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1. ABSTRACT

Essential oils are fragrances that occur in various parts of plants. Use in cosmetics, personal care products, and also in aromatherapy is known for a long time and is gaining more and more importance. Because of their highly concentration they mostly cannot be used undiluted. They can cause skin irritations and burns.

In the last years, many scientific studies on tolerability, toxicity and possible side effects of cosmetic products that are due to the essential oil components have been performed.

The aim of this paper is to summarize scientific literature over the past decade (2001 - 2012) and thus to update an existing report concerning incompatibilities of essential oils in cosmetics.

The focus is mainly on side effects such as rashes and eczema which are caused by the essential oil components in cosmetic products.

2. ZUSAMMENFASSUNG

Ätherische Öle sind Duftstoffe, die in verschiedenen Pflanzenteilen vorkommen. Die Anwendung in der Kosmetik, in Körperpflegeprodukten und auch in der Aromatherapie ist schon lange bekannt und gewinnt immer mehr an Bedeutung. Dabei handelt es sich um hochprozentige Konzentrate, die fast nie unverdünnt verwendet werden dürfen. Sie können Hautreizungen und Verätzungen hervorrufen.

In den letzten Jahren sind viele wissenschaftliche Studien über Verträglichkeit, Toxizität und mögliche Nebenwirkungen von Kosmetika, die man auf die ätherischen Ölkomponenten zurückführen kann, durchgeführt worden.

Ziel dieser Arbeit ist es, wissenschaftliche Berichte der letzten zehn Jahre (2001 – 2012) zusammenzufassen und somit vorhandene Berichte über Unverträglichkeit von ätherischen Ölen in Kosmetika zu aktualisieren.

Der Schwerpunkt liegt vor allem auf Nebenwirkungen, wie Ausschläge und Ekzeme, die durch das Auftragen bzw. Verwenden bestimmter kosmetischer Produkte aufgrund ätherischer Ölkomponenten zustande gekommen sind.

3. INTRODUCTION

Essential oils are volatile and liquid aroma compounds from natural sources, which can be obtained from various parts of the plants, like flowers, petals, roots, bark, leaves and stems. They are natural chemicals found in plants and get obtained as fragrant and oily volatiles, e.g. by steam distillation.

Essential oils are not oils in a strict sense, but often share with oils a poor solubility in water, and are soluble in alcohol. They are widely used in cosmetic and household products, and in aromatherapy, phytotherapy and in all the alternative medicines. Very odorant essential oils are used in perfumes, cosmetics, soaps as a fragrance and also for flavoring of food and drink.

Chemically, essential oils are highly complex mixtures of hundreds of individual aroma compounds. Mostly they belong to the huge family of terpenes, which are ubiquitous in the plant world. Terpenes are very complex chemicals. Essential oils tend to consist of rather shorter sequences known as monoterpenes and sesquiterpenes or ring-like structures. Besides, they contain also derivatives of phenylpropanes and simple aliphatic compounds.

Science regards essential oils in terms of functionality - they are considered as the chemical weapons of the plant world, as their compounds may attract pollinators or deter harmful insects, or protect the plant against bacterial or fungal attacks.

4. FRAGRANCE OILS vs. ESSENTIAL OILS

Fragrance oils can be natural, partly natural and partly artificial or fully artificial. If the product contains an essential oil mixed with carrier oils in varying concentration, it can be called natural. The second category contains products, which have both essential oils and artificial fragrances (chemical compounds that mimic essential oils). Most of the fragrance oils often contain several components, which produce a different fragrance, when blended. Even essential oils can be part of fragrance oils. It has been observed that many perfumes contain more than hundred components. In short, most of the fragrance oils are a mixture of aroma chemicals, some of which can cause fragrance allergies in people.

Studies show that there are around 150 types of essential oils today, whereas aroma chemicals, which are used to make fragrance oils are more than 500. The basic difference between fragrance oils and essential oils is that while, the latter are purely natural, the former can be considered as partly natural or fully artificial (if only aroma chemicals are used). [1]

A drop of pure liquid essential oil, when placed on a paper, will evaporate and does not leave an oil spot, fragrance oils do not leave any oil spots as well. Fragrance oils also may cause skin irritation, as they are chemicals. Essential oils must be used in a proper way to avoid any possible side effects.

Ref:

[1] www.buzzle.com/articles/fragrance-oils-vs-essential-oils.html, June 2013

5. DEFINITION OF „Cosmetic“

Cosmetic products are important consumer products with an important role in everyone's life: apart from "traditional" cosmetic products, such as make-ups and perfumes, there are also products for personal hygiene, for example tooth-care products, shampoos and soaps included. [2]

Cosmetic products are substances or mixtures of substances intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, etc.) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors.

Today's cosmetic market is driven by innovation including new color, treatments targeted to specific skin types and unique formulas concentrating on different needs.

If a product which complies with the requirements of the EU-regulation presents or could present a serious risk to human health, the competent national authority shall take all necessary provisional measures to withdraw, recall or restrict the availability of the product on the market.

Ref:

[2] http://ec.europa.eu/consumers/sectors/sectors/cosmetic-products/sunscreen-products/index_en.htm, June 2013

Limitations for certain substances [3]

The main part of the EU-directive are the different lists of substances in the annexes (see the following text in italics).

- *Annex II: Substances that are banned from use in cosmetics*
- *Annex III: +*
- *Substances that are subject to restrictions on their use. Such substances might only be permitted for certain types of cosmetics, or in certain concentrations, etc.*
- *Annex IV: Permitted colourings*
- *Annex VI: Permitted preservatives*
- *Annex VII: Permitted UV filters.*

COSMETICS DIRECTIVE 76/768/EEC

Member States shall prohibit the marketing of cosmetic products containing:

- (a) substances listed in Annex II;*
- (b) substances listed in the first part of Annex III, beyond the limits and outside the conditions laid down;*
- (c) preservatives other than those listed in Annex VI, Part 1;*
- (d) preservatives listed in Annex VI, Part 1, beyond the limits and outside the conditions laid down, unless other concentrations are used for specific purposes apparent from the presentation of the product;*
- (e) ingredients or combinations of ingredients tested on animals after 30 June 2000 in order to meet the requirements of this Directive.*

(f) ingredients or combinations of ingredients tested on animals after 30 June 2000 in order to meet the requirements of this Directive.

Consumer information

Product labelling contributes to consumer protection. Containers or packaging must bear written information in indelible, easily legible and visible lettering. This information concerns:

- the name or registered name and the address of the responsible person;*
- the country of origin for imported products;*
- the weight or volume of the content at the time of packaging;*
- a use-by date for products kept in appropriate conditions;*
- precautions for use, including for cosmetics for professional use;*
- the batch number of manufacture or the reference for identifying the cosmetic product;*
- the list of ingredients, i.e. any substance or mixture intentionally used in the product during the process of manufacturing.*

The language of the information shall be determined by the Member State where the product is made available to the end user.

Animal testing

Animal testing must be replaced by alternative methods. The Regulation prohibits the performance of animal testing in the European Union for:

- finished products,*
- ingredients or combinations of ingredients.*

The EU-Regulation also prohibits the placing on the European Union market of: [4]

- *"products where the final formulation has been the subject of animal testing;*
- *products containing ingredients or combinations of ingredients which have been the subject of animal testing.*

If there has been insufficient progress in developing satisfactory methods to replace animal testing, and in particular in those cases where alternative methods of testing, despite all

reasonable endeavours, have not been scientifically validated as offering an equivalent level of protection for the consumer, taking into account OECD toxicity test guidelines.(Organisation for Economic cooperation and Development)

Member States shall allow the marketing of cosmetic products containing:

(a) the substances listed in Annex III, Part 2, within the limits and under the conditions laid down;

(c) the preservatives listed in Annex VI, Part 2, within the limits and under the conditions laid down may be used in other concentrations for specific purposes apparent from the presentation of the product;

The inventory shall be divided into two sections: one concerning perfume and aromatic raw materials and the second concerning other substances.

2. The inventory shall contain information on:

— the identity of each ingredient, in particular its chemical name, the CTFA name (Cosmetic, Toiletry, and Fragrance Association), the European Pharmacopoeia name, the international non-proprietary names recommended by the World Health Organisation, the EINECS (European Inventory of Existing Commercial Substances), IUPAC (International Union of Pure and applied chemistry), CAS (Chemical Abstract Service) and colour index numbers.

— the usual function(s) of the ingredient in the final product,

— where appropriate, restrictions and conditions of use and warnings which must be printed on the label by reference to the Annexes.

1. Member States shall take all measures necessary to ensure that cosmetic products may be marketed only if the container and packaging bear the following information in indelible, easily legible and visible lettering; the information mentioned in point (g) may, however, be indicated on the packaging alone:

(c) the date of minimum durability. The date of minimum durability of a cosmetic product shall be the date until which this product, stored under appropriate conditions, continues to fulfil its initial function. The date of minimum durability shall be indicated by the words: "Best used before the end of ..." followed by either:

— the date itself, or

— details of where the date appears on the packaging.

If necessary, this information shall be supplemented by an indication of the conditions which must be satisfied to guarantee the stated durability.

The date shall be clearly expressed and shall consist of the month and the year in that order. Indication of the date of durability shall not be mandatory for cosmetic products the minimum durability of which exceeds 30 months;

(d) particular precautions to be observed in use, "Conditions of use and warnings which must be printed on the label" Precautionary information on cosmetic products for professional use, in particular in hairdressing. Where this is impossible for practical reasons, an enclosed leaflet, label, tape or card must contain that information to which the consumer is referred either by abbreviated information.

(f) the function of the product, unless it is clear from the presentation of the product;

(g) a list of ingredients in descending order of weight at the time they are added. That list shall be preceded by the word "ingredients".

The following shall not, however, be regarded as ingredients:

- impurities in the raw materials used,*
- subsidiary technical materials used in the preparation but not present in the final product,*
- materials used in strictly necessary quantities as solvents or as carriers for perfume and aromatic compositions.*

Perfume and aromatic compositions and their raw materials shall be referred to by the word "perfume" or "flavour". Ingredients in concentrations of less than 1% may be listed in any order after those in concentrations of more than 1%.

