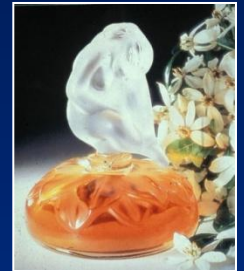


Fragrances as skin sensitizers: mechanistic and clinical insights



Prof. An Goossens

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Department of Dermatology

University Hospital

K.U. Leuven

Leuven, Belgium

No conflict of interest

IDEA August 2013

Fragrances as skin sensitizers

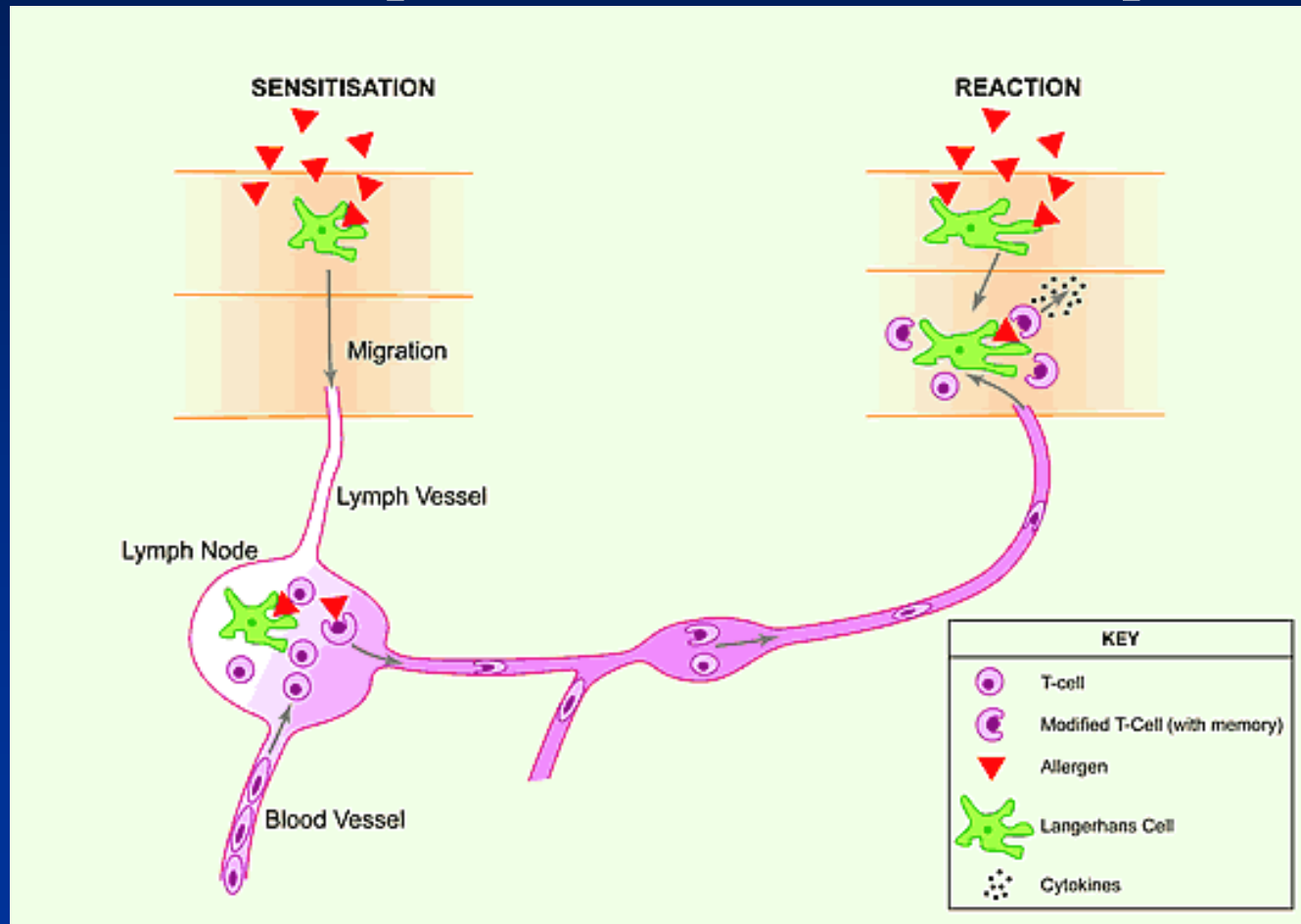
- Mechanisms
- Diagnosis
- Frequency
- Clinical aspects



Mechanisms of skin sensitization

Sensitization phase

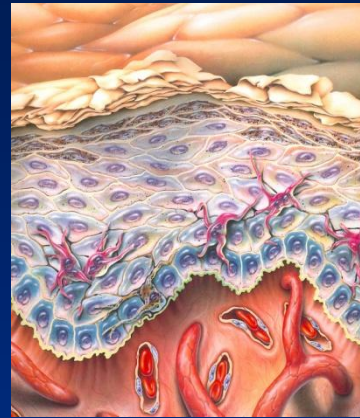
Elicitation phase



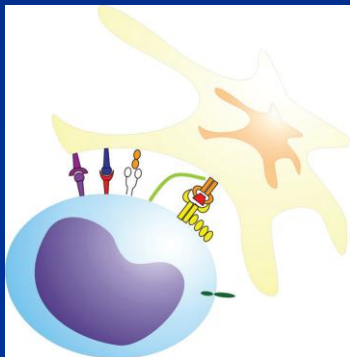
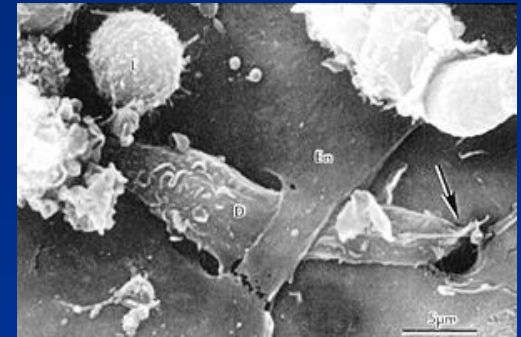
Mechanisms of skin sensitization

Sensitization phase:

