

Further important sensitizers in patients sensitive to fragrances

II. Reactivity to essential oils

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In order to find sensitizers additional to the current fragrance mix (FM) a series of fragrance materials (series II) was evaluated in 6 dermatological centres in Europe. 11 of the test materials were essential oils, the remaining 7 being either mixtures of isomers or simple chemicals of frequent usage in the perfume industry. 1606 patients were consecutively tested with series II and 8% FM. Each patient was classified regarding a history of adverse reactions to scented products: certain, probable, questionable, none. Reactions to FM occurred most frequently in 11.4% of the subjects. The 6 materials with the highest reactivity after the FM were ylang-ylang oil (YY) I (2.6%), YY II (2.5%), lemongrass oil (1.6%), narcissus absolute (1.3%), jasmine absolute (1.2%) and sandalwood oil (0.9%). 48 (3.0%) of the patients reacted only to materials of series II and not to FM. 6.0% of 1606 patients gave a history of adverse reactions to fragrances which was classified as certain. This group reacted to FM only in 22.9%, to series II and FM in 15.6% and to series II only in 5.2%. 63.5% of the patients reacting to both FM and 1 of the materials of series II had some type of positive fragrance history, which was higher in comparison to those with isolated reactions to FM (46.2% of 121) or to series II, respectively, (45.8% of 48). However, this difference was not statistically significant. In conclusion, the materials of series II identified a further subset of patients with a fragrance problem, which would have been missed by the current FM as the single screening tool for patch testing.

Key words: contact allergy; essential oils; fragrance mix; fragrances; history of fragrance sensitivity; patch testing. © Blackwell Munksgaard, 2002.

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In 2 previous publications (1, 2) our research group on contact allergy to fragrances has emphasized the need to supplement the fragrance mix (FM) of Larsen (3) in the diagnostic procedure of patch testing. In our search for possible candidates based on literature reports and own experience we have tested 18 materials (series II) after series I (2). Series II contained in the majority essential oils rather than well-defined single chemicals. Essential oils are still widely used in perfumery because of their unsurpassed richness in natural odours. Essential oils such as ylang-ylang (YY) or sandalwood oil have gained special attention in aromatherapy. They are often applied directly to the skin

in high concentrations for the treatment of headache, muscular pains, arthritis, etc. The results of our study show that it is indeed worthwhile to test some of these oils. Further relevant sensitizations will be identified which would have been missed by testing only with the FM.

Material and Methods

Fragrance materials

The materials were obtained from leading manufacturers. Test concentrations were determined according to guidelines in the literature (4) and on the basis of pilot studies in Dortmund, Malmö,

Table 1. Test concentrations

Fragrance compound	Chemical name	CAS Reg. No.	Supplier ^s	Test concentration
1. Patchouli oil (Indonesian)		8014-09-3	1	10%
2. Dwarf pine needle oil		97676-05-6	1	2%
3. Ylang-ylang oil (fraction I)		8006-81-3	2	10%
4. Ylang-ylang oil (fraction II)		8006-81-3	2	10%
5. Sandalwood oil (East India)		8015-65-4	1	10%, 2%
6. Limonene	1-methyl-4- (1-methylethenyl)-cyclohexene	138-86-3	1	3%
7. α -Irone	4- (2, 5, 6, 6-tetramethyl-2-cyclohexen-1-yl)-3-buten-2-one	79-69-6	1	10%
8. Peppermint oil (American)		8006-90-4	1	2%
9. Spearmint oil (American)		8008-79-5	1	2%
10. Lemongrass oil (East India)		8007-02-1	1	2%
11. Cedarwood oil (Moroccan and Chinese 1:1)		85085-41-2	3	10%
12. Jasmine absolute		84776-64-7	1	5%
13. Narcissus absolute		8023-75-4	4	2%
14. α -Damascone and β -damascone (rose ketones)	1- (2, 6, 6-trimethyl-2-cyclohexenyl)-2-buten-1-one	43052-87-5	2	0.2% (mixture of α - and β -isomers, 0.1% of each)
15. Piperonal (heliotropin)	1, 3-benzodioxole-5-carboxyaldehyde	120-57-0	2	5%, 1%
16. β -Caryophellene, natural	2-methylene-6, 10, 10-trimethylbicyclo-[7.2.0]undec-5-ene	87-44-5	1	5%
17. Hedione	methyl dihydrojasmonate	24851-98-7	1	5%
18. α -Terpineol, natural	1-p-menthen-8-ol	98-55-5	1	5%

