universität wien

# DIPLOMARBEIT

Titel der Diplomarbeit

„Compilation of toxicological data of major volatile essential oil components“

Verfasserin

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angestrebter akademischer Grad

Magistra der Pharmazie (Mag.pharm.)

Wien, 2012/13

| | |
|---|---|
| Studienkennzahl lt. Studienblatt: | A 449 |
| Studienrichtung lt. Studienblatt: | Diplomstudium Pharmazie |
| Betreuerin / Betreuer: | Prof. Dr. Gerhard Buchbauer |

# Danksagung

Ich möchte mich in erster Linie bei meinem Betreuer Prof. Dr. Buchbauer bedanken, der mich mit viel Engagement und Ermutigung zum wissenschaftlichen Arbeiten unterstützt hat und stets für mich ansprechbar war.

Des weiteren danke ich meinen Eltern, die mir dieses Studium ermöglicht haben und mich immer voll Stolz in allem unterstützen. Meinem Bruder und meiner Schwester danke ich dafür dass sie mir mit Rat und Tat in den Bereichen medizinisches Fachwissen, Englisch und Formatierung zur Seite standen.

Meinem Verlobten danke ich für seine Liebe und für seine Geduld. Schließlich gilt mein Dank meinen lieben Freunden, dafür dass sie mich immer motiviert haben und für ihre Treue.

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**Abstract**

Essential oils have been used since centuries in worldwide folk medicine to treat various diseases. But also in the perfume, cosmetics and food industries many essential oils are important additives. They play a main role as fragrances, flavour enhancers or as concealers of unpleasant odours. Obviously their toxicity is often underestimated or their toxic properties are not even known. Therefore, severe intoxications, which could be lethal, occur often (mainly in children).

This compilation serves as summary of the current toxicilogial data from the most important volatile essential oil components. Furthermore, the main forms of use are summarised and the current investigations have been touched on.

## Zusammenfassung

Seit Jahrhunderten werden ätherische Öle in der Volksmedizin weltweit verwendet um diverse Krankheiten zu therapieren. Auch in den Parfum-, Kosmetik- und Nahrungsmittelindustrien sind viele ätherische Öle essentielle Zusatzstoffe. Sie spielen unter anderem als Duftstoffe, Geschmacksverstärkter oder als Maskierer von unangenehmen Gerüchen eine Rolle. Doch leider wird die Toxizität von ätherischen Ölen oftmals unterschätzt, bzw. sind ihre toxischen Eigenschaften meist nicht bekannt. Es kommt daher häufig zu schweren Vergiftungen die auch, vor allem bei Kindern, tödlich enden könnten.

Diese Arbeit dient als Zusammenfassung von den aktuellsten toxikologsichen Daten der wichtigsten flüchtigen Komponenten von ätherischen Ölen. Weiters wurden die gängigsten Anwendunsgarten summiert und die aktuellsten Forschungsgebiebte angeschnitten.

# Introduction

Essential oils are aromatic and volatile liquids. The preparation is carried out by steam distillation of plant material, for instance flowers, roots, bark, leaves, seeds, peels, fruits, wood or the whole plant (Sánchez et al., 2010) and by pressing of the peels of citrus fruits (Schmidt, 2010). "*Essential oils are natural, complex, multi-component systems composed mainly of terpenes in addition to some other non-terpene components*" (Edris, 2007).

Since ancient times they have been widely used as symbolic articles in religious and social ceremonies (Smith et al., 2005), in medicine, perfumery and cosmetics as well as in spices or herbs, as additives to food. "*Almost 3000 different essential oils are known, and 300 are used commercially in the flavor and fragrances market*" (Burt, 2004). Additionally, they are often used only to mask unpleasant natural odours of basic ingredients in some products (Johansen et al., 2002).

Investigations about the therapeutic potentials of essential oils reported about their positive effects in aromatherapy, chemoprevention, cardiovascular disease, and as antidiabetic agents and skin penetration enhancers (Edris, 2007). They are often accepted as multifunctional agents. During their long history of use over a wide range of human exposures, no adverse effects were known. Therefore, essential oils relish a high degree of confidence and are presumed to be safe. The public do not scrutinise whether the essential oil products they use are safe. Indeed toxic, genotoxic and carcinogenetic properties were observed at high levels of exposure to several constituents (Smith et al., 2005).

The European Commission registered several essential oil components for their use as flavouring agents in food products. Those accepted components are for instance linalool, thymol, eugenol, carvone, cinnamaldehyde, vanillin, citral, and limonene, "*all of which are considered to present no risk to the health of the consumer. The United States Food and Drug Administration (FDA) also classifies*

*these substances as generally recognized as safe (GRAS)*." Moreover, the FDA limited the acceptable daily intake of essential oils and their compounds (Hyldgaard et al., 2012). Thus it could be concluded that the essential oil compounds do not pose a significant risk to human health at low levels, when used as flavouring substance, indeed in higher quantities some compounds exhibit toxicity. But the majority of essential oil constituents that are used as flavouring agents even do not pose any risk at doses that are much higher that their daily intake (Smith et al., 2005).

Furthermore, contact allergy is considered to be the most frequent adverse reaction caused by fragrances, which is believed to be an underestimated problem (Cuesta et al., 2010). "*Fragrances may be responsible for clinical conditions, including irritant contact dermatitis, allergic contact dermatitis, photosensitivity, immediate contact reactions (contact urticaria), and pigmented contact dermatitis*" (De Groot&Frosch, 1997 op.cit. Cuesta et al., 2010). This unawareness of consumers about the irritation and sensitization potential of fragrances is problematic, mainly because the use of plant products are increasingly favoured (Thomson&Wilkinson, 2000).

The European Commission's Scientific Committee on Consumer Safety made up a list of 26 fragrances that are common allergens. Detergents, cosmetics, lacquers, metalworking fluids and others were included as sources of exposition. "*It is concluded that several preservatives and fragrances with well-known skin-sensitizing potential are common in shampoos, hair conditioners, liquid soaps, wet tissues, washing-up liquids, and multi-purpose cleaners. Such products may be used several times a day by consumers and workers, leading to repeated exposure to some of the most important causes of contact allergy, often in combination with other allergens and skin irritants*" (Yazar et al., 2011). Depending of the exposure location, the dermatitis occurs anywhere on the body. Many of the essential oils contain compounds like terpinene, geraniol, linalool or limonene which develop (stronger) irritation potency when they are air exposed and auto-oxidized. Therefore the EU considered the regulation of the

content or peroxides in materials containing terpene and terpenoid materials (Karlberg et al., 2008).
The data above suggest that herbal treatments are never free of adverse effects (Ernst, 2000).

This compilation serves as summary of toxicological data from the most important volatile essential oil components, between 2000 and 2012. The data include information about the irritation and sensitization potential, as well as the genotoxic, hepatotoxic and carcinogenic propterties, and about ID50 and LD50 values (oral, dermal and intraperitoneal). Furthermore, the common kinds of use and the recent investigations of several components were summarised in this review.

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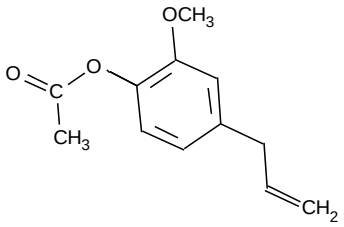
## Acetyleugenol




Acetyleugenol is, beside eugenol one of the main components of the traditional Chinese medicament *Eugenia caryophyllata* Thunb. (Myrtaceae) (clove oil). The most important application of the medicinal plant are gastrointestinal disorders like diarrhea or problems of the digestion (Yang et al., 2003; Kim et al., 2003). Clove oil is also used as skin permeation enhancer, e.g to improve the permeation of Ibuprofen. The request to such skin permeation enhancer is to be harmless and to exhibit a low skin irritation-potential. The content of acetyleugenol in clove oil is about 8% and the content of eugenol nearly 82%, hence the enhancing effect of clove oil most likely due to those two components. The application of a 3% (w/v) clove oil formulation did not cause neither redness nor discoloration nor swell. There was no visible affection on the morphology of the skin tissues. Even after 24, 48 and 72 hours after the application no signs of skin irritation were found. "*The results indicated that clove oil might possess low skin irritation and therefore well tolerated by the rabbits*". More studies would be necessary to prove much more the harmlessness of clove oil as skin permeation enhancer (Shen and Li, 2007).

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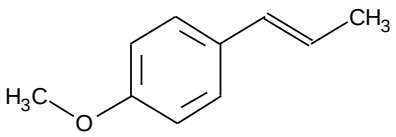
**Anethole**




Anethole is the main constituent of anise, star anise and sweet and bitter fennel oils, which are used in sweet foods or rather the herb fennel in savoury foods. It is also found in cosmetic products such as lipsticks or soaps, but also in flavoured toothpastes and liquid medicines. By consumption of food containing anethole, there were no reports about contact allergies (Saino, 1995 op.cit. Poon & Freeman, 2006). Indeed there have been cases of persistent cheilitis – in the form of erythema of the upper and lower lips – caused by contact allergy to anethole, as content of flavoured toothpaste. Therefore, it is important to consider that in any case of peri-oral contact allergy with no clear cause, the flavouring contents of the toothpaste may play an essential role (Poon & Freeman, 2006).

The evaluation of the toxic effect of anethole as food flavour additive was evaluated in Tameda et al. 2005. The intake of hight doses of trans-anethole was associated with hepatotoxicity linked to an increase of ALT and AST parameters in rats (Abd El-Wahab & Moram, 2012).

Beside estragole, anethole is also a main compound of *Croton zehntneri* L. (Euphorbiaceae), an aromatic plant native to Northeastern Brazil, which is used in folk medicine for the treatment of gastrointestinal problems. Another quality of its essential oil is the antinociceptive effect. This analgesic action was evaluated in mice. The mechanism of *Croton zehntneri* may be specified through acting in the central nervous system or an indirect mechanism like an anti-inflammatory effect. Further investigations are needed to describe the mechanism and to denominate *C. zehntneri* as potential therapeutic. Definitely the oral LD50 is indicated as >2.5 g/kg. Doses lower than 300 mg/kg do not cause any depressant effects (Oliveira et al., 2007).

The evaluation of the LD50 of *Croton zehntneri* L. and *Lippia sidoides*

Cham. (Verbenaceae) in mice, in the Fontenelle 2005 – study also indicated that these essential oils did not provoke any toxic effects until a dose of 3 g/kg (Camurca-Vasconcelos et al., 2007). The essential oil of *Ocimum selloi* Benth. (Lamiaceae) has also been traditionally used to flavour food and cosmetic hygiene products, but also in folk medicine to treat stomach aches and as anti-inflammatory and analgesic agent, to treat fevers, cough, bronchitis and also as emmenagogue and emetic (Vieira & Simon, 2000). Anethole is here also one of the major compounds. To investigate acute toxicity and skin irritant potential, the essential oil was tested on mice. A single dose of 1250 mg/kg did not show any signs of toxicity or death. At doses as high as 1500 mg/kg symptoms like hypoactivity, ataxia, lethargy and cyanotic extremities were observed, that potentially lead to death and coma. Mentionable is that males were more resistant to *Ocimum selloi* than females (De Paula et al., 2003). In former investigations the LD50 of trans-anethole was reported to be between 1850 and 5000 mg/kg (Newberne et al., 1999 op.cit. De Paula et al., 2003) which is not so far away from the data of the present study. The skin irritation potential of *O. selloi* was evaluated too. The results suggested that a single short topic application of four hours of the essential oil did not cause any irritation reactions to human skin. In any case the results show in conclusion that the essential oil of *O.selloi* owns a low acute toxicity and seems not to have any irritating potential to human skin (De Paula et al., 2003).

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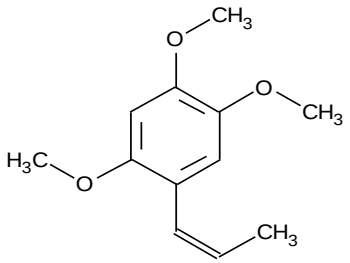
**β-Asarone**



As main compound of *Acorus calamus* L. (Acoraceae), an aromatic plant native to Central Asia and Eastern Europe, β-asarone limits the possibility of its use. The reason is the carcinogenic character of β-asarone (Bertea et al., 2005). There have been reports about its carcinogenic properties, such as duodenal tumour induction (Taylor et al., 1967 op.cit. Bertea et al., 2005), as well as antiproliferative and immunosuppressive (Mehrotra et al., 2003 op.cit. Bertea et al., 2005) and central nervous system inhibitory effects (Koo et al., 2003 op.cit. Bertea et al. 2005).

The essential oil of *Acorus calamus* is mainly used in the pharmaceutical and oenological industries (Bertea et al., 2005). The Scientific Committee for Food of the European Commission ECC determined a maximum dose of 0.1 mg/kg in flavourings for foodstuff such as desserts and beverages. In alcoholic beverages such as beer or liqueurs and bitters the limit is 1 mg/kg (ECC, 1968, 2002 op.cit. Bertea et al., 2005). The pharmaceutical use of *A. calamus* bases upon the European folk medicine, where it is used as “Amarum aromaticum”. The indication areas are such as gastrointestinal disorders, like acute and chronic dyspepsia, gastritis, intestinal colic and anorexia (Wichtl et al., 2009). Otherwise the Ayurvedic medicine and traditional Chinese medicine use the drug to treat the central nervous system, relating to epilepsy, insanity, mental weakness or insomnia (Khare, 2004 op.cit. Zaugg et al., 2011). Therefore, there are some in vivo studies which support the sedative and tranquillizing action of its essential oil. (Dandiya et al., 1959 op.cit. Zaugg et al., 2011). Other studies show that β-asarone has significant pharmacological effects on the central nervous system through

attenuation of ischemia-reperfusion-induced autophagy in rat brains and of neuronal apoptosis. Therefore, it may play an important role in neuroprotection (Liu et al., 2012) .

Because of the vast use of *A. calamus* there have been experiments to oxidise the toxic phenylpropanoid β-asarone to the bioactive isoacoramone. This metabolite reveals to be non-toxic up to 60 mg/kg (Sinha et al., 2004).

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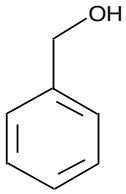
**Benzyl alcohol**




Benzyl alcohol, an aromatic, naturally produced alcohol is generally found in certain essential oils like jasmine or hyacinth, but also as constituent of balsam of Peru (Nair, 2001). It has a widespread use as preservative in topical preparations, as fragrance component in cosmetic formulations such as soaps or shampoos and also as solvent, anaestheticum (Curry&Warshaw, 2005) and antipruritic (Ramirez-Santos et al., 2008). The benzyl alcohol lotion 5% (BAL5%) is a safe and effective head lice treatment with a low incidence of eye and skin irritation. Due to its non-neurotoxicity it is also convenient for children, with a short application time (Meinking et al., 2010).

As component of cosmetic products, benzyl alcohol was the fifth most common allergen discovered in moisturizers. Moisturizers are used as cosmetic products by patients with dry skin conditions. Those products are considered to be safe, although skin reactions may appear. Other contact allergy reactions have been reported from hair dye, injectable medication and anesthetic spray (Zirwas&Stechschulte, 2008). In the MOAHLFA index 2004, benzyl alcohol was reported to be one of many allergens that are associated with occupational leg dermatitis in concentrations higher than 20%. The function of this epidemiological index is to give hints regarding causal exposures (Schnuch et al., 2011).

Many background preservatives, such as benzyl alcohol, are specific contact allergens. The allergy prevalence of benzyl alcohol is unknown. But there have been reported delayed-type hypersensitivity reactions to benzyl alcohol as preservative in creams and other topical agents (Sestini et al., 2004). Symptoms like facial dermatitis, characterized by pruritic erythematous scaly plaques, have been reported with a persistence of two month (Curry&Warshaw, 2005). Because benzyl alcohol is a constituent of the balsam of Peru, it is

essential to avoid the treatment of a potent dermatitis, caused by the balsam of Peru, with benzyl alcohol containing crèmes. The end effect would be, for instance, the worsening of an eyelid dermatitis (Jacob&Stechschulte, 2008). The high incidence of allergy of the balsam of Peru suggests the wariness to benzyl alcohol preserved injectable products (Amado&Jacob, 2007). As ingredients of topical products, benzyl alcohol could be used safely at concentrations up to 5% (Wenninger et al., 2000 op.cit. Nair, 2001). 1995 the European Union (EU) has determined the maximum concentration of 1%, when used as preservative (Nair, 2001). Dermal studies with cats resulted with a LD50 of 2.93 g/kg (Graham&Kuizenga, 1945 op.cit. Scognamiglio et al. 2012). The result of the irritancy potential examination of benzyl alcohol as pharmaceutical penetration enhancers in a 10% solution in nude mice, was an unacceptably severe skin irritation (Lashmar et al., 1989 op.cit. Scognamiglio et al. 2012), while Hausen et al. (1992) reported that 10% of benzyl alcohol is a moderate sensitizer in guinea pigs (Hausen et al., 1992 op.cit. Scognamiglio et al. 2012). Anyway it is also important to mention the investigations of the systemic toxicity of benzyl alcohol. The World Health Organization (WHO) determined the acceptable daily intake ADI at 5 mg/kg for Benzyl alcohol. It can be found in OTC drug preparations and it is also used as food additive (Nair, 2001).

The acute oral LD50 values for benzyl alcohol were about 1.580 g/kg for mice, between 1.230 and 3.200 g/kg for rats and about 1.040 g/kg for rabbits (Flavour and Extract Manufacture's Association, 1984 op.cit. Nair, 2001). In the male animals lethargy and rough coats were observed. The United States Environmental Protection Agency EPA calculated the doses for rats and mice into human doses between 39 and 84 mg/kg/day. For the chronic oral toxicity the LD50 was determined with a dose of 58 mg/kg/day for humans (EPA 1989 op.cit. Nair, 2001). Relating to the acute parenteral toxicity the LD50 values were determined between 100 and 400 mg/kg in mice. Clinical signs of toxicity were convulsion, dyspnoea and reduced motility. A mentionable factum is that undiluted benzyl alcohol was ranked as the

most toxic of five solvents tested (Montaguti et al., 1994 op.cit. Scognamiglio et al., 2012).