Interaction of
exogenous molecules
with skin structures



Role of DC's



Hapten-specific
T lymphocytes



Mechanisms of skin sensitization

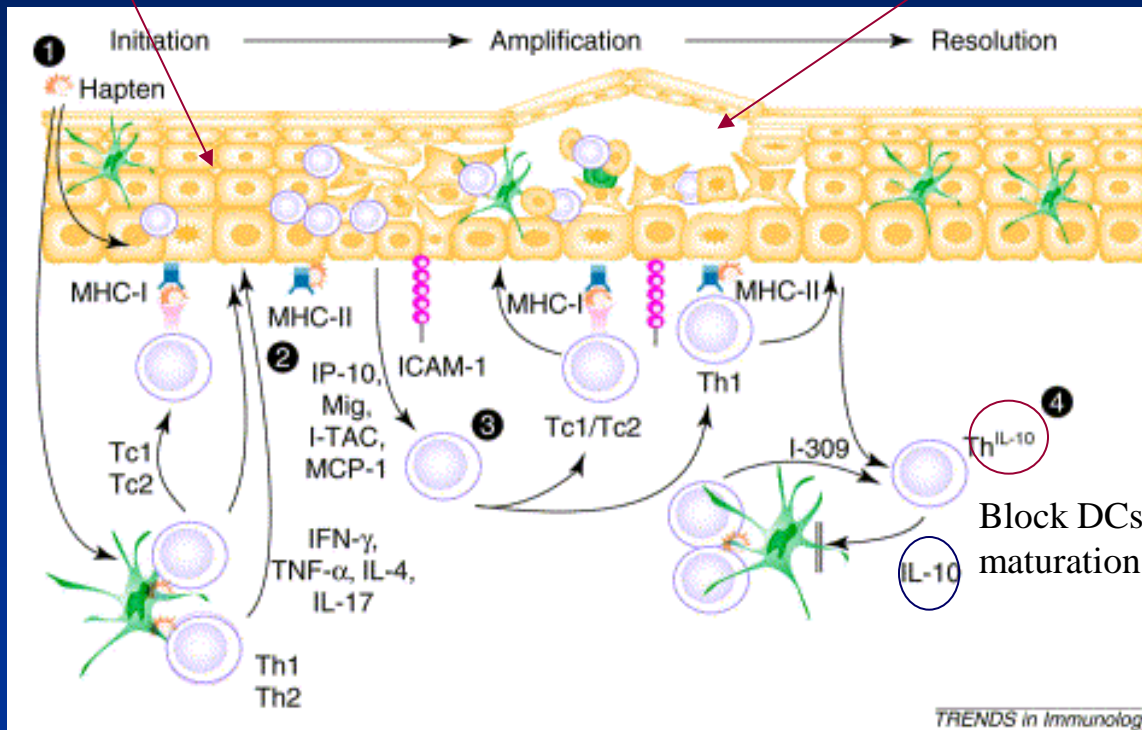
Elicitation phase:

IL-1, TNF- α , GM-CSF,
IP-10, Mig, I-TAC, MCP-1, RANTES

Keratinocyte damage



“allergic contact dermatitis”



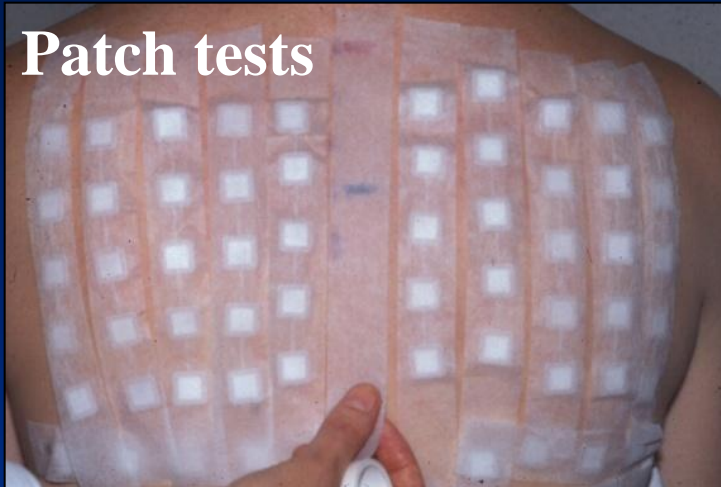
Cavani A, Trends in Immunology 2001

Cumberbatch M, J Immunol 2005

Fragrances as skin sensitizers

- Mechanism
- **Diagnosis**
- Frequency
- Clinical aspects

Fragrances as skin sensitizers: diagnosis



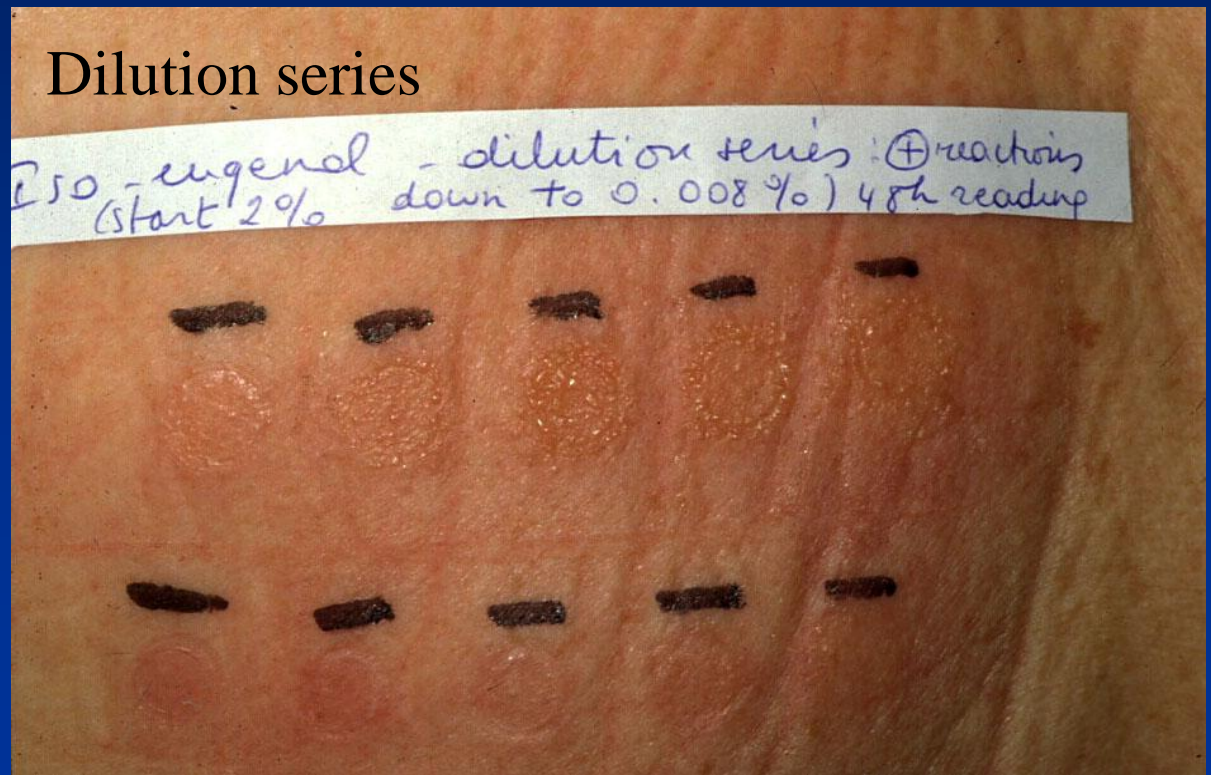
- Patch tests

Fragrances as skin sensitizers: diagnosis



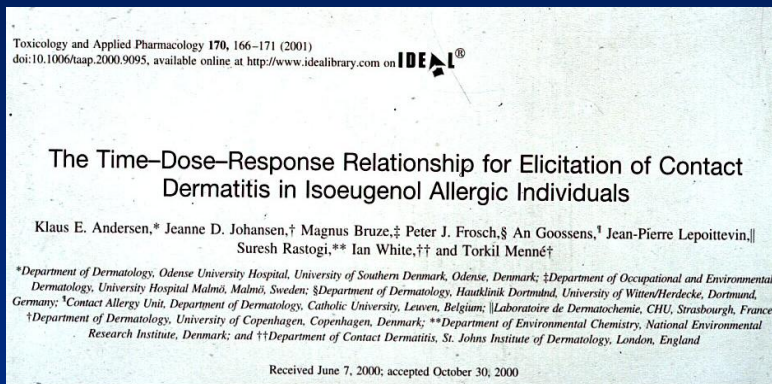
- Patch tests
- **ROAT's (Repeated Open Application Tests)**
- **Usage tests (original site)**

Testing in already sensitized subjects: Detection of sensitivity level (ROAT's/ Dilution series)



