydroperoxides) respectively.<sup>2,3</sup> It is unclear whether the differences in the rates of allergy shown in this audit reflects a true difference in regional rates of allergy or differences in interpretation of patch tests between centres.

Testing to non-oxidized terpenes appears to be less useful. There were a total of 422 patients with positive reactions, 411 to the hydroperoxides of limonene and linalool and 11 to the stabilized terpenes alone. Therefore testing to the terpene hydroperoxides alone captures the majority (97%) of positive reactions. A significant rate of irritant reactions to hydroperoxides of limonene and linalool was found with 7.3% recorded overall and up to 27% in one centre. This was not found in a

recent multicentre European study of oxidized limonene, where there was a rate of only 0.86% irritant reactions to oxidised limonene 3% pet. (Lim-OOH 0.33%).<sup>2</sup> However, the authors found a significant rate of 'doubtful' reactions (7%). Importantly, in our audit a doubtful reaction was classed as irritant. It is possible that the doubtful reactions may have been weak positive reactions. It is the authors' consensus that interpreting and classifying terpene patch test reactions (particularly distinguishing irritant from allergic reactions) is more difficult than with other allergens, for reasons that are unclear.

The duration of the dermatitis prior to patch testing in these patients (a mean of 3.4 and 3.5 years for linalool and limonene respectively) suggests considerable morbidity. Specific products associated with allergy to the terpene hydroperoxides, suggesting clinical relevance of the positive patch tests, were not recorded in many patients. However, where such items were recorded, not just fine fragrances but moisturising creams and detergents were frequently implicated products which patients might not otherwise suspect to contain fragrance.

The female predominance, age group and body sites affected in patients allergic to hydroperoxides of limonene and linalool reflect those affected by fragrance allergy in general. The predominance of retired individuals, office workers and healthcare workers is typical of allergy to other fragrances.<sup>11</sup> As with Fragrance Mix I, atopy does not appear to confer an overall increased risk of sensitization to fragrance terpenes.<sup>12</sup> 48% of patients with allergic reactions to one or both terpene hydroperoxides were atopic. This is similar to the 60% rate of atopy in a large UK patch test population.<sup>12</sup> Current rates of allergy to Fragrance Mix I in Europe range from 3.7-10.4%, allergy to Fragrance Mix II from 1.9-7.9%, and to hydroxyl-isohexyl cyclohexene carboxaldehyde from 1.8-2.5%.<sup>13-15</sup> Both limonene and linalool hydroperoxides give rates of allergic reactions in consecutive patients comparable to or greater than to these, meeting the criteria for inclusion in an extended baseline patch test series.

Patch testing to oxidized limonene and linalool is not routinely carried out. Due to the number of irritant reactions, the optimum concentration for testing remains to be established. Further, our results show allergy to the terpene hydroperoxides in isolation and not in the context of fragrance allergy to multiple fragrance markers. Concomitant reactions to other fragrance markers would make clinical relevance of allergy to terpene hydroperoxides more likely and assist in the interpretation of doubtful or weak positive reactions. We are carrying out a further study recording whether patients reacting to the terpene hydroperoxides are also allergic to other fragrance markers. In addition, to assist in determining clinical relevance, this study will document products associated with dermatitis, the patient's current exposure to terpenes, whether symptoms improved after avoidance of terpenes and a detailed history of reactions to fragrances and personal care products. It is hoped that such a study will also determine the optimum concentration for patch testing to minimise reactions that are difficult to interpret. As commercial preparations of oxidized limonene and linalool are now available, we recommend that oxidized limonene and linalool be tested as part of an extended standard series in all patch test patients.

#### **What's already known about this topic?**

- Limonene and linalool auto-oxidize on air exposure and their oxidation products can cause contact allergy
- A significant rate of allergy to oxidized limonene and linalool has been shown in multicentre European studies and 1 small single-centre UK study

### What does this study add?

- This is the first multicentre audit to show a significant rate of allergy to oxidized terpenes throughout the UK
- There is a high rate of irritant reactions to the oxidized terpenes
- We recommend that oxidized limonene and linalool be added to an extended baseline patch test series in the UK
- The optimum concentration of the terpene hydroperoxides for patch testing has yet to be determined.