^s1— Dragoco, Holzminden, (Germany); 2—Haarmann & Reimer, Holzminden, (Germany); 3—Adrian, Marseille (France); 4—Charbot & Cie, Grasse, (France).

and London (Table 1). The vehicle for dilution was petrolatum (pet.).

Patients and patch testing

Consecutive testing of patients attending the patch test clinic of 6 European departments of dermatology was performed. For details the reader is referred to our previous publication (2). This study was carried out on new patients after series I in the time period between November 1998 and May 2000.

Results

A total of 1606 patients were tested; the range between the centres was 145–381 patients (Tables 2 and 3).

FM produced the highest reactivity in all centres (mean 11.4%; range 9.3–17.9%). YYI oil and YY II oil were the front runners of series II, with 2.6% and 2.5% positive reactions, respectively. Lemongrass oil, jasmine absolute and narcissus absolute ranged between 1.2% and 1.6%. Lemongrass oil, however, produced the highest proportion of reactions considered doubtful or irritant (2.2%), although this was still much lower

than the corresponding figure for the FM (5.0%). The other materials of series II were all below the 1% margin of positive reactions. The lowest reactivity was observed with α -terpineol, yielding only

Table 2. Results of series II obtained by testing 1606 consecutive patients. Listed are numbers of observed reactions

Fragrance	<i>n</i>	+	++	+++	Total	%	
FM 8%	80	5.0	96	67	21	184	11.4
Ylang-ylang I oil 10%	22	1.4	16	18	8	42	2.6
Ylang-ylang II oil 10%	18	1.1	18	16	7	41	2.5
Lemongrass oil 2%	35	2.2	12	12	1	25	1.6
Narcissus abs. 2%	20	1.2	13	7	1	21	1.3
Jasmine abs. 5%	15	0.9	14	4	2	20	1.2
Sandalwood oil 10%	23	1.4	9	6	0	15	0.9
Patchouli oil 10%	11	0.7	5	6	2	13	0.8
Spearmint oil 2%	25	1.5	4	9	0	13	0.8
Dwarf pine needle oil 2%	12	0.7	7	3	2	12	0.7
Caryophyllene 5%	13	0.8	3	5	2	10	0.6
Cedarwood oil 10%	15	0.9	6	3	1	10	0.6
Limonene 3%	7	0.4	5	4	0	9	0.6
Peppermint oil 2%	12	0.7	4	3	2	9	0.6
α -Damascone 0,2%	7	0.4	2	5	1	8	0.5
Sandalwood oil 2%	11	0.7	4	3	0	7	0.4
Piperonal 5%	7	0.4	3	3	0	6	0.4
α -Irone 10%	8	0.5	2	2	1	5	0.3
Hedione 5%	9	0.6	1	2	0	3	0.2
Piperonal 1%	6	0.4	1	1	0	2	0.1
α -Terpineol 5%	11	0.7	1	0	0	1	0.1