Testing in already sensitized subjects: Detection of sensitivity level (ROAT's/ Dilution series)

Tox Appl Pharmacol 2001; 170: 166-71

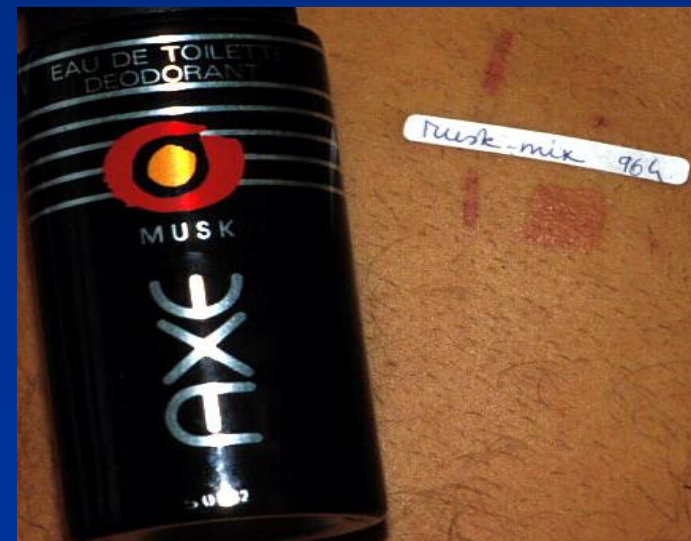


- *highly significant correlation between patch test thresholds and the nr of days until a + ROAT*

- *for low concentrations of the allergen or low degree of sensitivity, the allergic contact dermatitis may develop after several weeks of exposure! Therefore, a negative ROAT after 7 days may be false-negative!*

Fragrances as skin sensitizers: diagnosis

- Results of patch testing with
 - baseline series
 - additional “fragrance” series
 - individual fragrance allergens, essential oils, ...
- Results of patch (and other) tests with fragrances used (and presumed or known ingredients)



Screening agents for fragrance allergy

(baseline series)

- Fragrance Mix 1



- *Myroxylon pereirae* (balsam of Peru)

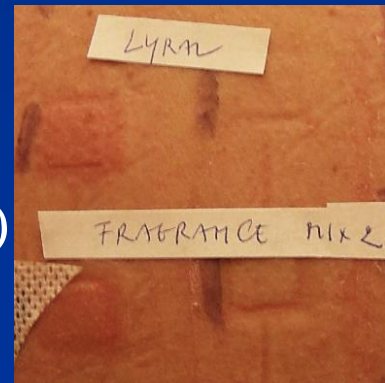


- Colophonium



- Fragrance Mix 2

- Hydroxyisohexyl cyclohexene carboxaldehyde (Lyrall®)



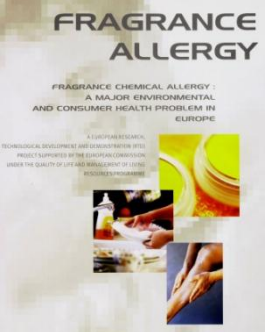
Screening agents for fragrance allergy

Fragrance mix 1

- Amyl cinnamal
- Cinnamal
- Cinnamylalcohol
- Hydroxycitronellal
- Eugenol
- Iso-eugenol
- Geraniol
- **Oakmoss**

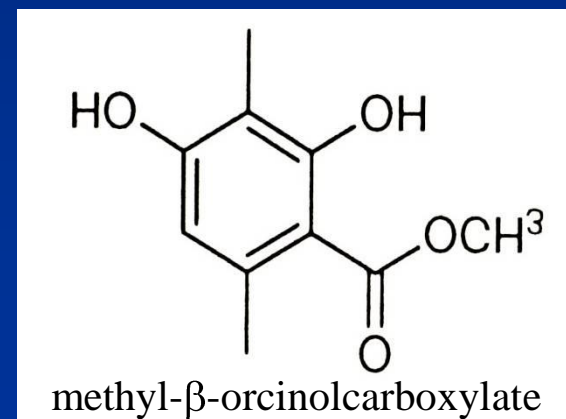
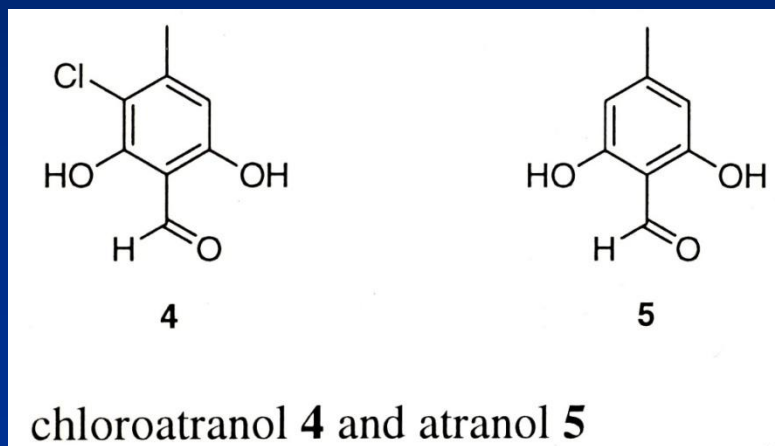
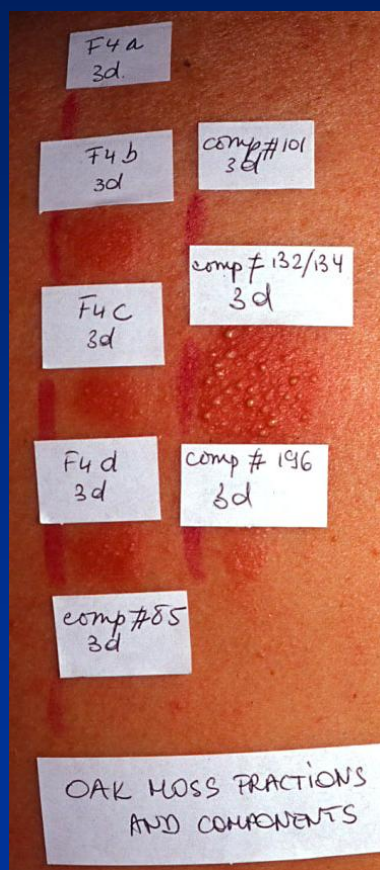
} *7 individual fragrance chemicals
and oak moss, a natural extract*





Fragrance Mix I: Oak moss

Contains extremely strong allergens, i.e. atranol and chloroatranol, and to a lesser extent methyl- β -orcinol carboxylate and β -orcinol, ...



Screening agents for fragrance allergy

Fragrance mix 2

- Alpha-hexyl cinnamic aldehyde
- Citral
- Citronellol
- Coumarin
- Farnesol
- Hydroxyisohexyl 3- cyclohexenecarboxaldehyde (HICC)*

Wir bieten Ihnen
100% Wirkung
bei **0,3%**
Einsatz.

Farnesol

Dieser zeitgemäÙe patentierte Wirkstoff zeigte im KWI-Test nach Prof. Hees schon bei einer Konzentration von nur 0,3% seine überragende Wirkung: Farnesol hemmt die Entstehung von Körpergeruch – ohne die natürliche Hautflora negativ zu beeinflussen.