### References:

1. Buckley DA. Allergy to oxidised linalool in the UK. *Contact Dermatitis* 2011; **64**: 240-1
2. Christensson J, Andersen KE, Bruze M, et al. An international multicentre study on the allergenic activity of air oxidized R-limonene. *Contact Dermatitis* 2013;**68**: 214-23
3. Christensson J, Andersen KE, Bruze M, et al. Air-oxidized linalool: a frequent cause of fragrance contact allergy. *Contact Dermatitis* 2012; **67**:247-59
4. Wilkinson DS, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm. Venereol* 1970;50(4),287–292
5. Buckley DA. Fragrance ingredient labelling in products on sale in the UK. *Br J Dermatol* 2007;**157**:295-300
6. Matura M, Skold M, Borje A et al. Selected oxidized fragrance terpenes are common contact allergens. *Contact Dermatitis* 2005; **52**: 320-328
7. Belsito D, Bickers D, Bruze M, et al. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. *Food Chem Toxicol* 2008; 46 Suppl 1; S1-S71
8. 7th amendment of the EU Cosmetics Directive ([http://pharmacos.eudra.org/F3/cosmetic/pdf/vol\\_1en.pdf](http://pharmacos.eudra.org/F3/cosmetic/pdf/vol_1en.pdf))
9. Nardelli A, Thijs L, Janssen K, Goossens A. Rosa centifolia in a 'non-scented' moisturizing body lotion as a cause of allergic contact dermatitis. *Contact Dermatitis*. 2009; 61: 306-9
10. Nilsson J, Emilsson K, Hagvall L, et al. Quantification of allergenic terpene hydroperoxides in perfumes. *Contact Dermatitis* 2010; 63 (suppl 1): 18
11. Buckley DA, Rycroft RJ, White IR, McFadden JP. Fragrance as an occupational allergen. *Occup Med (Lond)*. 2002; 52: 13-6.
12. Buckley DA, Basketter DA, Kan-King-Yu D, et al. Atopy and contact allergy to fragrance: allergic reactions to the fragrance mix I (the Larsen mix). *Contact Dermatitis* 2008; 59: 220-5
13. Uter W, Aberer W, Armario-Hita JC, et al. Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007-2008. *Contact Dermatitis* 2012; **67**: 9-19
14. Schnuch A, Geier J, Uter W. Is hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitization declining in central Europe? *Contact Dermatitis* 2012; **67**: 47-9
15. Heisterberg MV, Laurberg G, Veien NK, et al. Prevalence of allergic contact dermatitis caused by hydroxyisohexyl 3-cyclohexene carboxaldehyde has not changed in Denmark. *Contact Dermatitis* 2012; **67**: 49-51

Table 1. Scoring of patch tests according to the International Contact Dermatitis Research Group

| Score           | Reaction                                                                                     |
|-----------------|----------------------------------------------------------------------------------------------|
| <b>- (0)</b>    | Negative reaction                                                                            |
| <b>?+, +/-</b>  | Doubtful reaction; erythema only                                                             |
| <b>+ (1+)</b>   | Weak (non-vesicular) positive allergic reaction; erythema, infiltration and possibly papules |
| <b>++ (2+)</b>  | Strong (vesicular) positive allergic reaction; erythema, infiltration, papules and vesicles  |
| <b>+++ (3+)</b> | Extreme positive allergic reaction; bullous reaction                                         |
| <b>IR</b>       | Irritant reaction                                                                            |

Table 2. Total number of patients from each test centre and the number and percentage of positive reactions and irritant reactions to hydroperoxides of limonene 0.3% pet and hydroperoxides of linalool 1% pet. (NA = not recorded) Irritant reactions were recorded in 9 of 13 centres (n=3297)

| Centre        | Total no. tested | No. Positive         | % Positive | No. Irritant         | % Irritant |
|---------------|------------------|----------------------|------------|----------------------|------------|
| Aberdeen      | 259              | 38                   | 14.7       | 71                   | 27         |
| Bath          | 233              | 18                   | 7.7        | 23                   | 9.8        |
| Bristol       | 485              | 10                   | 2.1        | NA                   | NA         |
| Cardiff       | 265              | 20                   | 7.5        | NA                   | NA         |
| Dundee        | 666              | 96                   | 14.4       | 33                   | 5          |
| Leeds         | 578              | 92                   | 15.9       | 48                   | 8.3        |
| Leicester     | 321              | 13                   | 4          | 10                   | 3.1        |
| Liverpool     | 284              | 16                   | 5.6        | NA                   | NA         |
| London        | 51               | 5                    | 9.8        | 8                    | 15.7       |
| Middlesbrough | 300              | 25                   | 8.3        | 17                   | 5.7        |
| Newport       | 610              | 35                   | 5.7        | 13                   | 2.1        |
| Oxford        | 400              | 15                   | 3.8        | NA                   | NA         |
| Sheffield     | 279              | 28                   | 10         | 19                   | 6.8        |
| <b>Totals</b> | <b>4731</b>      | <b>411 (of 4731)</b> | <b>8.7</b> | <b>242 (of 3297)</b> | <b>7.3</b> |