For decorative cosmetic products marketed in several colour shades, all colouring agents used in the range may be listed, provided that the terms "may contain" are added.

In the case of soap, bath balls and other small products where it is impracticable, for reasons of size or shape, to appear on a label, tag, tape or card or in an enclosed leaflet, those particulars shall appear on a notice in immediate proximity to the container in which the cosmetic product is exposed for sale."

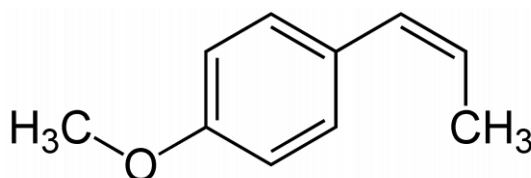
Reference for the text on the the pages 9-14

[3] See, for example, Commission Directive 2008/42/EC of 3 April 2008 amending Council Directive 76/768/EEC, concerning cosmetic products, for the purpose of adapting Annexes II and III thereto to technical progress. OJEC L93 of 2008-04-04, pp. 13–23. Corrigendum. OJEC L136 of 2008-05-24, p. 52.

[4] http://ec.europa.eu/consumers/sectors/cosmetics/cosmetic-products_en.html, June 2013

6. INDIVIDUAL FRAGRANCES

6.1. Anethol in cosmetic products



Anethol is a very common use as a flavoring substance. It is a main component of the essential oils of anise, star anise, and fennel (*Foeniculum vulgare* Mill., Apiaceae). Anethol exists as both cis-trans isomers, the trans isomer is more used as the cis.

It is very sweet, about 13 times sweeter than sugar. Anethol is used in alcoholic drinks like Ouzo, in oral hygiene products, and in small quantities in natural berry flavors [5]. Anethol shows an antimicrobial and a bacteriostatic and bactericidal effect. It is also used as an insect repellent against mosquitoes [6].

Allergy

It was reported that anethol is a flavoring agent used in toothpaste. In some cases it caused cheilitis by contact allergy to anethol in spearmint flavored toothpaste [7].

There was a report about a 63-year old woman presented with a 6 year history of persistent cheilitis. Cheilitis is a common problem of patient with recalcitrant cheilitis, the most common diagnosis was irritant contact dermatitis caused by liplicking. The patient complained about persistent itch, pain and blistering lips. She did not use any lipsticks, only lip balms. She had used a

toothpaste brand "Trileaf Spearmint" manufactured in China for many years [8]. The packaging of the toothpaste did not contain a list of ingredients. She was patch tested to possible allergic contact dermatitis to her lip balm and toothpaste. There was a positive reaction to anethol, which was in the toothpaste brand "Trolab Hermal, Reinbek, Germany". The patient was instructed to replace her toothpaste with an unflavored hypoallergenic one.

It was found that anethol is used in cosmetic products, particularly in lipsticks and soaps.

Nevertheless, anethol is an uncommon cause of allergic contact dermatitis. In large quantities, anethol is slightly toxic and may act as an irritant [9,10].

Ref:

[5] <http://en.wikipedia.org/wiki/Anethole>, June 2013

[6] Philip R. Ashurst (1999). *Food Flavorings*. Springer. p. 460. ISBN 978-0-8342-1621-1.

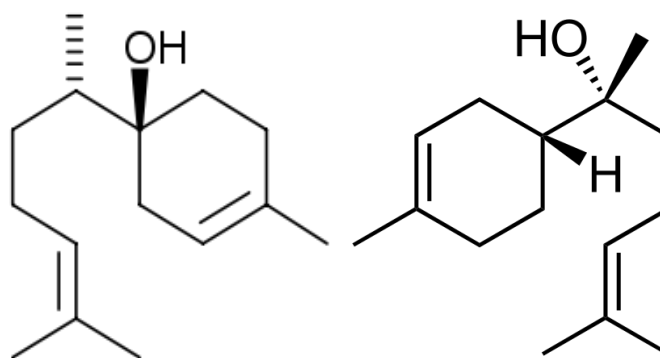
[7] Padilha de Paula J, Gomes-Carneiro MR, Paumgarten FJ (2003). "Chemical composition, toxicity and mosquito repellency of *Ocimum selloi* oil". *J Ethnopharmacol* **88** (2-3): 253-60. doi:10.1016/S03788741(03)00233-2. PMID 12963152

[8] Terence SC Poon, Freeman S. (2006) "Cheilitis caused by contact allergy to anethole in spearmint flavoured toothpaste" *Australasian Journal of Dermatology* (2006) **47**, 300-301

[9]. Newberne P, Smith RL, Doull J, Goodman JI, Munro IC, Portoghese PS, Wagner BM, Weil CS, Woods LA, Adams TB, Lucas CD, Ford RA (1999). "The FEMA GRAS assessment of trans-anethole used as a flavouring substance. Flavour and Extract Manufacturer's Association". *Food Chem. Toxicol.* 37 (7): 789-811. doi:10.1016/S0278-6915(99)00037-X. PMID 10496381.

[10] Waddell WJ (2002). "Thresholds of carcinogenicity of flavors". *Toxicol. Sci.* 68 (2): 275-9. doi:10.1093/toxsci/68.2.275. PMID 12151622.

6.2. Bisabolol



β -Bisabolol

α -Bisabolol

Bisabolol is also known as levomenol (α -bisabolol), it is a monocyclic sesquiterpene, which is the main component of the essential oil from *Matricaria recutita* (Asteraceae). Bisabolol has a sweet floral aroma and is used in many fragrances, in cosmetics like facial make ups, skin care, hair products and also in personal care products [11].

Why is bisabolol used in cosmetic products?

Bisabolol is used in cosmetic products because of his skin-healing, anti-irritant, anti-inflammatory and anti-microbial effect. [11]

It is a common component of moisturizers ointments, lotions, cleansers, sunscreens, and also of antiperspirants.

Bisabolol improves the appearance of dry or damaged skin.

Allergy

Contact dermatitis and contact cheilitis from bisabolol in lipstick has been reported. It was found in a study that a 20 year old woman was complaining of dry cheilitis of both lips. Related to allergic contact cheilitis, the patient should stop using lipsticks,

and her symptoms disappeared in a few days. Her lipstick was tested on her inner arm, and 3 days later there was an eczema. The lipstick "*Forever Metallic 40 pink mercury (Maybelline NY, L'Oreal, Paris)*" was tested. The young woman was patch-tested, and after 4 days they found a positive reaction to bisabolol [12]. On the other hand bisabolol has been assessed by the Cosmetic Ingredient Review (CIR). It was concluded that they evaluated scientific data and found that bisabolol was safe as used in cosmetics and personal care products [13].

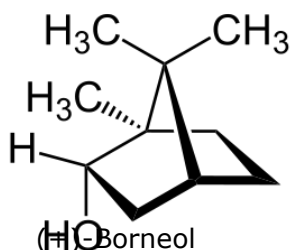
Ref:

[11] http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=300, July 2013

[12] Pastor N, Silvestre JF, Mataix J, Lucas A, and Pérez M, (2008) "Contact Cheilitis from bisabolol and polyvinylpyrrolidone/hexadecene copolymer in lipstick in lipstick", *Contact Dermatitis* **58**: 178–179

[13] http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=300, July 2013

6.3. Borneol



Borneol is a bicyclic monoterpene and it exists in two enantiomers. The main component in nature is (+)-borneol and will be found in several species of *Artemisia absinthium*, (Asteraceae), *Cinnamomum Camphora* (Lauraceae), *Rosmarinus officinalis* (Lamiaceae), and *Blumea balsamifera* (Asteraceae).

Borneol is a component of many essential oils, and it is a natural insect repellent [14].

Borneol is a fragrance ingredient used in decorative cosmetics, shampoos, toilet soaps and other toiletries and also in non-cosmetic products like household cleaners and detergents.

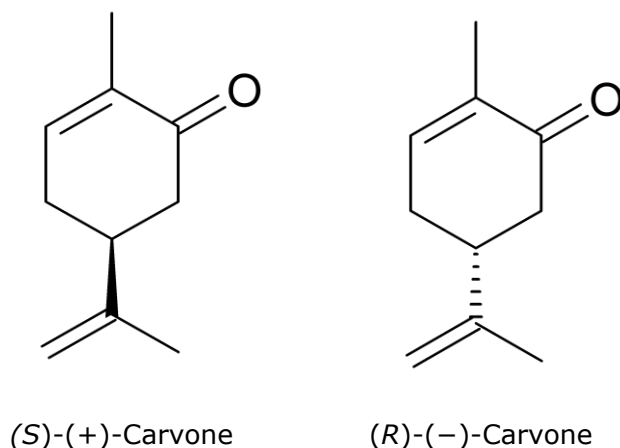
Studies showed that a 48-h closed patch test was conducted on healthy male and female. (L)-Borneol at 20% in vaselinum album or unguentum hydrophilicum was applied on the back and one irritation report out of 35. "No irritation was reported by using (L)-Borneol at 2% in vaselinum album or unguentum hydrophilicum" [15].

Ref:

[14] <http://sun.ars-grin.gov:8080/npgspub/xsql/duke/chemdisp.xsql?chemical=BORNEOL>, July 2013

[15] Bhatia SP, Letizia CS, Api AM, (2008) "Fragrance material review on borneol" *Food and Chemical toxicology* **46**, S77-S80

6.4. Carvone



Carvone is a monocyclic terpenoid, it is found naturally in many essential oils, especially in *Carum carvi* (Apiaceae), resp. *Mentha crispa* (or *M. spicata*) (Lamiaceae).

There exists two enantiomers of carvone:[16]

(R)-(-)-Carvone smells like spearmint.

(S)-(+)-Carvone smells like caraway (*Carum carvi*).

The fact is that the two enantiomers possess different odors. (S)-(+)-carvone is the constituent of the oil from *Carum Carvi* (Apiaceae) and it also occurs in the essential oil from *Anethum graveolens* (Apiaceae). Carvone is the main compound in the essential oil from several species of mint, "particularly spearmint oil (*Mentha spicata*, Lamiaceae) which contains 50-80% R-(-)-carvone". In commercial applications (R)-(-)-carvone is mostly used, it is synthesized from limonene.

