

# Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and *Myroxylon pereirae* and colophonium, over a 21-year period

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## Summary

**Background.** The frequency of fragrance contact allergy has shown a fluctuating trend over the years.

**Objectives.** To describe the frequency of positive reactions to the baseline screening agents and fragrance mix (FM) 1 and 2 components, to determine trends of the latter over the years, and to evaluate simultaneous reactions.

**Patients and methods.** This was a cross-sectional study on patch test results of 13 332 patients from January 1990 to December 2011.

**Results.** Of the total population, 9.6% reacted positively to FM 1, and 6% of 3416 tested with FM 2 reacted positively. Of those tested with both, 30.4% of 349 FM 1-positive patients reacted to FM 2, and 51.7% of 205 FM 2-positive patients reacted to FM 1. Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) and FM 2 were tested simultaneously in 3401 patients: 6 reacted to HICC alone. Nine hundred and forty patients were tested with FM 1 ingredients and 205 with FM 2 ingredients; *Evernia prunastri* was the most frequent FM 1 allergen, and HICC was the most frequent FM 2 allergen. Simultaneous reactions were frequently observed.

**Conclusions.** Fragrance-allergic subjects often show multiple positive reactions, some of which are highly significantly associated. Recently, there has been a decreasing trend in positivity for both *Evernia prunastri* and HICC, whereas a slight increase for cinnamyl alcohol has been observed.

**Key words:** allergic contact dermatitis; colophonium; epidemiology; fragrance mix; fragrances; hydroxyisohexyl 3-cyclohexene carboxaldehyde; *Myroxylon pereirae*; trends.

Sensitivity to fragrance ingredients is recognized as a common and clinically important problem in Europe. It has been shown that 7–11.5% of individuals with eczematous skin conditions (1, 2), and at least 1–3% of the general population, are allergic (delayed hypersensitivity)

to baseline indicators of fragrance allergy (3). This makes contact sensitization to fragrances among the most common causes of allergic contact dermatitis, next to nickel and preservative agents. Although progress has been made in improving the safety standards of fragrances, the figures on adverse effects reported by dermatologists worldwide suggest that they are far from sufficient.

The currently used fragrance mix (FM) 1 (containing *Evernia prunastri*, isoeugenol, cinnamal, cinnamyl alcohol, hydroxycitronellal, eugenol, geraniol, and  $\alpha$ -amylcinnamal) in the European baseline patch test series fails to detect a substantial number of clinically

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relevant fragrance allergies. It has been estimated that at least 15% of relevant cases of perfume allergy are not recognized by routine patch testing with FM 1 (4). However, Larsen et al. have reported that as much as 33% of fragrance sensitivity may be missed if FM 1 is used as the only test substance (5), a percentage that might be even higher, as it depends on other fragrance components (and products) tested. For this reason, since 2005, a mixture of six additional fragrance materials has been commercialized for introduction into the baseline series (officially introduced in 2008) (6), known as FM 2 [tested at 14% in petrolatum, i.e. hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), citral, farnesol, coumarin, citronellol, and  $\alpha$ -hexylcinnamal]. These are all fragrance components with known sensitization properties, and are widely used in cosmetics, household products, and industrial products, and also in topical pharmaceutical products (7).

The pattern of fragrance contact allergy has changed over time, because of industry developments, changing fashion trends, and regulatory interventions (8). The frequency of FM 1 contact allergy has shown a fluctuating trend over the years, either increasing or decreasing (9). In Denmark, an increase in the frequency of FM 1 contact allergy was observed from 1985–1986 to 1997–1998 in both men and women, followed by a decrease in 2006 (2). In a recent European multicentre study, FM 1 showed a wide frequency range, depending on the countries studied; this ranged from 3.7% to 10.4%. The prevalence of sensitization to FM 1 was lowest in the southern countries (Italy and Spain) and Lithuania, and highest in western and central Europe (10).

This article describes the frequency of positive reactions to FM 1 and FM 2, and to the individual components, along with trends in their frequency over the years in our department. Furthermore, this study was also set up to evaluate associations between positively reacting FM I ingredients and *Myroxylon pereirae* and colophonium.

## Materials and Methods

### Study population

This was a cross-sectional study for which all data were retrieved from, and evaluated with, in-house-developed databases in our contact allergy unit (11). The patient database contains patient information and results of patch tests of 13 332 patients investigated for contact allergy between January 1990 and December 2011.