Table 3. Top 10 of series II in 6 European centres

	Dortmund <i>n</i> = 381	Gentofte <i>n</i> = 303	London <i>n</i> = 208	Malmö <i>n</i> = 258	Leuven <i>n</i> = 145	Odense <i>n</i> = 311
FM	13.4%	9.6%	11.5%	9.7%	17.9%	9.3%
Ylang-ylang I	2.4%	1.6%	6.2%	2.7%	2.1%	1.6%
Ylang-ylang II	2.6%	1.3%	6.2%	2.3%	2.1%	1.6%
Lemongrass oil	0.3%	1.6%	2.9%	1.9%	2.7%	1.3%
Jasmine abs.	0.8%	0.9%	2.4%	2.2%	2.7%	0.0%
Narcissus abs.	0.8%	0.7%	1.9%	1.2%	3.4%	1.3%
Sandalwood oil 10%	0.5%	0.7%	0.5%	1.2%	2.1%	1.3%
Patchouli	1.3%	0.3%	0.9%	1.2%	0.7%	0.9%
Spearmint oil	0.5%	0%	0%	1.9%	1.4%	1.3%
Dwarf pine needle oil	0.3%	0.3%	0.9%	1.9%	0.7%	0.6%
Caryophyllene	0.3%	0%	0.5%	0.8%	0.7%	1.3%

Table 4. History of adverse reactions to fragrances of each patient related to positive patch test results to fragrance mix and series II. The total of 1606 patients was separated into 4 groups of fragrance history

	History	FM positive only	Series II and FM positive	Only series II positive
Certain	96/1606 (6.0%)	22/96 (22.9%)	15/96 (15.6%)	5/96 (5.2%)
Probable	172/1606 (10.7%)	19/172 (11.0%)	19/172 (11.0%)	9/172 (5.2%)
Questionable	171/1606 (10.6%)	15/171 (8.8%)	6/171 (3.5%)	8/171 (4.7%)
None	1167/1606 (72.7%)	65/1167 (5.6%)	23/1167 (2.0%)	26/1167 (2.2%)

Table 5. Patients positive to fragrance mix and series II in relationship to their history

History	FM positive only (<i>n</i> = 121)	Series II and FM positive (<i>n</i> = 63)	Series II positive only (<i>n</i> = 48)
Certain	22/121 (18.2%)	15/63 (23.8%)	5/48 (10.4%)
Probable	19/121 (15.7%)	19/63 (30.1%)	9/48 (18.7%)
Questionable	15/121 (12.4%)	6/63 (9.5%)	8/48 (16.7%)
None	65/121 (53.7%)	23/63 (36.5%)	26/48 (54.2%)

1 positive and 11 doubtful reactions. The majority of reactions were in the + and ++ class, but very strong +++ reactions were also observed, particularly to YY oil.

As can be seen in Table 3, there were marked variations between the results of the individual centres. Leuven showed the highest reactivity to all materials, particularly to FM, lemongrass oil and narcissus absolute. The highest prevalence rate to YY oil was observed in London, the lowest in the 2 Danish centres (Gentofte and Odense). Reactivity to these oils was generally lower in the Scandinavian centres but +++ reactions were also observed in Malmö (5) and in Odense (1). The figures of the German centre Dortmund lay in the intermediate range; it had the lowest rate of positive reactions to lemongrass oil (only 3+ reactions and 3?+). It is noteworthy that to this material a high number of ?+ reactions were recorded in Odense (6.4%) in comparison to only 4≥+ reactions (1.3%).

Tables 4 and 5 provide the data of patch test results in relationship to the history of adverse reactions to fragrances. 6.0% of the total population

were classified as having a certain history. Of these, 22.9% reacted to FM only, 15.6% to FM and series II and 5.2% were only positive to 1 of the materials of series II (Fig. 1). Reactivity to FM declined with the probable and questionable groups, but was still 7.6% in those without a history of adverse reactions to scented products. In the group of patients reacting to series II only, the corresponding figures were lower, particularly in those with a negative history (2.2%). A significantly higher proportion of those with a history (any type) had a positive patch test to FM, FM and series II or series II

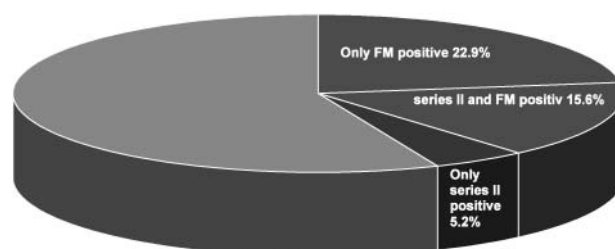


Fig. 1. History of adverse reactions to fragrances and benefit of series II. Test results of 96 patients with a certain history.

alone than those without a history, chi-square ($p < 0.01$).