Spezifische Eigenschaften:

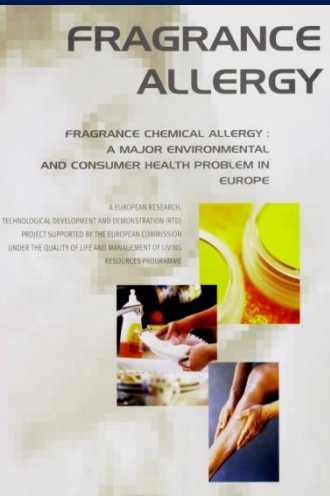
- Besonders sanfte, natürliche Wirkung
- Gute Haut-/Schleimhautverträglichkeit
- Hohe Ergiebigkeit,
- Leichter, fein-blumiger Duft
- Ideal für alle Deodorantien


DRAGOCO



* Lyrall, also tested separately in the baseline series

Additional markers for fragrance allergy needed!



Contact Dermatitis, 2001, 45, 221-225
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CONTACT DERMATITIS
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Fragrance chemicals in domestic and occupational products

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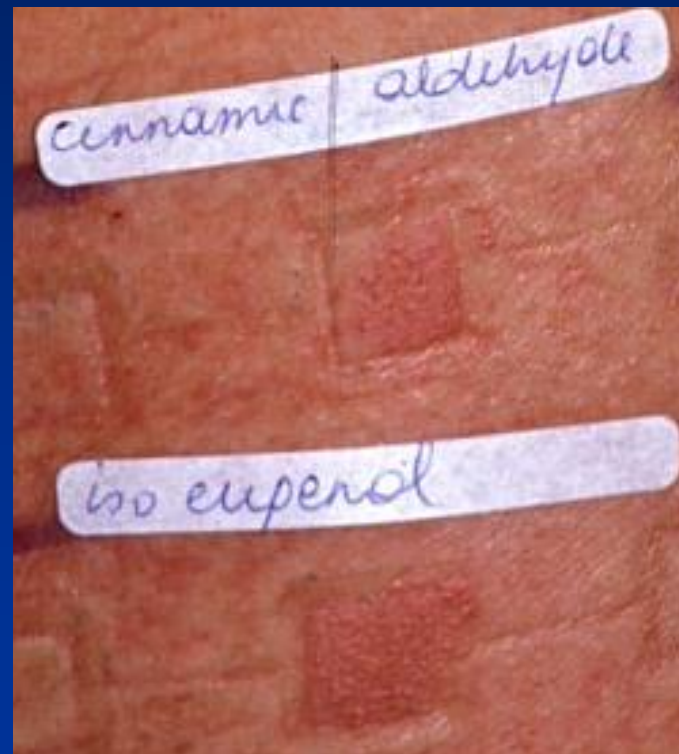
³SEAC Toxicology, Unilever Research, Sharnbrook, UK

with and without anti-oxydants...

Multiple positive reactions to fragrance components

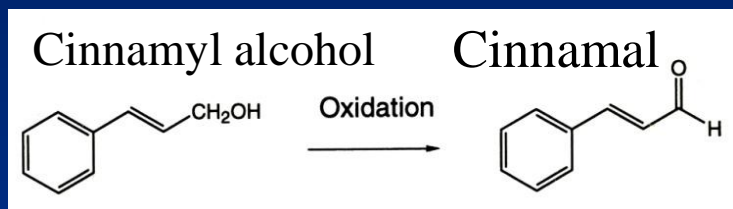
Fragrance mix allergens : Statistically significant associated positive tests

<u>Correlated substances</u>	<u>p-values</u>
Amylcinnamal - Cinnamyl alc.	$p < 0.001$
Cinnamyl alcohol - Cinnamal	$p < 0.001$
Eugenol - Isoeugenol	$p < 0.001$
Geraniol - Hydroxycitronellal	$p < 0.1$
Geraniol - Isoeugenol	$p < 0.1$
Geraniol - Oakmoss	$p < 0.05$
Isoeugenol - Oakmoss	$p < 0.01$



Multiple positive reactions to fragrance components

- concomitant/subsequent sensitization
- common metabolite(s) formed



- cross-reactions between chemically- related agents
- presence of common ingredients (natural products)

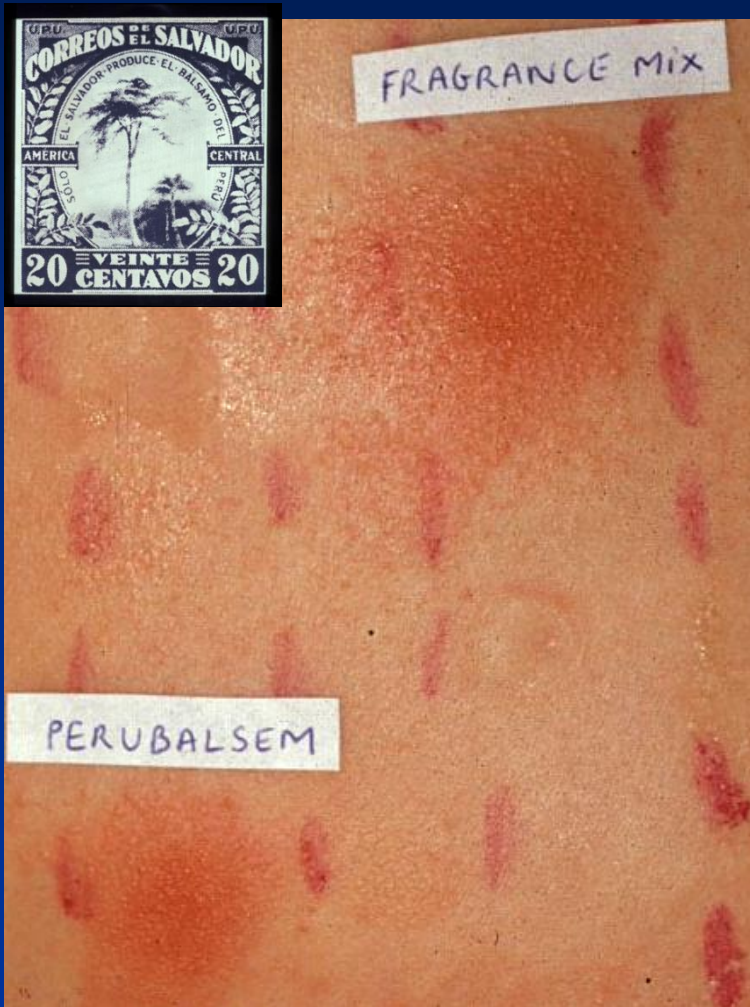


Multiple positive reactions to fragrance components

Myroxylon pereirae (Balsam of Peru)

components:

- benzyl cinnamate
- eugenol
- methyl cinnamate
- benzyl benzoate
- vanillin
- cinnamic acid
- cinnamic alcohol
- cinnamal
- benzyl salicylate



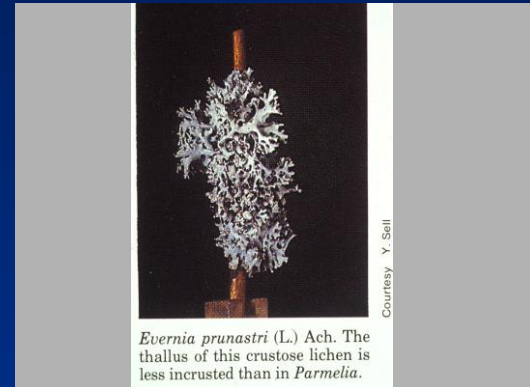
(Larsen, Arch. Derm. 1977, 113:623-6)

Multiple positive reactions to fragrance components

Beside (chloro)atranol, etc., also air-oxidized resin acids, i.e. abietic and dhydroabietic acids in oak moss - as contaminants from tree moss...