### Patch testing

All subjects had been tested with the European baseline series (Trolab, Hermal, Reinbeck, Germany) containing

FM 1, *M. pereirae* (balsam of Peru), and colophonium. Since 2002, 3927 have been tested with HICC 5% pet., and from 2005, 3416 have been tested with FM 2. The patients reacting to FM 1 and FM 2 were, in most cases, tested with the individual ingredients, and some of the subjects were occasionally also tested with other fragrance components.

The patch tests were administered with Van der Bend® patch test chambers (Van der Bend, Brielle, The Netherlands) applied on the back with Micropore™ (3M Health Care, Borken, Germany), and fixed with Fixomull® (Beiersdorf, Hamburg, Germany), and later with Mefix® (Mölnlycke Health Care, Göteborg, Sweden). The patch test readings were performed according to the international guidelines of the International Contact Dermatitis Research Group (12) after 2 days, 3 days (exceptionally), and 4 days, and sometimes later.

### Statistical analysis

The fragrance ingredients present in FM 1 and FM 2 were studied in an explorative way. The study of simultaneous positive reactions to FM 1 ingredients and to *M. pereirae* and colophonium are shown in a  $2 \times 2$  contingency table. As an appropriate statistical measure to compute the strength and the direction of the association, we used the odds ratio (OR), expressing the occurrence of positive reactions in one group as compared with another group, and the corresponding 95% confidence interval (CI). If the CI is different from 1, there is a significant association between the row and the column variable. As this was an explorative study, we did not correct for multiple tests. The statistical analysis in the patch tested patients was performed with SAS™ version 9.2 (SAS Institute, Cary, NC, USA).

## Results

Of the 13 332 patients who underwent patch testing between January 1990 and December 2011, 7486 (56%) showed at least one positive patch test reaction. One thousand two hundred and fifty-nine (9.6% of 13 114 patients tested) of them reacted positively to FM 1, and 205 (6% of 3416 patients tested) to FM 2. Three thousand three hundred and eighty patients were tested with both FM 1 and FM 2: 106 (30.4%) of the 349 FM 1-positive patients also reacted to FM 2, and 106 (51.7%) of the 205 FM 2-positive patients also reacted to FM 1. Eighty-two patients (2.09% of 3927 tested) showed a positive reaction to HICC (Table 1). Eighteen HICC-allergic patients did not react to FM 1. During the period 2005–2011, HICC and FM 2 were tested simultaneously in 3401 patients: only 6 were positive to HICC alone.

**Table 1.** Positive reactions to fragrance mix (FM) 1, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), and FM 2

|                    | Patients tested<br>with FM 1<br>(n = 13 114)* | Patients tested<br>with HICC<br>(n = 3927) <sup>†</sup> | Patients tested<br>with FM 2<br>(n = 3416) <sup>‡</sup> |
|--------------------|-----------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| Positive reactions | 1259                                          | 82                                                      | 205                                                     |
| Percentage         | 9.6                                           | 2.09                                                    | 6                                                       |

\*Between 1990 and 2011.

<sup>†</sup>Between 2002 and 2011.<sup>‡</sup>Between 2005 and 2011.**Table 2.** Positive reactions to the constituents of fragrance mix (FM) 1 between 1990 and 2011

| Constituents             | Total (n = 940)* | Percentage |
|--------------------------|------------------|------------|
| <i>Evernia prunastri</i> | 230              | 24.6       |
| Isoeugenol               | 160              | 17         |
| Cinnamyl alcohol         | 129              | 13.7       |
| Eugenol                  | 118              | 12.6       |
| Cinnamal                 | 66               | 7          |
| Geraniol                 | 52               | 5.5        |
| $\alpha$ -Amylcinnamal   | 30               | 3.2        |
| Hydroxycitronellal       | 24               | 2.6        |

\*Nine hundred and forty patients were tested with the FM 1 ingredients.