In Table 5 and Fig. 2 it can be seen that in the group with a positive reaction to FM only 46.3% provided a history, but 53.7% denied any type of adverse reactions to scented materials in the past. The figures were similar with the patients reacting to series II only. However, in the group of patients reacting to both FM and 1 of the materials of series II, the proportion with any type of history was considerably higher (63.5%), though this difference was not statistically significant.

Table 6 shows that in the majority of cases there were positive reactions to both FM and 1 of the materials of series II (for reasons of clarity, only the data for the top 6 of series II are shown). It is seen, however, that the FM was negative in several cases, particularly with positive reactions to jasmine absolute, lemongrass oil and YY.

Sandalwood oil was tested in 2 concentrations (10% and 2%). 15 patients reacted to the higher concentration and only 7 to the lower. However, 6/15 with a positive reaction to 10% sandalwood oil had no history of adverse reactions to scented products (3/7 for 2% sandalwood oil). In the 6 patients without a history, 4 had also reacted to FM. In the group of 15 patients with positive reactions to 10% sandalwood oil, 1 with a certain history would have been missed by testing only with 2% sandalwood oil.

The test results with piperonal at 2 concentrations also showed marked differences (6 positives at 5% *versus* only 2 at 1%). All 6 patients had no history of adverse reactions to scented products, although 5 of them also showed a reaction to FM.

Discussion

The results of this study show that the current FM should be supplemented by at least 4 essential oils producing positive test reactions in consecutive pa-

tients at a frequency of over 1%: YY oils I and II, lemongrass oil, narcissus absolute and jasmine absolute. As discussed in previous publications (1, 2), the prevalence of positive reactions would have been higher if aimed testing of patients with suspected or known histories of adverse reactions to fragrances had been performed. If we focus on those patients in our population who provided a history of adverse reactions to scented products considered certain according to our criteria, the gain of testing with series II was 5.2%, i.e. this proportion of patients would have been missed if they had been tested with FM only. If we take the benefits of series II and series I of our previous publication (2) together, we identify another 12% of hitherto unrecognized definitely fragrance-sensitive individuals. This percentage is even higher if we include those with probable and questionable histories (9.9% and 7.5%, respectively).

In the group of patients with positive reactions to 1 of the top 6 of series II (jasmine absolute, narcissus absolute, patchouli oil) and a negative reaction to FM, there were 2 men and 1 woman with a certain history of adverse reactions to fine perfumes (Table 6). A further 9 patients gave a history which was considered certain or probable, primarily due to deodorants and fine perfumes. It is noteworthy that a considerable portion of patients with any type of fragrance history reacted to both the FM and 1 of the materials of series II. This can be explained by sensitizations to substances present in both groups. Eugenol, isoeugenol, and cinnamic aldehyde are major constituents of FM, if the results of breakdown testing are considered (5–7). These substances are also present in many essential oils (8). Concentrations of the main constituents of essential oils vary with the origin of the plants, time of harvesting and method used for extraction (8, 9). It is therefore difficult to standardize the quality of essential oils, which would be an essential aspect if used for a diagnostic procedure. However, the perfume industry relies on some criteria which have worked in practice for decades (e.g. physical constants such as density, refractive index, optical rotation, and melting point) (8). Recently, determination of chemical parameters such as ester and carbonyl numbers is increasingly being supplemented by chromatographic procedures such as gas chromatography – mass spectrometry (10, 11).