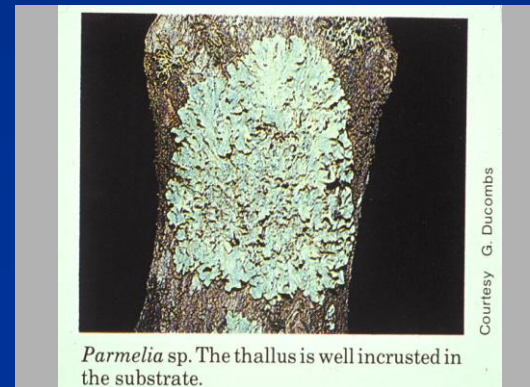
Oak moss



Evernia prunastri (L.) Ach. The thallus of this crustose lichen is less incrustated than in *Parmelia*.

Courtesy Y. Sell

Tree moss



Parmelia sp. The thallus is well incrustated in the substrate.

Courtesy G. Ducombs

Multiple positive reactions to essential oils

Statistically significant associated positive tests

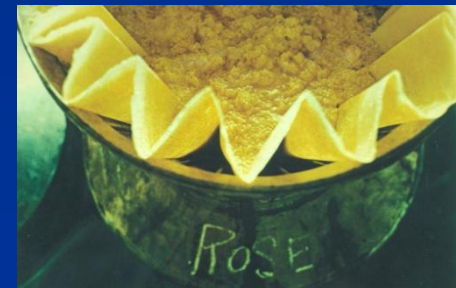
<u>Correlated substances</u>	<u>p-values</u>
Lavender oil - Geranium oil	$p < 0.05$
Jasmin oil - Cananga oil	$p < 0.1$
Jasmin oil - Ylang ylang oil	$p < 0.1$
Jasmin oil - Geraniol	$p < 0.05$
Jasmin oil - Hydroxycitronellal	$p < 0.1$
Cananga oil - Ylang ylang oil	$p < 0.001$
Cananga oil - Geraniol	$p < 0.001$
Ylang ylang oil - Rose oil	$p < 0.05$
Rose oil - Geraniol	$p < 0.01$
Rose oil - Benzyl alcohol	$p < 0.05$
Geraniol - Benzyl alcohol	$p < 0.01$
Geraniol - Hydroxycitronellal	$p < 0.05$
Benzyl alcohol - Hydroxycitronellal	$p < 0.001$
Hydroxycitronellal - Cinnamyl alc.	$p < 0.05$



Multiple positive reactions to essential oils: air-oxidized terpenes

Common ingredients of essential oils

	<u>geraniol</u>	<u>limonene</u>	<u>linalool</u>
Geranium oil	+	+	+
Jasmin oil	-	-	+
Lavender oil	+	+	+
(Bitter) Orange oil	-	+	+
Rose oil	+	-	-
Pine oil	-	+	-
Ylang ylang oil	+	-	+



“Natural” ingredients such as essential oils in “fragrance-free” cosmetics...



The example of *Rosa centifolia*



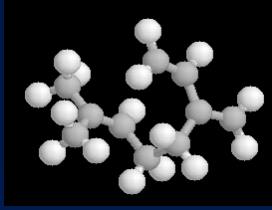
“Natural” ingredients in “fragrance-free” cosmetics...



Rosa centifolia (not used as a fragrance) → labeling = **CONFUSING!**



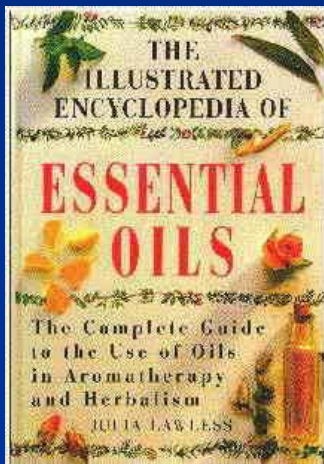
Air-oxidized terpenes



Essential oils



Many plants, fruits, ...





Air-oxidized terpenes in fragrances and *Compositae* or *Asteraceae* plants



Colophonium and *compositae* mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, *colophonium* and *compositae* plant extracts. Paulsen et al. *Contact Dermatitis* 2005; 53, 285

Air-oxidized terpenes

Spices



NUTMEG: volatile oil: myristicin, pinene, camphene, dipentene, safrol, eugenol, isoeugenol, alcohols.
fixed oil: trimyristin

- *Myroxylon pereirae* (balsam of Peru)/FM 1: = sometimes marker for spice allergy

Fragrances as skin sensitizers

- Mechanism
- Diagnosis
- Frequency
- Clinical aspects

Fragrances as skin sensitizers

- Frequency of contact allergy:

- ± 2 % in the general population
- 8 -15 % in routinely tested patients

- not all patients with contact allergy do suffer from allergic contact dermatitis

FM 1 and 2, and HICC (KULeuven study)

Positive reactions observed to FM 1, HICC and FM 2

	Patients tested with FM 1 (n=13114) 1990-2011	Patients tested with HICC (n=3927) 2002-2011	Patients tested with FM 2 (n=3416) 2005-2011
Positive reactions	1259	82	205
Percentage (%)	9.6	2.09	6

Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and *Myroxylon pereirae* and colophonium over a 21-year period. A Nardelli, A Carbonez, J Drieghe, and A Goossens *Contact Dermatitis* 2013; 68: 307-11

Testing to both FM 1 and 2 (n= 3380)

FM 2: 106 (30,4%) + out of 349 FM 1 +

FM 1: 106 (51,7%) + out of 205 FM 2 +



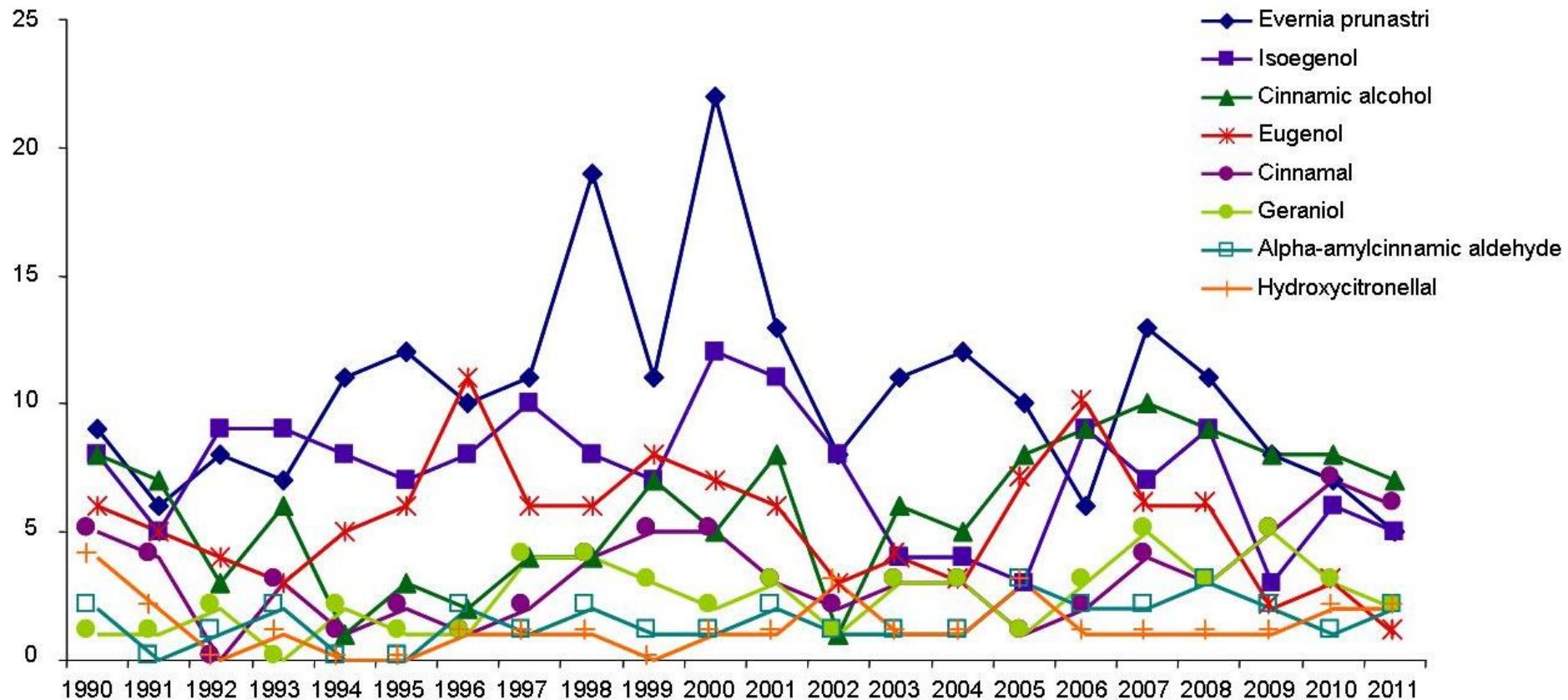
FM 2 = also an interesting marker in the baseline series