Althogether benzyl alcohol is considered to have a low incidence of sensitisation, although it may induce urticarial, immediate and systemic reactions. But the majority of those reported reactions have been the result of repetitive application and the constant use of moisturizers (Scheman et al., 2008).

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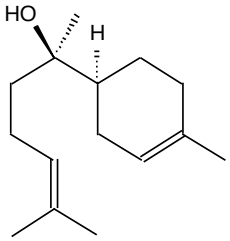
**α-Bisabolol**




The monocyclic sesquiterpene alcohol α-bisabolol is found in the essential oil of various plants such as chamomile, arnica, salvia and other plants. It has a vast use in dermatological and cosmetic formulations like hand- and body-lotions, sun-care- and baby creams (Jequier et al., 1980 op.cit. Gomes-Carneiro et al. 2005), due to its pleasant floral-sweet odour and apparent harmlessness.

The essential oil of chamomile has a high content of α-bisabolol. Chamomile teas have long been used in European folk medicine to treat inflammatory disorders, fever, diarrhoea and to allay menstrual pains (Moreno-Fernandes et al., 1992 op.cit. Gomes-Carneiro et al., 2005). Some animal studies show that α-bisabolol has gastric-protective properties too. The gastro-protective and anti-ulcerogenic mechanism is reported to be multifactorial (Bezerra et al., 2009).

The acute oral toxicity in rats was determined with a LD50 between 14.9 and 15.6 ml/kg, while sedation and ataxia was already observed at 6.35 ml/kg. The lowest toxic oral dose for foetuses and dams was reported to be between 1.0 and 3.0 ml/kg (Habersang et al., 1979 op.cit. Bhatia et al., 2008).

Because of its anti-inflammatory action, α-bisabolol may serve as a source for the development of drugs for skin inflammatory diseases, such as psoriasis and atopic or contact dermatitis. Another reason is that it has been generally regarded as relatively nontoxic for topical use (Leite et al., 2011). The International Fragrance Association IFRA (2006) reported that the maximum concentration of α-bisabolol in fine fragrances is 0.08%. The calculated maximum daily exposure on the skin is 0.0001 mg/kg (Bhatia et al., 2008). But patients with myeloproliferative disorders have to be aware of topical herbal

applications like arnica, because they can cause Sweet's syndrome with necrotic skin lesions of the face and the legs (Ernst, 2000).

Another promising future of α-bisabolol is the chemotherapy. Because of its selectivity it plays a role in the research and development of targeted anti-tumour drugs. The results of recent studies confirm that α-bisabolol is able to induce apoptotic cell death in tumour cells (Cavalierei et al., 2004). The absence of toxicity towards normal cells provides a basis for the development of safe and efficient anti-tumour drugs. Further studies are needed (Darra et al., 2008).

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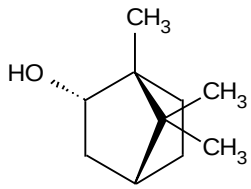
**Borneol (Camphol)**




The monoterpenoid alcohol borneol is a fragrance in decorative cosmetics, fine fragrances, shampoos, toilet soaps, etc., but it is also a content of household cleaners and detergents. The IFRA reported 2004 that the maximum skin level in formulations like fine fragrances is 0.3%. The maximum daily exposure on the skin is 0.0041 mg/kg (Bhatia et al., 2008). The irritation potential of borneol was tested in albino mice. The irritation dose ID50 was determined to be 0.667 µg/5 µl (Saeed&Sabir, 1994 op.cit. Bhatia et al., 2008).

Borneol is one of the main compounds of *Salvia libanotica* Boiss. et Gaill. (Lamiaceae) which is an important plant in Lebanese folk medicine. The essential oils of *S. libanotica* are used as infusions and teas or are inhaled to treat fractured bones, headaches, stomach aches and many other disorders (Gali-Muhtasib et al., 2000). The oral LD50 of borneol in rabbits was determined with a value of 2 g/kg (Budvari, 1989 op.cit. Gali-Muhtasib et al., 2000). Adverse reactions like nausea, vomiting, mental confusion and convulsion were reported (Rice&Wilson, 1976 op.cit. Gali-Muhtasib et al., 2000). In traditional Chinese medicine the semi-volatile borneol is used for preventing and curing cardiovascular and cerebrovascular disease (Huang&Lv, 2008). As component of plants such as *Dryobalanops aromatica* Gaertn.f.nom cons. (Dipterocarpaceae), or *Blumea balsamifera* Linn DC. (Asteraceae), borneol played for long time an important role in analgesic therapy with a mechanism which is related to the central nervous system (Park et al., 2003). Previous studies investigated a double side effect of borneol on the central nervous system. But the mechanism is still unknown and further studies are needed to assess the effect of borneol (Li et al., 2012). As corneal penetration enhancer borneol is used in products at a concentration of 0.1% which is safe

and does not cause any eye irritation in rabbits. Mentionable is that the drug permeability effect of synthetic borneol is stronger than the effect of the natural one. Synthetic borneol is a mixute of (+)-, (-)-borneol and isoborneol (Yang et al., 2009).

(-)-Borneol

The maximum skin concentration of (-)-borneol in skin formulations, such as fine fragrances and others was determined by the IFRA, 2004 with 0.32%. The maximum daily exposure on the skin was reported to be 0.0046 mg/kg (Bhatia et al., 2008). In albino rats the acute oral toxicity was determined with a LD50 of 6.5 g/kg. Clinical signs such as hyperactivity and loss of righting reflex were reported. At doses about 7.8 g/kg all tested animals died (RIFM, 1972 op.cit. Bhatia et al., 2008).

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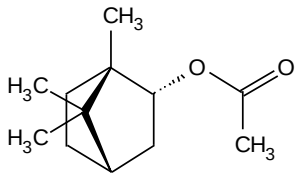
## Bornyl acetate




There are only few toxicity reports about bornyl acetate. It is the main component of the essential oil of the silver fir, *Abies alba* Mill. (Pinaceae), which is known to help respiratory system and to have easing and soothing effect for muscles. Further studies are needed to identify its exact bioactivity to get a basis for its potential for industrial application. Because of its distinctive and refreshing pine-forest fragrance, the interest for the silver fir as aromatherapy is also growing.

The essential oil of silver fir has no toxic effect at low concentrations for 24 hours. But there is no available information about the cytotoxicity of the oil, for the direct use on human skin (Yang et al., 2009).

Bornyl acetate is also the main compound of the Iranian plant *Ferulago macrocarpa* Boiss. (Apiaceae), but this plant has not been subject of any study (Sajjadi et al., 2012).

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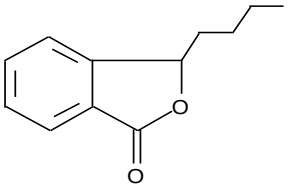
**3-n-Butylphthalide**




3-n-Butylphthalide, one of the most important volatile odorant components in the seeds of celery *Apium graveolens* L. Var. *dulce* (Kurobayashi et al., 2006), is able to reduce beta-amyloid-induced neuronal toxicity in cultured neuronal cells. The natural free radical scavenger was recommended by State Food and Drug Administration (SFDA) of China as profitable for the therapy of ischemic stroke (Xiong et al., 2012). It has been reported that 3-n-butylphthalide has antithrombotic activities and can inhibit platelet aggregation. In higher doses it is able to inhibit thrombus formation ex vivo (Peng et al., 2004).

Therapeutic effects were demonstrated with no mentionable side reactions in 590 patients with acute cerebral ischemia. A dose of 100 mg/kg increased the bleeding time on rats, while the effects of (-)-3-n-butylphthalide is much more potent than the effects of (+)-3-n-butylphthalide. In addition it is relatively safe (Peng et al., 2004) mainly in comparison with the NMDA receptor antagonist Memantin, relating to the adverse reactions (Ma et al., 2009). "*A series of studies indicated that 3-n-butylphthalide attenuate cerebral ischemic damage in experimental rats with no marked toxicity*" (Liu and Feng, 1995; Chong and Feng, 1997, 1999a; Xiong and Feng, 1999 op.cit. Zhao et al., 2003). Only an overdose of 3-n-butylphthalide - about 250mg/kg/d - can be toxic on rats (in vitro data) and may cause adverse reactions. But any dosage below 100mg/kg/d in rats and below 10 mg/kg/d in humans rarely cause any adverse reactions (NBP Pharmaceutical Co., Li et al.,2009 op.cit. Xiong et al., 2012).

Although the primary mechanism is not definite, with the decreasing of the acetylcholine activity and the attenuation of the learning and memory damages in aged rats, 3-n-butylphthalide could be a new long-term drug to treat neurodegeneration desease (Ma et al., 2009).

Even if it has been approved to be neuroprotective in cerebral ischemia, vascular dementia and Alzheimer's disease, it is still necessary to investigate the new drug before moving into clinical trials (Feng et al., 2012).

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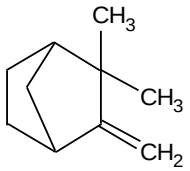
**Camphene**




The bicyclic monoterpene camphene is a compound of several essential oils like cypress oil, citronella oil, turpentine oil (Jeffery et al., 1983 op.cit. Tiwari&Kakkar, 2009) and diverse plants such as apricot, carrots, cinnamon, ginger, nutmeg, cardamom and turmeric. It has a vast use as flavouring food additive as well as in the preparation of fragrances, cosmetics, plasticizers and lacquers (Verschueren, 2011 op.cit. Tiwari&Kakkar, 2009). The individual daily intake was reported to be 0.05 µg/kg/day. The Council of Europe Committee of Experts on Flavouring Substances appropriated the limit for camphene in foodstuff as 20 mg/kg (Burdock&Fenaroli, 2004 op.cit. Tiwari&Kakkar, 2009).

As minor component of the essential oil of Chios mastic gum, a resin produced by *Pistacia lentiscus* L. var Chia (Anacardiaceae), camphene may play an important role as alternative hypolipidemic drug. "*Disorders of lipid metabolism are the primary risk factor for cardiovascular disease*." Since some patients do not tolerate the successful, cholesterol-lowering statins, the interest for more effective drugs from natural origin with low toxicity is growing. In vivo studies demonstrated the hypolipidemic activity of camphene with a process that is independent of inhibition of HMG-CoA reductase. While statins cause liver injury, the treatment with camphene did not induce any cytotoxicity in human hepatic cells. In animals there was no toxicity observed, even after receiving the highest dose of 30 mg/kg of camphene. The OECD High Volume Chemicals Programme determined 1993 in a Screening Information Data Set a LD50 of
5 g/kg in rats. For the development of camphene as hypolipidemic agent, further investigations are needed (Vallianou et al., 2011).

Other studies improved the protective effect of camphene against oxidative stress by reducing the lipid peroxidation and the NO

production of cells. With this property camphene is potent for the development of drugs for oxidative-damage-induced disease like lung inflammatory disease. It could be used as prophylactic agent or as adjuvant therapy (Tiwari&Kakkar, 2009). In combination with the terpene geraniol, hepatotoxicity could be prevented. The pre-administration of camphene and geraniol promised more protection in mitochondria than silymarin. In vivo studies in rats show that the effective, non-toxic dose of this combination was 1/10 of the effective silymarin dose (Singh et al., 2012).

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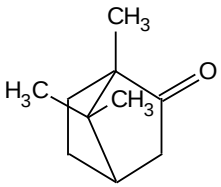
**Camphor**




The cyclic terpene camphor occurs naturally in the camphor laurel tree. It could be also produced synthetically from turpentine oil (Roberston&Hussain, 1969 op.cit. Jankelowitz et al., 2009). In Asia it is used as food-flavouring agent, but it is also an ingredient of many Ayuverdic medicines (Bhaya&Beniwal, 2007).

Due to its pleasant odour it is used in cosmetics like skin lotions. Camphor has analgesic and anti-pruritic properties and is used to treat haemorrhoids (Ragucci et al, 2007). In addition it has mild expectorant effects and is also an active ingredient in mothballs, which could be a good source for poisoning. Camphor owns a high toxicity. Notable is that camphor toxicity is well-documented in paediatric literature, but rare in adults (Jankelowitz et al., 2009). For instance in adults there was an unique report about the toxic effect of camphor, direct on the myocardium. But this myocarditis was associated with the ingestion of a large camphor-dose (Bhaya&Beniwal, 2007).

The camphor usage in the community was largely unrecognized. Such products had a vast use for medicinal, spiritual and aromatic purposes. Parents often used camphor products to treat common childhood ailments. Due to its highly lipophilic properties, camphor can be easily absorbed through the skin (Khine et al., 2009). It crosses also the placental barrier and has embryotoxic effects. The toxic dose is estimated to be between 15 and 30 mg/kg or above 500 mg in humans. Although there are enough reports about camphor toxicity, it continues to be a source of paediatric exposure (Manoguerra et al., 2006 op. cit. Guilbert et al., 2007).

Symptoms of toxicity occur within minutes and include burning of the mouth, throat, nausea and vomiting. Serious intoxication lead to

neurological irritability, tonic muscle contraction, seizures, coma, apnoea and death, due to respiratory failure or status epilepticus. Such intoxication could only be treated symptomatically. The main problem is, that there are no supportive antidotes also because the exact mechanism of action of camphor toxicity is not well understood. Therefore, the US Food and Drug Administration determined in 1982 that no product can contain more than 11% camphor (Jankelowitz et al., 2009).

Camphor is also an important compound of *Salvia libanotica* Boiss.&Gaill (Lamiaceae). The essential oil of *S. libanotica* owns a characteristically camphor-like odour and tastes very bitter. The sage plant is widely used in traditional Lebanese medicine. But the essential oil has to be handled with precaution (Gali-Muhtasib et al., 2000). The toxicity of the essential oil has been mainly attributed to camphor and thujone (Millet et al., 1981 op.cit. Gali-Muhtasib et al., 2000). The LD50 values of a intraperitoneal injection of camphor are reported to be 3000 mg/kg in mice and 200 mg/kg in rats (Budavari, 1989 op.cit. Gali-Muhtasib et al., 2000). Other studies reported that the intraperitoneal injection of 2200 mg/kg was the minimum lethal dose in mouse, and that an intraperitoneal injection of 300 to 400 mg/kg in rats did not cause any toxic effects (Cirainnati, 1999 op.cit. Nikravesh&Jalali, 2004). Obviously the reports about its toxicity vary. However, an interesting point is that the non-toxic dose of 100 mg/kg of camphor has an effect on the reproductive system of male mice. It has been identified to alter the process of spermatogenesis (Goel et al., 1985 op.cit. Nikravesh&Jalali, 2004). This property of camphor as a suppressor of sexual activity was an old supposition of the Iranian traditional medicine. But further studies are needed to know the exact mechanism of this effect (Nikravesh&Jalali, 2004). On the research of natural anticarcinogenic agents, *Artemisia capillaris* Thunb. (Asteraceae) has been tested. Camphor is an important constituent of this plant. But further studies are needed to identify the anticarcinogenic mechanism of *A. capillaris* or of particular constituents of this oriental plant (Kim et al., 2008).

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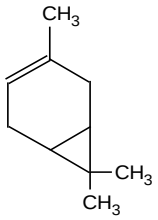
KIM Y.S., BAHN K.N., HAH C.K., GANG H.I., HA Y.L., 2008. Inhibition of 7,12 Dimethylbenz[a]anthracene-Induced Mouse Skin Carcinogenesis by Artemisia capillaries. Journal of Food Science 73(1), 16-20.

Nikravesh M.R.&Jalali M., 2004. The Effect of Camphor on the Male Mice Reproductive System Urology Journal. UNRC/IUA 1(4), 268-272.

Ragucci K.R., Trangmar P.R., Bigby J.G., Detar T.D., 2007. Camphor ingestion in a 10 year old male. The Southern Medical Journal 100(2), 204–207.

**3-Carene**




The bicyclic monoterpene 3-carene is commonly used as a fragrance component. Due to its fragrancy it is used, as many other monoterpenes, in perfumes, cosmetics, food additives and household products (Lastbom et al., 2003). It is a potent skin sensitizer. Inhalation of 3-carene has been shown to induce bronchoconstriction. In previous studies it has been found that there is a connection between skin sensitisation and increased lung reactivity with 3-carene. 3000 mg 3-carene/m³ caused bronchoconstriction in skin-sensitised guinea pig lungs (Lastbom et al., 2000). In the follow up, three years later, it was reported that 1900 mg 3-carene/m³ already caused the same effect on the lung. These results are not only important for people who are exposed to 3-carene by fragrant detergents or perfumes, but also for people working with industrial chemicals, cleaning products and people working in the wood industry. It occurs for instance in saw mills, particle-board plants or carpentry shops. Coniferous wood is rich of such monoterpenes (Lastbom et al., 2003). The following repeated contact with such substances may cause irritant and allergic contact dermatitis. Additionally their airborne exposure own large irritant properties (Lotti et al, 1998 op.cit. Erikkson&Wiklund, 2004). It was considered that the dermal exposure of monoterpenes like 3-carene could be relatively high for people working in the wood industry (Eriksson&Wiklund, 2004). Therefore the increasing skin irritation during work shift in a sawmill could be explained. Sawing fume is also irritaiting to eyes and mucous membranes. It causes chronic bronchitis, extrinyic allergic alveolitis and dust toxic syndrome (Demers et al., 1997 op.cit. Rosenberg et al., 2002). An exposure, ranged from 10 to 160 mg/m³, caused an increase in eye irritation symptoms during the work shift (Erikkson et al., 1996 op.cit. Rosenberg et al., 2002). Concentrations of 0.13

mg/m³ already showed slight inflammatory reactions of the upper airway (Dahlqvist et al., 1996 op.cit. Rosenberg et al., 2002). The International Agency for Research on Cancer (IARC) classified 1995 wood dust as a human carcinogen. The symptoms, including rhinitis, all occurred after long term exposition of wood dust (Rosenberg et al., 2002). For the acute exposition, the possible chemosensory irritative and odour perception effects from short-time exposure to relatively high levels of volatile organic compounds, emitted from oriented strand board panels, including 3-carene, was investigated. Healthy human volunteers were tested. The results showed that an acute exposure to oriental strand board emission for two hours did not cause any sensory irritation or plenary effects up to a volatile organic compound concentration of 9 mg/m³ (Gminski et al., 2010).