Most patients underwent a full breakdown test when a positive reaction to either FM 1 or FM 2 occurred. Nine hundred and forty patients were tested with the FM 1 ingredients: the frequency of positive reactions, in descending order, was: 24.6% (n = 230) to *E. prunastri*, 17% (n = 160) to isoeugenol, 13.7% (n = 129) to cinnamyl alcohol, 12.5% (n = 118) to eugenol, 7% (n = 66) to cinnamal, 5.5% (n = 52) to geraniol, 3.2% (n = 30) to  $\alpha$ -amylcinnamal, and 2.6% (n = 24) to hydroxycitronellal (Table 2). When the breakdown constituents of FM 2 were tested in 205 subjects, HICC was by far the most common sensitizer (n = 58), followed by farnesol (n = 27), citral (n = 23), hexylcinnamal (n = 20), citronellal (n = 11), and coumarin (n = 9) (Table 3).

The absolute numbers in frequency of the different ingredients of FM 1 (1990–2011) and FM 2 (2005–2011) obtained over the years are given in Figs. 1 and 2, respectively.

The associated positive test results observed with the different ingredients of FM 1, *M. pereirae* and colophonium are given in Table 3, showing associations for all comparisons reported. When an association was significant, the OR was computed. As an example, an OR of 915.09 (Table 4) means that the odds of a positive reaction to cinnamyl alcohol is 915 times higher for

**Table 3.** Positive reactions to the constituents of fragrance mix (FM) 2 between 2005 and 2011

| Constituents  | Total (n = 205)* | Percentage |
|---------------|------------------|------------|
| HICC          | 58               | 28.3       |
| Farnesol      | 27               | 13.2       |
| Citral        | 23               | 11.2       |
| Hexylcinnamal | 20               | 9.7        |
| Citronellol   | 11               | 5.4        |
| Coumarin      | 9                | 4.4        |

HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

\*Two hundred and five patients were tested with the FM 2 ingredients.

patients with a positive reaction to cinnamal than for the non-cinnamal-allergic patients.

## Discussion

We observed a frequency of 9.6% positive reactions to FM 1, with its ingredients showing a fluctuating trend. *E. prunastri* was the most frequent allergen among them, with remarkable peaks in 1997 and 2000, the pattern of which could be attributed to the fashionable use of it in some cosmetic products, especially aftershave and hydroalcohols. Among the > 100 constituents identified in *E. prunastri*, atranol and chloroatranol (degradation products of atronorin and chloroatranorin) figure as the most potent allergens (13); in view of their extreme sensitization potencies, the EU's Scientific Committee for Cosmetic Products (SCCP) came to the conclusion that both substances could not be used at all in cosmetic products (SCCP/0847/04) (14). In addition, significant associations have previously been observed for colophonium and *E. prunastri* (with *Evernia furfuracea* as a contaminant or substitute), because of the potential common presence of resin acids, that is, abietic acid and dehydroabietic acid, and their oxidized derivatives (13). Moreover, a recent study by Uter et al. identified two subgroups of *E. furfuracea*-sensitized patients: first, those with sensitization to (oxidized) resin acids, as indicated by positive patch test reactions also to colophonium; and second, those non-sensitized to resin acids, but sensitized to common constituents of *E. prunastri* and *E. furfuracea* (15). Furthermore, colophonium, *M. pereirae* and FM 1 also cross-react with other terpene-containing substances, among which are essential oils, and also with Compositae plants (16) (data on file).

Crude *M. pereirae* as such has not been used in perfumery since 1982, when the International Fragrance Association (IFRA) advised against its use in fragrances. Since 1995 (17), *M. pereirae* has been incorporated in

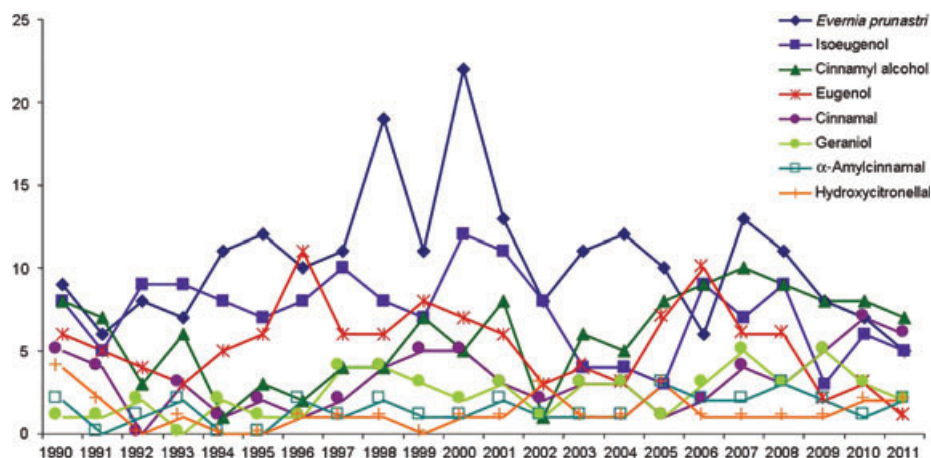


**Fig. 1.** Evolution of the absolute numbers in frequency over the years of positive reactions to the different ingredients of fragrance mix 1 (1990–2011).

