

Allergic contact dermatitis from fragrance components in specific topical pharmaceutical products in Belgium

ANDREA NARDELLI¹, ELLEN D'HOOGHE¹, JACQUES DRIEGHE¹, MARC DOOMS² AND AN GOOSSENS¹

¹Department of Dermatology, University Hospital, and ²University Hospital, Hospital Pharmacy, Katholieke Universiteit Leuven, Leuven, Belgium

Objectives: To determine which topical pharmaceutical products marketed in Belgium contain fragrances and to examine the nature of the fragrance allergens in specific pharmaceutical products having caused iatrogenic contact dermatitis.

Methods: All topical pharmaceutical products marketed in Belgium, that is 3820 products, were examined as to their fragrance content as labelled. Data of 18 960 patients investigated for contact allergy between 1978 and 2008 were retrieved from our database, including information on the nature of the topical pharmaceutical products used, the results of patch tests, and the sensitization sources.

Results: Three hundred and seventy (10%) of 3280 of the topical pharmaceutical products were found to contain a total of 66 fragrance substances. Among 3378 patients suffering from iatrogenic allergic contact dermatitis, 127 were found to react to 48 specific products, for which 38 different fragrance substances gave relevant positive reactions. Women were more affected than men, and legs, hands, and face were the most commonly affected body sites.

Conclusions: Fragrances, the presence of which is in most cases unnecessary, do contribute to iatrogenic allergic contact dermatitis. Moreover, sensitized patients have difficulties in avoiding their specific allergens because standardized labelling of the ingredients in pharmaceutical products is lacking.

Key words: allergic contact dermatitis; colophonium; essential oils; fragrances; iatrogenic; *Myroxylon pereirae*; topical pharmaceutical products. © 2009 John Wiley & Sons A/S.

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Contact allergy to fragrances is common, the frequency of which in the general population is estimated to be around 1.5% (Denmark, 1.1% and Norway, 1.8%) (1–3) and between 6.5% and 10.4% in contact dermatitis patients (4, 5). The real incidence of adverse reactions to topical medications is not known, and most of the data about prevalence are quite old with a frequency estimated to be between 14% and 18% among patients investigated for contact allergy (6). In our contact allergy unit, topical pharmaceutical products account for about 33% of all contact allergies, the allergenic culprits being active prin-

ciples, preservatives, vehicles, and also fragrance components (6, 7).

Labelling of all pharmaceutical products has been required in Belgium since the end of the 19th century, that is active principles and also inactive ingredients (8). Regarding the fragrances, their precise nature or a statement such as 'perfume' can be found, either on the packaging or on the notice (leaflet). In Europe, such labelling has been required since 1965, and only the active ingredients needed to be taken into account (9). The list of ingredients to be labelled in 1965 was, however, revised in 2001: additional particulars

needed to be stated on the outer packaging of medicinal products, such as the list of all excipients in the case of injectable products or of topical or eye preparations (10). However, there is no restriction as to the presence of fragrance allergens nor are the ingredient names standardized.

The fragrances present may be natural products, such as essential oils (e.g. orange flower oil and lavender oil), resins [e.g. benzoin and balsam of Peru (*Myroxylon pereirae*)], semisynthetic chemicals (produced from isolates through chemical reactions, such as terpineol from pinene and hydroxycitronellal from citronellal), and synthetic chemicals (11, 12).

The importance of fragrance components as allergens in specific topical pharmaceutical products has not been reported before.

The aims of this retrospective study were:

- (1) To determine which and how many topical pharmaceutical products marketed in Belgium contain fragrance components.
- (2) To examine the nature of the fragrance allergens in specific pharmaceutical products that have caused iatrogenic contact dermatitis.

Materials and Methods

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 (8, 13). The database on topical pharmaceutical products, first developed in 1978, contains information on the complete composition (including fragrance ingredients) of 3820 products marketed in Belgium (preparations by pharmacists not included) in which the nature of the fragrance allergens (as labelled) was examined. An ingredient was considered to be a 'fragrance' according to its classification as a fragrance or 'aroma' by the International Cosmetic Ingredient Dictionary and Handbook (14) (Table 1).