Apart from its irritation potential, 3-carene is, a potent inhibitor of AChE. This could be an interesting fact for the search of bioactive natural compounds for the treatment of Alzheimer's disease (Miyazawa&Yamafuji, 2005).

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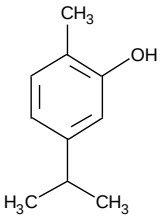
**Carvacrol**




The monoterpenic phenol carvacrol is an isomer of thymol. Both are widely used in folk medicine and aromatherapy (Lemos et al., 1990 op.cit. Azirak&Rencuzogullari, 2008). Carvacrol is an important and main component of many essential oils of plants including *Origanum* L. (Lamiaceae), *Satureja* L. (Lamiaceae), *Thymbra* L. (Lamiaceae) and *Thymus* L. (Lamiaceae) species. These have been used for years as source of flavour and food (Krimer et al., 1995 op.cit. Cho et al., 2011). It is responsible for the various biological activities of oregano like antitumour, antimutagenic, analgesic, anti-inflammatory and antispasmodic activities. Oregano water is orally used to treat gastrointestinal disorders like heartburn (Baser, 2008). The Council of Europe determined that carvacrol could be added to foodstuff at a level of 2 ppm in beverages and 25 ppm in candies. It has been generally considered as safe for consumption (De Vincenzi et al, 2004). Investigating its anti-obesity effects, a diet with 0.1% supplemented carvacrol did not have any harmful effects on mice (Cho et al., 2011). The median lethal oral dose of carvacrol has been reported to be 810 mg/kg in rats (Hagan et al., 1967 op.cit. Cho et al., 2011). Acute administration of higher doses of carvacrol significantly reduced plasma estradiol levels in female rats. In this context it might have prodepressive properties (Trabace et al., 2011). Because of its peripheral and central antinociceptive properties (Guimaraes et al., 2010), it is suggested that this monoterpene could be an interesting candidate for the development of natural drug treatment of painful conditions associated with inflammation. But the exact mechanism still has to be elucidated (Guimaraes et al., 2012). Another interesting quality is the protective effect of carvacrol on rat liver. Therefore, it may be used as alternative drug for the medicinal treatment of liver injury. It was also shown that it is not hepatotoxic (Uyanoglua et al.,

2008). Otherwise in vivo studies in rats show that carvacrol has a high genotoxic effect at the minimum concentration of 10 mg/kg. For this reason it is important to be careful, using carvacrol in food, cosmetics and in the drug industry (Azirak&Rencuzogullari, 2008).

There have to be further investigations about the future of carvacrol as a potential therapeutic agent in periodontal disease (Botelho et al., 2009) or as efficient anticancer agent (Jayakumar et al., 2011).

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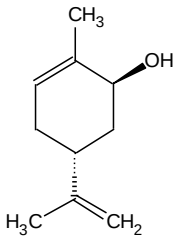
**Carveol**




The cyclic monoterpene alcohol carveol is a component of herbs like caraway, spearmint and dill. Monoterpene alcohols like carveol are ingredients in food, cosmetics and herbal medicinal products (Lin et al., 2006). There are no reports about the maximum skin level of carveol in dermal formulations. A default value of 0.02% is used. With this default level, the maximum daily exposure of 0.0005 mg/kg on the skin could be calculated for high end users. There is no data about acute toxicity (Bhatia et al., 2008). Tests of the repeated dose toxicity in rats show that a 1% carveol supplemented ration caused reduction in food intake and body weight. Whereas the liver weight and cholesterol level increased (Imaizumi et al., 1985 op.cit. Bhatia et al., 2008). In vivo studies show that (-)-carveol decrease the volume of distribution and increase the blood concentration of propofol.
(-)-Carveol is supposed to inhibit the metabolism of propofol by competitive metabolism and to enhance its anaesthetic effect. But
(-)-carveol itself could not induce anaesthetic effects.

(-)-Carveol

There are available data about the acute oral toxicity of (-)-carveol. At 5.0 g/kg eight out of ten rats died. Ataxia was observed in all tested doses. The oral LD50 was determined to be 3.0 g/kg. Dermal studies in rabbits showed that the dermal LD50 was 5.0 g/kg. Skin irritation reactions were observed (RIFM, 1972 op.cit. Bhatia et al., 2008). Another study showed that a 10% (-)-carveol in olive oil formulation caused irritation in guinea pigs (Karlberg et al., 1992 op.cit. Bhatia et al., 2008).

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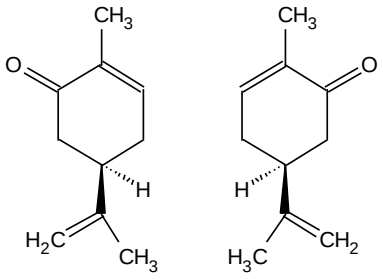
**Carvone**




(R) (S)

The monoterpene ketone (R)-(-)-carvone is the main active compound of spearmint oil. It is distilled from the leaves of *Mentha spicata* L. (Lamiaceae), a relative common mint (De Sousa et al., 2007). Its enantiomer (S)-(+) is a constituent of dill and caraway oils. The racemate is a content of ginger grass oil (Brocksom et al., 2005 op.cit. De Sousa et al., 2007). The enantiomers are used in cosmetics, pharmaceutical preparations and food industry. Because of the chiral recognition by receptors and enzymes it is important to know the central and toxicological effects of the two enantiomers. In vivo tests in mice show that (S)-(+)-carvone was less toxic than (R)-(-)-carvone. Both had the same depressant effects on the animals which were dull, calm and relaxed. The LD50 values in mice, of (S)-(+)-carvone was reported to be 484.2 mg/kg and of (R)-(-)-carvone 426.6 mg/kg. The tests show that (R)-(-)-carvone was slightly more antinociceptive than its enantiomer (De Sousa et al., 2007). This analgesic activity may be associated with the decreased peripheral nerve excitability. The most effective dose in rats was 200 mg/kg of (R)-(-)-carvone (Goncalves et al., 2008).

As main compound of the chemotype II of the Central and South American shrub *Lippia alba* (Mill.) N.E. Brown (Verbenaceae) (Hennebelle et al., 2008), (R)-(-)-carvone plays an important role in its anxiolytic activities (Hatano et al., 2012). Previous studies have already shown that carvone, an important ingredient of essential oils used in folk medicine and phytotherapy, has sedative or tranquilising properties. It acts as a potent depressor of the central nervous system. It was reported that the inhalation of the two enantiomers decreased

the locomotor activity in mice (Buchbauer et al., 2005 op.cit. Hatano et al., 2012).

Carvone in toothpaste is well known to cause urticarial reactions, resulting in cheilitis. Only few minutes after the contact with toothpaste the symptoms, like swelling and pruritus of the lips, occur. In this report the patient reacted with the same strength to both stereoisomers (Hansson et al., 2011).

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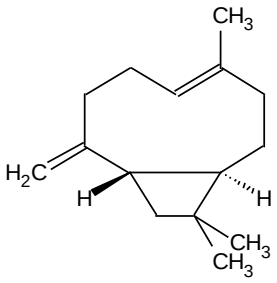
**β-Caryophyllene**




β-Caryophyllene, a volatile bicyclic sesquiterpene, has been detected in the essential oil of plants like *Salvia* L. (Lamiaceae), *Artemisia* L. (Asteraceae) and *Eugenia* L. (Myrtaceae), but also in several spices such as clove, oregano, thyme, pepper and cinnamon. In the middle of the last century an anti-emetic effect was investigated. Lately in vivo studies have shown its anti-inflammatory and ant-mutagenic properties, as well as the protection of gastric damages and oxidative stress. It is supposed to be local anaesthetic, anti-carcinogen and potent compound against acne (Di Sotto et al., 2008). Up to 5 g/kg of β-caryophyllene there was no sign of toxicity in testing the acute oral LD50 in animals. These experiments about the acute toxicity show that β-caryophyllene could be safely used for industrial and therapeutic purposes, although further studies are needed to confirm the LD50-values (Molina-Jasso et al., 2009). There have been also studies about the use of β-caryophyllene in the prevention of treatment of colitis. It was observed to be effective in suppressing the chronic diarrhoea and in ameliorating the gross rectal bleeding. But further studies are needed to appropriate the exact mechanism (Cho et al., 2007).

Due to its pleasant fragrance β-caryophyllene alcohol is commonly used in decorative cosmetics, fine fragrances, shampoos, soaps, cremes as well as in household cleaners and detergents. The maximum skin level in dermal formulations has not been reported. A default value of 0.02% is used therefore the maximum daily exposure on the skin is calculated to be 0.0005 mg/kg (Bhatia et al., 2008). In human skin subjects β-caryophyllene did not cause any skin irritation

or sensitization up to 4%. The acute dermal LD50 in rabbits was as well as the oral LD50 in rats 5g/kg. Because of its low toxicity it has received the “generally recognized as safe” (GRAS) status by the Flavor and Extract Manufactures Association (FEMA), 1997 (Cho et al., 2007). Otherwise the auto-oxidation products of common fragrance chemicals are often causes of allergic contact dermatitis. After air exposition of the unsaturated hydrocarbon β-caryophyllene, the sensitising caryophyllene oxide was found to be the main oxidation product. In guinea pig experiments it was shown to be an allergen of moderate strength. But it is a rather rare sensitiser compared to oxidized R-limonene and linalool (Skold et al., 2006).

As main component in plants, such as the North Brazilian *Lippia sidoides* Cham. (Verbenaceae), β-caryophyllene plays a role as topical antiseptic. The essential oil may be a promising source in the research for new phytopharmaceutical drugs, because of its efficacy and low toxicity. The acute oral LD50 level of the essential oil in mice was 3 g/kg. (Carvalho et al., 2003 op.cit. Fontenelle et al., 2007). But also as main component of the (sub)tropical *Piper aleyeanum* C.DC (Piperaceae), which is used as an immune modulator, analgesic, and antidepressant in folk medicine. More studies show that the plant is potent for the development of safe drugs with antinociceptive, anti-inflammatory and gastroprotective effects (Lima et al., 2012).

It is also determined that β-caryophyllene has an anxiolytic like activity as major compound of the Brazilian shrub *Spiranthera odoratissima* A.St.Hil (Rutaceae) (Galdino et al., 2012), which is also used in folk medicine as appetite stimulant, to treat stomach ache, head ache and hepatic dysfunction (Silva, 1998 op.cit. Galdino et al., 2012).

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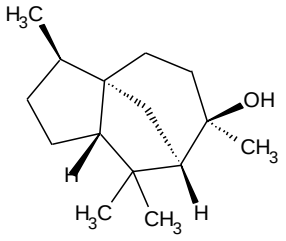
**Cedrol**




The sesquiterpene alcohol cedrol is a crystalline natural substance derived from the cedar wood oil of *Junipeus virginiana* L. (Cupressaceae). The essential oil has a weak aroma and has been commonly used as an ingredient of cosmetics, soaps, essences and others (Funk&Amir, 2000 op.cit. Dayawansaa et al., 2003). The essence was suggested to change the cardiovascular parameters. It causes an increase of parasympathetic activity and suppression of sympathic activity with alteration of respiratory functions. Collectively cedrol has a relaxant effect with a decrease of heart rate, of respiratory rate and of blood pressure. Further studies are needed to investigate the direct effects of cedrol on the cardiovascular system (Dayawansaa et al., 2003). Cedrol has also a sedative effect on the autonomic nervous system. The exact mechanism of sedation is not clear and needs further investigations (Yada et al., 2007). According to these results, cedrol may be a new agent for the therapy of essential hypertension and sleep apnea (Kara et al., 2003).

The maximum skin level of cedrol in dermal formulations has been reported to be 1.51%. The maximum daily exposure on the skin has been calculated to be 0.0331 mg/kg for high end users (IFRA, 2006 op.cit. Bhatia et al., 2008). After a single dermal application, the acute dermal LD50 of cedrol in rabbits was determined to be 5 g/kg (RIFM, 1973 op.cit. Bhatia et al., 2008).

Cedrol is also a subject in the investigations of natural agents with antiproliferative effects in human renal adenocarcinoma and amelanotic melanoma cells (Loizzo et al., 2008).

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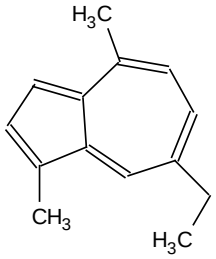
Yada Y., Sadachi H., Nagashima Y., Suzuki T., 2007. Overseas Survey of the Effect of Cedrol on the Autonomic Nervous System in Three Countries. Physiol Anthropol 26(3), 349–354.

**Chamazulene**




Chamazulene is a sesquiterpene hydrocarbon. It is one of the main compounds of *Chamomila* L. (Asteraceae), *Achillea* L. (Asteraceae) species and other important plants in the Mediterranean and Pacific North American areas. It is generally recognized as safe by consumers (Militello et al., 2011). Chamazulene has relevant industrial importance, possessing anti-inflammatory properties (Salamon, 2009 op.cit. Militello et al., 2011).

Chamomile is one of the most commonly consumed single ingredient herbal teas. It has been used traditionally for medicinal purposes. In folk medicine it is used because of its antiallergy, anxiolytic, carminative, diuretic, sedative, spasmolytic and vulnerary properties (McKay&Blumberg, 2006).

Chamomile tea has been reported to cause severe allergic reactions like contact dermatitis, from its dermal as well as oral use (Rodriguez-Serna et al., op.cit. McKayy&Blumberg, 2006). Compresses of chamomile tea caused angioedema which was associated with contact urticaria (Foti et al., 2000 op.cit. McKay&Blumberg, 2006). Additionally chamomile is able to increase the CNS depressant effects of other sedative drugs (Abebe, 2002).

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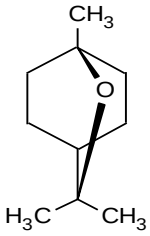
**1,8-Cineole**




The essential oil component and terpenoid oxide 1,8-cineole (Eucalyptol, Cajeputol (Santos and Rao, 2000)), used as medicament also in aromatherapy, shows antibacterial (Pattnaik et al., 1997 op.cit. Gali-Muhtasib et al., 2000) and insecticide (European Pharmacopoeia, 1971 op.cit. Gali-Muhtasib et al. 2000) properties. It is also used as skin penetration enhancer (Williams and Barry, 1991 op.cit. Gali-Muhtasib et al., 2000) and to treat renal and biliary calculus (Laude et al., 1994 op.cit. Gali-Muhtasib et al., 2000). Amongst others it is the component of the Middle Eastern plant *Salvia libanotica* Boiss. et Gaill (Lamiaceae), which is used as treatment of common diseases like abdominal pain and colds (Gali-Muhtasib et al. 2000). Otherwise the usage as spice to flavour meat is conventional (Morton, 1976 op.cit. Gali-Muhtasib et al. 2000). Local irritation was denoted for the favoured essential oil on rats, with "*inflammatory edema in the hind paw*" (Santos and Rao, 1997 op.cit. Gali-Muhtasib et al., 2000). The dosage which causes this edema is not mentioned. 1,8-cineole is the major component of many active plants, such as *Lippia alba* Mill. (Verbenaceae) and *Callistemon lanceolatus* Sm. (Myrtaceae). Regarding the high $LD_{50}$-values on mice: 11049.2 µL $kg^{-1}$ for *L. alba* and 14 626.3 µL $kg^{-1}$ for *C. lanceolatus*, either could be approved as save and non-mammalian toxic (Shukla et al., 2011).

Also *Rosmarinus officinalis* L. (Lamiaceae) a favoured folk-medicine-plant counts 1,8-cineole to one of the main constituents. It is investigated to be hepatoprotective in rats with an effective dose about 200mg/kg, while higher doses may arouse toxic effects (Sotelo-Félix et al., 2002). The $LD_{50}$-values of the commonly used oil of *R. officinialis* in mice are 1.000 mg/kg (i.p.) and 3.000 mg/kg (p.o.). Due

to those high values it is declared to be relatively safe to animals (Takaki et al., 2008).

The effective vasorelaxant essential oil of *Alpinia zerumbet* K. Schum (Zingiberaceae) contains as major component 1,8-cineole. For the oral acute toxicity of the oil of *A. zerumbet* in rats was reported a $LD_{50}$ about 2,5 g/kg (Pinho, 2002 op.cit. Pinto et al., 2009) and merely for 1,8-cineole to be lethal at a dose of 2.85 ±0.33 g/kg (Santos, 1999 op.cit. Pinto et al., 2009). Those high $LD_{50}$-values encourage the use of *A. zerumbet* as additional therapy of hypertension (Pinto et al., 2009).