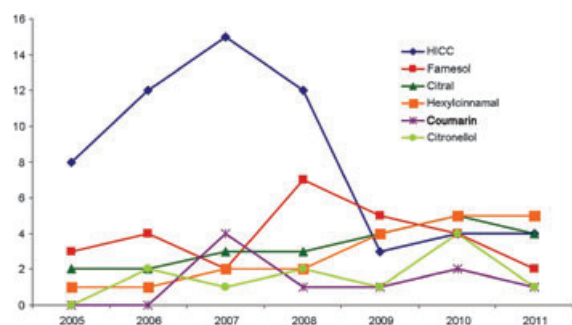


**Fig. 2.** Evolution of the absolute numbers in frequency over the years of positive reactions to the different ingredients of fragrance mix 2 (2005–2011). HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

fragrances as an extract or distillate, but patch testing has shown that *M. pereirae*-sensitized subjects react even more strongly to these extracts. Exposure to *M. pereirae*, or to some of the single constituents, is apparently frequent, so this 'historical' screening agent is still important for detecting fragrance sensitivity (9).

In the current study, FM 2 identified 6% of the subjects suffering from fragrance allergy, and 99 fragrance-allergic patients would have been missed if only FM 1 had been tested. There was also a fluctuating trend in the frequency of allergy to FM 2's ingredients; HICC was the most frequent allergen, with a peak in 2007, but a descending trend since 2009. In the case of hexylcinnamal, a moderate increase was observed in the last year. The high frequency could be attributable to the common use of HICC in deodorants and other cosmetic products in the EU at rather high use concentrations, that is, >3.0% in certain perfumes, which resulted in positive reactions in 1–2.7% of consecutively patch tested

patients (18–22). In North America, the prevalence was found to be only 0.4%, which was considered to be mainly because of the presence of the ingredient at much lower concentrations in deodorants in the United States than in the EU (6). Recently, Schnuch et al. (23) also observed a slight decrease in the number of positive reactions to HICC, which may be a consequence of reduced exposure resulting from its use in fewer products and at lower concentrations, the latter having been recommended by the IFRA ([www.ifraorg.org](http://www.ifraorg.org)), which, since 2009, has provided guidance in this regard: 0.02% for deodorants, lip products, and intimate wipes; and 0.2% for all other leave-on and rinse-off cosmetics (24). However, in agreement with our results, in a recent study in which the 26 labelled fragrance ingredients were investigated, HICC still remained among the most frequent allergens (25).

Significant associations between cinnamal and cinnamyl alcohol, as well as with *M. pereirae*, in which both are present, were observed (Table 4). The IFRA restricts the use concentration in cosmetic products of cinnamyl alcohol to 0.1% for deodorants and lip products, whereas cinnamal has specific concentration restrictions of 0.02% for deodorant and lip products and of 0.05% for the other cosmetic categories (43rd Amendment, IFRA standard 2009). It has been reported that cinnamal and cinnamyl alcohol may generate a common hapten. This may be because of either their close chemical relationship, causing cross-sensitization, or their combined presence in many cosmetic products, leading to concomitant sensitization. It is thought that cinnamyl alcohol is a 'prohapten', transformed by alcohol dehydrogenase in the skin to cinnamal. However, we found cinnamic alcohol to be a more important allergen than cinnamal,