Table 3. Distribution of the strength of positive patch test reaction to hydroperoxides of limonene 0.3% pet. according to centre

| <b>Hydroperoxides of Limonene 0.3% pet</b> |                         |                     |            |           |               |           |
|--------------------------------------------|-------------------------|---------------------|------------|-----------|---------------|-----------|
| <b>Centre</b>                              | <b>Total no. tested</b> | <b>No. positive</b> | <b>+</b>   | <b>%</b>  | <b>++/+++</b> | <b>%</b>  |
| Aberdeen                                   | 259                     | 16                  | 16         | 100       | 0             | 0         |
| Bath                                       | 233                     | 12                  | 4          | 33        | 8             | 67        |
| Bristol                                    | 485                     | 5                   | 3          | 60        | 2             | 40        |
| Cardiff                                    | 265                     | 9                   | 9          | 100       | 0             | 0         |
| Dundee                                     | 666                     | 57                  | 54         | 95        | 3             | 5         |
| Leeds                                      | 578                     | 66                  | 56         | 85        | 10            | 15        |
| Leicester                                  | 321                     | 5                   | 4          | 80        | 1             | 20        |
| Liverpool                                  | 284                     | 10                  | 9          | 90        | 1             | 10        |
| London                                     | 51                      | 2                   | 2          | 100       | 0             | 0         |
| Middlesbrough                              | 300                     | 17                  | 16         | 94        | 1             | 6         |
| Newport                                    | 610                     | 15                  | 15         | 100       | 0             | 0         |
| Oxford                                     | 400                     | 10                  | 9          | 90        | 1             | 10        |
| Sheffield                                  | 279                     | 13                  | 13         | 100       | 0             | 0         |
| <b>Totals</b>                              | <b>4731</b>             | <b>237</b>          | <b>210</b> | <b>89</b> | <b>27</b>     | <b>11</b> |

Table 4. Distribution of the strength of positive patch test reactions to hydroperoxides of linalool 1% pet. according to centre

| <b>Hydroperoxides 1% Linalool pet.</b> |                         |                     |            |           |               |           |
|----------------------------------------|-------------------------|---------------------|------------|-----------|---------------|-----------|
| <b>Centre</b>                          | <b>Total no. tested</b> | <b>No. positive</b> | <b>+</b>   | <b>%</b>  | <b>++/+++</b> | <b>%</b>  |
| Aberdeen                               | 259                     | 29                  | 25         | 86        | 4 (14)        | 14        |
| Bath                                   | 233                     | 15                  | 5          | 33        | 10 (67)       | 67        |
| Bristol                                | 485                     | 7                   | 6          | 86        | 1 (14)        | 14        |
| Cardiff                                | 265                     | 15                  | 15         | 100       | 0             | 0         |
| Dundee                                 | 666                     | 69                  | 65         | 94        | 4 (6)         | 6         |
| Leeds                                  | 578                     | 52                  | 45         | 86        | 7 (14)        | 14        |
| Leicester                              | 321                     | 11                  | 9          | 82        | 2 (8)         | 8         |
| Liverpool                              | 284                     | 7                   | 6          | 86        | 1 (14)        | 14        |
| London                                 | 51                      | 3                   | 3          | 100       | 0             | 0         |
| Middlesbrough                          | 300                     | 13                  | 12         | 92        | 1 (8)         | 8         |
| Newport                                | 610                     | 29                  | 29         | 100       | 0             | 0         |
| Oxford                                 | 400                     | 6                   | 5          | 84        | 1 (16)        | 16        |
| Sheffield                              | 279                     | 25                  | 25         | 100       | 0             | 0         |
| <b>Totals</b>                          | <b>4731</b>             | <b>281</b>          | <b>250</b> | <b>89</b> | <b>31</b>     | <b>11</b> |