The patient database contains information (including sex, localization of the lesions, the topical pharmaceutical products used, the results of patch tests, and the sensitization sources) of 18 960 patients investigated for contact allergy between January 1978 and June 2008. They were patch tested with the European baseline patch test series (Trolab, Hermal, Reinbeck, Germany), additional series, and individual substances when indicated. In order to detect the allergenic culprits in patients suspected of iatrogenic contact dermatitis, whenever possible, the topical pharmaceutical products used along with their ingredients were tested as well. The subjects included in this

study were those who presented with iatrogenic contact dermatitis from a specific pharmaceutical product and for whom a positive reaction was found to a fragrance allergen present.

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 AG, Hamburg, Germany) and later on with Mefix® (Mölnlycke Health Care, Göteborg, Sweden) as adhesive tape. The patch test readings were performed according to the international guidelines by the International Contact Dermatitis Research Group (15) after 2, 3 (exceptionally), and 4 days and sometimes later.

Results

A total of 18 960 patients were investigated for contact allergy, that is 12 419 (65.5%) women and 6541 (34.5%) men, for whom the MOAHLFA index (16, 17) was: M (male), 34.5%; O (occupational dermatitis), 19.7%; A (atopic dermatitis), 22.9%; H (hand dermatitis), 40.2%; L (leg dermatitis), 5%; F (face dermatitis), 32.4%; and A (40 years and older), 43.7%. At least one of the allergens tested produced a positive reaction in 10 249 (54%) patients, that is 6103 (60%) women and 4146 (40%) men. Of 10 249, 3378 (33%) suffered from iatrogenic contact dermatitis, that is 2268 (67%) women and 1110 (33%) men. One hundred and twenty-seven patients, that is 92 (72%) women and 35 (28%) men, reacted to 48 specific topical pharmaceutical products in which fragrance components were identified as relevant allergens.

Legs ($n = 57$), hands ($n = 39$), and face ($n = 28$) were the most commonly affected body sites in these patients, particularly in women.

We identified 66 different fragrance components (Table 1) in 370 (10% of the total) topical pharmaceutical products marketed in Belgium. Table 2 lists the nature of 48 specific products that have caused iatrogenic contact dermatitis in 127 patients, along with the nature of the 38 different fragrance components these products contain. These are products with wound healing, antiseptic or antimicrobial properties, non-steroidal anti-inflammatory drugs (NSAIDs), antihemorrhoidal preparations, and even corticosteroid-containing medications [e.g. Mycolog® (Triadacortyl® in the UK) (Sanofi-Aventis, Diegem, Belgium), Scheriproct® and Ultralan® (both from Schering, Diegem, Belgium)]. So-called parapharmaceutical products, that is products not officially registered as pharmaceutical products, were excluded from

Table 1. Fragrance components^a identified in 370 topical pharmaceutical products marketed in Belgium