**Table 4.** Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the different fragrance mix 1 ingredients and *Myroxylon pereirae* and colophonium

| Allergens                                             | OR (95% CI)        |
|-------------------------------------------------------|--------------------|
| Cinnamyl alcohol by cinnamal                          | 915.0 (428–1955)   |
| Isoeugenol by eugenol                                 | 140.6 (92–215)     |
| Cinnamyl alcohol by amylcinnamal                      | 98.7 (45–217)      |
| Amylcinnamal by hydroxycitronellal                    | 56.4 (23–138)      |
| Cinnamal by amylcinnamal                              | 55.1 (20–152)      |
| Geraniol by hydroxycitronellal                        | 50.9 (24.18–107.5) |
| <i>Myroxylon pereirae</i> by eugenol                  | 46.9 (31–72)       |
| Isoeugenol by <i>Evernia prunastri</i>                | 42.9 (30–62)       |
| Eugenol by cinnamyl alcohol                           | 38.3 (23–63)       |
| Isoeugenol by geraniol                                | 33.3 (17–66)       |
| Hydroxycitronellal by <i>Evernia prunastri</i>        | 32.5 (15–68)       |
| Eugenol by <i>Evernia prunastri</i>                   | 29.7 (19–46)       |
| Isoeugenol by hydroxycitronellal                      | 28.7 (17–50)       |
| Amylcinnamal by <i>Evernia prunastri</i>              | 28.5 (13–64)       |
| Eugenol by cinnamal                                   | 26.4 (13–54)       |
| <i>Myroxylon pereirae</i> by isoeugenol               | 25.4 (18–36)       |
| Geraniol by <i>Evernia prunastri</i>                  | 25.2 (16–39)       |
| Cinnamyl alcohol by <i>Evernia prunastri</i>          | 25.1 (16–39)       |
| Cinnamal by hydroxycitronellal                        | 24.5 (11–56)       |
| Cinnamyl alcohol by hydroxycitronellal                | 22 (12–42)         |
| Geraniol by eugenol                                   | 21.4 (9–49)        |
| Geraniol by cinnamal                                  | 17.4 (5–58)        |
| Eugenol by hydroxycitronellal                         | 16.4 (8.21–33)     |
| Isoeugenol by cinnamyl alcohol                        | 14.4 (8–26)        |
| Isoeugenol by amylcinnamal                            | 14.1 (5–41)        |
| <i>Myroxylon pereirae</i> by geraniol                 | 13.6 (7–25)        |
| <i>Myroxylon pereirae</i> by cinnamic alcohol         | 13 (9–19)          |
| <i>Myroxylon pereirae</i> by cinnamal                 | 12 (7–21)          |
| Colophonium by amylcinnamal                           | 11.8 (5–26)        |
| Cinnamal by <i>Evernia prunastri</i>                  | 11.6 (6–24)        |
| Isoeugenol by cinnamal                                | 10.5 (4–25)        |
| <i>Myroxylon pereirae</i> by <i>Evernia prunastri</i> | 9.3 (7–13)         |
| Eugenol by amylcinnamal                               | 8.4 (2–36)         |
| <i>Myroxylon pereirae</i> by amylcinnamal             | 7.7 (3–17.22)      |
| Colophonium by geraniol                               | 6.9 (3–14)         |
| <i>Myroxylon pereirae</i> by hydroxycitronellal       | 6.4 (4–11)         |
| Colophonium by cinnamyl alcohol                       | 6 (4–10)           |
| Colophonium by eugenol                                | 5.9 (4–9)          |
| Colophonium by <i>Evernia prunastri</i>               | 5.8 (4–8)          |
| Colophonium by isoeugenol                             | 4.4 (3–7)          |
| Colophonium by hydroxycitronellal                     | 3.9 (2–7)          |
| Colophonium by cinnamal                               | 3.5 (2–8)          |

which could be explained by an additional sensitization mechanism (26, JP Lepoittevin, pers. comm. 2012). Moreover, in agreement with the literature (27, 28), cinnamyl alcohol contact allergy is very often related to ketoprofen photosensitization (which explains its recent slight increase in frequency): during the study period, 48 of 81 ketoprofen-positive patients were also tested with cinnamyl alcohol, and 37 reacted positively, whereas only 6 of 45 patients tested with cinnamal reacted to it; this makes cinnamyl alcohol a potential marker

for ketoprofen sensitization. Some authors (29–31) have considered possible cross-sensitization between ‘an aldehyde function’ in the ketoprofen molecule and cinnamal, or the formation of common metabolites (29). However, a clear explanation for this phenomenon is still lacking.