The essential oil of *Ocimum gratissimum* L. (Lamiaceae) is commonly used in Brazil for gastrointestinal disorders (Matos, 2001 op.cit. Interaminenese et al., 2007) and has beside the hypotensive also antinociceptive properties which due to 1,8-cineole. The effective dose is 400 mg/kg in rats, which do not provoke any neuronal toxicity after oral administration (Santos and Rao, 2000). In this context the oral acute toxicity of 1,8-cineole in rats is announced to be greater than 2000 mg/kg (Santos and Rao, 1999 op.cit. Interaminenese et al., 2007)

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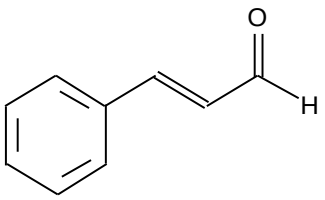
**Cinnamaldehyde**




The aromatic aldehyde cinnamaldehyde is the main compound of bark extract of *Cinnamomum verum* J.S. Presl. (Lauraceae) (Holley&Patel, 2005) and *Cinnamomum cassia* Nees. (Lauraceae). Cinnamon has been used in traditional herbal medicine for centuries. It is suggested that it is one of the oldest spices used in naturopathic medicine. In Ayurvedic and Chinese medicine it is traditionally used to treat diabetes (Modak et al., 2007 op.cit. Huang et al., 2011). Cinnamon has a vast use in food, cosmetics and pharmaceutical industries. Cinnamaldehyde is supposed to be the main allergen in cinnamon. Workers handling with food containing cinnamon have to be aware, even though an occupational contact allergy to cinnamon is rare. Due to its sensitizing properties, the use of cinnamon-oil in perfumeries is limited. (Ackermann et al., 2009). Basketter et al., described cinnamaldehyde as a moderate sensitizer (Basketter et al., 2005). It is known to induce nociception and mechanical allodynia (Rodriguesa et al., 2012). As constituent of fragrance mixes, cinnmaldehyde was the most likely cause of anaphylaxis reactions (Diba&Statham, 2003). Such mixtures of allergens are often found in fragrances and hair dyes. In a dermal study in mice, it was reported that there was a stronger challenge response to cinnamaldehyde as content of an allergen mixture than to cinnamaldehyde alone because of the synergistic elicitation of the ingredients (Bonefeld et al., 2011). The use of up to 3% cinnamaldehyde in dermal formulation, can induce skin irritation in humans. Anyway in some cosmetic products 10% cinnamaldehyde could be found (Bickers et al., 2005). Dermal studies in animals show that the acute dermal LD50 of cinnamaldehyde in rabbits is determined to be >1000 mg/kg. The dermal irritation symptoms in all of the rabbits were severe erythema, eschar and edema (RIFM, 1997 op.cit. Bickers et al., 2005). In oral studies an acute oral LD50 of

2200 mg/kg in rats and of 1200 mg/kg in guinea pigs have been reported (Jenner et al., 1964 op.cit. Bickers et al., 2005). In mice the acute oral toxicity was determined to be more than 2.500 mg/kg (Ministry of Health PR China, 2003 op.cit. Wei et al., 2011). Altogether, it could be concluded that cinnamaldehyde has a low order of toxicity by the oral and dermal route of exposure in acute studies. Based on the subchronic and chronic feeding studies, for instance in NTP, 2004, mortality, induced by cinnamaldehyde would not be expected at a dose of 2.5 mg/kg (Bickers et al., 2005).

It was reported that cinnammaldehyde significantly reduced the body weight and feed efficiency in obese mice. It is also able to improve insulin sensivity and to reduce plasma lipids. Due to these results, cinnamaldehyde could be a candidate for new therapeutic strategies for lipid disorders. Further investigations are needed to know the mechanism of cinnamaldehyde by moderating lipid metabolism (Huang et al., 2011).

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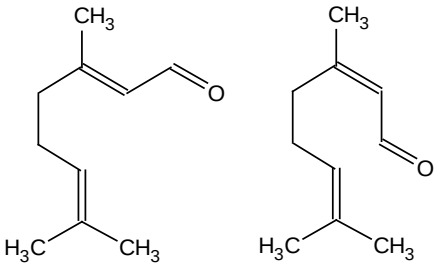
**Citral**




Geranial Neral

The acyclic monoterpene aldehyde citral has a characteristic lemon-like odour and a bittersweet taste. It is widely used as fragrance and flavour material. In essential oils with strong lemon odours (Heydorn et al., 2003), citral is the main two-compound mixture in the proportion 2:1 (Rauber er al., 2005), for instance lemongrass *Cymbopogon citrates* DC.Stapf. (Poaceae), *Melissa officinalis* L. (Lamiaceae) *Verbena officinalis* L. (Verbenaceae) (Dudai et al., 2005) and *Litsea cubeba* Pers. Oil (Lauraceae). In tropical countries lemongrass is widely used as treatment of hypertension, gastrointestinal disorders, anxiety and epilepsy (Quintans-Júnior et al., 2008). It is popularly used in Brazil, due to its depressant action on the central nervous system. Lemongrass could be an interesting source of new drugs for the treatment of central disturbances such as epilepsy (Silva et al., 2010). It contains a high concentrations of citral. Lemongrass oil is one of the most frequent sensitizers (Uter et al., 2010).

Citrus fruits contain aliphatic aldehydes such as citral. The essential oils of citrus fruits is expected to be used to flavour food and beverages as well as soaps, perfumery and household products (Matsuura et al. 2006).

Citral has been accorded GRAS – generally recognized as safe – status. It has been approved by the Food and Drug Administration FDA for use in foods. Due to its allergenic potential the International Fragrance Association IFRA has determined 1980, a standard on the use of citral in fragrance formulations. It is suspected to cause allergic contact dermatitis and is associated with cutaneous anaphylaxis and prostatic hyperplasia (Lalko&Api, 2008). Tests in guinea pigs and

mice showed that citral is a weak to moderate contact sensitizer. The highest chronic dose that induces sensitization in humans was reported to be 1400 µg/cm² (Basketter et al., 2005).

Citral used in lip balm has been reported to cause cheilitis (Hindle et al., 2007). Heydorn et al., issued that citral could be described as an allergen as well as an irritant (Heydorn et al., 2003). It has been reported that the autoxidation product of the isomer geranial found to be a strong sensitizer (Hagvall et al., 2011).

Apart from its irritation potential, citral as a compound of *Aloysia triphylla* Paláu (Verbenaceae), plays an important role in the alternative treatment of menstrual colic, mainly to avoid the side effects of NSAIDs like the aggressive gastric injury. In this context citral has been reported to have spasmolytic and anti-inflammatory properties in rats (Ponce-Monter et al., 2010).

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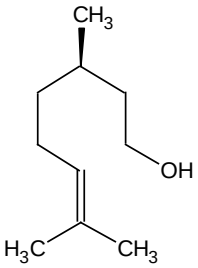
**Citronellol**




The acyclic monoterpene alcohol citronellol is the main compound of essential oils of many aromatic plants, such as *Cymbopogon winteriaus* Jowitt (Poaceae) (Rao et al., 2004). It occurs naturally as two isomeric optical forms, the R-(+)- and the S-(-)-isomer, which is much less common (Hierro et al., 2004 op.cit. de Sousa et al., 2006). Medicinal plants containing citronellol are widely used. Citronellol was reported to have a vasorelaxant activity and to lower blood pressure. Due to those cardioprotective effects, it could be a potent substance for antihypertensive treatment (Bastos et al., 2009).

With 20%, citronellol is one of the most frequently used fragrances in cosmetic products and other toiletries. It could be also found in detergents such as washing-up liquids and multi-purpose cleaners. Those products are used by a large part of the population (Yazar et al., 2010). Relating to induced contact dermatitis, citronellol has a minor importance, compared with other ingredients (Krautheim et al., 2010).

There is no report about the maximum skin level from (R)-(+)-citronellol in dermal formulations. A default value of 0.02% is used. With this value the maximum daily exposure on the skin was calculated to be 0.0005 mg/kg for high end users of such products. There are no available data about the toxicity of (R)-(+)-citronellol (Lapczynski et al., 2008). (-)-Citronellol was classified as a mild-irritant (RIFM, 1973 op.cit. Lapczynski et al., 2008). At concentrations higher than 0.5%, irritation reactions could be observed in albino guinea pigs (RIFM, 1993 op.cit. Lapczynski et al., 2008). The acute oral toxicity of (±)-citronellol in rats was determined to be 3.45 g/kg. At a dose of 5.0 g/kg all animals died. The acute dermal LD50 in rabbits was reported to be at 2.65 g/kg. All animals died at a dose of 5.0 g/kg.

(RIFM, 1973 op.cit. Lapczynski et al., 2008). The intramuscular LD50 in mice was calculated to be 4.0 g/kg (Northover&Verghese, 1962 op.cit. Lapczynski et al., 2008), while the subcutaneous LD50 value in mice was reported to be 0.88 g/kg ± 0.05 (Nozawa, 1952 op.cit., Lapczynski et al., 2008). In various pain models it could be shown that citronellol has effective analgesic and anti-inflammatory properties. The mechanism of citronellol on nociception is not clear. Therefore, further investigations are necessary (Brito et al., 2012). Citronellol was reported to have anticonvulsant properties. In conclusion, it could be suggested to act as a neuroprotective drug (De Sousa et al., 2006).

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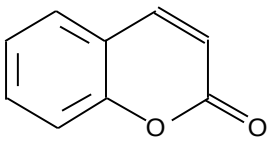
**Coumarin**




The heterocyclic organic compound coumarin is naturally found in various plant species like *Coumarona odorata* Aubl. (Fabaceae) (Feuer, 1974 op.cit. Pereira et al., 2009), which have a pleasant spicy odour of fresh hay, woodruff, or vanilla (Pereira et al., 2009). Coumarin is widely used as fragrance enhancer and stabilizer. It has also clinical administrations (Lake et al., 1994 op.cit., Born et al., 2000). For instance up to 0.1 – 5g daily are administered to treat kidney and skin cancers (Sharifi et al., 1993 op.cit. Born et al., 2000).

Coumarin is a content in foodstuffs like cinnamon, peppermint and green tea. It was found to be carcinogenic (Lake, 1999 op.cit. Born et al., 2000). Coumarin in generally recognized to be a liver toxicant in rats. More than 5000 ppm resulted in an increased incidence of liver cell tumours in rats (Carlton et al., 1996 op.cit. Born et al., 2000). In vivo studies in rats showed that a dose of 200 mg/kg increased the plasma levels of liver parameters and necrosis of liver cells (Kienhuis et al., 2006). Mentionable is that coumarin from cinnamon tea may pose a higher risk compared with coumarin in tablets or in meals (Abraham et al., 2011).

The European Food Safety Authority EFSA determined a tolerable daily intake TDI of 0.1 mg coumarin/kg bw./ day (EFSA, 2004). Current investigations showed its antidiabetic activities in type 2 diabetes (Rajarajeswari&Pari, 2011) and the possibility of the therapeutic use of coumarins in neurodegenerative disease (Pereira et al., 2009). It was also reported to reduce the extension of lesions in acute colitis in rats (Luchini et al., 2008) and to play a positive role in the regulation of hyperthyroidism in rats, at a safe dose below 50 mg/kg (Panda&Kar, 2007).

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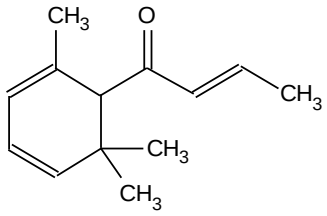
## Damascenone




Damascenone is one of a series of structurally related compounds, the “rose ketones”. It is essential to the quality of rose oil. The powerful odorant was first isolated from the essential oil of *Rosa damascena* Mill. (Rosaceae) (Williams, 2002 op.cit. Sefton et al., 2011). Damascenone is a natural product in various sources, but it occurs more commonly in a wide variety of processed food products and beverages. As an important component of perfumes, it is an indispensable ingredient in the international perfume industry (Sefton et al., 2011). It is used in many fragrance compounds, such as decorative cosmetics, fine fragrances, shampoos, toilet soaps as well as detergents and household cleaners. The maximum skin level of damascenone in dermal formulations has been reported to be 0.02%. The maximum daily exposure on the skin has been calculated to be 0.002 mg/kg/day for high end users of these products (IFRA, 2002 op.cit. Lapczynski et al., 2008). The acute oral toxicity in rats was determined with a LD50 value greater than 2.0 g/kg (RIFM, 1986 op.cit. Lapczynski et al., 2008). Dermal tests in rabbits resulted with an acute dermal LD50 greater than 2.0 g/kg. Damascenone was classified as a mild sensitizer (RIFM, 1979 op.cit. Lapczynski et al., 2008). Based on the results of a local lymph node assay in mice, damascenone was classified as a moderate sensitizer (RIFM, 2002 op.cit. Lapczynski et al., 2008).

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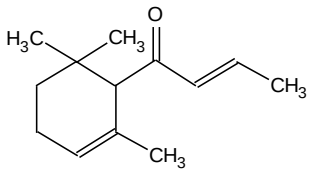
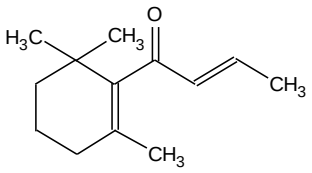
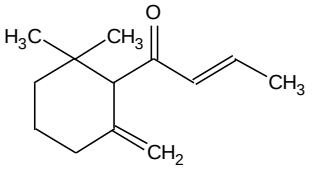
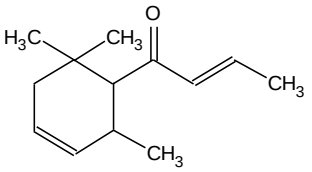
**Damascone**

α   β

γ   δ

Damascone and all its isomers are fragrance ingredients, that are used as compounds in decorative cosmetics, fine fragrances, shampoos, toilet soaps as well as non-cosmetic products, for instance household cleaners and detergents (Lapczynski et al, 2008).

The maximum skin level of α-damascone in dermal formulations was reported to be 0.07%. The calculated maximum daily exposure on the skin was 0.0031 mg/kg for high end users (IFRA, 2003 op.cit. Lapczynski et al., 2008). The acute oral LD50 in rats was reported to be 1.67 g/kg. At a dermal application of 4.64 g/kg on rabbits, all animals died. The acute dermal LD50 value was determined to be 2.9 g/kg. α-Damascone was not considered to be a primary irritant (RIFM, 1979 op.cit. Lapczynski et al., 2008). Whereas the results of the local lymph node assay in mice showed that it is a skin sensitizer (RIFM, 2001 op.cit. Lapczynski et al., 2008).

β-Damascone is a compound of *Rosa damascena* Mill. (Rosaceae) (Huang et al., 2009). It is used in tobacco, wine and whisky products (Boido et al., 2003). For both isomers of β-damascone the oral LD50 in rats was reported to be 2920 mg/kg (Adams et al., 1996 op.cit. Kaufman et al., 2011). The maximum skin level of both isomers in dermal formulations was reported to be 0.02%. The maximum daily exposure was calculated to be 0.0018 mg/kg for high end users (IFRA, 2002 op.cit. Lapczynski et al., 2008, Lalko et al., 2007). Additionally, there are reports about the toxicity of the two separated isomers. The acute oral LD50 of trans-β-damascone in rats was reported to be

greater than 2 g/kg (RIFM, 1986 op.cit. Lapczynski et al., 2008). Dermal studies in rabbits resulted in a dermal LD50 greater than 2 g/kg. In the dermal studies trans-β-damascone was classified as a mild sensitizer (RIFM, 1979 op.cit. Lapczynski et al., 2008). Concerning the results of the local lymph node assay in mice, trans-β-damascone was considered to be a sensitizer (RIFM, 2001 op.cit. Lapczynski et al., 2008). In ten out of fifty guinea pigs slight to moderate erythema was observed after dermal application of a 5% preparation of cis-β-damascone. These reactions were not irritant but they were considered to be sensitization reactions (RIFM 1992, op.cit. Lalko et al., 2007).

In dermal formulations the maximum skin level of γ-damascone was reported to be 0.02%. Calculating the maximum daily exposure on the skin, the result was 0.005 mg/kg for high end users (IFRA, 2002 op.cit. Lalko et al., 2007). The acute oral toxicity in rats was reported to be greater than 2.0 g/kg. Side reactons such as piloerection and perinasal staining were observed. At a dose of 5.0 g/kg five out of ten animals died. The acute dermal LD50 value was either reported to be greater than 2.0 g/kg. γ-Damascone was considered to be an irritant (RIFM, 1987 op.cit. Lalko et al., 2007). After a local lymph node assay in mice, it was classified as a weak sensitizer (RIFM, 2001 op.cit. Lalko et al., 2007).

For δ-damascone the maximum skin level in skin formulations was reported to be 0.02%. The calculated maximum daily exposure on the skin was 0.0024 mg/kg (IFRA, 2002, op.cit. Lalko et al., 2007). In acute toxicity tests the results showed an acute oral LD50 of 1.8 g/kg in mice. Systemic effects, such as lethargy, urinary incontinence, salivation, hyperactivity, tremors and ataxia were observed (RIFM, 1978 op.cit. Lalko et al., 2007).

Testing the acute oral toxicity of trans,trans-δ-damascone in mice, all animals died at a dose of 1.9 g/kg. Clinical signs, such as decreased activity, salivation, anorexia, ataxia, tremors, urinary incontinence and decreased respiration were observed in all doses given to the mice.

The acute oral LD50 was reported to be 1.6 g/kg (RIFM, 1979 op.cit. Lapczynski et al., 2007).

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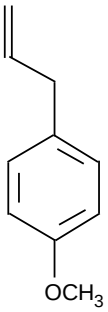
**Estragole**




The alkenylbenzene estragole is used as a flavouring substance and food additive in baked goods, non-alcoholic beverages and candy (SCF, 2001 op.cit. Jeurissen et al., 2007). It occurs naturally in *Artemisia dracunculus* L. (Asteraceae), *Ocimum basilicum* L. (Lamiaceae), *Foeniculum vulgare* Mill. (Apiaceae), *Pimpinella anisum* L. (Apiaceae) and *Illicium verum* Hook.f. (Schisandraceae). Data show that estragole is genotoxic and carcinogen in experimental animals after chronic exposure of after repeated doses. Due to carcinogenicity studies on rats and mice, a limit of 0.05 mg/kg is recommended in food (De Vincenzi et al, 2000).