Fragrance components	Number of topical pharmaceutical products
Menthol	99
Lavandula Angustifolia (lavender) Oil (Lavender oil)	68
Mentha Piperita (Peppermint) Oil (Peppermint oil)	54
'Perfume'	51
Camphor	48
Eucalyptol (Cineole/Eucalyptol)	47
Rose Flower Oil (Rose oil)	33
Citrus Medica Limonum (Lemon) Peel oil (Lemon oil)	24
Cymbopogon Nardus (Citronella) Oil (Citronella oil)	24
Pinus Sylvestris Leaf Oil (Pine needle oil)	21
Geranium Maculatum oil (Geranium oil)	20
Eucalyptus Globulus Leaf Oil (Eucalyptus oil)	17
Citrus Aurantium Bergamia (Bergamot) Fruit Oil (Bergamot Fruit oil)	17
Eugenol	15
Thymus Vulgaris (Thyme) Oil (Thyme oil)	14
Citrus Aurantium Dulcis (Orange) Flower Oil (Orange flower oil)	13
Myroxylon Pereirae (Balsam Peru) resin (Balsam Peru)	13
Turpentine (Turpentine oil)	12
Rosmarinus Officinalis (Rosemary) Leaf Oil (Rosemary oil)	11
Illicium Verum (Anise) Oil (Anise oil)	11
Styrax Benzoin Gum (Benzoin)	10
Thymol	9
Colophonium	9
Benzyl alcohol	9
Anethole (Anethol)	9
Vanillin	8
Terpineol	7
Myristica Fragrans (Nutmeg) Kernel Oil (Nutmeg oil)	6
Musk Ketone	6
Linalool	6
Citrus Aurantium Amara (bitter orange) Oil (Neroli oil or Petitgrain Oil Organic)	6
Benzyl acetate	6
Melaleuca Quinquenervia oil (Niaouli oil)	5
Linalyl acetate	5
Hydroxycitronellal	5
Dihydrocoumarin	5
Cinnamyl alcohol	5
Mentha Viridis (Spearmint) Leaf Oil (Spearmint oil)	4
Melaleuca Leucadendron Cajaputi Oil (Cajeput oil)	4
Benzyl benzoate	4
Melaleuca Leucadendron Cajaputi Oil (Cajeput oil)	4
Origanum Majorana Leaf oil (Sweet marjoram oil)	3
Melissa Officinalis (Balm Mint) Leaf Oil (Balm mint oil)	3
Citrus Nobilis (Mandarin Orange) Peel oil (Mandarin oil)	3
Isoamyl Acetate (Isoamyl ethanoate)	3
Cupressus Sempervirens Oil (Cypress oil)	3
Cinnamomum Cassia Leaf (cinnamon) Oil (Cinnamon oil)	3
Cedrus Atlantica (Cedarwood) Bark Oil (Cedarwood oil)	3
Shorea Robusta Resin (Damar)	2
Cymbopogon Schoenanthus oil (Lemongrass oil)	2
Laurus Nobilis oil (Laurel oil)	2
Foeniculum vulgare (Fennel) oil (Fennel oil)	2
Coriandrum Sativum (Coriander) Fruit Oil (Coriander oil)	2
Benzyl cinammate	2
Cinnamal	1
Melaleuca Alternifolia (Tea Tree) Leaf Oil (Tea tree oil)	1
Jasminum Officinale (jasmine) Oil (Jasmine oil)	1
Sassafras Officinale Root Oil (Sassafras oil)	1
Santalum Album (Sandalwood) Oil (Sandalwood oil)	1
Hyssopus Officinalis Leaf oil (Oil of hyssop)	1
Dipentene (Limonene)	1
Heliotropine (Piperanol)	1
Canarium Luzonicum Gum Oil (Canarium Luzonicum – Elemi)	1
Ocimum Basilicum (Basil) oil (Basil oil)	1
Anise alcohol	1
Amyl Cinnamal	1

^aThe fragrance components are named here with the International Nomenclature of Cosmetic Ingredients name (which is not the case on the labels, on which many different names for the same components could be used) as well as the technical/trade names in bracket.

Table 2. The 48 fragrance-containing topical pharmaceutical products marketed in Belgium, found to be responsible for iatrogenic allergic contact dermatitis in 127 patients, along with their pharmacological activity and the fragrance ingredients present^a