Figure 1. Venn diagram showing the relationship between allergic reactions to the stabilized terpenes and hydroperoxides of linalool and limonene in 4,731 patients tested; 422 positive reactions in total

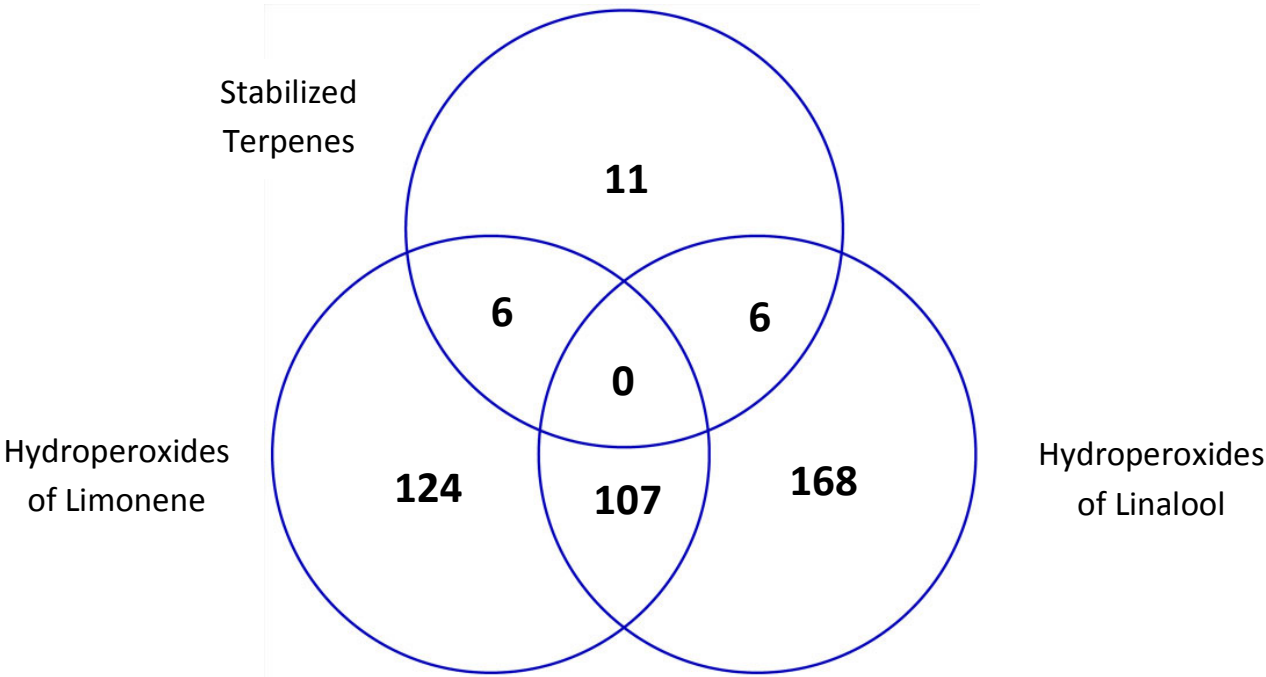


Figure 2. Sites affected in 411 patients with positive reactions to hydroperoxides of limonene and/or linalool