Both enantiomers are used in food and flavor industry. (R)-(-)-carvone is also used for air freshening products, in aromatherapy and in toothpaste [17].

Allergy

Contact allergy to toothpaste is uncommon [18]. Most reported cases concerning contact dermatitis are about cheilitis caused by the flavors of toothpaste. But there are also some reports on contact urticaria caused by flavors of toothpaste, it has induced bronchospasm, and in another report rhinitis.

There was a report about a 33-year old man with a 6 month history of swelling lips within minutes of contact with toothpaste. After that he noticed a swelling of his gingiva and shortness of breath. He tried different brands, but there was the same symptom. By using children fruit-flavored toothpaste, the patient showed no symptoms.

The report shows a patch test with the substances mixed in petroleum. [19]

Open test result

Table 1:

Substance	% in pet.	2 min	15 min	30 min
Benzoic acid	5	---	---	Weak infiltration
Salicylic acid	1	---	---	---
Citric acid	1	---	---	---
Peppermint oil Brand A/B	2	---	Flare, Infiltration 10 mm	Strong flare 10mm more infiltration
Eucalyptus oil	2	---	---	---
(+)-Limonene	1	Weak flare	Flare, infiltration 10mm	Strong flare, 10mm more infiltration
R/S-Carvone	5	Strong, wheal 10mm	Strong, wheal 10mm	Strong, wheal 25mm

Readings were performed after 2, 15 and 30 min. No further reactions were seen later. It was found that there was a fast and strong reaction to carvone after 2 minutes. After 15 min, there

was a wheal 10 mm in diameter with both (*R*)-carvone and (*S*)-carvone.



“Urticarial reactions at open testing with carvone 5% in pet. and read after 15 min. The names (D)-carvone and (L)-carvone used in the figure correspond to (S)-carvone and (R)-carvone, respectively, used in the text”

The report shows that most of the reactions have been related to peppermint. Menthol and limonene are the major components of peppermint oil. (*R*)-Carvone is the main substance in spearmint oil. It is well known that carvone in toothpaste causes cheilitis allergy [20].

The toothpaste was labeled with “taste of mint”, but pure carvone was not declared.

Another study also reported about cheilitis due to toothpaste. Again carvone was the main component of the flavor additive, and responsible for the contact sensitization [21].

Conclusion

Carvone has been often reported as an allergen, usually in flavoring products. Reports also show that it is an ingredient of hair conditioner with a mint scent and which also leads to contact dermatitis.

Ref:

[17] <http://de.wikipedia.org/wiki/Carvon>, May 2013

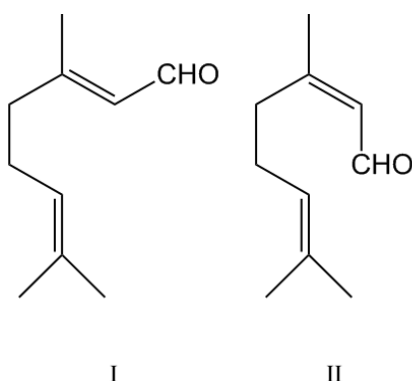
[18] Simonsen, J. L. (1953). "*The Terpenes*" **1** (2nd ed.). Cambridge: Cambridge University Press. pp.394–408.

[19] Wiley J. and Sons A/S, Hansson Ch, Bergendorff O, Wallengren J. "Contact urticaria caused by carvone in toothpaste" (2011) *Contact Dermatitis*, **65**, 359–368.

[20] Quertermous J, Fowler JF Jr., 2010 "Allergic contact dermatitis from carvone in hair conditioners" *Contact Dermatitis*. **21(2)**:116-7.

[21] Hausen B.M. "Toothpaste allergy" (1984); *Dtsch med Wochenschr*. **109(8)**: 300-302.

6.5. Citral



Citral is a mixture of a pair of terpenoid aldehydes, the two compounds are double bond isomers. The (*E*)-isomer is known as geranial or citral A (I) and the (*Z*)-isomer is known as neral or citral B (II).

Citral is an oil component of several plants, for instance lemongrass (75–85%), lemon tea tree, *Ocimum gratissimum* (Lamiaceae), lemon balm, lime, lemon, and orange [22,23].

Geranial (citral A) has a strong lemon odor and neral (citral B) is less intense, but sweeter. Therefore, citral is an aroma compound used in perfumery and also used as a flavor. It is also used to mask the smell of smoke.

Allergy

It was frequently reported about allergies to citral. The international Fragrance Association (IFRA) recommends the use of citral only in association with substances that prevent a sensitizing effect.

A study reported about a 30-year-old lady presented with a 5-year history of cheilitis. She was patch-tested to face series, flavors series, her own toothpaste, her own nail varnish, her own

lip products and the standard series including fragrance mix II. The patient had a lot of positive reactions, to fragrance mix II, oil of lemongrass, petroleum and her own nail varnish. Subsequently she had a positive reaction to citral [24].

After that the patient reported that she always applied petroleum (normal soft paraffin) to her lips. The product was tested and it was found to be Vaseline lip balm with *Aloe vera*. It was listed as an ingredient on the lip balm package.

Citral is recognized as an allergen and as an irritant. Previous studies showed patch-tested patients with hand eczema due to citral.

Fragrance mix II has recently been added to the standard series, and by testing with this.

What is Fragrance Mix II and where is it found?

Fragrances can be found in most products, especially cosmetics, as they are used to add scent or flavor.

Fragrance Mix II contains:

- lylal,
- citral,
- citronellol,
- farnesol,
- coumarin
- hexyl cinnamic aldehyde;

These are chemicals which are commonly used in perfumes, cosmetics, laundry detergents and personal hygiene products. Further research may identify additional product or industrial usages of this chemical.

List of 26 Fragrance Allergens Designated by the European Union
[24]

- Alpha isomethylionone
- Amyl cinnamal
- Amylcinnamyl alcohol
- Anisyl alcohol
- Benzyl alcohol
- Benzyl benzoate
- Benzyl cinnamate
- Benzyl salicylate
- Butylphenyl methylpropional (Lilial®)
- Cinnamal
- Cinnamyl alcohol
- **Citral**
- Citronellol
- Coumarin
- Eugenol
- Farnesol
- Geraniol
- Hexyl cinnamal
- Hydroxycitronellal
- Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall)
- Isoeugenol
- **Limonene**
- **Linalool**
- Methyl 2-octynoate
- *Evernia furfuracea* (Treemoss) extract
- *Evernia prunastri* (Oakmoss) extract

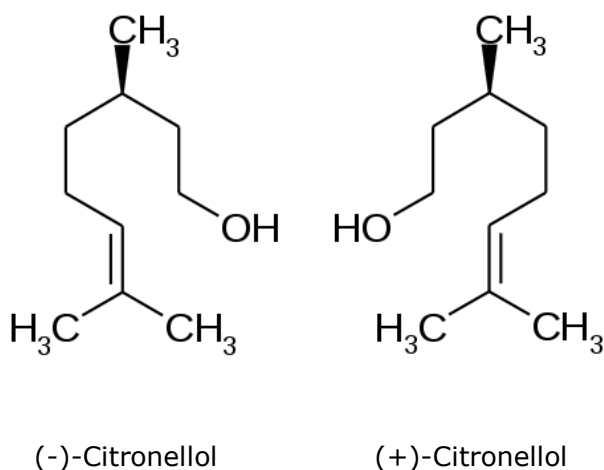
Ref:

[22] <http://en.wikipedia.org/wiki/Citral>, Juli 2013

[23] Lawless, J., *The Illustrated Encyclopedia of Essential Oils*, ISBN 1-85230-661-0

[24] E. Hindle, J. Ashworth and M.H.Beck "Chelitis from contact allergy to citral in lip salve" (2007) *Contact Dermatitis*:**57**: 125-126, ,

6.6. Citronellol



Citronellol, or dihydrogeraniol, is a natural acyclic monoterpenoid and it exists in two enantiomers (+)-citronellol and (-)-citronellol [25].

(+)-Citronellol, which is found in citronella oil, including *Cymbopogon nardus* (Poaceae), is the more common isomer. (-)-Citronellol is found in the oils of rose and *Pelargonium geranium* (Geraniaceae).

Citronellol is used in perfumes and insect repellents and also as flavor additive in foodstuff. In perfumes citronellol can cause allergic reactions but it is disputed. Citronellol is produced by hydrogenation of geraniol.

Allergy

The effect of citronellol is moderately irritating to the skin of humans, and seriously irritating the skin of rabbit and guinea pig. The critical effect of citronellol is assessed to be contactallergy. Because of the allergenic potential of citronellol, humans allergic to the substance should avoid skin contact, as there is no lower limit for this adverse effect [26,27,28].

Ref:

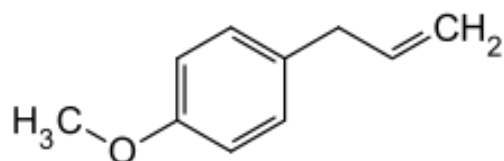
[25] Taylor WG, Schreck CE. (1985). "Chiral-phase capillary gas chromatography and mosquito repellent activity of some oxazolidine derivatives of (+)- and (-)-citronellol". *J. Pharm Sci.* **74** (5): 534–539. doi:10.1002/jps.2600740508. PMID 2862274.

[26] http://www.ifraorg.org/en-us/standards_restricted/s3/p3, July 2013

[27] J. G. de Vries and C. J. Elsevier, Robert H. Morris, Survey and health assessment of chemical substances in massage oils
"Ruthenium and Osmium" in *The Handbook of Homogeneous Hydrogenation*. (2007) WILEY-VCH, Weinheim. ISBN: 978-3-527-31161-3

[28] Lowless, J., "The Illustrated Encyclopedia of Essential Oils" ISBN 1-85230-661-0 <http://en.wikipedia.org/wiki/Citronellol>, July 2013

6.7. Estragole



Estragole (p-allylanisole, methyl chavicol) is a phenylpropene, a natural organic compound. Its chemical structure consists of a benzene ring substituted with a methoxy group and a propenyl group. It is an isomer of anethol, differing to the location of the double bond.