The Scientific Commitee on Food of the European Union SCF determined that estragole is genotoxic and carcinogenic. The SCF estimated the average intake of estragole to be 4.3 mg/day, corresponding to 0.07 mg/kg bw/day. (SCF, 2001 op.cit. Jeurissen et al.,2007). Otherwise the Expert Panel of the Flavour and Extract Manufactures' Association of the United States (FEMA) defined that the exposure of estragole from food does not pose a significant cancer risk. The FEMA estimated the mean daily intake for estragole to be less than 0.6 mg/kg/day (Smith et al., 2002). 2005 the Committee of Experts on Flavouring Substances estimated the total intake from all sources to be 1 mg/kg/day. But the exposure in infants could be higher (Martins et al., 2012). The estimated exposure in infants just from fennel herbal tea could be up to 51 µg/kg/day (Raffo et al., 2011). Fennel herbal tea is traditionally used for the treatment of gastrointestinal disorders and symptoms of the respiratory tract (EMEA, 2008 op.cit. Raffo et al., 2001).

The results of a 3-month toxicity study of estragole in male rats caused cancer of the liver, after an oral application of 600 mg/kg (NTP, 2010 op.cit. Martins et al., 2012). The daily dose rate in
mg/kg body weight/day that is sufficient to induce tumours in half of the tested animals, TD50, was reported to be 51.8 mg/kg in mice (Zhou et al., 2007). As main compound of *Croton zehntneri* Pax et Hoff. (Euphorbiaceae), an aromatic plant native to Brazil, estragole may play a role in its antinociceptive, analgesic effects. *C. zehnteri* is often used in folk medicine for the treatment of gastrointestinal problems. The oral LD50 of the essential oil was indicated to be greater than 2.5 g/kg (Oliveira et al., 2001). In this context, estragole was reported to cause hypotension and bradycardia in rats in higher doses, between 10 and 20 mg/kg (De Siqueira et al., 2006). Estragole is also the main compound of the Brazilian plant *Ocimum selloi* Benth (Lamiaceae), which owns a vast use in folk medicine. At doses greater than 1500 mg/kg of the essential oil, symptoms like ataxia, lethargy and death occurred in mice. The LD50 of the essential oil of *O. selloi* is 1250 mg/kg (De Paula et al., 2003), the same as the LD50 value for estragole (Jenner et al., 1964 op.cit. De Paula et al., 2003). As compound of *Artemisia dracunculus*, estragole plays arole in its antidiabetic, blood sugar lowering effect (Weinoehrl et al., 2011). The essential oil of *A. dracunculus* was shown to be toxic in rodents. It is normally used as spice and as tea, therefore the maximum daily dose is reported to be below 10 g/day, which corresponds to minor amounts of estragole (Obolskiy et al., 2001).

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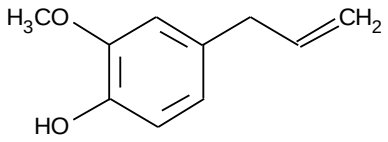
**Eugenol**




Eugenol is a phenylpropene and is the main compound of clove oil, nutmeg, cinnamon, basil and bay leaf. It is a common flavour and fragrance ingredient (Doty et al., 1978 op.cit. Wise et al., 2012). It could be found in food items, drinks and household materials (Nibret&Wink, 2010). It serves as stimulus either as an odourant or as masker of another odourant (Wise et al., 2012). It is widely used as a spice because of its strong odour. Due to its detergent-like effect it is used as dental antiseptic (Tai et al., 2002). Eugenol is generally regarded as safe by the Food and Agricultural Oragnization of the United Nations because of its nonmutagenic and noncarcinogenic properties. The acceptable daily intake was reported to be up to 2.5 mg/kg in humans (FAO, 1982 op.cit. Gülcin, 2011). Eugenol is suggested to induce relaxant and antispasmodic effects. It shows a low acute toxicity (Limaa et al., 2011). It is suggested to have an acute oral LD50 greater than 2.000 mg/kg (OECD, 2001 opi.cit. Santin et al., 2011). On the search of an anti-gastric ulcer agent with less side effects, the essential oil of *Syzygium aromaticum* (L.) Merrill & Perry (Myrtaceae), with eugenol as main compound could be an interesting candidate. Clove oil and eugenol are reported to provide gastroprotective activity (Santin et al., 2011). As main compound of *Ocimum gratissimum* L. (Lamiaceae), eugenol plays a role in its cardiovascular effects in rats. The essential oil is used as hypotensive agent in folk medicine (Lahlou et al., 2004).

In a study about the elicitation of contact dermatitis by eugenol, it was classified to be a weak sensitizer. Using a lower concentration of eugenol of 0.5%, no dermatitis was elicited (Svedman et al., 2012).

In various pain models eugenol shows antinociceptive properties (Park et al., 2011). At a daily dose of 40 mg/kg of eugenol, no signs of ill effects occurred in tested animals. Therefore, eugenol could be an

interesting candidate for the treatment of neuropathic pain (Lionnet et al., 2010).

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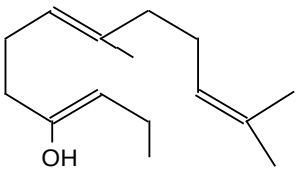
**Farnesol**




Farnesol, an isoprenoid alcohol is naturally occurring in various plants like rose, chamomile, lavender and lilac (He et al., 1997 op.cit. Horn et al., 2005). It is a fragrance ingredient used in decorative cosmetics, fine fragrances, shampoos, toilet soaps as well as non-cosmetic products (Lapczynski et al., 2008).

It has been reported to be carcinogen in mice (Balaji&Chempakam, 2010). A daily oral administration (28 days) of farnesol at doses up to 1000 mg/kg/day was minimally toxic to rats (Horn et al., 2005). The acute oral LD50 in albino mice was reported to be greater than 20 ml/kg. Signs of toxicity were decreased motor activity, coordination disturbance, piloerection and diarrhoea (RIFM, 1976 op.cit. Lapczynski et al., 2008). In rats the acute oral LD50 was determined to be greater than 5.0 g/kg (RIFM, 1974 op.cit. Lapczynski et al, 2008). The intraperitoneal LD50 value in mice was calculated to be 0.327 g/kg (RIFM 1981 op.cit. Lapczynski et al., 2008). Farnesol has the potential to induce contact allergic dermatitis. It is listed on the European Unions' 26 fragrance allergens that must be named on cosmetic detergents and product labels (Buckley, 2007). The acute dermal LD50 was reported to be greater than 0.015 g/kg in rats (RIFM, 1983 op.cit. Lapczynski et al., 2008). A concentration of 100% caused irritation in rabbits (RIFM, 1995 op.cit. Lapczynski et al., 2008). In conclusion farnesol should be regarded as one of the most important fragrance allergens (Schnuch et al., 2004).

Studies show that farnesol significantly reduced serum triglycerides in rats (Duncan&Archer, 2008).

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Horna T.L., Longa L., Cwika M.J., Morrissey R.L., Kapetanovic I.M., McCormicka D.L., 2005. Modulation of hepatic and renal drug metabolizing enzyme activities in rats by subchronic administration of farnesol. Chemico-Biological Interactions 152, 79–99.

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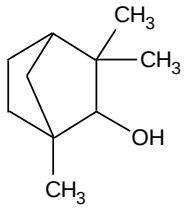
Schnuch A., Uter W., Geier J., Lessmann H., Frosch P.J., 2004. Contact allergy to farnesol in 2021 consecutively patch tested patients. Results of the IVDK. Contact Dermatitis 50, 117–121.

## Fenchyl alcohol




As fragrance ingredient, fenchyl alcohol is used in decorative cosmetics, fine fragrances, shampoos and other toiletries. It could be also found in household cleaners and detergents. The maximum skin level of fenchyl alcohol in dermal formulations was reported to be 0.06%. the maximum daily exposure on the skin was calculated to be 0.0013 mg/kg for high end users of such products (IFRA, 2004 op.cit. Bhatia et al., 2008).

In acute oral toxicity tests in rats all animals died at doses between 3.2 g/kg and 5.0 g/kg. Clinical signs, such as lethargy, ataxia, tearing, comatose and flaccid were observed in all dosed given to the animals. Irritation studies in guinea pigs showed moderate erythema and edema (RIFM, 1976 op.cit. Bhatia et al., 2008).

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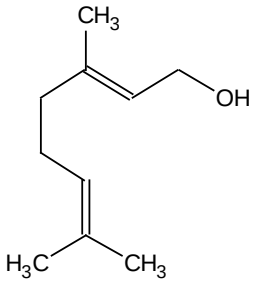
**Geraniol**




Geraniol is a widely used fragrance terpene. It occurs naturally in high concentrations in the essential oils of rose, citronella and palmarosa. It is one of the most common fragrance ingredients in consumer products on the European market (Rastogi et al., 2008 op.cit Hagvall et al., 2012). It was found to have one of the highest maximum daily exposures from different sources (Belsito et al., 2008). The essential oil of geraniol is colourless and owns a scent of roses (De Groot et al., 1988 op.cit. Mineoka et al., 2007). Geraniol is widely used in perfumes. Additionally it is listed in the Euopean Unions' 26 fragrance allergens that must be named on cosmetic and detergents product labels. There have been many reports about allergic contact dermatitis of geraniol (Buckley, 2007) and that patient developed cheilitis on exposure to certain foods. Food additives should be considered as a possible cause of allergic contact dermatitis (Mineoka et al., 2007).

The exposure of geraniol in workplace of masseurs caused severe hand eczema that developed in some cases into chronic eczema (Hagvall et al., 2012). At concentrations of 50% or 100% irritation was observed in guinea pigs (RIFM, 1992 op.cit. Lapczynski et al., 2008). At 100% of geraniol eye irritation was observed in rabbits (RIFM, 2000 op.cit. Lapczynski et al., 2008). The acute LD50 was reported to be greater than 5g/kg in rabbits (RIFM 1972 op.cit. Lapczynski et al., 2008). Subcutaneous studies in mice resulted with a LD50 of 1.1 g/kg (Nozawa, 1952 op.cit. Lapczynski et al., 2008). It is considered to be a weak allergen (Schnuch et al., 2002). The sensitizing potency of geraniol increases by air exposure and its formation to an allergenic oxidation product. Experiments show that geraniol hydroperoxide

owns the main allergenic activity after autooxidation of geraniol. It has a moderate sensitizing capacity (Hagvall et al., 2007).

Geraniol is not only used in cosmetics, but also in sweet foods such as ice cream and candy (Murphy&White, 2003). Studies about the acute oral toxicity resulted with a LD50 of 3.6 g/kg in rats. Clinical signs such as depression, wet fur and coma were observed (Bar&Griepentrog, 1967 op.cit. Lapczynski et al., 2008).

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Belsito D., Bickers D., Bruze M., Calow P., Greim H., Hanifin J.M., Rogers A.E., Saurat J.H., Sipes I.G., Tagami H., 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem Toxicol 46 (11), 1–71.

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Hagvall L., Bäcktorp C., Svensson S., Nyman G., Börje A., Karlberg A-T., 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.

Hagvall L., Karlberg A-T., Christensson J.B., 2012. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. Contact Dermatitis 67, 20–27.

Lapczynski A., Bhatia S.P., Foxenberg R.J., Letizia C.S., Api A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46, 160–170.

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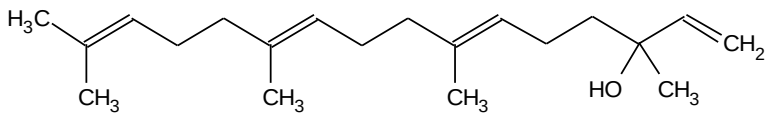
Tamagawa-Mineoka R., Katoh N., Kishimoto S., 2007. Allergic contact cheilitis due to geraniol in food. Contact Dermatitis 56, 242–243.

## Geranyl linalool




Geranyl linalool is widely used as fragrance ingredient in cosmetic preparations as well as in non-cosmetic products. From its use in dermal formulations, the maximum skin level has been reported to be 0.008%. The maximum daily exposure was calculated to be
0.001 mg/kg for high end users of such dermal products (IFRA, 2004, op.cit., Lapczynski et al., 2008). Testing the acute oral toxicity in albino mice, clinical symptoms like oily anogential area, brown staining on the nose/mouth and diarrhoea occurred. The LD50 value in albino mice was reported to be greater than 5.0 g/kg (RIFM, 1982 op.cit. Lapczynski et al., 2008). Other studies about the acute oral toxicity in mice reported about a LD50 of 14.63 g/kg ± 0.849 g/kg (RIFM, 1967 op.cit. Lapczynski et al., 2008). The intraperitoneal LD50 value in mice was calculated to be greater than 2.00 g/kg (RIFM, 1978 op.cit. Lapczynski et al., 2008). In irritation tests in rabbits, primary irritation with slight to moderate edema and erythema were observed (RIFM, 1988 op.cit. Lapczynski et al., 2008).

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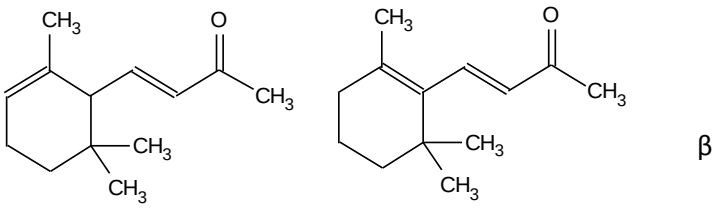
Lapczynski A., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on geranyl linalool. Food and Chemical Toxicology 46, 176–178.

**Ionone**

α  β

Ionone and its isomers are cyclic isoprenoids (Liu et al., 2008). As fragrance ingredients they are used in many fragrance compounds like various toiletries, cosmetic products and fine fragrances as well as in house-hold cleaners and detergents. The use of ionone in dermal formulations resulted in a maximum skin level of 1.57% in dermal formulations. The calculated maximum daily exposure for high end users of such products resulted in a value of 0.08 mg/kg (IFRA, 2002 op.cit. Lalko et al., 2007). The acute oral toxicity tests in rats resulted with a LD50 of 4.6 g/kg. Toxic signs like depression and tremors were observed (Bar&Griepentrog, 1967 op.cit. Lalko et al., 2007). The acute oral LD50 in mice was reported to be 10 g/kg. Clinical signs, such as stress, laboured breathing, uncoordinated movement, hypothermia, lacrimation and bloated stomach occurred (RIFM, 1980 op.cit. Lalko et al., 2007). The intraperitoneal LD50 in mice was calculated to be 2.3 g/kg (Sporn et al., 1963 op.cit. Lalko et al., 2007). General toxic signs, after a subcutaneous application in albino mice, were extreme excitement, convulsions, respiratory depression and death. The subcutaneous LD50 was determined to be 2.6 g/kg (Wenzel&Ross, 1957 op.cit. Lalko et al., 2007). Tests in rabbits showed that ionone is an irritant (RIFM, 1979 op.cit. Lalko et al., 2007). Also in rats very slight erythema and edema were observed in all concentrations (RIFM, 1981 op.cit. Lalko et al., 2007). Some studies also report about the separate isomers of ionone:

The maximum skin level of α-ionone in formulations for the skin was reported to be 1.00%. Calculating the maximum daily exposure on the skin, the result was 0.05 mg/kg/day for high end users of these products (IFRA, 2002 op.cit. Lalko et al., 2007). Acute oral studies in

mice resulted with a LD50 of 7.0 g/kg (RIFM, 1980 op.cit. Lalko et al., 2007). The chronic LD50 value in rats was considered to be 10 mg/kg/day (RIFM 1983 op.cit. Lalko et al., 2007). After an intraperitoneal application of 1.8 g/kg of α-ionone in mice, all animals died. Clinical signs such as lethargy, piloerection and hunched position were observed. The maximum tolerated dose was estimated to be 1.2 g/kg (RIFM, 2006 op.cit. Lalko et al., 2007). In skin irritation studies in guinea pigs as well as in humans, α-ionone was found to be a moderate irritant, while in albino rats it produced severe irritation reactions (Motoyoshi et al, 1979 op.cit. Lalko et al., 2007).

The use of β-ionone in dermal preparations resulted in a maximum skin level of 2.34%. The maximum daily exposure of such products on the skin was calculated to be 0.11 mg/kg for high end users (IFRA, 2002 op.cit. Lalko et al., 2008). The acute oral LD50 value of β-ionone in mice was reported to be 2.0 g/kg ±3.2 g/kg. In rats the acute oral LD50 varied between 7.12 g/kg within a 24-h period and 3.29 g/kg within a 10 day period. Intraperitoneal studies in mice resulted with a LD50 value of 1.33 g/kg within a 24 h period and 0.7 g/kg within a 10 day period (RIFM, 1980 op.cit. Lalko et al., 2007).

Testing the anticancer activity of β-ionone, rats were fed with doses up to 36.0 mmol/kg. No toxicity was observed during the experiment, while tumour incidence was decreased. β-Ionone was shown to be a potent, side-effect-free chemopreventive agent in rats. Obviously there are no data about its effect in humans (Liu et al., 2008).

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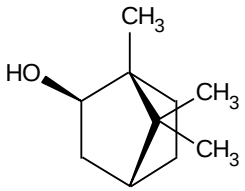
Lalko J., Lapczynski A., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on β-ionone. Food Chem Toxicol 45, 241–247.

Lalko J., Lapczynski A., Politano V.T., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on α-ionone. Food Chem Toxicol 45, 235–240.