Topical pharmaceutical product (number of patients reacting)	Company	Application	Fragrance ingredients
Mycolog (cream) ^b (<i>n</i> = 34)	Sanofi-Aventis, Diegem	Antibiotic–corticosteroid	'Perfume'
Fastum (gel) (<i>n</i> = 19)	Menarini, Zaventem	Anti-inflammatory (NSAID)	Lavender oil, neroli oil
Flexium (cream) (<i>n</i> = 9)	Melisana, Brussels	Anti-inflammatory (NSAID)	Benzyl alcohol, eucalyptus oil, pine needle oil
Dermophil Indien (ointment) (<i>n</i> = 5)	Couvreur, Brussels	Wound healing	<i>Myroxylon pereirae</i> , rose oil
HAC (solution) (<i>n</i> = 5)	SSL Healthcare Belgium, Groot-Bijgaarden	Antiseptic–disinfectant	Benzyl benzoate, terpineol
Cicatrisan (ointment) (<i>n</i> = 4)	Unda, Brussels	Wound healing	<i>Myroxylon pereirae</i>
Calendula (ointment) (<i>n</i> = 4)	Unda, Brussels	Wound healing	Rose oil
Homeoplasmine (ointment) (<i>n</i> = 3)	Unda, Brussels	Wound healing	Benzoin, benzyl alcohol
Newderm (ointment) (<i>n</i> = 3)	Wolfs, Sint-Niklaas	Wound healing	Geranium oil
Polyseptol (ointment) (<i>n</i> = 3)	Qualiphar, Bornem	Antibiotic	Bergamot fruit oil, geranium oil
Borostyrol (solution) (<i>n</i> = 2)	A.C.P., Brussels	Wound healing	Benzoin, bergamot fruit oil, menthol, thymol
Phenergan (cream) (<i>n</i> = 2)	Sanofi-Aventis, Diegem	Antihistaminic	Lavender oil
Reparil (gel) (<i>n</i> = 2)	Madaus, Brussels	Anti-inflammatory, vascular disorders	Lavender oil, neroli oil
Madecassol (cream) (<i>n</i> = 2)	Bayer, Brussels	Wound healing	Geranium oil, lavender oil
Anusol (ointment) (<i>n</i> = 2)	Pfizer Consumer Health, Brussels	Antihemorrhoids	<i>Myroxylon pereirae</i>
Hibitane (cream) (<i>n</i> = 2)	SSL Healthcare Belgium, Groot-Bijgaarden	Antiseptic–disinfectant	Pine needle oil
Oxyplastine (ointment) (<i>n</i> = 1)	Bournonville Pharma, Brussels	Wound healing	<i>Myroxylon pereirae</i>
Murazyme (ointment) (<i>n</i> = 1)	Grünenthal, Sint-Stevens-Woluwe	Wound healing	Lavender oil
Biogaze HN (bandage) (<i>n</i> = 1)	OJG Cons Care, Sint-Martens-Latem	Wound healing	Niaouli oil
Vitamorrhaine (ointment) ^c (<i>n</i> = 1)	PCB	Wound healing	Bergamot fruit oil, lavender oil
Vegebom (ointment) (<i>n</i> = 1)	Bournonville Pharma, Brussels	Wound healing	Cajeput oil, cedarwood oil, laurel oil, nutmeg oil, turpentine oil
Groene Duivel (plaster) (<i>n</i> = 1)	Colin, Blegny	Wound healing	Colophonium, turpentine
Reumatrix (plaster) (<i>n</i> = 1)	Beiersdorf, Anderlecht	Wound healing	Colophonium
Baume Contre Brulures (ointment) ^c (<i>n</i> = 1)	Qualiphar, Bornem	Wound healing	<i>Myroxylon pereirae</i>
Advantan (cream) (<i>n</i> = 1)	Schering, Diegem	Corticosteroid	Benzyl alcohol
Amicla (cream) (<i>n</i> = 1)	ERFA, Etterbeek	Corticosteroid	Benzyl alcohol
Dermaspray (solution) (<i>n</i> = 1)	Roche, Anderlecht	Antiseptic–disinfectant	Benzyl alcohol
Neo-Sabenyl (solution) (<i>n</i> = 1)	Qualiphar, Bornem	Antiseptic–disinfectant	Lavender oil

(Continued)