Fragrance mix 1 ingredients

Positive reactions to the constituents of FM 1 between 1990-2011

Constituents	Total (n=940)	Percentage (%)
Evernia prunastri	230	24.57
Isoeugenol	160	17.02
Cinnamic alcohol	129	13.73
Eugenol	118	12.55
Cinnamal	66	7
Geraniol	52	5.5
α amylocinnamal	30	3.2
Hydroxycitronellal	24	2.56
(Sorbitan Sesquioleate)	21	2.24

Fragrance mix 1 ingredients: trends over the years



- Cinnamyl alcohol more important than cinnamal, particularly in recent years (relation with ketoprofen!)

Multiple allergic reactions following ketoprofen photosensitization

*



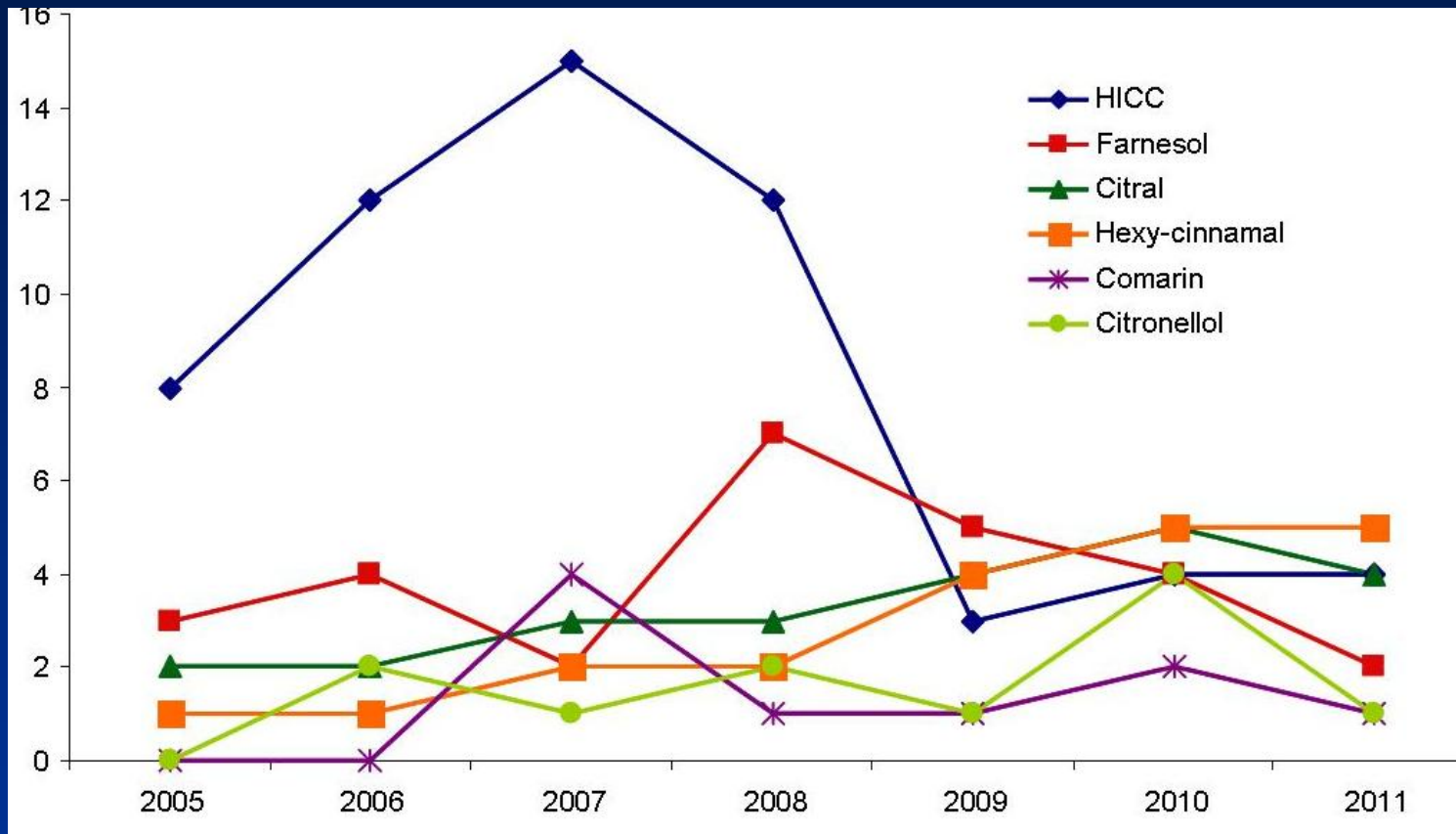
* 89% of photo-allergic ketoprofen patients also reacting to cinnamic alcohol (*Marmgren et al., ESCD 2010*)

Fragrance mix 2 ingredients

Positive reactions to the constituents of FM 2 between 2005-2011

Constituents	Total (n=205)	Percentage (%)
HICC	58	2.4
Farnesol	27	0.61
Citral	23	0.31
Hexyl cinnamal	20	0.19
Citronellol	11	0.19
Coumarin	9	0.19

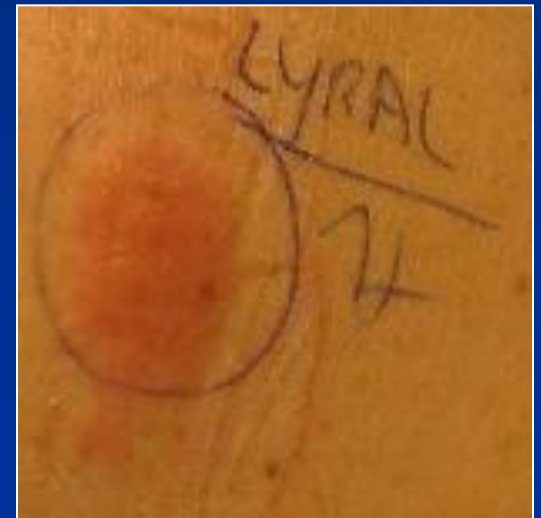
Fragrance mix 2 ingredients: trends over the years