Liu J-R., Sun X-R., Dong H-W., Sun C-H., Sun W-G., Chen B-G., Song Y-Q., Yang B-F., 2008. β-ionone suppresses mammary carcinogenesis, proliferative activity and induces apoptosis in the mammary gland of the Sprague-Dawley rat. Int. J. Cancer. 122, 2689–2698.

**Isoborneol**

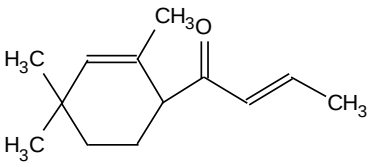



The IFRA reported 2006 that the maximum skin level of isoborneol in dermal formulations is 0.34%. The maximum daily exposure was calculated to be 0.0140 mg/kg (Bhatia et al., 2008). Toxicity studies identified the acute oral LD50 of 5.2 g/kg in rats, while the acute dermal LD50 value was about 5 g/kg in rabbits. Adverse reactions like lethargy, ptosis, blood on nose, pilo-erection and diarrhoea were reported. The results of the necropsy showed abnormalities in lungs, liver, kidney intestine and stomach (RIFM, 1977 op.cit. Bhatia et al., 2008).

References:

Bhatia S.P., Mc Ginty D., Letizia C.S., Api A.M., 2008. Fragrance material review on isoborneol. Food and Chemical Toxicology 46, 182–184.

## Isodamascone




As fragrance ingredient, isodamascone is used in may fragrance compounds. It could be found in cosmetic products, shampoos and toiletries, as well as detergents and household cleaners. Relating to the maximum skin level, the IFRA reported a concentration of 0.02% in dermal formulations. The calculated maximum daily exposure on the skin for high end users of such products was reported to be 0.005 mg/kg/day (IFRA, 2002 op.cit. Lalko et al., 2007). There are reports about the separate isomer α-isodamascone, that the calculated maximum daily exposure on the skin was 0.0010 mg/kg/day for high end users of dermal products (IFRA, 2002 op.cit. Lapczynski et al., 2007).

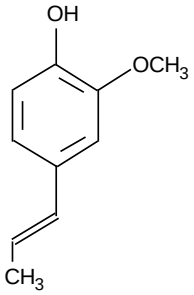
In a 100% application of isodamascone in guinea pigs, slight to moderate erythema was observed. After an intradermal injection of 2.5% and 5% of isodamascone in water, severe erythema with black discoloration at the injection site occurred in the guinea pigs' skin. Therefore the intradermal induction concentration was determined to be 1% (RIFM, 1991 op.cit. Lalko et al., 2007). Testing the acute oral toxicity in rats, clinical signs included decreased activity, irritability, abnormal gate, diarrhoea, salivation and piloerection occurred at all doses. At doses between 7.94 and 12.6 g/kg all animals died. The acute oral LD50 value was determined to be 6.3 g/kg (RIFM, 1979 op.cit. Lalko et al., 2007).

References:

Lalko J., Lapczynski A., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on isodamascone. Food and Chemical Toxicology 45, 258–262.

Lapczynski A., Lalko J., McGinty D., Bhatia S.P., Letizia C.S., Api A.M., 2007. Fragrance material review on α-isodamascone. Food and Chemical Toxicology 45, 267–271.

**Isoeugenol**




Isoegenol is used in many kinds of cosmetics. It is a fragrance compound with a spicy, carnation-like scent (Schnuch et al., 2004). It is an important fragrance sensitizer (Johansen et al., 2003), which is well-known to be a moderate sensitizer to humans. Sensitizing reactions have also been reported in mice and guinea pigs (Tanaka et al., 2004). Due to this sensitizing properties, isoeugenol was recommended from the fragrance industry not to exceed the concentration of 0.02% (200 ppm) in finished cosmetic products (White et al., 1999 op.cit. Rastogi et al., 2007). But the mean concentration of isoeugenol in fine fragrances was reported to be 0.17% (Johansen et al., 1996 op.cit. Rastogi et al., 2007). This explains why – despite this recommendation – there is an increase of allergic reactions to isoeugenol (White et al., 2004). Another explanation could be an increase in the frequency of use of products containing the potent allergen, like perfumes or deodorants.

As main compound of *Evernia prunastri* L.Ach (Parmeliaceae) (oak moss absolute), isoeugenol plays a role in the allergic reactions of this widely used fragrance (Buckley, 2007).

References:

Buckley D.A., 2007. Fragrance ingredient labelling in products on sale in the U.K. British Journal of Dermatology 157, 295–300.

Johansen J.D., Andersen K.E., Svedman C., Bruze M., Bernard G., Giménez-Arnau E., Rastogi S.C., Lepoittevin J.P., Menné T., 2003. Chloroatranol an extremely potent allergen hidden in perfumes–a doseresponse elicitation study. Contact Dermatitis 49, 180–184.

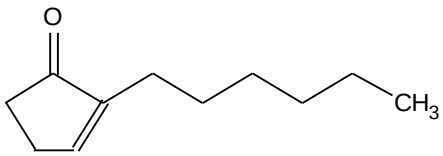
Rastogi S.C., Johansen J.D., Bossi R., 2007. Selected important fragrance sensitizers in perfumes – current exposures. Contact Dermatitis 56, 201–204.

Schnuch A., Lessmann H., Geier J., Frosch P.J., Uter W., 2004. Contact allergy to fragrances: frequencies of sensitization from 1996 to 2002. Results of the IVDK. Contact Dermatitis. 50(2), 65-76.

Tanaka S., Royds C., Buckley D., Basketter D.A., Goossens A., Bruze M., Svedman C., Menné T., Johansen J.D., White I.R., McFadden J.P., 2004. Contact allergy to isoeugenol and its derivatives: problems with allergen substitution. Contact Dermatitis 51(5-6), 288-91.

White J.M., White I.R., Glendinning A., Fleming J., Jefferies D., Basketter D.A., McFadden J.P., Buckley D.A., 2001. Frequency of allergic contact dermatitis to isoeugenol is increasing: a review of 3636 patients tested from 2001 to 2005. Br J Dermatol. 157(3), 580-2.

## Isojasmone



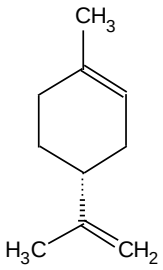

The fragrance ingredient isojasmone can be found in many fragrance mixtures as compound of cosmetic products as well as non-cosmetic products. The odour of isojasmone has been described to be floral, fruity, minty, warm, diffusive and oily (Arctander 1969 op.cit. Scognamiglio et al., 2012). The maximum skin level in dermal products has been reported to be 0.01%. The calculated maximum daily exposure would result in 0.00025 mg/kg for high end users of such products (IFRA, 2007 op.cit. Scognamiglio et al., 2012). The Flavour and Extract Manufactures' Association FEMA determined isojasmone as GRAS as a flavour ingredient (FEMA, 1978 op.cit. Scognamiglio et al., 2012).

The acute oral LD50 in rats was reported to be greater than 5.0 g/kg. Dermal tests in rabbits showed that the dermal LD50 value was either greater than 5.0 g/kg. In all tested rabbits slight to severe redness and moderate edema were observed (RIFM, 1974 op.cit. Scognamiglio et al., 2012).

References:

Scognamiglio J., Jones L., Letizia C.S., Api A.M., 2012. Fragrance material review on isojasmone. Food and Chemical Toxicology 50(3), 586-91.

## Limonene




The terpene limonene is found in several plants and essential herb oils like rosemary, eucalyptus, lavender, caraway, lemon grass and peppermint as well as in turpentine oil and tea tree oil (Ippen, 1998 op.cit. Matura et al., 2002). Limonene is one of the five most frequently used fragrances in domestic and occupational products (Rastogi, 2001). It belongs to the group of fragrance chemicals that must be labelled on cosmetic products when used in high concentrations (EEC, 2003 op.cit. Christensson et al., 2008). Due to its skin sensitizing capacity the isomer R-(+)-limonene is one of the most commonly used fragrance materials. It is the main constituent of peel oil from citrus fruits. In technical products and fine fragrances it is often used in higher concentrations than other fragrances (0.005-2%) (Matura et al., 2002). R-(+)-Limonene itself if an irritant in high concentrations. It is reported to cause allergic contact dermatitis and coetaneous and respiratory disease (Schnuch et al., 2007).

Auto-oxidation of R-(+)-limonene results in a fragrance allergy with a greater extent than non-oxidized R-(+)-limonene. The most likely sources of sensitization with the oxidized limonene might be scented cleaning products, care products and cosmetics (Matura et al., 2002). The primary oxidation products are the hydroperoxides (Christensson et al., 2008). The oxidation product (+)-limonene epoxide caused adverse reactions like ataxia, hyperventilation, sedation and mortality after intraperitoneal application of high does in mice. The acute oral LD50 was reported to be 4000 mg/kg. Therefore (+)-limonene epoxide is a slight toxic agent. The dose of the non-observed-adverse-effect of (+)-limonene epoxide was determined with 1000 mg/kg.

Additionally (+)-limonene epoxide showed anxiolytic-like effects in mice. It is suggested to be responsible for most of the central effects of limonene (De Almeida et al., 2012).

References:

Christensson J.B., Johansson S., Hagvall L., Börje C.J.A., Karlberg A-T., 2008. Limonene hydroperoxide analogues differ in allergenic activity. Contact Dermatitis 59, 344–352.

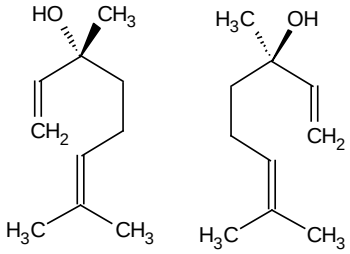
De Almeidaa A.A.C., Costab J.P., De Carvalhoa R.B.F., De Sousac D.P., De Freitasb R.M., 2012. Evaluation of acute toxicity of a natural compound (+)-limonene epoxide and its anxiolytic-like action. BRAINRESEARCH 1 448, 56–62.

Matura M., Goossens A., Bordalo O., Garcia-Bravo B., Magnusson K., Wrangsjö K., Karlberg A-T., 2002. Oxidized citrus oil (R-limonene): A frequent skin sensitizer in Europe. J AM ACAD DERMATOL 47, 5.

Rastogi S.C., Heydorn S., Johansen J.D., Basketter D.A., 2001. Fragrance chemicals in domestic and occupational products. Contact Dermatitis 45, 221–225.

Schnuch A., Uter W., Geier J., Lessmann H., Frosch P.J., 2007. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis 57, 1–10.

**Linalool**

(S)-(+)  (R)-(-)

In Europe the monoterpene linalool is one of the most frequently used fragrance compounds in fine fragrances and household products such as soaps, cleaners and conditioners. It is a common ingredient in lavender oil (Rastogi et al., 2001). The essential oil of lavender is almost colourless and owns a sweet floral odour (Lis-Balchin, 2002). It has also been used for centuries in traditional herbal medicine, due to its smooth muscle relaxing, sedative and antidepressive effects. It is still widely used in aromatherapy (Cavanagh&Wilkinso, 2002 op.cit. Hagvall et al., 2008).

The maximum skin level from (R)-(-)-linalool in dermal formulations was reported to be 0.31%. The calculated maximum daily exposure on the skin results with a value of 0.0720 mg/kg for high end users of such products (IFRA 2004, op.cit Lapczynski et al., 2008).

The maximum skin level from (S)-(+)-linalool in dermal formulations was reported to be 0.13%. The calculated maximum daily exposure on the skin results with a value of 0.0459 mg/kg for high end users of such products (IFRA 2004, op.cit Lapczynski et al., 2008).

Linalool itself has limited allergenic properties. It can auto-oxidize upon air exposure in to hydroperoxides (Sköld et al., 2002). Oxidized lavender oil is a source of exposure to allergenic hydroperoxides and can elicit allergenic contact dermatitis (Hagvall et al., 2008). Linalool hydroperoxides are strong sensitizers in mice, while the other oxidation products are moderate sensitizers or non-sensitizers. The fact that linalool is the most often used fragrance chemical, might explain the high frequency of contact dermatitis (Sköld et al., 2004). Workers at perfume factories are often victims of allergic contact dermatitis caused by linalool hydroperoxides (Schubert, 2006). The

International Fragrance Research Association IFRA determined that linalool should only be used when the peroxide level is as low as possible (IFRA, 2009 op.cit. Christensson et al., 2010).

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Christensson J.B., Matura M., Gruvberger B., Bruze M., Karlberg A-T., 2010. Linalool – a significant contact sensitizer after air exposure. Contact Dermatitis 62, 32–41.

Hagvall L., Sköld M., Christensson J.B., 2008. Lavender oil lacks natural protection against autoxidation, forming strong contact allergens on air exposure. Contact Dermatitis 59, 143–150.

Lapczynski A., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on l-linalool Food and Chemical Toxicology 46, 195–196.

Lapczynski A., Letizia C.S., Api A.M, 2008.. Fragrance material review on d-linalool. Food and Chemical Toxicology 46, 193–194.

Lis-Balchin M., 2002. Miscellaneous uses of lavender and lavender oil. Use in hair products, food flavouring, tissanes, herbal pillows and medicinal products. Med Aromatic Plants Ind Profile 29, 200–205.

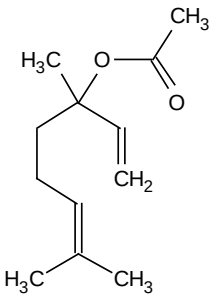
Rastogi S.C., Heydorn S., Johansen J.D., Basketter D.A., 2001. Fragrance chemicals in domestic and occupational products. Contact Dermatitis 45, 221–225.

Schubert H.J., 2006. Skin diseases in workers at a perfume factory. Contact Dermatitis 55, 81–83.

Sköld M., Börje A., Harambasic E., Karlberg A.T., 2004. Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. Chem Res Toxicol 17, 1697–1705.

Sköld M., Börje A., Matura M., Karlberg A-T., 2002. Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hydroperoxide. Contact Dermatitis 46, 267–272.

**Linalyl acetate**




Linalyl acetate is a non-conjugated ester of linalool. It is a commonly used fragrance chemical. It is present in high concentrations in lavender oil, which is widely used as fragrance in cosmetic products (Sköld et al., 2008). Linalyl acetate was found to be the third most common fragrance material in the USA (Fenn, 1989 op.cit. Woronuk et al., 2011). Lavender was reported to help restrain the decrease of vigilance. In this context linalyl acetate has been reported to have a tranquilising effect (Shimizu et al., 2008). The acute oral LD50 of linalyl acetate was determined to be 10 ml/kg in rats. Clinical signs like dyspnoea, apathy and anxiety were observed (RIFM, 1969 op.cit. Letizia et al., 2003). The acute oral LD50 value in mice was reported to be 13.360 mg/kg (Jenner et al., 1964 op.cit. Leticia et al., 2003).

The maximum skin level of linalyl acetate in dermal formulations have been reported to be 4.6%. The maximum daily exposure has been calculated to be 0.33 mg/kg for high end users of such products (IFRA, 1998 op.cit. Letizia et al., 2003). The dermal LD50 in rabbits was determined to be 5.0 g/kg (RIFM, 1972 op.cit. Leticia et al., 2003). Linalyl acetate was reported to be a weak sensitizer. Its allergenic activity increases after air exposure by the formation of allergenic hydroperoxides. Many cases of contact dermatitis caused by such hydroperoxides have been reported (Sköld et al., 2008).

References:

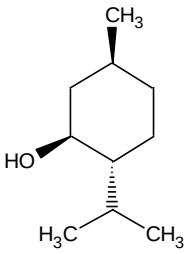
Letizia C.S., Cocchiara J., Lalko J., Api A.M., 2003. Fragrance material review on linalyl acetate. Food and Chemical Toxicology 41, 965–976.

Shimizi K, Gyokusen M, Kitamura S., Kawabe T., Kozaki T., Ishibashi K., Izumi R., Mizunoya W., Ohnuki K., Kondo R., 2008. Essential Oil of Lavender Inhibited the Decreased Attention during a Long-Term Task in Humans. Biosci. Biotechnol. Biochem. 72 (7), 1944–1947.

Sköld M., Hagvall L., Karlberg A-T., 2008. Autoxidation of linalyl acetate, the main component of lavender oil, creates potent contact allergens. Contact Dermatitis 58, 9–14.

Woronuk G., Demissie Z., Rheault M., Mahmoud S., 2011. Biosynthesis and Therapeutic Properties of Lavandula Essential Oil Constituents. Planta Med 77, 7–15.

**Menthol**




(-)

The monocyclic terpenoid alcohol menthol plays a role as analgesic and anti-inflammatory drug. It has cooling analgesic and local anaesthetic effects and is a penetration enhancer (Jain&Panchagnula., 2005). It is the main compound of plant oils of the mint family for instance *Mentha piperita* L. (Lamiaceae). At concentrations between 1 and 16%, menthol is used in analgesic and antipruritic balms (Knight&Draper, 2007 op.cit. Klein et al., 2012). At such concentrations in topical preparations it is considered by the Food and Drug Administration FDA as a safe substance (Patel et al., 2007). Menthol owns biphasic effects. At low concentrations it has a cooling effect on the skin, while at high concentrations about 40% menthol reduces the cold-evoked response (Klein et al., 2012). At this concentrations menthol is associated with erythema and spontaneous burning (Cal, 2008). Orally, menthol is able to induce burning mouth syndrome, stomatitis or oral lichenoid reactions (Ale et al., 2002 op.cit. Nakagawa et al., 2009). It is a widely used constituent in various foods, cosmetic products, soaps and toothpastes. It has been reported to induce asthma, urticaria, rhinitis (Andersson&Hindsn, 2007) and anaphylaxis after using such products containing menthol (Paiva et al., 2010). The maximum skin level of menthol has been reported to be 0.52%. The maximum daily exposure was calculated to be
0.0074 mg/kg for high end users of menthol containing products (IFRA, 2004 op.cit. Bhatia et al., 2008). The acute oral LD50 was reported to be 0.94 mg/kg in rats and 2.65 mg/kg in mice (RIFM, 1975 op.cit. Bhatia et al., 2008). Studies show that 0.1% menthol is a safe and potential permeability enhancer in ocular drug delivery. It does not cause any toxic or irritant effects in the eye (Xu et al., 2011).