Table 2. Continued

Topical pharmaceutical product (number of patients reacting)	Company	Application	Fragrance ingredients
Dettol (solution) (<i>n</i> = 1)	Reckitt Benckiser, Brussels	Antiseptic–disinfectant	Perfume, terpineol
Reflex (gel) (<i>n</i> = 1)	Boots, Louvain la Neuve	Anti-inflammatory (NSAID)	Benzyl alcohol, menthol
Nifluril (ointment) (<i>n</i> = 1)	Upsa Medica SA, Waterloo, Belgium	Anti-inflammatory (NSAID)	Perfume
Lotriderm (cream) (<i>n</i> = 1)	Schering Plough, Brussels	Antimycotic	Benzyl alcohol
Mycospor (cream) (<i>n</i> = 1)	Bayer, Brussels	Antimycotic	Benzyl alcohol
Pevaryl (cream) (<i>n</i> = 1)	Janssen-Cilag, Berchem	Antimycotic	Rose oil
Chloramphenicol (cream) (<i>n</i> = 1)	SKF-Rit, Rixensart	Antibiotic	Neroli oil
Sarnol (lotion) (<i>n</i> = 1)	Stiefel, Herverlee	Antipruritus/analgesic	Camphor, menthol, perfume
Vicks Vaporub (<i>n</i> = 1)	Procter & Gamble, Stombeek-Bever	To inhale (to relieve symptoms of bronchitis, sinusitis, etc.)	Camphor, eucalyptus oil, menthol, nutmeg oil, thymol, turpentine
Duofilm (solution) (<i>n</i> = 1)	Stiefel, Heverlee	Keratolytic	Colophonium
Scheriproct (ointment) (<i>n</i> = 1)	Schering, Diegem	Analgetic, anti-inflammatory	Cypress oil
Caladryl (ointment) (<i>n</i> = 1)	Omega Pharma, Nazareth	Antipruritic	Lavender oil
Benzoeoplossing (solution) ^c (<i>n</i> = 9)	ABL	Degreaser	Benzoin, benzyl alcohol, rose oil
Maturosan (ointment) ^c (<i>n</i> = 4)	Sam	Wound healing	Benzoin, benzyl alcohol, elemi resin, turpentine, turpentine oil
Madecassol (ointment) ^c (<i>n</i> = 3)	Laroche Navarron, Brussels	Wound healing	Geranium oil, lavender oil
Pyal (ointment) ^c (<i>n</i> = 3)	Sanico, Turnhout	Antibiotic	Bergamot fruit oil, lavender oil
Oxyplastine (ointment) ^c (<i>n</i> = 2)	Promedy	Wound healing	Geranium oil, lemongrass oil, <i>Myroxylon pereirae</i> , origanum oil, thyme oil
Ultralan Vet Gras (ointment) ^c (<i>n</i> = 1)	Schering, Diegem	Corticosteroid	Bergamot fruit oil, cinnamyl alcohol, citronella oil, piperonal, hydroxycitronellal, ionone, lavender oil, linalool, musk ketone, neroli oil
Desinfecterende en helende zalf (ointment) ^c (<i>n</i> = 1)	Unda, Brussels	Antiseptic–disinfectant	<i>Myroxylon pereirae</i>
Inhalene (solution) ^c (<i>n</i> = 1)	Alcon, Breendonk	Cold symptoms, laryngitis, sinusitis	Cajeput Oil, cypress oil, eucalyptol, eucalyptus oil, musk ketone, lavender oil, peppermint oil, pine needle oil

^aDuring the period 1978–2008, the names of the manufacturers or the companies marketing these topical pharmaceutical products as well as the content of the products may have changed over the years.

^bMycolog[®] cream is marketed in the UK as Triadcortyl[®].

^cSome of them are no longer commercially available, hence no companies in Belgium anymore.

this list. The fragrance allergens, for which the presence was all or not confirmed, but that produced positive patch test results in this population, along with the corresponding literature references for each compound, are listed in Table 3.

With regard to the fragrance allergens identified among the 127 patients, fragrance mix I (FM I) [containing cinnamyl alcohol, cinnamal, eugenol, amyl cinnamal, hydroxycitronellal, geraniol, iso-eugenol, and *Evernia prunastri* (oakmoss) absolute] was the most frequent allergen found in the European baseline patch test series, that is 87 reactions (Table 3), followed by *M. pereirae* with 59 positive reactions, both reacting concomitantly in 40 cases. To a lesser extent, colophonium was found with 21 reactions, reacting concomitantly to FM I and *M. pereirae* in 11 cases and with FM I alone in 4 more cases.

Since 2005, a mixture of six additional fragrance materials has been available for introduction into the baseline series, that is fragrance mix II (FM II) (containing hydroxyisohexyl 3-cyclohexene carboxaldehyde, citral, citronellol, farnesol, coumarin, and hexyl cinnamal) (4, 18), for which we detected three relevant positive reactions. Two patients reacted to citronellol, and the third patient reacted to farnesol, for which no relevant explanation was found, and to eucalyptus oil (cf. below) present in Flexium[®] gel (Melisana, Brussels, Belgium). All three also reacted to FM I, one of whom to cinnamyl alcohol present in it.