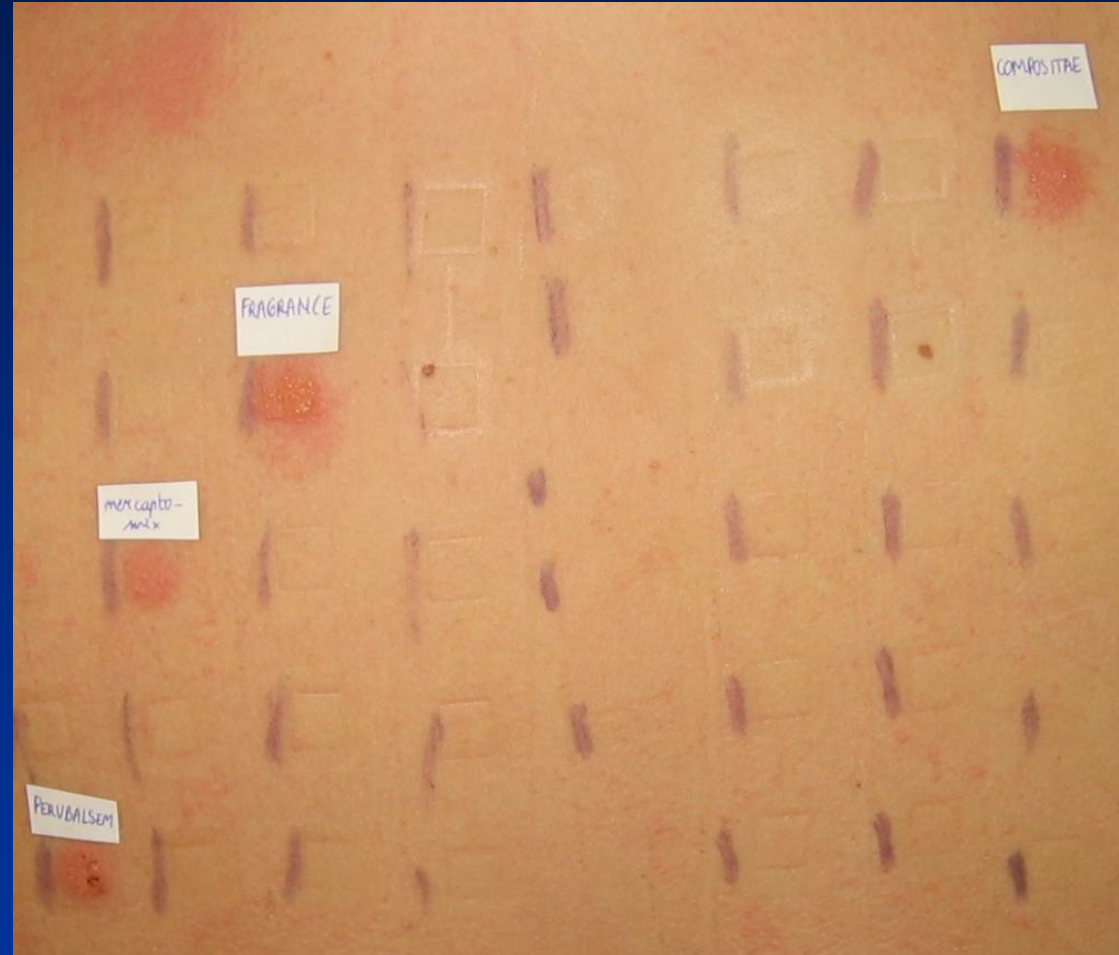
- Farnesol and HICC going down since 2008

Hydroxyisohexyl cyclohexene carboxaldehyde (HICC) (n= 3927)

- 18/82 HICC + did not react to FM 1
- 6 out of 3401 tested to both FM 2 and HICC
+ to HICC only



Cross-reactions between colophonium, MP, fragrance-mix 1, and (air-oxidized)terpene-containing compositae plants



Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and Myroxylon pereirae and colophonium, over a 21-year period. A Nardelli, A Carbonez, J Drieghe and A Goossens. Contact Dermatitis 2013; 68: 307-11

Fragrances as skin sensitizers

- Mechanism
- Diagnosis
- Frequency
- Clinical aspects

Fragrances as skin sensitizers: Clinical aspects

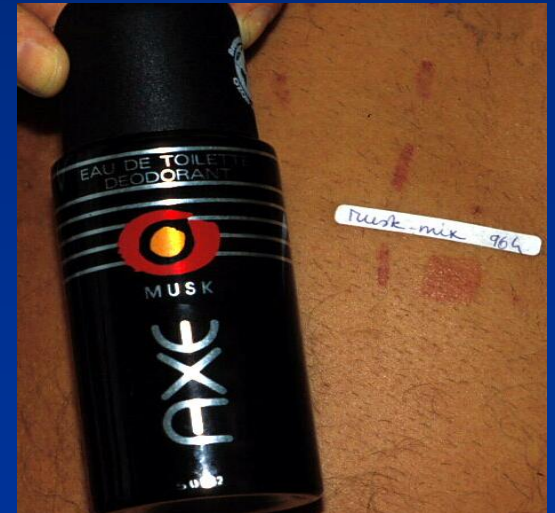


Micro-traumata from shaving
facilitate (photo-)contact dermatitis



Occlusion facilitates skin
sensitization to deodorants

Fragrances as skin sensitizers: Clinical aspects

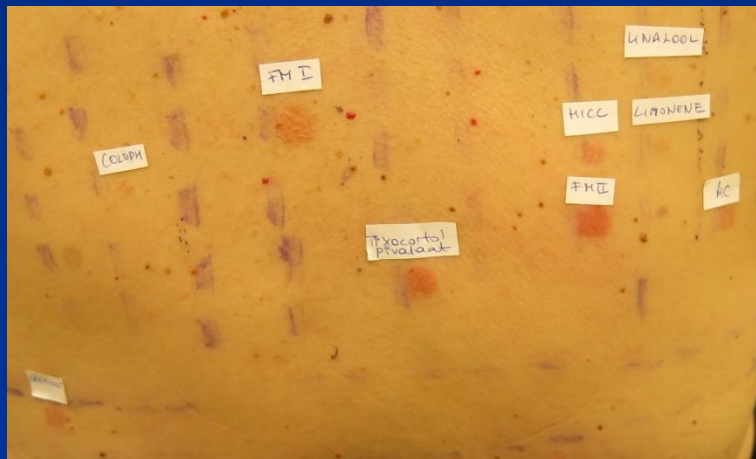


Fragrances as skin sensitizers: Clinical aspects



Hand eczema is common in
fragrance-sensitive patients

Fragrances as skin sensitizers: Clinical aspects



Fragrances as skin sensitizers: Clinical aspects



Fragrances as skin sensitizers: Clinical aspects

(B) Alcoholvrij
(B) Sans alcool
Ohne Alkohol

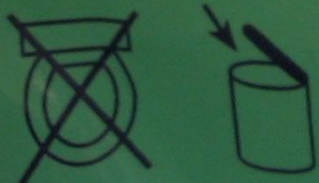


Ingredients:

Aqua, Glycerin, Methyl Gluceth-10, Imidazolidinyl Urea, PPG-26 Buteth-26, PEG-40 Hydrogenated Castor Oil, Tetrasodium EDTA, Chlorhexidine Digluconate, Citric Acid, Bisabolol, Methylisothiazolinone, Methylchloroisothiazolinone, Parfum, Alpha Isomethyl Ionone, Amyl Cinnamal, Benzyl Benzoate, Benzyl Salicylate, Butylphenyl Methylpropional, Cinnamyl Alcohol, Citronellol, Coumarin, Eugenol, Hexyl Cinnamal, Isoeugenol, Linalool.