Significant associations were also found between isoeugenol and eugenol, the former of which is recognized as a strong sensitizer, with its concentration in cosmetics being restricted by the IFRA since 1998. In 2009, the IFRA standard (43rd Amendment) changed the restrictions on isoeugenol to 0.01% for deodorants and lip products, and to 0.02% for hydroalcohols, aftershaves, and women’s facial and hand creams, intimate wipes, and make-up removers. On the other hand, eugenol is a much weaker sensitizer (26). They do not, in fact, cross-react, despite their close chemical similarity, and they are both prohaptens that are metabolized in the skin. According to our results, the OR of simultaneous association was still important (140.6), but considerably lower than with the cinnamyl derivatives. Moreover, simultaneous reactions were found with *M. pereirae*, which contains, among other components, both eugenol and isoeugenol.

With regard to other significant associations (Table 4), no molecular explanation can be put forward, but concomitant sensitization seems likely; indeed, fragrance-allergic subjects tend to show multiple sensitivities.

A significant number of subjects (n = 131) reacted negatively to the breakdown constituents but positively to FM 1, a phenomenon also noted by others (3, 18, 26). Possible explanations are as follows:

- false-positive reaction to the mix
- each constituent acts as an irritant, which lowers the elicitation threshold for other allergens when tested in combination
- false-negative reactions to the individual constituents of the FM, because the concentrations tested are too low, or the skin penetration of FM 1 is increased by the emulsifier sorbitan sesquileate (also present in *E. prunastri*) (26)
- the existence of ‘compound allergy’ to a combination of two or more ingredients of FM 1, that is, by the formation of a new allergen (18)
- different evaporation potentials of individual components than of the mixture. The conditions under which the fragrance test preparations are stored when applied in test chambers may affect the diagnostics of fragrance contact allergy, resulting in false-negative reactions. As many fragrance compounds are volatile, application to the test chamber should be performed as close in time to the patch testing as possible, and storage in a refrigerator is recommended (32)

- cinnamal and cinnamyl alcohol were found (32) to be more stable when analysed as ingredients in FM 1 than when analysed in individual preparations.

A recent study by Bonefeld et al. (33) has indeed shown that mixtures have increased potency in sensitization and the elicitation of contact allergic reactions as compared with isolated fragrance allergens. These results may explain why fragrance allergy is a prevalent phenomenon in spite of the fact that many fragrance allergens are categorized as weak sensitizers. The authors consider that mixtures of fragrances, i.e. FM 1 and FM 2, not only reflect normal exposure to perfumes, but also provide the optimal stimulus to the immune system, and thereby have high diagnostic ability. Hence, in the light of the Bonefeld study, false-negative reactions to the ingredients certainly also accounts for this phenomenon (33).

### Limitations of the study

The main limitation of our study is that the individual ingredients of FM 1 and/or FM 2 were not tested in all subjects reacting to the mixes. This is because testing was only performed with the individual ingredients when the FM-sensitive patients were able to come back for later readings. Second, this was a single-centre study. Therefore, only a relatively low number of patients were positive to the individual ingredients of the mixture. However, we consider that the present study on fragrance materials expands on previous work from our unit (8), and provides

a current perspective on the frequency of sensitization to FM 1 and FM 2 in the European baseline series and their ingredients, as well as simultaneous reactions observed to *M. pereirae* and colophonium.

### Conclusions

*E. prunastri* and isoeugenol were found to be the most common single fragrance allergens in FM 1, whereas HICC and, to a lesser extent, farnesol were the most common fragrance allergens in FM 2.

Positive reactions to *M. pereirae* and FM 1 are frequently associated, because they share common components, that is, eugenol, isoeugenol, cinnamal, and cinnamyl alcohol. The association between colophonium and FM 1 is partly attributable to the presence of resin acids in *E. prunastri*, but together with *M. pereirae*, also to (oxidized) terpenes, which are also present in essential oils and Compositae plants.

A fluctuating trend in the frequency of positive reactions has been observed with the individual ingredients of the mixes, with a recent slight increase for cinnamyl alcohol, associated with ketoprofen photosensitization, and a descending trend particularly for *E. prunastri* and HICC. This could be explained by concentration restrictions (e.g. HICC), fashionable fragrance composition changes, and last, but not least, by avoidance of the use of the components that are legally required to be labelled on the cosmetic packaging by the perfume industry.

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