Forty-five patients presented with 82 reactions to one or more essential oils (Table 3); seven of them did not react to FM I, *M. pereirae*, or colophonium. In addition, in those subjects who were tested with some of the individual ingredients of essential oils, we found following positive reactions: three to (oxidized) limonene in patients positive to lavender oil and two to geraniol in patients reacting to geranium oil; of five patients reacting to rose oil, one had a positive reaction to benzyl alcohol, one to citronellol, one to limonene, and one to geraniol. The reactions to citronellol (as a component of FM II, cf. above) were relevant too for contact allergy to rose and geranium oil, present in Calendula[®] ointment (Unda, Brussels, Belgium) and Polyseptol[®] ointment (Qualiphar, Bornem, Belgium), respectively.

There were 34 patients who reacted to the perfume present in Mycolog cream. According to data obtained from the company, this perfume contains 28 ingredients, among which one (hydroxycitronellal) and three (citral, citronellol, and coumarin) are also present in FM I and FM II, respectively. Not all patients reacting to this perfume were tested with the fragrance mixes or

Table 3. The fragrance allergens identified in 127 patients reacting to the 48 specific topical pharmaceutical products

Allergens	PC	PNC	Literature references
FM I	36	51	(26, 28, 42, 63, 71–75)
Cinnamyl alcohol	2	4	(64, 71, 73)
Cinnamal	2	3	
Geraniol ^a	4	2	(74–78)
Hydroxycitronellal ^a	3		(64)
<i>Evernia prunastri</i> (Oak moss) ^a		10	
Eugenol ^a	4	2	(79)
Isoeugenol ^a	3	3	
FM II	2	1	
Citral ^a	1	1	
Citronellol ^a	2		
Essential oils			(11, 12)
Lavender oil	24	2	(12, 48, 75, 80)
Neroli oil	14		(48, 12)
Eucalyptus oil	10		(12)
Cananga Odorata Flower (ylang ylang) oil		2	(12)
Cinnamon oil		1	(48)
Jasmine oil		1	(11, 12)
Geranium oil	12		(11, 12)
Laurel oil	2		(12, 53–55)
Niaouli oil		2	(3)
Pine needle oil	4		(32, 35)
Tea tree oil	2		
Lemon oil		1	
Rose oil	5		
Other allergens			
<i>Myroxylon pereirae</i>	21	38	(25–28, 42, 57)
Resin (balsam of Peru)			
Colophonium	7	14	(42)
Perfume (Mycolog [®])	34		(23, 24, 64, 81)
Perfume (Nifluril [®])	1		
Amyl cinnamic alcohol ^a	2	1	
Thymol	1		
Camphor	2		
Limonene	7	2	
Tree moss		1	
(<i>Evernia furfuracea</i>)			
<i>Styrax</i> Benzoin Gum	19		(60, 61)
(Benzoin)			
Benzyl alcohol	5		(49, 58, 64)
Benzyl benzoate	1		
Terpineol	5	1	(34)
Turpentine	2		

FM I, fragrance mix I; FM II, fragrance mix II; PC, presence confirmed in the causal pharmaceutical product; PNC, presence not confirmed.

^aThese allergens were not listed in Table 1 as they were tested because of their presence in FM I or FM II, or in Mycolog[®] 'perfume'. However, all patients were not tested with all individual components.

with other fragrance ingredients, but of the six tested, one presented with a positive reaction to citral, three to amylcinnamal, two to limonene, and one to benzyl alcohol. Two subjects also reacted to lavender oil, which, besides limonene (not tested in these cases), might share also other common ingredients with lavandin oil (*Lavandula Hybrida*) present in Mycolog cream.

We found 19 patients with positive reactions to benzoin, 7 of them because of a degreasing solution, 5 to wound healing preparations, and 7 to an ointment preparation against fissures. Of 19, 9 presented simultaneous reactions to both FM I and *M. pereirae* and another 4 to FM I, *M. pereirae*, and colophonium.

Simultaneous reactions to *M. pereirae* and propolis were found in 5 patients and to the fragrance components of FM I and *M. pereirae* (one of them also to colophonium) and Compositae mix (Trolab, Hermal) in 7 patients, of whom 6 reacted to arnica and 2 to sesquiterpe-lactone mix.