In the European standard series for patch testing there are also some materials which are mixtures of many chemicals, e.g. colophonium or balsam of Peru (Myroxylon Pereirae resin). These are still used for screening purposes because, even when the main constituents and allergens are known, no single chemical of these can replace

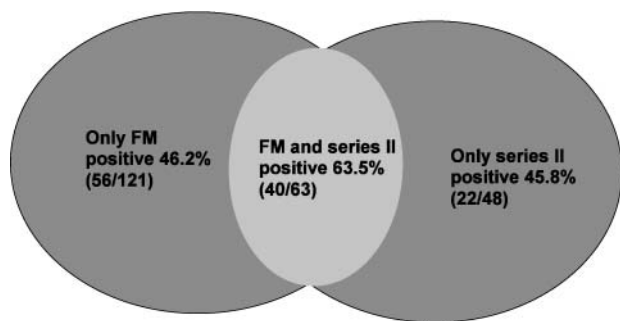


Fig. 2. Patients positive to fragrance mix and series II in relationship to any type of history of fragrance sensitivity (certain, probable, questionable).

Table 6. Reactions to FM in comparison to those of series II (Top 6)

	Ylang I	Ylang II	Lemongrass	Jasmine	Narcissus	Patchouli
FM positive	32	30	18	11	16	8
Doubtful	4	3	0	0	2	1
Negative	6	8	7	9	3	4

testing with the whole mixture. Abietic acid, for example, is the main sensitizer in colophonium, but it is not positive in all patients allergic to colophonium. We are therefore convinced that at this stage, with big knowledge gaps in the field of fragrance allergy, patch testing with essential oils is necessary in order to identify relevant cases. This conviction gains further support from the fact that in the perfume industry to this day rather crude extractions of various plants and woods are used. One reason is the low price for mass products such as soaps or household products. Another reason is the full body of odour that some plant extracts deliver, e.g. YY or lemongrass oil. Despite impressive advances in synthetic chemistry and increasing knowledge about odour-generating constituents, experienced perfumers still appreciate natural oils. Allergic reactions to the oils we have tested have previously been reported by others. In Portugal, 2600 patients were tested over 10 years with FM and in selected cases with a series of 10 essential oils. YY headed the list of positive reactions (13.4%), followed by clove oil, cananga oil, geranium oil Bourbon and sandalwood oil (6.6%). Lemon oil, which is derived from the peel of ripe citrus fruits, was relatively low in this series (12). In the worldwide trial of Larsen et al. (13) in 8 centres, 178 patients with a known patch test proven fragrance sensitivity were evaluated by an extensive fragrance series of 20 materials. Nearly 80% reacted to FM, next were jasmine absolute 10% pet. (16.9%), geranium oil Bourbon (8.4%), citronellol (5.6%) and spearmint oil (5.0%).

In an earlier study, the same group tested a mix of 'natural' ingredients containing jasmine absolute, ylang-ylang oil, narcissus absolute, sandalwood oil and spearmint oil (2% each) (14). Of 754 consecutive patients, 8.9% reacted to FM and 6.3% to the 'natural' mix. A mixture of jasmine and 24 further ingredients, including the FM constituents, was positive in 8.4%.

YY is a major cause of allergic contact dermatitis in Asian countries, where it is frequently followed by hyperpigmentation (15). In Japan a sharp increase in sensitivity to lavender oil was found during a 10-year period due to intensive use of lavender in aromatherapy (16). YY, farnesol P, hydroxycitronellal and jasmine absolute were also prominent in this series. In London we have ob-

tained the highest prevalence rates for YY, probably due to extensive use in this metropolis with a high proportion of Asians. This centre reported occupational allergic contact dermatitis in 2 aromatherapists caused by essential oils such as YY, citrus neroli, lavender oil and others (17). Further cases of occupational contact allergy due to YY have been observed in Spain and Finland (18, 19).