Estragole is a colorless liquid, and can appear yellow in pure samples. It is a component in the essential oil of various herbs and is used in the preparation of fragrances [29].

In a cosmetic product estragole can be present when being part of the following “botanical” ingredient:

- *ARTEMISIA DRACUNCULUS EXTRACT*
- *FOENICULUM VULGARE EXTRACT, fruit, oil*
- *ILLICIUM VERUM OIL*
- *OCIMUM BASILICUM EXTRACT, oil*
- *PIMPINELLA ANISUM EXTRACT*

Estragole is also used in perfumes and as a food additive for flavor.

Hundreds of tones of basil oil are produced annually by steam distillation of *Ocimum basilicum* (Lamiaceae). The main component of this oil is estragole but also contains linalool. It is the primary constituent of essential oil of tarragon, pine oil, turpentine, fennel, anise and *Zyzygium anisatum* (Myrtaceae) [30].

Allergy

Estragole is suspected to be carcinogenic and genotoxic, as is indicated by the European Union, Committee on Herbal Medicinal Product [31].

Several studies have established that the profiles of metabolism, metabolic activation, and covalent binding are dose dependent. In particular, studies show that these events are minimal in the dose range of 1–10 mg/kg body weight, which is approximately 100-1000 times the anticipated human exposure to this substance. For these reasons it is concluded that the present exposure to estragole resulting from consumption of herbal medicinal products does not pose a significant cancer risk in short time uses. In the meantime exposure of estragole to sensitive groups such as young children, pregnant and breastfeeding women should be minimized [32].

Ref:

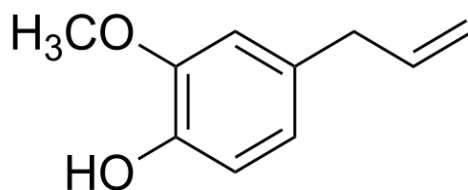
[29] Fahlbusch KG, Hammerschmidt FJ, Panten J, Pickenhagen W, Schatkowski D, Bauer, Garbe D, Surburg H (2002) "Flavors and Fragrances" in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim: 2002. Published online: 2003; doi:10.1002/14356007.a11_141.

[30] Philip R. Ashurst (1999). "Chavicol - Food Flavorings". *Springer*. p. **11**.

[31]<http://www.ema.europa.eu/pdfs/human/hmpc/13721205en.pdf>, July 2013

[32] http://ec.europa.eu/food/fs/sc/scf/out104_en.pdf, July 2013

6.8. Eugenol



Eugenol is a phenylpropene. It is a clear to pale yellow oily liquid extracted from clove oil, cinnamon, basil and bay leaf.

Eugenol is slightly soluble in water and soluble in organic solvents. It has a spicy clove-like aroma. Eugenol occurs in *Eugenia aromaticum* or *Eugenia caryophyllata* (Myrtaceae) [33].

It is used in perfumeries, flavorings, essential oils and in medicine as a local antiseptic and anesthetic.

Eugenol is also used in the production of isoeugenol for the manufacture of vanillin.

Allergy

Studies shows that potential fragrance allergens used in daily products should have a concentration limited to levels that are at, or below, acceptable exposure levels based on the quantitative risk assessment for the induction of dermal sensitization. [34,35]

The relationship between the allergen concentration and the time to elicit allergic contact dermatitis in eugenol-sensitized patients was studied. The products used to elicit allergic contact dermatitis had a concentration of eugenol that was equal to, or below, the International Fragrance Association standard.

Volunteers were patch-tested with various concentrations of eugenol.

The result of the report shows that allergic contact dermatitis which could not be elicited by any of the concentrations studied, including in those patients where the patch tests were positive.

When tested in a 3-week trial, eugenol did not induce reactions even in those people known to be sensitized. Whether this represents a false-negative result for a weak allergen is unknown. [36]

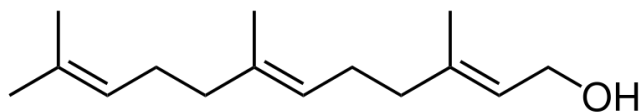
Another study reported that patients sensitized to eugenol, with the maximum allowed concentration of eugenol and after 4 weeks they had a clear allergic contact dermatitis.

As some people may become sensitized to eugenol, its use in perfumery is limited. However, the degree to which eugenol can cause an allergic reaction in humans is disputed. [37]

Ref:

- [33] Md. Nazrul Islam Bhuiyan, Begum J, Nandi NC, Akter F, (2010) "Constituents of the essential oil from leaves and buds of clove (*Syzigium caryophyllatum* (L.) Alston)" *African Journal of Plant Science* Vol. **4(11)**, pp. 451-454
- [34] Mallavarapu GR, Ramesh S,. Chandrasekhara RS, Rajeswara Rao BR, Kaul PN, Bhattacharya AK, (1995) "Investigation of the essential oil of cinnamon leaf grown at Bangalore and Hyderabad" *Flavour and Fragrance Journal* Volume **10**, Issue 4, pages 239–242
- [35] Zheljazkov VD, Callahan A, Cantrell CL (2008) "Yield and Oil Composition of 38 Basil (*Ocimum basilicum* L.) Accessions Grown in Mississippi" *J. Agric. Food Chem.*, **56** (1), pp 241–245
- [36] Jadhav BK, Khandelwal KR, Ketkar AR, Pisal SS. (2004). "Formulation and evaluation of mucoadhesive tablets containing eugenol for the treatment of periodontal diseases". *Drug Dev Ind Pharm.* **30** (2): 195–203. doi:10.1081/DDC-120028715. PMID 15089054
- [37] <http://www.ncbi.nlm.nih.gov/pubmed/22653067>, July 2013

6.8. Farnesol



Farnesol is a natural organic compound; it is an acyclic sesquiterpene alcohol.

It is present in several essential oils, like citronella, neroli, lemongrass, rose. Farnesol is used in perfumery to emphasize odors of sweet floral perfumes. It is a co-solvent that regulates the volatility of the odorants, used especially in lilac perfumes. Farnesol is also a flavoring ingredient of cigarettes and it is included in the fragrance mix II [38].

The commercial source of farnesol is *Vachellia farnesiana* (Fabaceae). This is a particular acacia species, which was found in the botanical gardens in Rome.

It was found that farnesol has a chemopreventive and an antitumor effect [39]. It is also used as a deodorant in cosmetic products because of its antibacterial activity. As some people may become sensitized to farnesol, its use is limited in perfumery. However, the evidence that farnesol can cause an allergic reaction in humans is disputed.

Allergy

Reports show that farnesol is a significant contact allergen. Therefore, it was decided by the European Union to label products containing farnesol.

Farnesol was patch-tested, and it shows allergic reaction, especially hand and face were more often affected. In total,

"2021 patients were patch-tested with farnesol (5% pet.), 1243 females and 778 males. Of these, 22 (1.1%, 95% CI: 0.7–1.6%)" had a positive reaction to farnesol.

The result shows that the frequency of sensitization (1.1%) must be interpreted with caution, because there was no information about patients with contact dermatitis. [40]

Another study presented a case report about a 30-year-old woman with an itchy erythema for 3 weeks in both axillae [41]. This was the result after using a deodorant, which she had been using for several weeks. The woman was patch-tested and the result shows positive reactions too, the deodorant and farnesol. The perfume in the deodorant was negative.

Farnesol is used in deodorants at 0.3% as a bacteriostatic, where it inhibits body odor without negatively affecting skin flora [42].

It is also present in perubalsam, where it has a weak sensitization potential. Reports show that contact allergy to farnesol is rarely, and when it comes to an allergy, it is associated with perubalsam.

Ref:

[38] <http://quitsmoking.about.com/cs/nicotineinhaler/a/cigingredients.htm>
Mai 2013

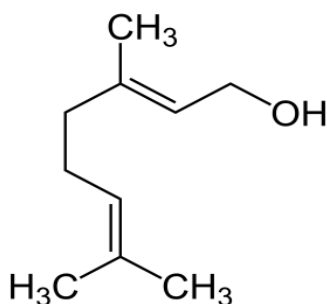
[39] Joo JH, Jetten AM (2009). "Molecular mechanisms involved in farnesol-induced apoptosis". *Cancer Lett.* **287** (2): 123–35.
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"Release of antimicrobial actives from microcapsules by the action of axillary bacteria". *Int J Cosmet Sci* **28** (2): 103–108.doi:10.1111/j.1467-2494.2006.00283.x. PMID 18492144.

[42] A. Goosens and L. Merckx, (1997) "Allergic contact dermatitis from farnesol in a deodorant", *Department of Dermatitis*, Volume **37**, Issue 4 p 179-180

6.9. Geraniol



Geraniol is a monoterpenoid alcohol. It is the main component of rose oil, palmarosa oil and citronella oil. And it occurs also in geranium, lemon and many other essential oils. Geraniol is insoluble in water, but soluble in organic solvents. It has a rose-like scent and is often used in perfumes and flavors such as peach, raspberry, grapefruit, red apple, lime, orange, lemon, watermelon, pineapple and blueberry. Because of its fresh flowery odor, geraniol is widely used. [43]

Geraniol is used in the formulation of aftershave lotions, bath products, bubble baths, hair products lipsticks, moisturizers, perfumes and colognes, skin care products cosmetics and personal care products. It is also found in deodorants, and household products.

Besides other flavor compounds geraniol was found in well-aged tobacco. *"It is listed in a 1994 report from cigarette companies as one of the 599 additives to cigarettes to improve their flavor"* [44].

Allergy

Geraniol is tested in the baseline series in fragrance mix I. It is a pro-hapten and a pre-hapten. Antigen formation is normally considered to take place between an electrophilic hapten and

nucleophilic moieties in amino acid side chains in skin proteins. Geraniol is not electrophilic and should consequently not possess any contact allergenic activity [45,46].

Geraniol shows the potential to autoxidize on air exposure and form allergenic compounds analogous to other monoterpenes such as limonene and linalool.