N = 411

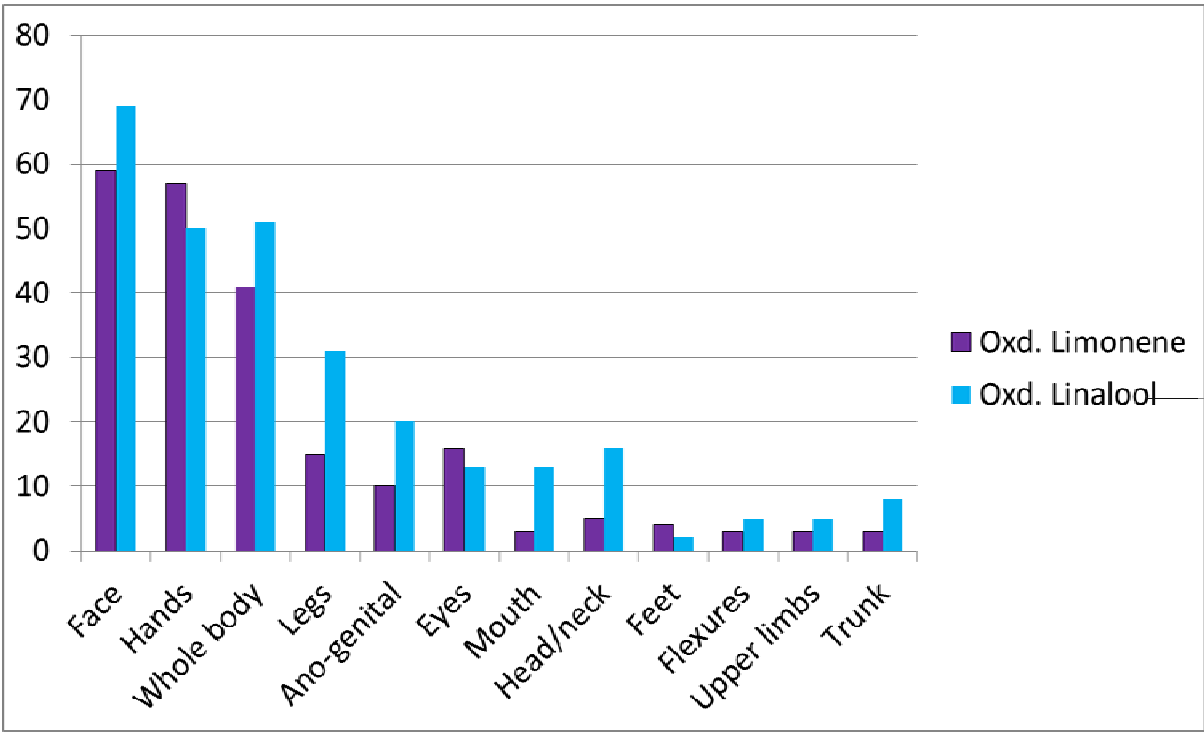


Figure 3. Occupation of 411 patients with positive reactions to hydroperoxides of limonene and/or linalool

N = 411

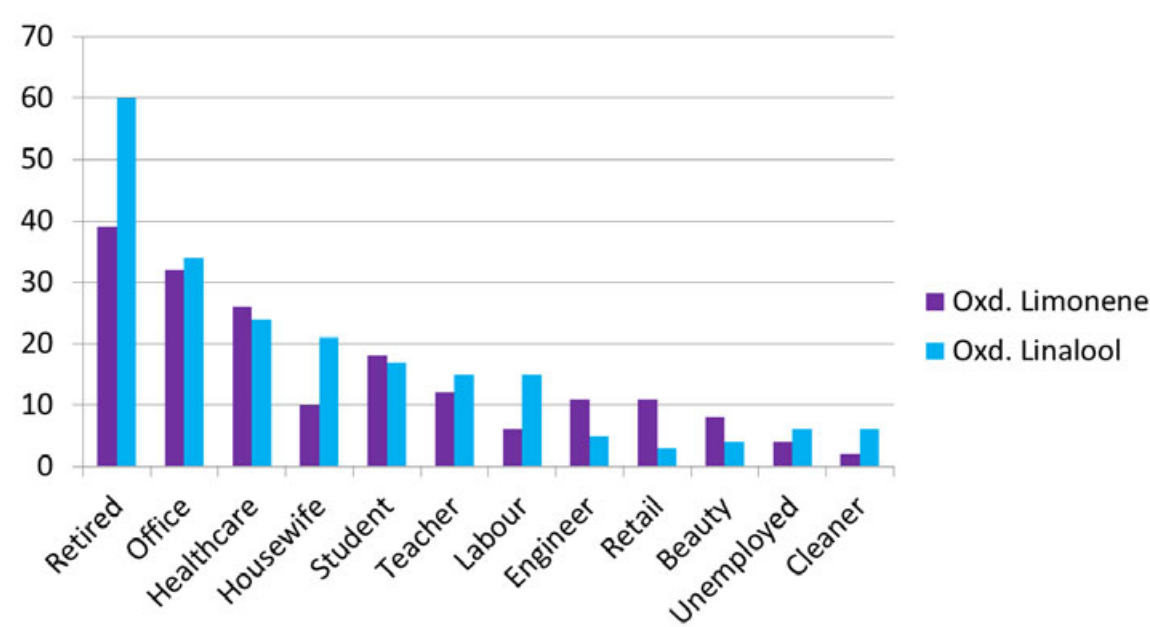


Figure 4. Products giving allergic reactions in 152 of the 411 patients with positive reactions to hydroperoxides of limonene and/or linalool.

N = 152