YY is produced by steam distillation of the freshly early morning-picked flowers of *Cananga odourata*. Modern distilleries produce 4 grades of YY oil: extra, 1st, 2nd and 3rd, with quality and price decreasing in the same order. The annual world consumption of extra YY is estimated at over 30 metric tons. It is used as a fragrance component in soaps, detergents, creams, lotions and perfumes (usually at a level of 1%). The oil is also used as a flavouring agent (beverages, candy, frozen dairy desserts, etc. usually at below 0.003%). The essential oils obtained by steam distillation from fresh flowers contain up to 3 × more monoterpenes and lightly oxygenated components than those distilled 24 h after the flowers have been collected. Aromatic oxygenated compounds are primarily p-methylanisole, methyl benzoate, ethyl benzoate and benzyl acetate (20). Monoterpenols (linalool, α -terpineol, geraniol) and their acetates are remarkably higher in fresh flowers compared to dry flowers. Furthermore, the maturity of the flowers influences the concentration of these compounds. The first distillation fraction (40–60 min) from fresh undamaged flowers corresponds to the so-called extra grade YY (20). Extra was not tested in this series because of the high price. This type contains the highest concentrations of the above-listed components which are partially known as allergens. Other chemicals identified in YY are anethole, cinnamyl acetate (E, E)-farnesyl acetate, α -pinene, camphene, β -pinene, limonene, eugenol, isoeugenol, and β -caryophyllene. Cananga oil resembles YY III but has a higher content of caryophyllene. In general, sesquiterpenes are higher in concentration with increased fractionation (> 70% in YY III) (21). In a study of 21 patients known to be sensitive to perfumes, Meynadier et al. (22) found the highest degree of reaction to balsam of Peru (= 13), followed by YY (= 8), cananga oil (= 7) and patchouli oil (= 3). It was not specified by

the authors which type of YY was used (presumably grade I and II because cananga oil, which is comparable to grade III, was tested separately).

Although YY I and II differ chemically to some extent, biologically this does not seem to play a major role because the test results were nearly identical with both types. For practical reasons a 1:1 mixture of YY (10% pet.) may be used for patch testing in the future. It is remarkable that the strongest reactions we have observed in series II were primarily caused by the YY. This should be studied further in order to identify the main sensitizers and possibly produce safer YY by reducing or eliminating the culprits.

Lemongrass oil is distilled from the fresh or partly dried grass of 2 species cultivated in India, China, Brazil and Guatemala. It has a refreshing lemon-like odour. It contains about 80% citral, together with citronellal, geraniol, methylheptenone, n-decyl-aldehyde and probably linalool. It is mainly used in low-cost lemon soap perfumes (23). About 1000 tons/year are produced. According to the studies of the Research Institute of Fragrance Materials (RIFM, Englewood, NJ, USA), a patch test concentration of 4% is non-irritating (24). De Groot et al. (4) recommend 2% pet. based on reports of Mendelsohn (25) and Rudzki & Grzywa (26). It caused a high degree of reactions that were regarded as doubtful. As discussed previously, this problem can be solved only by further investigations. Irritancy and low levels of sensitization could be distinguished by dose-response studies and repeated open application tests over at least 2 weeks (27). Possibly some of the reactions were linked to citral, which was found to be one of the top 6 reactors in series I.

Narcissus absolute contains numerous substances (Table 7) (28). It also elicited strong allergic reactions in our patients and was associated with a certain history of fragrance sensitivity in some cases. In this context, it is important to realize that 2 of these constituents were tested as well-defined chemicals in this series, caryophyllene and α -terpineol. These chemicals produced much fewer reactions than narcissus absolute. This finding suggests that other substances than terpineol and caryophyllene may carry more weight for the allergenicity of narcissus absolute.

Terpineol is extracted from pine oil and also found in more than 200 derivatives of leaves, herbs and flowers. It is also present in oil of Bergamot, neroli, petit grain and limette oil. Commercial terpineol contains mainly α -terpineol and a considerable amount of γ -terpineol. It emits a strong lilac odour and is one of the most frequently used fragrance compounds. It is stable, inexpensive and used primarily for soaps and various cosmetics. In

Table 7. Major components of important essential oils used in series II (28)