The autoxidation of geraniol follows two paths, from allylic hydrogen abstraction near the two double bonds starting with primarily hydrogen peroxide is formed together with aldehydes geranial and neral via a hydroxyhydroperoxide. In addition, small amounts of a hydroperoxide are formed, analogous to the formation of the major linalool hydroperoxide. The hydroperoxide form is maybe the major contributor to allergenic activity, together with the aldehydes geranial and neral.

Studies showed that oxidized geraniol is a better marker for patch testing than pure geraniol. The result of the studies was that *"655 patients were patch-tested with pure and oxidized geraniol at 4.0%, 6.0% and 11.0%"* [47]. It was shown that pure geraniol has a *"positive reaction in 0.15-1.1% of the patients"*, and oxidized geraniol detected positive reaction *"in 0.92-4.6%"* of the patients. The conclusion was that by means of increasing the test concentration of pure and oxidized geraniol more cases of contact allergy were reported. Oxidized geraniol causes more patients with pure geraniol but patch-testing with only oxidized geraniol is not responsible for all cases of contact allergy due to metabolic activation of geraniol.

It was found that it is *"responsible for 5% of the positive patch test reactions to the individual compounds of FM I"*.

The Flavor and Extract Manufacturers Association (FEMA) Expert Panel has reviewed the safety of geraniol and determined that it is "Generally Recognized as Safe" (GRAS) for use as a flavoring substance.

In Europe, geraniol is included into the list of allergenic substances. It must be in the list of ingredients if they are present above certain levels in the product especially if it exceeds "*0.001% in leave-on and 0.01% in rinse-off products*" [47a].

Other studies like Hostynek & Maibach found that there were no cases where patients had been brought to a clinic because of geraniol contact dermatitis. They discussed patch-testing mixtures, where concentrations of geraniol were too high. Consumers get an allergic reaction after everyday exposure to low doses of geraniol, which are only revealed under patch-testing conditions [47a].

Ref:

[43] <http://en.wikipedia.org/wiki/Geraniol>, May 2013

[44] <http://quitsmoking.about.com/cs/nicotineinhaler/a/cigingredients.htm>
May 2013

[45] Hagvall I, Karlberg AT, Christensson JB, (2013). "Finding the optimal patch test material and test concentration to detect contact allergy to geraniol". *Contact Dermatitis*.; **68(4)**:224-31. doi: 10.1111/cod.12033
Department of Dermatology, Sahlgrenska Academy, University of Gothenburg, 40530 Gothenburg, Sweden.

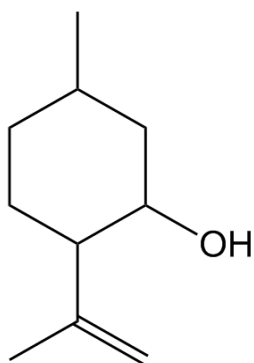
[46] Lina Hagvall,[†] Carina Backtorp,[‡] Sophie Svensson,[§] Gunnar Nyman,[‡] Anna Borje,[†] and Ann-Therese Karlberg* (2007) "Fragrance Compound Geraniol Forms Contact Allergens on Air Exposure. Identification and Quantification of Oxidation Products and Effect on Skin Sensitization" *Chem. Res. Toxicol.* **20**, 807-814

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[47b] Hostynek J.J., Maibach H.I. (2004d) "Is there evidence that geraniol causes allergic contact dermatitis?" *Exog. Dermatol.* **3**(6), 318-331.

6.10. Isopulegol



Isopulegol is a fragrance component in decorative cosmetics, shampoos, toilet soaps and other toiletries, also in non-cosmetic products such as household cleaners and detergents. It was reported that in formula for cosmetic use isopulegol should be "0.027% (IFRA, 2004)" [48].

It was reported that citronellal can be easily cyclized to isopulegol in the presence of acidic mixed oxides.

Allergy

Studies showed no irritation to 8% isopulegol in petrolatum when applied for 48h on backs of healthy persons.

Summary of human irritation study:

Table 3:

Method	Dose (%)	Vehicle	Results	Reference
Maximization (pre-test)	8	Petrolatum	0/10	<u>RIFM (1971a)</u>
48-h Occluded patch test	10 and 20	Lanolin	0/30	<u>RIFM (1999a)</u>

Also isopulegol at 10% and 20% concentration in lanolin was patch-tested. It was applied on the upper arms and the result after 24h and 48h was no irritation [49].

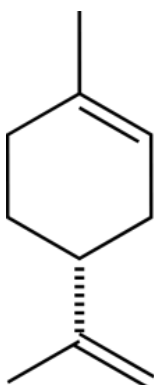
Ref:

[48] .Bhatia SP, McGinty D, Letizia CS, Api AM. (2008) "Fragrance Material Review on isopulegol" *Food Chem Toxicol.* **46** (11):S185-189

[49] Matteo Guidotti, Giuliano Moretti, Rinaldo Psaroa and Nicoletta Ravasioa Centro CNR, (2000) "One-pot conversion of citronellal into isopulegol epoxide on mesoporous titanium silicate"

"<http://pubs.rsc.org/en/content/articlelanding/2000/cc10.1039/b003397i#!divAbstract>, Mai 2013

6.11. Limonene



Limonene is a cyclic monoterpene, it is a colorless and liquid substance. It exists in (+) and (-) isomers. The more common (+)-isomer shows a strong smell of oranges. It is used in chemical synthesis as a precursor to carvone [50].

The name is taken from the lemon, as the rind of the lemon, like other citrus fruits, contains considerable amounts of limonene.

Limonene is often an ingredient in cosmetic products. (+)-limonene is also used in food, and some medicines, as a flavoring to mask the bitter taste of alkaloids, and as a fragrant in perfumery. It is also used as a botanical insecticide. It is added to cleaning products such as hand cleaners to impart them lemon-orange fragrance [51].

Allergy

It was reported that limonene and its oxidation products are skin and respiratory irritants, particularly limonene-1,2-oxide which is formed by aerial oxidation is a known skin sensitizer.[52]

In male rats, high doses of limonene lead to renal cancer. In some researchers limonene is considered to be a potential chemopreventive agent. There were no reports about

carcinogenicity or genotoxicity in humans. There is also no information about health effects of inhalation exposure to (+)-limonene in humans found.

Allergic contact dermatitis due to citrus fruits are rare, but are reported in cooks and bartenders. It was reported about a bartender with hand dermatitis who showed an allergic reaction to lime peel, fragrance mix I and fragrance mix II. The most reported cases about citrus allergy are due to (+)-limonene, which is the main component of peel oil. The patient showed an allergic reaction to geraniol, which is a minor component and present in the fragrance mix I. It was recommended to consider contact sensitivity to citrus oils in patients who show a positive reaction to fragrance mix I and II [53].

Product labeling is very important, as limonene is found in household products, to avoid allergic reactions.

In patch test studies on dermatitis patients, it was found that (+)-limonene is an indicator of fragrance-related contact allergy. Mixtures of both enantiomers were tested. The result showed that *“63 out of 2411 patients tested (2.6%) reacted to one or both preparations. Only 2.3% reacted to the oxidized (+)-Limonene and 2.0% to the oxidized (-)-Limonene”* [54].

It was reported that (+)-limonene itself does not lead to an allergic reaction, it forms allergenic products due to autooxidations during handling and storage.

Ref:

[50] Fahlbusch, Karl-Georg; Hammerschmidt, Franz-Josef; Panten, Johannes; Pickenhagen, Wilhelm; Schatkowski, Dietmar; Bauer, Kurt; Garbe, Dorothea; Surburg, Horst (2003). "Flavors and Fragrances". *Ullmann's Encyclopedia of Industrial Chemistry*. doi:10.1002/14356007.a11_141. ISBN 978-3-527-30673-2.

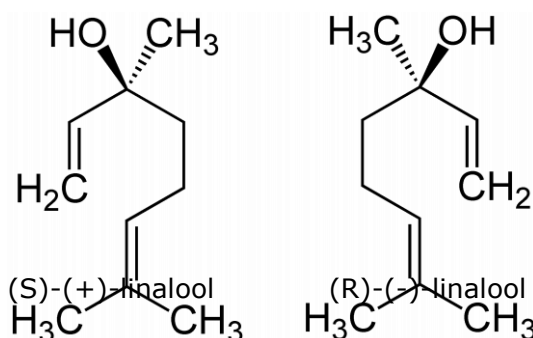
[51] Matura M, PhD,a An Goossens, Bordalo O, Begona Garcia-Bravo, Magnusson K, Wrangsjo K, and Karlberg AT, (2002) "Oxidized citrus oil (R-limonene): A frequent skin sensitizer in Europe", *J. Am Acad Dermatol*;47:709-14.

[52] Guarneri F, Barbuzza O, Vaccaro M, Galtieri G. (2008) "Allergic contact dermatitis and asthma caused by limonene in a labourer handling citrus fruits" *Contact Dermatitis* 58: 315–316

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[54]. Swerdlin A, Rainey D, Storrs FJ. (2010) "Fragrance mix reactions and lime allergic contact dermatitis" *Contact Dermatitis*.**21**(4):214-6. Department of Dermatology, Oregon Health & State University, Portland, OR, USA

6.12. Linalool



Linalool is a natural acyclic monoterpene alcohol and found in oils from berbs, leaves, flowers and wood. It is present in the oils of rosewood, bergamot, rose, jasmine, coriander and lavender. There are two stereoisomers : (R)-(-)-linalool is also known as licareol and (S)-(+)-linalool is also known as coriandrol. Linalool is widely used because of its fresh flowery odour.

Allergy

Studies showed the frequencies of the most common fragrance ingredients in cosmetic and other scented products and it was found that linalool is the most frequently fragrance. A study analysed 73 deodorants and found that 97% of these were containing linalool. It was found that contact allergy to linalool itself is rare, allergens are formed on handling and storage [55].

Linalool was tested in animal experiments before and after air exposure. It was found that *“during 10 weeks of air exposure the amount of linalool decreased to about 80%”* [56].

It was reported that pure linalool did not lead to any sensitizing to animals. After that animals were induced with oxidized linalool and became sensitized.

Another study shows that linalool can cause allergic reactions and eczema. The allergic reactions are due to the contact with oxygen. Linalool also can form allergic substances while storing for a long time. A new study shows that linalool is number three after nickel and cobalt which is responsible for eczema [55].