If only the baseline series had been tested, fragrance allergy would have been missed in 24 of 127 (19%) patients reacting to the 48 responsible products. They did react to perfume, terpineol, geranium oil, lavender oil, benzoin, pine needle oil, laurel oil, bitter orange oil, rose oil, laurel oil (oxidized), limonene, or thymol.

Figs 1 and 2 illustrate allergic contact dermatitis from HAC[®] solution (SSL Healthcare, Groot-



Fig. 1. Allergic contact dermatitis from terpineol in HAC[®] solution (SSL Healthcare, Groot-Bijgaarden, Belgium).



Fig. 2. Positive reaction to terpineol 5% petrolatum in the same patient.

Bijgaarden, Belgium) and the positive test to its ingredient α -terpineol. Fig. 3 shows residual permanent hyperpigmentation as a complication of allergic contact dermatitis from benzoin in a degreasing solvent applied under a cast. Besides benzoin, the patient also reacted to FM I and *M. pereirae*.

Discussion

Most patients reacting to 48 specific fragrance-containing topical pharmaceutical products reacted to FM I, followed by *M. pereirae*, and colophonium, the fragrance-allergy markers



Fig. 3. Residual permanent hyperpigmentation as a complication of allergic contact dermatitis from benzoin tincture in a degreasing solvent applied under a cast.

present in the European baseline patch test series. Reactions to them were often associated (19–23), which is explained by the presence of similar components. In 1977, Larsen even introduced FM I partly based on positive patch test results obtained with the fragrance components of Mycolog perfume (23, 24) to detect fragrance allergy.

Allergic contact dermatitis from *M. pereirae* in Dermophil Indien (Couvreur, Brussels, Belgium) was described by Foussereau (25) in 1975, and recent studies (26–28) indicate that the increased incidence of sensitization to *M. pereirae* observed is mainly because of fragrances present in topical medications for wound-healing or antimicrobial effects (29, 30). Most ingredients of *M. pereirae* are present in or related to other allergenic fragrance materials, for example three of them being present in FM I, that is cinnamyl alcohol, cinnamal, and eugenol. Furthermore, propolis, a resinous substance collected by bees (31), to which anti-inflammatory and antimicrobial properties are attributed, also shares several minor sensitizers with *M. pereirae*, which explains the concomitant reactions; according to Wohrl et al. (19), it is also a helpful indicator for fragrance allergy.

Colophonium may cross-react or co-react with other fragrance allergens (32–37) that also contain oxidized terpenes (38, 39); it is mostly found as an allergen in classical adhesive tapes (not taken into account in this study) but is also used as a vehicle component in wart medications, surgical paints (40), and Chinese herbal medicine (41, 42), the latter of which two such cases were included here. Such medications generally contain more fragrance allergens and plant extracts than topical pharmaceutical products sold in Europe (42). Moreover, modified colophonium is also present in wound dressings.

Essential oils are mainly constituted of terpenes such as α -pinene and β -pinene, citral, geraniol, linalool, citronellal, hydroxycitronellal, and limonene but also of other organic chemical compounds, including aromatics, aliphatics, alicyclics and heterocyclics. It has been shown that terpenes are not allergenic themselves but that their oxidation products are the strongest allergens formed being mainly hydroperoxides (43–46). Although patch test material of the oxidized forms of linalool and limonene are not commercially available yet (44, 45), we did test with aged materials and thus obtained positive patch test results. As shown in Table 2, essential oils are present in several pharmaceutical topical products, particularly in those that have been marketed several decades ago. Unfortunately, they are also found in more recently marketed preparations such as NSAIDs.

In a recent study performed in our department (47), 10 of 40 patients with positive photo-patch tests to Fastum[®] (Menarini, Zaventem, Belgium) presented with a contact allergy to the essential oils present in them. Moreover, 22 of 40 reacted to FM I and/or *M. pereirae* but not to the essential oils contained in these products. In agreement with the literature, fragrance allergy, and cinnamyl alcohol in particular, is indeed often related to photocontact allergy to ketoprofen, the reason for which is not clear (48, 49).