Narcissus absolute (odoriferous part 20%)	
α -Terpineol	23.7
<i>trans</i> -Isoeugenol methyl ether	20.0
Benzyl benzoate	19.4
Coumarin	6.9
Benzyl alcohol	5.0
Δ^3 -Carene	3.4
Phenylethyl alcohol	2.2
Ethyl palmitate	2.2
Cinnamic alcohol	2.2
Phenylpropyl acetate	1.7
1, 8-Cineole	1.5
Caryophyllene	1.0
Benzyl acetate	0.7
Total	89.9
Jasmine absolute	
Benzyl acetate	28.5
Benzyl benzoate	17.0
Linalool	7.7
Phytol	7.4
Isophytol	6.4
Phytol acetate	6.1
Indole	3.4
8-Geranyl linalool	3.2
<i>cis</i> -Jasmone	2.5
Eugenol	2.2
Methyl linolenate	2.0
Benzyl alcohol	1.9
Methyl palmitate	1.4
p-Cresol	1.0
<i>cis</i> -3-Hexenyl benzoate	1.0
Total	91.7

a series of 1200 Italian patients, α -terpineol produced only 2 positive reactions (29).

Jasmine absolute was found to be relevant in a recent worldwide trial in fragrance-sensitive individuals (13) and in a previous study on cosmetic allergy (30). Jasmine absolute contains methyl jasmonate, but not methyl dihydrojasmonate (hedione) (28). Hedione was also tested in our series. Most of the 20 patients positive to jasmine absolute did not react to hedione (only 3 positives, though 9 doubtful ones). Hedione is extensively used for floral compositions and extracted from tea. In a recent analysis of 59 domestic and occupational products, it was found in 14 products (31). In deodorants it was found in 65–86% depending on the type (32). Hedione can now be synthesized from 2-pentyl-cyclopenten-2-one and ethyl malonate. It is closely related to methyl jasmonate, which occurs in jasmine oil. *cis*-Jasmone is isolated from jasmine absolute. The huge effort required to obtain natural odours to this day can be appreciated from some figures for jasmine oil. 1000 kg of hand-picked flowers (approximately 8 million pieces) will deliver 2.3 kg jasmin concrète, which is further concentrated by alcohol to yield 1 kg absolute. For 80 tons of jasmine flowers picked

in the best region of Esterel, E10,000 (DM 20,000) per kg was the market price in 1980! The prices were considerably lower for other qualities from Italy, Egypt or Morocco. World production of jasmine absolute in that year was estimated at 5–6 tons (33).

The results obtained with sandalwood oil tested at 2 concentrations deserve comment. The number of both doubtful and allergic reactions at the 10% concentration were about $2 \times$ those seen at the 2% concentration. This suggests, as discussed previously, that there might be a problem with irritancy or low levels of sensitization not detected with the lower patch test concentration. In our patients we would have missed one with a certain history by testing only with 2% sandalwood oil. However, nearly 1/2 of the reactors to 10% sandalwood oil had no history. Sugai (34), based on a Japanese study on 327 patients, recommended 2% as the appropriate test concentration of sandalwood oil, although the differences in reactions obtained with 10% were not great (3 *versus* 5 regarding the positive and 7 *vs* 8 regarding the doubtful). Nakayama et al. (35) described an association of pigmented contact dermatitis with sensitization to sandalwood oil. This may be related to photosensitization, at least in some cases, as documented by de Leo et al. (36): in his series of 176 patients, 1 photoallergy and 2 contact allergies were found. Santucci et al. (29) reported only 1 positive reaction to 2% sandalwood oil in 1200 consecutively tested patients. Jasmine absolute (2% pet.) produced the highest reactivity after FM (16% pet.) (1.1% and 5.2%, respectively).

The main sensitizers in sandalwood oil have been identified as α - and β -santalol, which represent 66% of the oil (28); further compounds are geraniol and citronellol (8). Spearmint oil is extracted from *Mentha spicata* and *Mentha cardiaca*. The main constituents are limonene, 3-octanol, menthone and dihydrocarvone. The main uses are as flavours in toothpaste and chewing gum.