The conclusion of these studies was that more than 3.000 patients were patch-tested with oxidized linalool to find out the real cause of eczema. The result was that about 7% of the people were allergic to the oxidized form of linalool.

Linalool is present in too many products that are of a constant use, and this must be the main reason why the contact allergy to this substance is so common.

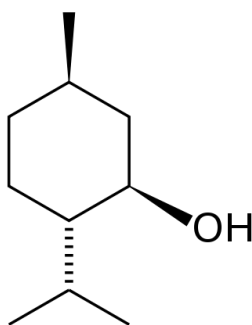
Legislation of European Union states that linalool must be labeled on hygiene and cosmetic products.

Ref:

[55] Sköld M, Börje A, Matura M, Karlberg AT, (2002) "Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hydroperoxide". *Contact Dermatitis*, **46**, 267-272

[56] Christensson JB, Matura M, Gruvberger B, Bruze M, Karlberg AT, (2010) "Linalool – a significant contact sensitizer after air exposure", *Contact Dermatitis* **62**:32-41

6.13. Menthol



(1R,2S,5R)-(-)-Menthol

Natural menthol exist as one pure stereoisomer, nearly always the (1R,2S,5R), which is (-)-menthol. Menthol is obtained from cornmint, peppermint or other mint oils. It is a crystalline substance, white in color, which is solid at room temperature and melts slightly above. Menthol has local anesthetic and analgesic effect, and it is widely used to relieve minor throat irritation. It also acts as a weak kappa opioid receptor agonist [57].

(-)-Menthol is also called "L-menthol", it occurs naturally in peppermint oil, which is obtained from *Mentha x piperita* (Lamiaceae) and it is mainly used in pharmaceutical products, tobacco and chewing gums.

(+)-Menthol is called "D-menthol", it is a fragrance ingredient used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries and also in household products, in refreshing creams and lotions, in toothpaste and mouth washes.

Allergy

Studies show no skin irritation in rabbits for "D-menthol", 5% menthol liquid and for 1% "L- and DL-menthol", while higher

concentrations and undiluted “L- and DL-menthol” show skin-irritations [58].

It was found that menthol as a component at high concentrations in consumer products such as cigarettes, toothpaste and topical medications, has led to sensitivity reactions.

Studies reported the maximum skin level to use “D-menthol” in formula in fine fragrance should be 0.20%, assuming use of the fragrance oil at levels up to 20% in the final product. In formula for use in cosmetics has been reported to be 2.25% which would result in a maximum daily exposure on the skin of 0.0573mg/kg/day for high end users of these products (see Table).

Table 4. Calculation of the total human skin exposure from the use of multiple cosmetic products containing *d*-menthol [59]

Type of cosmetic product	Grams applied	App-licat-ions per day	Reten-tion factor	Mixture Per product %	Ingred-ient/ mixture ^a	Ingredient mg/kg/day ^b
Body lotion	8.00	0.71	1.000	0.004	2.25	0.0085
Face cream	0.80	2.00	1.000	0.003	2.25	0.0018
Eau de toilette	0.75	1.00	1.000	0.080	2.25	0.0225
Fragrance cream	5.00	0.29	1.000	0.040	2.25	0.0218
Antipe-rspirant	0.50	1.00	1.000	0.010	2.25	0.0019
Shampoo	8.00	1.00	0.010	0.005	2.25	0.0002
Bath products	17.0	0.29	0.001	0.020	2.25	0.0000
Shower gel	5.00	1.07	0.010	0.012	2.25	0.0002
Toilet soap	0.80	6.00	0.010	0.015	2.25	0.0003
Hair spray	5.00	2.00	0.010	0.005	2.25	0.0002
Total						0.0573

a Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products.

b Based on a 60-kg adult.

It was concluded

It was concluded that the amount of menthol should not exceed 2% in cosmetic products, to avoid allergic reactions. Menthol should also not be used in baby products.

Ref:

[57] <http://en.wikipedia.org/wiki/Menthol>, January 2013

[58] Belsito, et al., 2008 D. Belsito, D. Bickers, M. Bruze, H. Greim, J.H. Hanifin, A.E. Rogers, J.H. Saurat, I.G. Sipes, R.L. Smith, H. Tagami A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients *Food and Chemical Toxicology*, 46 (11S) (2008), pp. S1–S71

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7. Essential oils

7.1. Bergamot oil

Bergamot oil is not extracted by steam distillation it is a cold-pressed essential oil of bergamot orange fruit. Bergamot orange (*Citrus aurantium var. bergamia*, Rutaceae) grows on small trees. “It is a cross between pear lemon and Seville orange or grapefruit” [60].

It is used as a fixative in the perfume industry. It was reported that one hundred of bergamot oranges fruits yield 85 grams of the essential oil.

The essential oil of bergamot is used extensively in perfumery for its sweet freshness. Bergamot oil is also used for flavoring purposes, e.g. Earl Grey tea and the so called althea drops, candy-making, and in aromatherapy.

Its scent is fruity-sweet with mild spicy note. Bergamot oil is used in production of both female and male perfumes, and in most fragrance groups, mainly in top notes. It was a component of the original Eau de Cologne developed in Germany in the 17th century, and today is used in different proportions in almost all modern perfumes. Perfumes of the so-called Chypre and Fougère types are not possible without bergamot oil [61,62].

Perfumes and Colognes With Bergamot [61]

- Gucci Rush Summer
- Armani Prive Cologne, Giorgio Armani
- Coco Mademoiselle Chanel
- Lacoste Essential
- Comme une Evidence, Limited Edition Yves Rocher

- Fahrenheit Summer 2006, Dior
- La Nuit de l'homme, Yves Saint Laurent
- Emporio Armani Red, Giorgio Armani
- Ck one Graffiti, Calvin Klein
- Instinct Ice, David & Victoria Beckham

The main components of the oil are limonene, linalyl acetate, linalool, γ -terpinene, β -pinene, geranial and β -bisabolene.

Several studies showed that the application of bergamot oil to the skin have a concentration-dependent phototoxic effect due to bergapten a furocoumarin derivate [63].

It was found that the photosensitivity to human skin starts after 2h sun exposure of perfume application. UVA sunscreen is more decreasing the phototoxic effect of bergamot oil than UVB sunscreen. However, it was shown that the protective effect of UVB and UVA sunscreens at low concentrations (0.5%-1%) in perfumes did not lead to phototoxicity [64].

Other studies reported about 2 people with contact allergy to bergamot oil. One person shows an allergic reaction because of his job in a perfume factory and the other one shows skin irritation due to cosmetic products. The result of the patch test shows a positive result to α -pinene and β -pinene [65].

Ref:

[60] http://en.wikipedia.org/wiki/Bergamot_oil, July 2013

[61] <http://www.fragrantica.com/notes/Bergamot-75.html>, July 2013

[62] Sawamura, Masayoshi; Onishi, Yuji; Ikemoto, Junko; Tu, Nguyen Thi Minh; Phi, Nguyen Thi Lan (2006). "Characteristic odour components of bergamot (*Citrus bergamia* Risso) essential oil". *Flavour and Fragrance Journal* **21** (4): 609–615. doi:10.1002/ffj.1604. ISSN 0882-5734.

[63] Girard J, Unkovic J, Delahayes J, Lafille C (1979). "Phototoxicity of Bergamot oil. Comparison between humans and guinea pigs". *Dermatologica* **158** (4): 229–43. PMID 428611.

[64] Kejllova K, Jirova D, Bendova H, Kandarova H, Weidenhoffer Z, Kolarova H, Liebsch M (2007). "Phototoxicity of bergamot oil assessed by in vitro techniques in combination with human patch tests". *Toxicology in Vitro* **21** (7): 1298–1303. doi:10.1016/j.tiv.2007.05.016 .PMID 17669618.

[65] Dubertret L, Serraf-Tircazes D, Jeanmougin M, Morlière P, Averbeck D, Young AR 1990 "Phototoxic properties of perfumes containing bergamot oil on human skin: photoprotective effect of UVA and UVB sunscreens", *J Photochem Photobiol B*. **7**(2-4):251-9.

7.2. Peppermint oil in Cosmetic products

Peppermint oil is an ingredient of *Mentha x Piperita* (Lamiaceae), which is a hybrid, a cross between *Mentha aquatic* and *Mentha spicata*. The plant has been for a very long time in cultivation [66].

The essential oil components of the plant are menthol, menthone and menthylesters, particularly menthylacetate. Dried peppermint contains 0.3-0.4% of volatile oil consisting of

- menthol 7-48%,
- menthone 20-46%,
- 1,8-cineole 3-6%,
- menthofurane 1-17%,
- menthylacetate 3-10%.

Furthermore, it contains limonene, pulegone, eucalyptol, caryophyllene and pinene. The main form of menthol in nature is the stereoisomer (-)-menthol, with (1R,2S,5R) configuration. (-)-Menthol has a sweet, minty, fresh, cooling effect. It activates cold-sensitive receptors which are responsible for the well-known cooling sensation when applied to the skin. Menthol is often used in tea and for food flavoring for example ice cream, chewing gum and toothpaste [66].

Peppermint oil can be found in sunblockers shampoos, soaps, skin care products and make ups. It can be used internally as well as externally. The internal uses are for digestive problems, cramps of the upper gastrointestinal tract, irritable bowel syndrome, and some people use peppermint for menstrual problems and also in aromatherapy [67].

Externally, peppermint oil has been used for myalgia and neuralgia. The topical application to infants and young children due to the menthol constituent can induce apnea, laryngeal and bronchial spasm, acute respiratory distress with cyanosis or respiratory arrest.

Why is peppermint oil used in sunblockers?

Sunscreen products have an important protective function against UV radiation.

The sun protection factor (SPF) is a measure of the efficacy of sunblockers. A sunblocker offers better protection against the ultraviolet radiation when the SPF is higher. Studies show that the SPF values were in between 1 and 7 for volatile oils.

"The in vitro SPF is determined according to the spectrophotometric method of Mansur et al. Hydroalcoholic dilutions were prepared, and in vitro photoprotective activity was studied by UV spectrophotometric method in the range of 290-320 nm." [68]

It was found that the SPF value of olive oil was the highest of the nonvolatile oils and peppermint oil was the highest among volatile oils.