Because of their pharmacological properties, such as antiseptic, analgesic, or anti-inflammatory effects, essential oils and their ingredients are often used for medical instead of cosmetic reasons. Currently, these substances are frequently found in aromatherapy (50–52) and are applied directly to the skin for the treatment of, for example, arthritis (53, 54), muscular pains (55), etc. In dentistry, for example, eugenol, an important chemical constituent of clove oil, is widely used because of its antiseptic properties (56). A Swedish study has reported that even *M. pereirae*, which also contains eugenol, is used in dental cement and indicated that the oral mucosa might also be a sensitization site (57).

Benzyl alcohol (58, 59) is present in *M. pereirae* at 1–2% concentration and is an aromatic preservative agent that also has anaesthetic, antipruritic, and viscosity-decreasing properties (58–60). Despite its widespread use, sensitization to this allergen is considered rare but has been responsible for allergic contact dermatitis from antibacterial and antimycotic creams, topical corticosteroids, sunscreens, analgesic sprays, and sclerosing agents (58, 59).

Benzoin is a balsamic resin obtained from *Styrax* benzoin Dryander and other species of *Styrax* (Faroo, Styraceae). The tincture is used (61, 62) to enhance the adhesive properties of tape and bandages, as an antiseptic, and also as a solvent for drugs, for example in podophyllin tincture, used in the treatment of venereal warts (61). The main constituents of benzoin are resin, benzoic acid, and cinnamic acids and their esters. In addition, traces of vanillin, benzaldehyde, styrol, and styacin are also present (61, 62). Cross-reaction between benzoin and similar allergens (FM I, *M. pereirae*, colophonium, and tea tree oil) have been reported (61, 62).

The observation of simultaneous reactions to fragrances and Compositae plant extracts (sesquiterpene lactones) can be explained by the common presence of terpenes (63, 64).

In agreement with the literature, multiple sensitization to several fragrances was also observed in this study population, and the risk becoming

higher because of the frequent application of topical pharmaceutical products also in chronic dermatological conditions in which the skin barrier is damaged: leg ulcer patients, patients with dermatitis on the hands (also direct contact when applying the products on the skin), patients with chronic facial dermatitis such as seborrhoeic or atopic dermatitis (26, 27, 65–67).

Since 1997, all cosmetic ingredients have been labelled in a uniform manner with the International Nomenclature of Cosmetic Ingredients name, except for fragrance. Since 2005, the EU has also required that 26 important fragrance allergens be labelled specifically (68). Moreover, restrictions have been made on the use concentrations of certain allergens, for example isoeugenol (69). Besides EU regulations, the International Fragrance Research Association gives advice as to the use of certain fragrance allergens by the perfume industry; for example, the use of crude *M. pereirae* in cosmetics has been banned since 1982 (70) (albeit that the extracts or distillates are not necessarily less allergenic). In contrast, in topical pharmaceutical products in Europe, there is no legislation regarding such labelling: the nomenclature of the ingredients has not been standardized (9), and several synonyms may appear on the label or on the notice. As to the presence of fragrance allergens, no restrictions have been made either.

Conclusions

The fragrance-allergy markers in the baseline series did pick up most of the patients sensitized to fragrance allergens present in the 48 specific topical pharmaceutical products to which they reacted. However, extended patch testing with the products used by the patient, along with the ingredients, is also needed because one fifth of them only reacted positively to an essential oil or to another fragrance allergen present. The possibility of testing all the components of a commercial product depends, of course, on the manufacturer's goodwill to provide all ingredients.

Because topical pharmaceutical products are applied on more vulnerable, and often diseased skin (wounds, leg ulcers, eczema, etc.), they thus constitute another important source of fragrance sensitization, which predisposes the patients to develop multiple sensitivities and to react also to fragrance-containing cosmetics (and other fragranced materials). Besides their use as a pharmacologically active ingredient in some cases, the use of fragrances in topical pharmaceutical products is unnecessary. In agreement with other authors (71, 72), we also urge for better legislative meas-

ures and a standardized labelling of all ingredients of such products.

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Address:

Prof An Goossens
Department of Dermatology
Contact Allergy Unit
University Hospital St Rafaël
Katholieke Universiteit Leuven
Kapucijnenvoer 33
B-3000 Leuven
Belgium
Tel: 00 32 16 33 78 60
Fax: 00 32 16 33 70 12
e-mail: an.goossens@uz.kuleuven.ac.be