12/26 fragrance ingredients to be labeled...



Distributed by:
INTIGENA AG · Baarerstrasse 25 · CH-
Made in the E.U.

Composition adapted



Fragrances as skin sensitizers also in children's cosmetics

Cinnamylalcohol (5x recommended conc. IFRA)

Hydroxycitronellal

Iso-eugenol

Geraniol



*Contact Dermatitis, 1999, 41, 84-88
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CONTACT DERMATITIS
ISSN 0105-1873*

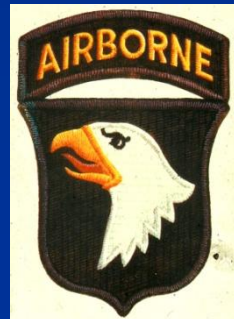
Contents of fragrance allergens in children's cosmetics and cosmetic-toys

S. C. RASTOGI¹, J. D. JOHANSEN², T. MENNÉ², P. FROSCH³, M. BRUZE⁴, K. E. ANDERSEN⁵,
J. P. LEPOITTEVIN⁶, S. WAKELIN⁷ AND I. R. WHITE⁷

Fragrances as skin sensitizers: Clinical aspects



Perfume sprays also causing airborne lesions





Fragrances as skin sensitizers: Clinical aspects



Airborne dermatitis caused by unintentional contact with
fragrance-containing consumer products



Fragrances as skin sensitizers: Clinical aspects



Linalyl acetate in Cedium chlorhexidine® :
an occupational allergen in a nurse

Fragrances as skin sensitizers: Clinical aspects

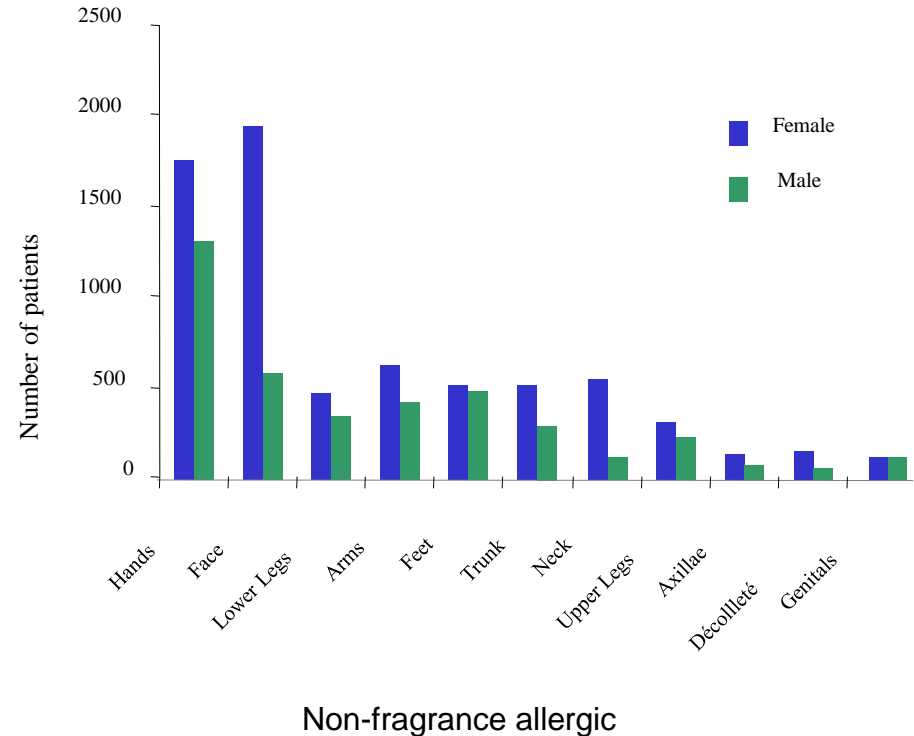
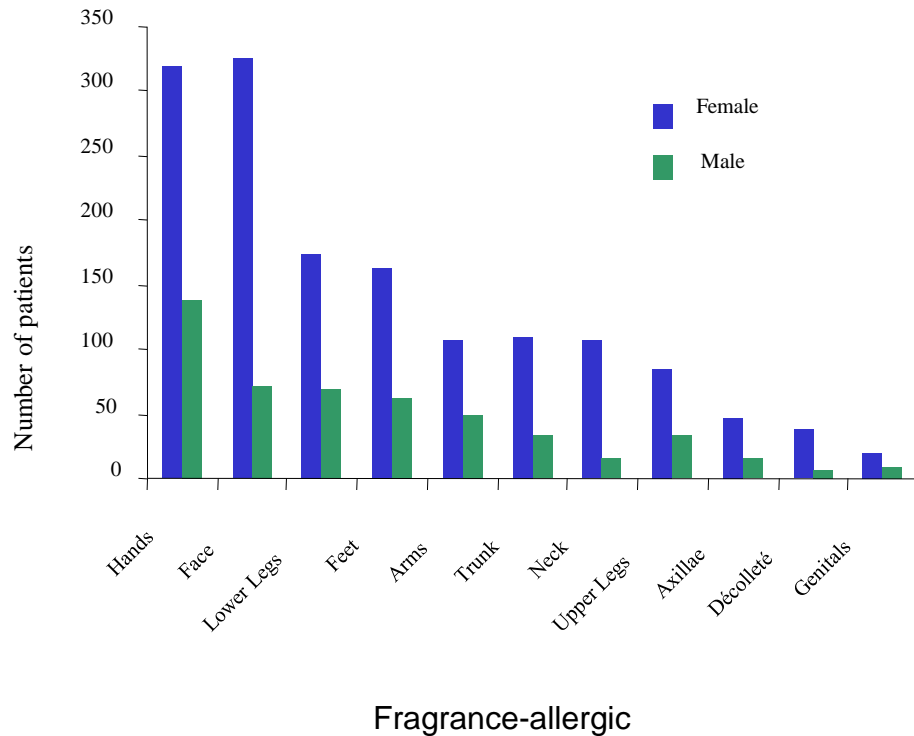


Dept. Dermatology, Nancy



“Connubial” dermatitis

Fragrances as skin sensitizers: Location of the lesions (1990 – 2005)



Fragrances as skin sensitizers: Location of the lesions

- 14.5% + out of 10,128 consecutively tested patients
 - **Face and hands** the most commonly affected body sites, but significant associations found for **legs (topical drugs*!), arms, and axillae**
 - Significant **associations** observed between between specific fragrance allergens and certain locations, e.g. **HICC and axillae** ♀



* 10% of topical pharmaceuticals in Belgium contain fragrance components

Fragrances as skin sensitizers:

Conclusions

- Fragrances are important allergens, both in men and women
- Fragrance-allergic subjects frequently have multiple sensitivities
- Different clinical manifestations and lesion locations
- Frequency probably still higher than reported (more screening agents needed)



*“A woman who does not use perfume,
has no future...”
(Paul Valéry)*