Piperonal (heliotropin) is used in many flowery-spicy fragrances and is also an important flavour component. It is found in a score of essential oils, though never as the main component (pepper oil, *Robinia pseudo-acacia*). It is also present in vanilla, camphor wood and violet flower extract (8). Larsen (37) described a 62-year-old woman with a perfume dermatitis of the face. When tested with 94 constituents of perfume she reacted strongly to angelica root oil and orange sweet terpeneless oil; heliotropin, YY and hydroxycitronellal produced + reactions. In a previous study, we did not observe any reactions to piperonal in 106 subjects (38). In this study we noted 6 reactions classified as allergic to 5% piperonal (7 doubtful ones); the

corresponding numbers for the lower concentration of piperonal 1% were 2 and 6. However, clinical relevance has not been ascertained, because all patients lacked a fragrance history. Further studies are needed with this compound. The material was found in 22% of 59 domestic and occupational products, even though at rather low concentrations (mean 76 ppm) (31).

Patchouli oil is produced by steam distillation of the dried leaves of *Pogostemon cablin* (Indonesia, China, Philippines) and is rich in the sesquiterpene alcohols (–)-patchoulol and norpatchoulol. The odour is powerfully woody and balsamic. About 30 constituents have been identified: α -, β -, γ -patchoulol (–)- α -guajene, (+)- α -bulnesene, cinnamic aldehyde, benzaldehyde, eugenol and caryophyllene (39). Hausen & Kunze (40) described a clear-cut case of contact allergy in a 29-year-old man who used patchouli oil behind the ear and in the axillae. In reviewing the literature they concluded that 10% pet. would be the appropriate test concentration for patchouli oil.

? α -Damascone (rose ketone) is a chemical whose use is restricted by the International Fragrance and Research Association (IFRA, Brussels, Belgium). It is recommended not to exceed a concentration $>0.02\%$ due to its sensitization potential. At 1% pet. it is an irritant if applied under occlusion in a repeated human patch test. At higher concentrations (30% pet.) it is a potent sensitizer and was considered an alternative to dinitrochlorobenzene for testing the immune competence of patients with malignant tumours (41); 8/30 patients and all 3 healthy subjects were sensitized. In our group of consecutive dermatological patients 0.5% were positive. This suggests that the IFRA limit may still be too high and does not prevent *de novo* sensitizations (assuming that all manufacturers follow the IFRA guidelines).

Cedarwood oil is produced in different varieties depending on the source: Texas, Atlas (Morocco), Virginia and China. In our study a 1:1 mixture of Atlas (Morocco) and Chinese was used. The major constituents are cedrene, cedrol (Texas), γ - and α -atlantone, α -ionone, α -caryophyllene alcohol (Atlas), cedrene, thujopsene, and cedrol (Virginia). Dermatitis from cedarwood pencils has been reported by Calnan (42). Rudzki & Grzywa (43) observed 6 positive reactions to 2% (Chinese) cedarwood oil in 450 patients tested. For further reports on contact allergies to series II, the reader is referred to reviews and some pertinent original articles (4, 44–48).

The authors considered this lengthy discussion to be necessary in order to balance the view on positive results in relationship to the complexity of the problem. Essential oils have been used for

centuries in large amounts. Extraction has been rather crude in former times and is now very refined. Major constituents are today synthesized in chemical laboratories. Although contact sensitization has been observed for a long time and reported in the scientific literature in numerous cases, no 'epidemics' of contact allergy to essential oils have been observed in contrast to nickel or preservatives such as chloromethylisothiazolinone + methylisothiazolinone (Kathon® CG, Rohm and Haas, Philadelphia). However, the top ranking oils of our test series are a matter of concern: YYI and II, lemongrass oil, narcissus absolute, jasmine absolute and possibly also sandalwood and patchouli oil. If human skin exposure to these is intensive, e.g. in aromatherapy, contact sensitization may develop. The clinician should therefore be alerted if a patient's history points in this direction. Furthermore, as essential oils are increasingly used for inhalation in pursuit of psychological effects, immediate-type contact reactions may be observed, as reported recently (49–52).

In conclusion, the results of our study show that it is indeed worthwhile to test some of these oils. Further relevant sensitizations will be identified which would have been missed by testing only with FM. We need additional screening agents including essential oils.

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