References:

Andersson M.&Hindsn M., 2007. Rhinitis because of toothpaste and other menthol-containing products. Allergy 62, 336–337.

Bhatia S.P., McGinty D.,. Letizia C.S, Api A.M., 2008. Fragrance material review on menthol. Food and Chemical Toxicology 46, 209–214.

Cal K., 2008. Skin Disposition of Menthol After its Application in the Presence of Drug Substances Biopharm. Drug Dispos. 29, 449–454.

Jain A.K.&Panchagnula R., 2005. Transdermal delivery of imipramine hydrochloride: development and evaluation (in vitro and in vivo) of reservoir gel formulation. Biopharm Drug Dispos 26, 41–49.

Klein A.H., Sawyer C.M., Takechi K., DAvoodie A., Ivanov M.A., Carstens M.I., Carstens E., 2012 TOPICAL HINDPAW APPLICATION OF L-MENTHOL DECREASES RESPONSIVENESS TO HEAT WITH BIPHASIC EFFECTS ON COLD SENSITIVITY OF RAT LUMBAR DORSAL HORN NEURONS Neuroscience 219, 234–242.

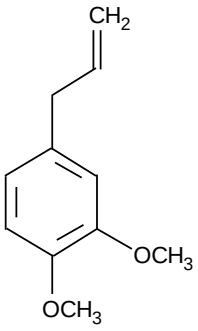
Nakagawa S., Tagami H., Aiba S., 2009. Erythema multiforme-like generalized contact dermatitis to l-menthol contained in anti-inflammatory medical compresses as an ingredient. Contact Dermatitis 61, 178–179.

Paiva M., Piedade S., Gaspar A., 2010. Toothpaste-induced anaphylaxis caused by mint (Mentha) allergy. Allergy 65 1201-2.

Patel T., Ishiuji Y., Yosipovitch G., 2007. Menthol: a refreshing look at this ancient compound. J Am Acad Dermatol 57, 873-878.

Xu X., Yu N., Bai Z., Xun Y., Jin D., Li Z., Cui H., 2011. Effect of menthol on ocular drug delivery. Graefes Arch Clin Exp Ophthalmol 249, 1503–1510.

**Methyleugenol**




Methyleugenol is naturally occurring in various aromatic plants such as *Acacia senegal* L.Willd. (Fabaceae), *Cinnamomum verum* J.S.Presl. (Lauraceae), *Gentiana lutea* L. (Gentianaceae), *Piper nigrum* L. (Piperaceae), *Melissa officinalis* L. (Lamiaceae), *Myristica odroata* L.Scop. (Myristicaceae) and *Rosmarinus officinalis* L. (Lamiaceae). It is used as flavouring agent in foodstuffs and in cosmetics (De Vincenzia et al., 2000). Methyleugenol is a colourless to pale yellow oily liquid. It owns a clove-carnation odour and a bitter taste (NTP, 2000 op.cit. Ding et al., 2011). It was classified as GRAS by the Flavor and Extract Manufactures Association FEMA 1965. It was concluded that its use should be restricted, because of its carcinogenic and genotoxic properties. (EC-SCF, 2001 op.cit. Jeurissen et al., 2006). Chronic studies in mice showed that a intraperitoneal injection of 150 mg/kg increased significantly the incidence of hepatoblastoma. A limit of 0.05 mg/kg bw methyleugenol is proposed. (De Vincenzia et al., 2000). The FEMA expected that the harmful effects of methyleugenol would be minimal at doses between 1 and 10 mg/kg, which was 100-1000 times the average daily intake of methyleugenol. The FEMA expected it to be 0.01 mg/kg bw/day (Smith et al., 2002). Otherwise the Scientific Committee on Food SCF supposed that the average daily intake of methyleugenol is 0.217 mg/kg bw/day (SCF, 2001 op.cit Al-Subeihi et al., 2012). Results of acute toxicity tests in rats showed that methyleugenol is a moderately toxic substance. The median lethal oral doses were between 0.81 and 1.56 g/kg bw (NTP, 1998 op.cit. Lahloua et al., 2004).

The International Fragrance Research Association IFRA established a limit for methyleugenol of 2.5 µg/kg bw/day (IFRA, 2009 op.cit. Al-Subeihi et al., 2012).

References:

Al-Subeihi A.A., Spenkelink B., Punt A., Boersma M.G., Van Bladeren P.J., RietjensI. M.C.M., 2012. Physiologically based kinetic modeling of bioactivation and detoxification of the alkenylbenzene methyleugenol in human as compared with rat. Toxicology and Applied Pharmacology 260, 271–284.

De Vincenzia M.,. Silanob U.M, Stacchinic P., Scazzocchioa B., 2000. Constituents of aromatic plants: I. Methyleugenol. Fitoterapia 71, 216-221.

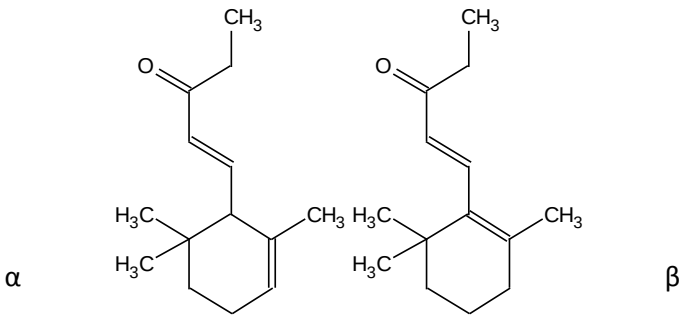
Ding W., Levy D.D., Bishop M.E., Lascelles E. L-C., Kulkarni R., Chang C-W., Aidoo A., Manjanatha M.G., 2011. Methyleugenol Genotoxicity in the Fischer 344 Rat Using the Comet Assay and Pathway-Focused Gene Expression Profiling. TOXICOLOGICAL SCIENCES 123(1), 103–112 .

Jeurissen S.M., Bogaards J.J., Boersma M.G., Ter Horst J.P., Awad H.M., Fiamegos Y.C., Van Beek T.A., Alink G.M., Sudhölter E.J., Cnubben N.H., Rietjens I.M., 2006. Human Cytochrome P450 Enzymes of Importance for the Bioactivation of Methyleugenol to the Proximate Carcinogen 1□-Hydroxymethyleugenol. Chem. Res. Toxicol. 19, 111-116.

Lahloua S., Figueiredoa A.F., Magalha˜esb P.J.C., Leal-Cardosoc J.H., 2004. Cardiovascular effects of methyleugenol, a natural constituent of many plant essential oils, in normotensive rats. Pinto Duarte Gloria Life Sciences 74, 2401–2412.

Smith R. L., Adams T.B., Doull J., Feron V.J., Goodman J.I., Marnett L.J., Portoghese P.S., Waddell W.J., Wagner B.M., Rogers A.E., Caldwell J., Sipes I.G., 2002. Safety assessment of allylalkoxybenzene derivatives used as flavouring substances - Methyl eugenol and estragole. Food Chem. Toxicol. 40, 851-870.

**Methylionone**




"*Methyl ionone is a fragrance ingredient used in many fragrance compounds. It may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents*". From the use of methyl ionone in dermal formulations resulted a maximum skin level of 5.64%. The calculated maximum daily exposure on the skin was reported to be 0.25 mg/kg for high end users of products containing methyl ionone (IFRA, 2001 op.cit. Lalko et al., 2007). Testing the acute oral toxicity in mice, all animals died at a dose of 10 g/kg bw. At that dose animals were cyanosed, somnolent, dehydrated and experienced heavy breathing. The acute LD50 value in mice was determined to be between 5 and 10 g/kg (RIFM, 1980 op.cit. Lalko et al., 2007). Dermal tests resulted with an acute dermal LD50 greater than 5 g/kg (RIFM, 1973 op.cit. Lalko et al., 2007).

According to the seperated isomer methyl-α-ionone, the maximum skin level was reported to be 0.001% in dermal formulations.

The maximum daily exposure on the skin was calculated to be 0.0004 mg/kg for high end users of such products (IFRA, 2001 op.cit. Lapczynski et al., 2007).

For methyl-β-ionone the maximum skin level of dermal formulations was reported to be 0.02%. Calculating the maximum daily exposure on the skin for high end user of products containing methyl-β-ionone resulted with a value of 0.0025 mg/kg (IFRA, 2001 op.cit. Lapczynski et al., 2007). Furthermore, the acute oral LD50 of the separated β-isomer has been determined to be greater than 2000 g/kg in rats (RIFM, 1988 op.cit. Lapczynski et al., 2007).

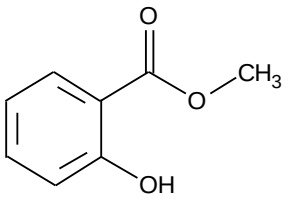
References:

Lalko J., Lapczynski A., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on methyl ionone (mixture of isomers). Food and Chemical Toxicology 45, 300–307.

Lapczynski A., Lalko J., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on methyl-a-ionone. Food and Chemical Toxicology 45, 276–279.

Lapczynski A., Lalko J., McGinty D., Bhatia S., Letizia C.S., Api A.M., 2007. Fragrance material review on methyl-b-ionone. Food and Chemical Toxicology 45, 290–293.

**Methylsalicylate**




"*Methyl salicylate is a liquid methyl ester of salicylic acid with a distinct characteristic odor. It is colorless of light pale in color, and commonly known as synthetic oil of wintergreen (made from the distillation of wintergreen leaves)*". Preparations of methyl salicylate are compounds of cosmetics, flavourings ad perfumes. But it is also used in medicine as a counter irritant, analgesic and local anaesthetic agent (Parker et al., 2004) in creams, ointments, lotions and oils to relieve musculoskeletal aches and pains. Methyl salicylate is known to be a potent toxic agent. Therefore the FDA determined that the label of any drug should not contain more than 5% methyl salicylate. Furthermore, the FDA suggested to keep products with high concentrations of methyl salicylate, safely out of the reach of children (FDA, 2004 op.cit. Davis, 2007), because it is a source of serious toxicity. First signs of an acute toxicity are gastrointestinal symptoms, diaphoresis, fever and tinnitus and could lead to multisystem organ dysfunction (Dabis, 2007). Salicylate toxicity could be characterized with a mixed acid-basic disturbance: " *a primary respiratory alkalosis and a primary metabolic acidosis*" (Buck et al., 1993 op.cit. Davis, 2007). Reports show that the lethal dose in children could be as little as 4 ml (Clauthen&Hester, 1989 op.cit. Parker et al., 2004).

The use of methyl salicylate in formulations of fine fragrances has been reported to be 0.29%. For high end users of such products, the maximum daily exposure was calculated do be 0.0034 mg/kg (IFRA, 2002 op.cit. Lapczynski et al., 2007).

The acute oral LD50 value in mice was determined to be

1.44 g/kg/day (NTP, 1984 op.cit. Lapczynski et al., 2007). In dermal tests in rabbits slight to moderate erythema and edema were observed in all animals tested. The acute dermal LD50 was reported

to be greater than 5.0 g/kg (RIFM, 1973 op.cit., Lapczynski et al., 2007). A dermal application of a 30% methyl salicylate formulation in ethanol caused irritation in humans (Green&Shaffer, 1992 op.cit Lapczynski et al., 2007).

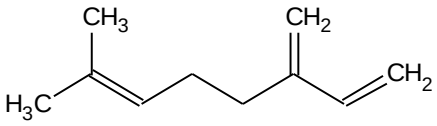
References:

Davis J.E., 2007. ARE ONE OR TWO DANGEROUS? METHYL SALICYLATE EXPOSURE IN TODDLERS. The Journal of Emergency Medicine 32(1), 63–69.

Lapczynski A., Jones L., McGinty D., Bhatia S.P., Letizia C.S., Api A.M., 2007. Fragrance material review on methyl salicylate. Food and Chemical Toxicology 45, 428–452.

Parker D., Martinez C., Stanley C., Simmons J., McIntyre I.M., 2004. The Analysis of Methyl Salicylate and Salicylic Acid from Chinese Herbal Medicine Ingestion. Journal of Analytical Toxicology 28.

**Myrcene**




The acyclic monoterpene myrcene is a content of essential oils of various plants, for instance lemongrass, hop, verbena and bay (De-Oliveria et al., 1997 op.cit. Ciftci et al., 2011). It is an important ingredient of cosmetics, shampoos, soaps and detergents (Ciftci et al., 2011). "*Myrcene exists as two isomers*". Like most natural terpenes the naturally occurring is the β-isomer (in the following only called "myrcene"). "*Myrcene is a colorless oil with a characteristic odor of geranium*". It is known to own low oral and dermal toxicity (Khamidulina et al., 2006 op.cit. Behr&Johen et al., 2009).

1965 the Flavor Extract Manufacturers' Association FEMA accorded it the GRAS status. The American Food and Drug Administration FDA approved myrcene as food additive (Behr&Johen, 2009). On air exposure myrcene is able to autoxidize. While the pure compound was found to be a nonsensitizer in animals, the oxidized one was reported to be a rare allergen (Matura et al., 2005).

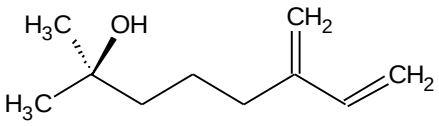
References:

Behr A., Johnen L., 2009. Myrcene as a Natural Base Chemical in Sustainable Chemistry: A Critical Review. ChemSusChem 2, 1072–1095.

Ciftci O., Ozdemir I., Tanyildizi S., Yildiz S. ,Oguzturk H. 2007. Antioxidative effects of curcumin, □-myrcene and 1,8-cineole against 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced oxidative stress in rats liver. *Toxicol Ind Health* 27, 447.

Matura M., Sköld M., Börje A., Andersen K.E., Bruze M., Frosch P., Goossens A., Johansen J.D., Svedman C., White I.R., Karlberg A.T., 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact Dermatitis 52(6),320-8.

## Myrcenol




Myrcenol is widely used as fragrance ingredient in cosmetic and non-cosmetic products. A default value of 0.02% of myrcenol is used as maximum skin level in formulations. The calculated maximum daily exposure of this default value is 0.0005 mg/kg for high end users of such dermal products (Lapczynski et al., 2008).

In acute oral toxicity tests in rats, all animals died at a dose of 7.8 g/kg. Clinical signs, such as ataxia, loss of righting reflex, lethargy and piloerection were reported. The LD50 was calculated to be 5.3 g/kg. Dermal studies in white rabbits resulted with a LD50 value greater than 5.0 g/kg. Slight to moderate edema and erythema were observed in all rabbits tested (RIFM, 1972 op.cit. Lapczynski et al., 2008).

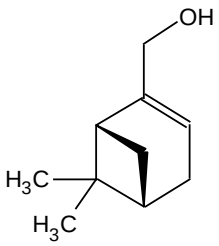
In vivo studies suggest that myrcenol potentiates the $GABA_A$ receptor. it was injected to mice which were administrated to pentobarbital before. As result myrcenol increased the pentobarbital-induced sleeping time (Aoshima et al., 2006).

References:

Aoshima H., Takeda K., Okita Y., Hossain S.J., Koda H., Kiso Y., 2006. Effects of Beer and Hop on Ionotropic ç-Aminobutyric Acid Receptors. J. Agric. Food Chem. 54, 2514-2519.

Lapczynski A., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on myrcenol. Food and Chemical Toxicology 46, 234–236.

## Myrtenol




The fragrance ingredient myrtenol is used in fine fragrances, cosmetics and toiletries as well as detergents. The maximum skin level has been reported to be 0.014% in formulations. The maximum daily exposure on the skin was calculated to be 0.0033 m/kg for high end users (IFRA, 2004 op.cit. Bhatia et al., 2008).

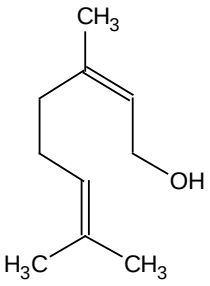
Tests about the acute oral toxicity in rats resulted with a LD50 value of 1.4 g/kg (RIFM, 2001 op.cit. Bhatia et al., 2008).

Dermal irritation tests showed that myrtenol causes irritations in guinea pigs at concentrations between 5 and 100% (RIFM, 1987 op.cit. Bhatia et al., 2008).

References:

Bhatia S.P., McGinty D., Letizia C.S., Api A.M., 2008. Fragrance material review on myrtenol. Food and Chemical Toxicology 46, 237–240.

**Nerol**



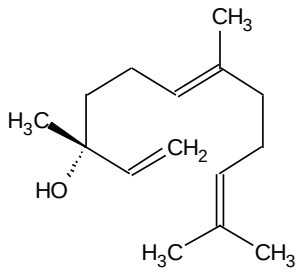

Nerol is a compound of many fragrances used in cosmetic products as well as in non-cosmetic products. The use of nerol in formulations resulted in a maximum skin level of 1.12%. The maximum daily exposure on the skin for high end users was calculated to be 0.06 g/kg (IFRA, 2003 op.cit. Lapczynski et al., 2008).

The acute oral LD50 in rats was determined to be 4.5 g/kg. At a dose of 9.8 g/kg all animals died. The dermal LD50 value in rabbits was reported to be greater than 5 g/kg. Slight to moderate edema were observed in all rabbits (RIFM, 1972 op.cit Lapczynski et al., 2008). The intramuscular LD50 in mice was calculated to be 3 g/kg (Northover&Verghese 1962 op.cit. Lapczynski et al., 2008). At a concentration of 100% nerol had an eye irritation potential in albino rabbits (RIFM, 1977 op.cit. Lapczynski et al., 2008).