To be effective in preventing sunburn and other skin damage, a sunblocker should have a wide range of absorbance, between 290-400nm.

Table 4 [68]

Spectrophotometrically calculated sun protection factor values of volatile oils

Name of volatile oil	SPF value
Peppermint oil	6.668
Tulsi oil	6.571
Lemon grass oil	6.282
Lavender oil	5.624
Orange oil	3.975
Lemon oil	2.810
Eucalyptus oil	2.625
Tea tree oil	1.702
Rose oil	0.248

The table shows that the SPF value was found between 1 and 7. Peppermint oil and tulsi oil (Tulsi or Tulasī (*Ocimum tenuiflorum*, Lamiaceae) or Holy basil is a sacred plant in Hindu belief) was found around 7 as opposed to tea tree oil around 2 and rose oil around 1.

It can be concluded that peppermint oil and tulsi oil have the best SPF value in regard to sunblockers.

Toxicology

Some studies reported that the peppermint plant may induce liver disease, and other studies found that it may protect against hepatic disease [69].

In addition to that, the toxicity varies from one cultivar to another. The reason for the toxicity depends on the pulegone concentration.

Therefore, the European Pharmacopoeia recommends a limitation of pulegone concentration that should not exceed 1%.

Preparations with this limitation are safe and can be used in cosmetic formulations.

Peppermint oil can cause allergic reactions to the skin, it leads to flush, headaches and contact dermatitis. Symptoms can be internally and externally. By using toothpaste, one may break out in a mouth and tongue rash.

The use of peppermint oil in cosmetics is the reason for medicinal qualities. Cosmetics products are applied to different parts of the body. The main use of peppermint oil in cosmetics is to treat skin problems. The main skin problems is associated with the face are acne and dark spots. It is also effective in the treatment of pimples and it is good to treat cracked lips. Therefore, it is used as a component of lip sticks and lip glosses.

The Food and Drug Administration (FDA) includes peppermint on its list of spices and other natural seasonings and flavoring considered Generally Recognized As Safe (GRAS). Peppermint is also on the list of GRAS essential oils, oleoresins and natural extractives.

Ref:

[66] http://en.wikipedia.org/wiki/Peppermint_oil, July 2013

[67] Chanchal Deep Kaur and Swarnlata Saraf, 2010, "In vitro sun protection factor for determination of herbal oils used in cosmetics" *Pharmacognosy Res* **2**(1): 22–25. doi: 10.4103/0974-8490.60586

[68] http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=300, July 2013

[69] Akdogan, M; Ozguner, M; Aydin, G; Gokalp, O (2004). "Investigation of biochemical and histopathological effects of *Mentha piperita* Labiatae and *Mentha spicata* Labiatae on liver tissue in rats". *Human & Experimental Toxicology* **23**(1): 21–8. doi:10.1191/0960327104ht412oa.PMID 15027812.

7.3. Peru balsam

Peru balsam is extracted from the cortex of the tree "*Myroxylon balsamum pereirae*" (Fabaceae), which grows in Central America. It is a fragrance mix and used as a flavor additive in foodstuffs. It has a weakly antiseptic effect and therefore it is used in pharmaceutical treatment and for skin problems, such as eczema and itching. It is also found in personal use and cosmetic products such as perfumes, bath essence, body sprays and deodorants, and aromatic skin or hair products [70].

Fragrances are primarily used as a pleasant aroma. They also work to camouflage a distasteful scent, which are called "masking fragrances" and found in products labeled "unscented". But they are also a trigger to allergic reactions.

The main components of Peru balsam are esters of cinnamic acid, benzoe acid with benzyl cinnamate, benzyl benzoate and cinnamyl cinnamate. There are also small amounts of vanillin and eugenol found. As there have been a great number of substances identified, the exact compositions of Peru balsam is not known [71].

Allergy

It was reported that Peru balsam contains several fragrances which are responsible to allergic reactions by skin contact. Fragrance allergens should be labeled on cosmetic products. Peru balsam is prohibited in cosmetic products due to annex 2 [72]. Studies showed that Peru balsam in concentrations of 25% caused moderate skin irritation in children and mild reaction in women. It also showed skin irritations in tests with rabbits.

A study of 101 children below 15 years 24% of the children showed allergic reaction to Peru balsam, and from 2000 adults 6% showed allergic reaction. Allergic reaction to Peru balsam manifests in nettle rash, which is not unusual. It was also reported that Peru balsam shows phototoxic reaction [73].

The main components in Peru balsam – benzyl cinnamate and benzyl benzoate has been registered in the Scientific Committee of European Union SCCP (Scientific Committee on Consumer Products) on the fragrance list. This list contains well known allergens. Studies reported about positive reactions to benzyl benzoate and benzyl cinnamate.

Today the substance is prohibited in cosmetic products. People who are allergic to Peru balsam should avoid skin contact.

Ref:

[70] <http://en.wikipedia.org/wiki/Myroxylon>, July 2013

[71] <http://www.pharmawiki.ch/wiki/index.php?wiki=Perubalsam>, July 2013

[72] <http://www.dermatitisfacts.com/allergic-contact-dermatitis/allergic-contact-dermatitis-balsam-of-peru.php>

[73] http://www2.mst.dk/common/Udgivramme/Frame.asp?http://www2.mst.dk/udgiv/publications/2006/87-7052-278-2/html/kap07_eng.htm, July 2013

7.4. Lavender oil

Lavender oil is obtained from "*Lavandula angustifolia* Mill." (Lamiaceae). The primary components of lavender oil are linalool (51%), linalyl acetate (35%) and β -caryophyllene. Other components are α -pinene, limonene, 1,8-cineole, cis- and trans-ocimene, 3-octanone, camphor, terpinen-4-ol and lavandulyl acetate [74].

There are two forms:

- Lavender flower oil, colorless oil, insoluble in water.
- Lavender spike oil, a distillate from the herb "*Lavandula latifolia*", it has a poor olfactory quality.

Lavender oil is not a pure compound, it is like all essential oils a complex mixture of naturally phytochemicals including linalool and linalyl acetate.

It is known that lavender oil has a sedative and spasmolytic effect. Therefore, it is used as a sedative, insomnia and nervousness. Due to these effects it is used in aromatherapy and as an ingredient of cosmetic products [75,76]. The essential oil is used in the production of perfume especially "*Lavandula delphineusis*". In diluted formulation on the skin it may help to relieve pain from tension headache. It was found that lavender oil treats sunburn and sunstroke and can also be used in massage oil mixtures. It is also a treatment in hair rinse mixture for head lice to eliminate hits.

Allergy

It was reported that lavender oil is a compound in a massage oil mixture. Due to the massage the main constituents of lavender oil – linalool and linalyl acetate - could be detected in the blood. Inhalation and penetration through the skin leads to a relaxing and sedative effect after a massage [77].

Another study reported cytotoxicity of lavender oil to human skin cells in vitro at a concentration of 0.25%.

Also a 2005 study reported that lavender oil and its constituents linalool and linalyl acetate are toxic to human skin cells in vitro. Contact dermatitis to lavender oil appears to occur at very low frequency. The relevance of the in vitro toxicity to dermatological application is unclear. It was also reported that lavender oil does not have a phytotoxic effect.

Lavender oil is also found as a component in shampoos and lotions. In this context it was reported that it may increase incidence of early breast development in girls particularly in puberty, as young boys and girls are sensitive to estrogenic and androgenic compounds. It was suspected that lavender oil is responsible for gynecomastia in boys.

The conclusion of this study shows that gynecomastia *"actually was caused by the essential oils in the products used by the three boys"*.

Terpenes are the components of lavender oil, they can oxidize in air. Oxidized terpenes have a great sensitizing potency of lavender oil. Studies showed positive patch-testing results to air-exposed lavender oil to oxidized linalyl acetate in patients with contact allergy to oxidized linalool [78].

Ref:

[74] http://en.wikipedia.org/wiki/Lavender_oil, May 2013

[75] Shiina Y, Funabashi N, Lee K, Toyoda T, Sekine T, Honjo S, Hasegawa R, Kawata T, Wakatsuki Y, Hayashi S, Murakami S, Koike K, Daimon M, Komuro I. (2008), "Relaxation effects of lavender aromatherapy improve coronary flow velocity reserve in healthy men evaluated by transthoracic Doppler echocardiography." *Int J Cardiol.*; **129**(2):193-7

[76] Hongratanaworakit T.,(2011)"Aroma-therapeutic effects of massage blended essential oils on humans". *Nat Prod Commun.* **6**(8):1199-204

[77] Hwang JH. (2006), "The effects of the inhalation method using essential oils on blood pressure and stress responses of clients with essential hypertension" *Taehan Kanho Hakhoe Chi.* **36**(7):1123-34

[78] Lina Hagval, Maria Sköld, Johanna Bråred-Christensson, Anna Börje, Ann-Therese Karlberg, (2008) " Lavender oil lacks natural protection against autoxidation, forming strong contact allergens on air exposure" *Contact Dermatitis.* ;**59**(3):143-50. doi: 10.1111/j.1600-0536.2008.01402.x

7.5. Tea tree oil

Tea tree oil, or melaleuca oil is an essential oil with fresh camphoraceous odour. It is extracted via steam distillation from the leaves of *Melaleuca alternifolia* (Myrtaceae), which is native in Australia. Tea trees will be used by the native people as a traditional medicine by inhaling the oils to treat coughs and colds. They also cover wounds with leaves and they prepare an infusion with tea tree leaves to treat sore throats or skin damages [79].

Tea tree oil is defined by international standard “*Oil of Melaleuca, Terpinen-4-ol type*” which specifies 15 components to define the oil as “tea tree oil”. There are more than 98 compounds detected in the oil.

Table 4 [80]
Tea tree oil composition,
as per ISO 4730 (2004)

Component	Concentration
terpinen-4-ol	30-48%
γ -terpinene	10-28%
α -terpinene	5-13%
1,8-cineole	0-15%
α -terpinolene	1.5-5%
α -terpineol	1.5-8%
α -pinene	1-6%
p-cymene	0.5-8%

"The table shows the component that must be contained in tea tree oil, according to the ISO standard (International Organization for Standardization) 4730-2004".

Tea tree oil is a very common ingredient of household and cosmetic products, including shampoos, massage oils, skin and nail creams, and laundry detergents. It also shows an antiseptic potential, and it was found that it is active against bacteria, fungi and viruses. Due to its menthol-like cooling effect it is a common ingredient in topical products and it is used at a concentration for 5-10%.

α -terpinene

The monoterpene α -terpinene is responsible for the antioxidant activity of tea tree oil. On air α -terpinene forms an allergenic compound due to autoxidation. It forms allergenic hydroperoxides and therefore the sensitization potency of α -terpinene will be increased after air-exposure. Thus, its suitability can be questioned when used in topical applications and also in cosmetics and skin care products [81].

Allergy

Several studies reported contact allergy to tea tree oil due to α -terpinene. It was found that α -terpinene and its oxidized products are skin-sensitizing [81].

Ref:

[79] http://en.wikipedia.org/wiki/Tea_tree_oil#On_humans , May 2013

[80] Hart, P.H.; Brand, C.; Carson, C.F.; Riley, T.V.; Prager, R.H.; Finlay-Jones, J.J. (2000). "Terpinen-4-ol, the main component of the essential oil of *Melaleuca alternifolia* (tea tree oil), suppresses inflammatory mediator production by activated human monocytes". *Inflammation Research* **49**(11): 619–26. doi:10.1007/s000110050639

[81] Johanna R, Moa Andresen B, Anna B, Ulrike LN, Ann-Therese K, Chem. Re. Toxicol., α -terpinene, an Antioxidant in Tea Tree Oil, Autoxidizes Rapidly to Skin Allergens on Air Exposure, 2012]

7.6. Rosemary oil

Rosemary oil is extracted from the flowering tops by steam distillation of "*Rosmarinus officinalis*" (Lamiaceae).

The chemical components are α -pinene, borneol, β -pinene, camphor, bornyl acetate, camphene, 1,8-cineole and limonene.

There are different chemotypes of Rosemary, with different components: [82]

- *Rosmarinus officinalis* var. *verbenone* contains less camphor and is safer for using in topical applications.
- *Rosmarinus officinalis* var. *cineole* is preferred in respiratory and circulatory issues.

Rosemary oil has an analgesic, antidepressant, astringent, carminative, cholagogue, digestive, diuretic, hepatic, and hypertensive, stimulant and tonic effect [83].

Reports show that rosemary oil should not be used during pregnancy and is unsuitable for people with epilepsy or high blood pressure. Rosemary oil in skin products helps to ease swelling and can also be used for acne, dermatitis and eczema. A very popular use is in hair products; it has a positive effect on increasing the circulation to the scalp and hair growth. As an ingredient to shampoo it also acts as a conditioner and tonic. Rosemary oil is also helpful in massage and arthritis; it helps to improve blood circulation.

Ref:

[82] <http://www.aromaweb.com/essential-oils/rosemary-oil.asp>, July 2013

[83] <http://www.essentialoils.co.za/essential-oils/rosemary.htm#Chemical> composition, July 2013

7.7. Sandalwood oil

Sandalwood (*Santalum album*, Santalaceae) essential oil provides perfumes with a wood base note. When used in smaller proportions in a perfume, it is an excellent fixative to enhance the head space* of other fragrances.

Sandalwood oil is widely used in India in cosmetic industries. The main source of true sandalwood (*S. album*, Santalaceae) is a protected species. Within the genus *Santalum* alone, there are more than nineteen species. Traders will often accept oil from closely related species, such as various species in the genus *Santalum*, as well as from unrelated plants such as West Indian Sandalwood (*Amyris balsamifera*, Rutaceae) or bastard sandalwood (*Myoporum sandwicense*, Myoporaceae). However, most woods from these alternative sources will lose their aroma within a few months or years [83a].

S. album has been the primary source of sandalwood and the derived oil. These often hold an important place within the societies of its naturalised distribution range. The high value of the plant has led to attempts of cultivation, this has increased the distribution range of the plant. The ISO Standard for the accepted characteristics of this essential oil is ISO 3518:2002. The long maturation period and difficulty in cultivation have been restrictive to extensive planting within the range. Harvest of the tree involves several curing and processing stages, also adding to the commercial value. These wood and oil have high demand and are an important trade item.

Sandalwood oil is also used in medicine for treatment of common colds, bronchitis, skin disorders, heart ailments, general weakness, fever, infection of the urinary tract, inflammation of the mouth and pharynx. It was found that α -santalol has an antioxidant potential.

Ref:

[83a] http://en.wikipedia.org/wiki/Santalum_album, July 2013

8. PARFUM

8.1. Definition

Perfume is a mixture of fragrances, essential oil or aroma compounds, fixatives and solvents which is used for a pleasant scent of the human body, food and living spaces. Perfumes exist since a very long time. *"Modern perfumery began in the 19th century with synthesis of aroma compounds such as vanillin or coumarin"*. Dumas and Pèligot identified in 1833 cinnamic aldehyde as the responsible scent of cinnamon oil – this was the starting point [84].

The most famous perfumes from the past were: [85]

- *"Jicky by Guerlain (1889) containing vanillin and linalool"*
- *"La rose Jacqueminot of Coty (1904) containing rhodinol"*
- *"Après Londe by Guerlain (1906) containing para-anisaldehyde"*
- *"Quelques Fleurs by Houbigant (1912) containing hydroxycitronellal"*
- *"Chanel 5" (1921) containing aldehydes C-10, C-110 and C-12"*

8.2. Antiperspirants and Deodorants

Deodorants, are substances which are applied to the body to mask body odor caused in armpits, feet and other areas of the body. Antiperspirants are a subgroup of deodorants, which are used to reduce the sweating amount. They are typically applied to underarms, while deodorants may also be used on feet and

other areas, using in form of body sprays. Deodorants are classified as cosmetics by the FDA (Food and Drug Administration), while antiperspirants are classified as drugs [86].

Allergy

Some components of antiperspirants and deodorants can cause axillary dermatitis. A study reported about a 42 year old man with such complains. He was patch-tested and there was one positive reaction found to fragrance mix 1 and peru balsam and 3 positive reactions to fragrance mix 2, and positive reactions to lylal[®] (4-hydroxy-4-methylpentyl)-1-cyclohex-3-enecarboxaldehyde), tea tree oil, and lavender oil [87].

107 deodorants and antiperspirants were included in the database, 97 of them contained fragrances which render them as most common allergens.

It was reported that the main constituents which are responsible for allergic contact dermatitis found in deodorants are geraniol, eugenol and hydroxycitronellal. They are all present in the fragrance mix [88].

8.3. Concentration

Perfume types reflect the concentration of aromatic compounds in a solvent, in fine fragrance which is ethanol or a mix of ethanol and water. Intensity and longevity of the aromatic components – natural essential oils, or perfume oils – are based on their concentration. Perfumes have different classifications:[84]

- "Perfume extract, or simply perfume: 15-40% (IFRA: 20%) aromatic compounds"
- "Esprit de Parfum (ESdP): 15-30% aromatic compounds"
- "Eau de Parfum (EdP), Parfum de Toilette (PdT): 10-20% aromatic compounds"
- "Eau de Toilette (EdT): 5-15% aromatic compounds"
- "Eau de Cologne (EdC): Chypre citrus type perfumes with 3-8% aromatic compounds. Original Eau de Cologne is a registered trademark"
- "Aftershave: 1-3% aromatic compounds"

Classical cologne is a basically citrus blend, it describes men's and women's fragrances. Men's colognes have a similar concentration to EdT and women's cologne are often the smallest concentration of women's fragrance product.

Essential oils are used in the perfume industry as fragrances to promote hormonal balance and to mask toxin reactions of the skin.

Chypre and Fougère types of perfumes are not possible without bergamot oil.

- Chypre: meaning "Cyprus" in French. It includes fragrances based on a similar accord consisting of bergamot, oakmoss, and labdanum.
- Fougère: meaning "Fern" in French, build on a base of lavender, coumarin and oakmoss.

Many men's fragrances belong to this family of fragrances, which is characterized by its sharp herbaceous and woody scent. Some well-known fougères are

- Fabergé Brut
- Guy Laroche, Drakkar Noir

8.4. Perfume intolerance

Perfume intolerance is a condition where people develop allergic reactions to ingredients of perfume. The most common allergic reaction to perfume is contact dermatitis. Results of studies showed that most of the people reported about irritations from air fresheners, or irritation by scented laundry products. It was found *“that 1.7-4.1% of the general population shows a contact allergic response to a mix of common perfume ingredients”* [89].

Allergy

Studies showed people with allergic contact dermatitis, irritant contact dermatitis and people with different strong reactions to various fragrances. It was reported that the main causes of allergic contact dermatitis were 2 perfume oils, and their ingredients were:[90]

- geraniol
- benzaldehyde
- cinnamic aldehyde
- linalool
- neroli oil
- terpenes of lemon oil and orange oil

Ref:

[84] <http://en.wikipedia.org/wiki/Perfume>, July 2013

[85] Patricia de Nicola, (2008) "A smelling Trip into the Past: The Influence of Synthetic Materials on the History of Perfumery" *Chemistry & Biodiversity*. **5**: 1137-1147

[86] <http://en.wikipedia.org/wiki/Antiperspirant>, July 2013

[87] Matthew J. Zirwas, MD, and Jessica Moennich, (2008), "Antiperspirant and Deodorant Allergy". *The Journal of Clinical and Aesthetic Dermatology* **3** (1): 38-44

[88] Scheman A, Jacob S, Zirwas M, et al. (2008) "Contact allergy: alternatives for the 2007 North American contact dermatitis" *Tray. Dis Mon.*; **54**(1-2):7-156.

[89] http://en.wikipedia.org/wiki/Perfume_intolerance, July 2013

[90] Schubert HJ. (2006) "Skin diseases in workers at a perfume factory". *Contact Dermatitis*.; **55**(2):81-3. Dermatological Practice, Erfurt, Germany. hans-juergen.schubert@arcor.de

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