References:

Lapczynski A., Foxenberg R.J., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on nerol. Food and Chemical Toxicology 46, 241–244.

**Nerolidol**




The natural aliphatic sesquiterpene alcohol nerolidol is also known as peruviol. It is an important compound of many essential oils of various plants (Péres et al., 2009), for instance *Baccharis dracunculifolia* DC (Asteraceae) (Koudou et al., 2005). Nerolidol has a vast use as flavour and aroma enhancer. There have been studies about its topical skin penetration enhancing effects (Lapczynski et al., 2008).

"*It may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents*". The use of nerolidol in formulations of fine fragrances resulted in a maximum skin level of 2.02%. The maximum daily exposure on the skin was calculated to be 0.0293 mg/kg for high end users of such products (IFRA, 2007 op.cit Lapczynski et al., 2008). The Flavor and Extract Manufacturers' Association FEMA accorded to nerolidol the GRAS status (FEMA, 1970 op.cit. McGinty et al., 2010). The acute oral LD50 value of nerolidol in mice was determined to be 10 g/kg (RIFM, 1967 op.cit. Lapczynski et al., 2008), while the value in rats was reported to be greater than 5 g/kg. Dermal tests in rabbits resulted with an LD50 value greater than 5 g/kg (RIFM, 1973 op.cit. Lapczynski et al., 2008). Irritation tests in guinea pigs showed at a concentration of 1% of nerolidol irritation reactions (Sharp, 1978 op.cit. Lapczynski et al., 2008). Sensitization tests in guinea pigs showed that nerolidol is a weak sensitizer at 3% (Hausen, 1992 op.cit. Lapczynski et al., 2008). Reports show that nerolidol has clastogenic and weak genotoxic properties (Píçulo et al., 2011).

It has been reported that nerolidol toxicity in animals differs based on the route of exposure. The American Environmental Protection Agency EPA classified nerolidol "*in ''Toxicity Category IV'' for acute oral toxicity, ''Toxicity Category III'' for acute dermal toxicity, primary eye irritation and primary dermal irritation, and ''Toxicity Category II'' for acute inhalation toxicity*" (Hollis&Jones, 2009 op.cit. Ferreira et al., 2012).

References:

Ferreira F.M., Palmeira C.M., Oliveira M.M., Santos D., Simões A.M., Rocha S.M., Coimbra M.A., Peixoto F., 2012. Nerolidol effects on mitochondrial and cellular energetics. Toxicol In Vitro. 26(2), 189-96.

Koudou J., Abena A.A., Ngaissona P., Bessiére J.M., 2005. Chemical composition and pharmacological activity of essential oil of Canarium schweinfurthii. Fitoterapia 76, 700–703.

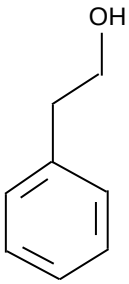
Lapczynski A., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on nerolidol (isomer unspecified). Food and Chemical Toxicology 46, 247–250.

McGinty D., Letizia C.S., Api A.M., 2010. Addendum to Fragrance material review on Nerolidol (isomer unspecified) Food and Chemical Toxicology 48, 43–45.

Péres V.F., Moura D.J., Sperotto A.R., Damasceno F.C., Caramão E.B., Zini C.A., Saffi J., 2009. Chemical composition and cytotoxic, mutagenic and genotoxic activities of the essential oil from Piper gaudichaudianum Kunth leaves. Food Chem. Toxicol. 47, 2389–2395.

Píciulo F., Macedo C.G., De Andradeb S.F., Maistroa E.L., 2011. In vivo genotoxicity assessment of nerolidol. J. Appl. Toxicol. 31, 633–639.

**Phenethyl alcohol**




Phenethyl alcohol is a fragrance ingredient that belongs to the group of aryl alkyl alcohols (AAA). "*The AAA fragrances demonstrate low acute and subchronic dermal and oral toxicity*". The FDA has designated phenethyl alcohol as GRAS for use as flavouring ingredient in food products (Belsito et al., 2012). The maximum dermal exposure of phenethyl alcohol has been reported to be 0.3198 mg/kg bw/day for high end users of cosmetic products (IFRA, 2004 op.cit. Belsito et al., 2012).

According to the acute oral toxicity, the LD50 in rodents has been reported to be 2540 mg/kg (Zaitsev&Rakhmanina, 1974 op.cit. Belstio et al., 2012), for guinea pigs alone the LD50 was determined to be between 400 and 800 mg/kg (Treon, 1963 op.cit. Belsito et al., 2012), for rats 1800 mg/kg (Rumyantsev et al., 1987 op.cit. Belsito et al., 2012) and for mice 2190 mg/kg (RIFM, 1974 op.cit. Belsito et al., 2012). The lowest observed adverse effect level in rats resulted in a value of 500 mg/kg bw/day. Symptoms like inactivity, ptosis, diarrhoea, poor grooming, abnormal stance, hypersensitivity and piloerection were observed (RIFM, 1982 op.cit. Belsito et al., 2012).

Tests about the acute inhalation toxicity resulted with LD50 values of 520 mg/kg in rats (RIFM, 1982 op.cit. Belsito et al., 2012) and
454 mg/kg in mice (RIFM 1974 op.cit. Belsito et al., 2012). An application of 25% phenethyl alcohol in ethanol on the eye caused moderate to severe conjunctival irritation with cornea opacity and iris congestion (RIFM, 1965 op.cit. Belsito et al., 2012). Dermal tests in rabbits resulted with an acute dermal LD50 of 2535 mg/kg (RIFM, 1983 op.cit. Belsito et al., 2012). In rats the acute dermal LD50 value

was determined to be greater than 5000 mg/kg (RIFM, 1982 op.cit. Belsito et al., 2012).

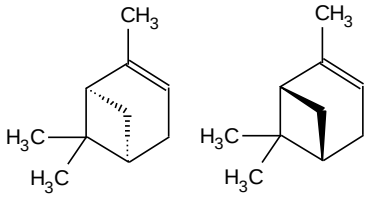
The result of intraperitoneal tests of phenethyl alcohol in rats, was a LD50 value of 0.55 mg/kg (RIFM, 1982 op.cit. Scognamiglio et al., 2012).

References:

Belsito D., Bickers D., Bruze M., Calow P., Dagli M.L., Fryer A.D., Greim H., Miyachi Y., Saurat J.H., Sipes I.G., 2012. A toxicological and dermatological assessment of aryl alkyl alcohols when used as fragrance ingredients. Food Chem Toxicol. 2, 52-99.

Scognamiglio J., Jones L., Letizia C.S., Api A.M., 2012. Fragrance material review on phenylethyl alcohol. Food Chem Toxicol. 2, 224-39.

**α-Pinene**

(-)-α  (+)-α

"*α-Pinene is a monoterpene and is a derivate of turpentine, an oleoresin that is exuded from many species of pine trees. It is widely distributed, and is one of the commonest constituents of essential oils from leaves, fruits, seeds, barks and woods of many plants*" (Read&Gunstone, 1958 op.cit. Wei et al., 2006). Turpentine oil has been used in traditional medicine for various sorts of indication, due to its anticarcinogenic, diuretic, immunostimulant, anti-convulsive, sedative and hypoglycaemic activities. α-Pinene is known to possess low irritancy potential and is generally regarded as safe (Mercier et al., 2009). Toxic effects have been reported in mice at a dose of 5 g/kg (Menezes et al., 2007). Testing the acute dermal irritation in guinea pigs, at 20% as well as a concentration of 100% of α-pinene caused erythema on the abdomens of the animals, 24 hours after the application (Wei et al., 2006). Studies show that exposure to α-pinene induces persistent sensory irritation effects on the upper respiratory tract in mice. In this context it was observed that (-)-α-pinene has higher systemic toxicity than (+)-α-pinene (Nielsen et al., 2005).

References:

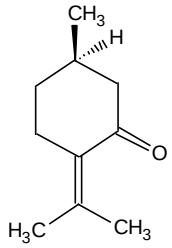
Menezes I.A., Marques M.S., Santos T.C., Dias K.S., Silva A.B., Mello I.C., et al., 2007. Antinociceptive effect and acute toxicity of the essential oil of Hyptis fruticosa in mice. Fitoterapia 78(3), 192–5.

Mercier B., Prost J., Prost M., 2009. The essential oil of turpentine and its major volatile fraction (α- and β-pinenes): a review. International journal of Occupational Medicine and Environmental Health 22, 331–342.

Nielsen G.D., Larsen S.T., Hougaard K.S., Hammer M., Wolkoff P., Clausen P.A., Wilkins C.K. Alarie Y., 2005. Mechanisms of Acute Inhalation Effects of (+) and (-)-a-Pinene in BALB/c Mice. Basic & Clinical Pharmacology & Toxicology 96, 420–428.

Wei Q., Harada K., Ohmori S., Minamoto K., Wie C., Ueda A., 2006. Toxicity Study of the Volatile Constituens of Myoga Utilizing Aute Dermal Irritaion Assays and the Guinea-Pig Maximization Test. J Occup health 48, 480-486.

## Pulegone




(R)-(+)

The monoterpene ketone pulegone is mainly found in the essential oil of *Mentha pulegium* L. (Lamiaceae) (pennyroyal) as well as in other species of mints (Franzios et al., 1997 op.cit. Chen et al., 2003). ‘‘*The mints are used as flavorings in food and beverages. A survey of mint products and herbal teas in the UK found pulegone at concentrations below the limit of detection (ca. 1 ppm) to 119 ppm*”. Pennyroyal tea is used to induce menstruation and abortion (MAFF 1996 op.cit. Chen et al., 2003).

There have been reports that the consumption of high doses of pennyroyal oil caused central nervous system toxicity, gastritis, hepatic and renal failure, seizure and coma (NTP, 2011 op.cit Da Rocha et al., 2012). At doses of 150 mg/kg of pulegone the incidence of urinary bladder neoplasm increases. The administration to rats caused urothelial necrosis (DA Rocha et al., 2012). The LD50 was determined to be 245 mg/kg (Moorthy et al., 1989 op.cit. Chen et al., 2003). ‘‘*Surprisingly, despite its reported toxic effects, pennyroyal oil is largely used as flavouring agent in chewing gums, toothpaste, and candies*” (Petrakis et al., 2009).

Mentionable is that earlier studies detected that R-(+)-pulegone is three time more hepatotoxic than the S-enantiomer (Gordon et al., 1982 op.cit. Madyastha&Ray, 2002).

References:

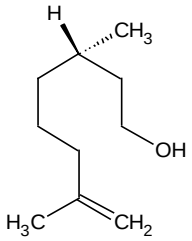
Chen L-J., Lebetkin E.H:, Burka L.Z., 2003. COMPARATIVE DISPOSITION OF (R)-(+)-PULEGONE IN B6C3F1 MICE AND F344 RATS. DMD 31, 892–899.

Da Rocha M.S., Dodmane P.R., Arnold L.L., Pennington K.L., Anwar M.M., Adams B.R., Taylor S.V., Wermes C., Adams T.B., Cohen S.M., 2012. Mode of action of pulegone on the urinary bladder of F344 rats. Toxicol Sci. 128(1), 1-8.

Madyastha K.M.& Raj C.P., 2002. Stereoselective hydroxylation of 4-methyl-2-cyclohexenone in rats: its relevance to R-(+)-pulegone-mediated hepatotoxicity Biochemical and Biophysical Research Communications 297, 202–205.

Petrakis E.A., Kimbaris A.C., Pappas C.S., Tarantilis P.A., Polissiou M.G.J., 2009. Quantitative determination of pulegone in pennyroyal oil by FT-IR spectroscopy. J. Agric. Food Chem. 57, 10044–10048.

## Rhodinol



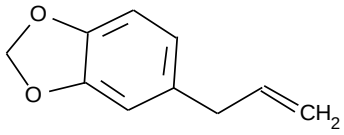

The non-cyclic terpene alcohol rhodinol is a fragrance ingredient, which is used in decorative cosmetics, fine fragrances, shampoos, toilet soaps as well as in household cleaners and detergents (Lapczynski et al., 2008). The acute oral toxicity was tested in rats and the acute LD50 resulted to be greater than 5 g/kg. Slight lethargy was observed as adverse reaction. Dermal studies in rabbits led to a dermal LD50 value of 3.6 g/kg. Three of four animals died at a dose of 5 g/kg. At all dose levels slight to moderate erythema and edema were observed (RIFM, 1973 op.cit. Lapczynski et al., 2008). The intramuscular LD50 was investigated in mice and was calculated to be 4.0 g/kg (Northover, 1962 op.cit. Lapczynski et al., 2008).

Since rhodinol is used as fragrance in dermal products, the skin irritation potential was tested on the upper arm of human volunteers. With a 5% preparation of rhodinol in Vaseline, in 18 of 40 volunteers irritation reactions were observed after 24 hours (RIFM, 1971 op.cit. Lapczynski et al., 2008).

References:

Lapczynski A., Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on rhodinol. Food and Chemical Toxicology 46, 259–262.

**Safrole**




Safrol occurs naturally in the essential oils of plants like sassafras, sweet basil, cinnamon as well as in spices (Ioannides et al., 1981 op.cit. Jin et al., 2011). The alkenylbenzene is used as food flavour and could also be found in aromatic oils, perfumes and detergents (Smith et al., 2002).

There have been many reports about the nephrotoxicity and hepatotoxicity of safrole. The gentoxicity was not confirmed and still needs further investigations (Jin et al., 2011). "*Safrole and sassafras oil were banned as food additives and flavouring agents by the FDA in 1960 because of their carcinogenic potential*". The European Council Directive on food flavouring determined a limit of 1 ppm for safrole in foodstuffs and beverages. The Committee of Experts on Flavoring Substances (CEFS) of the Council of Europe concluded 1997 that efforts should be made to reduce the consumption of safrole through foods and beverages as far as possible (Martati et al., 2011). "*The Scientific Committee for Food of the European Union estimated the average daily intake of safrole to be 0.3 mg/day, equivalent to 5 µg/kg body wt/day for a 60 kg person*" (SCF, 2002 op.cit. Martati et al., 2011).

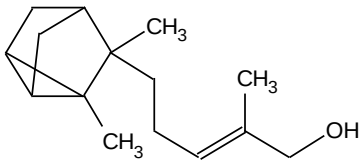
References:

Jin M., Kijima A., Suzuki Y., Hibi D., Inoue T., Ishii Y., Nohmi T., Nishikawa A., Ogawa K., Umemura T., 2011. Comprehensive toxicity study of safrole using a medium-term animal model with gpt delta rats. Toxicology. 290(2-3),312-21.

Martati E., Boersma M.G., Spenkelink A., Khadka D.B., Punt A., Vervoort J., Van Bladeren P.J., Rietjens I.M., 2011. Physiologically based biokinetic (PBBK) model for safrole bioactivation and detoxification in rats. Chem Res Toxicol. 24(6), 818-34.

Smith R.L., Adams T.B., Doull J., Feron V.J., Goodman J.I., Marnett L.J., Portoghese P.S., Waddell W.J., Wagner B.M., Rogers A.E., Caldwell J., Sipes I.G., 2002. Safety assessment of allylalkoxybenzene derivatives used as flavouring substances – methyl eugenol and estragole. Food Chem. Toxicol. 40, 851–870.

**α-Santalol**




The sesquiterpene α-santalol is a major compound of sandalwood oil (Bommareddy et al., 2012). "*The essential oil emulsion or paste of sandalwood is routinely used in India as an ayurvedic medicine to inflammatory and eruptive skin diseases*"（Dwivedi& Ghazaleh, 1997 op.cit. Paulpandia et al., 2012) as well as food-additve and as ingredient of cosmetics and perfumes (Jellin, 2002 op.cit. Bommareddy et al., 2012). "*Sandalwood and its oil have a long history of use without any reported adverse effects; therefore consumption of sandalwood oil as an added food ingredient is considered safe at present use levels*" (Paulpandia et al., 2012).

The use of α-santalol in skin formulations resulted in a maximum skin level of 0.10% that go into fine fragrances. The maximum daily exposure was calculated to be 0.0038 mg/kg for high end users of products containing α-santalol (IFRA, 2004 op.cit. Bhatia et al., 2008). Sensitization studies in guinea pigs resulted with mild sensitization reactions after an application of a 10% α-santalol containing formulation (Ishihara et al., 1986 op.cit. Bhatia et al., 2008).

Investigations about the anticancer activity of α-santalol demonstrated that it could inhibit the growth of human prostate cancer cells (Bommareddy et al., 2012).

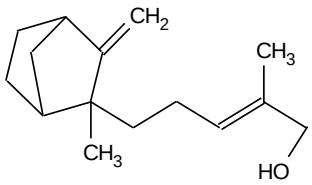
References:

Bhatia S.P., McGinty D., Letizia C.S., Api A.M., 2008. Fragrance material review on α-santalol Food and Chemical Toxicology 46, 267–269.

Bommareddya A., Rulea B., VanWerta A.L., Santhab S., Dwivedi C., 2012. α-Santalol, a derivative of sandalwood oil, induces apoptosis in human prostate cancer cells by causing caspase-3 activation. Phytomedicine 19, 804– 811.

Paulpandia M., Kannana S., Thangamb R., Kaverib K., Gunasekaranb P., Rejeetha C., 2012. In vitro anti-viral effect of α-santalol against influenza viral replication. Phytomedicine 19, 231– 235.

**β-Santalol**




The bicyclic sesquiterpene alcohol β-santalol (Sell, 2000 op.cit. Stappen et al., 2008) is beside α-santalol the main constituent of natural sandalwood oil.

It contributes up to 30% to the essential oil and is responsible for the typical sandalwood note with powerful woody, milky and urinous tonalities (Brocke et al., 2008). The essential oil is produced by distillation of the wood from *Santalum album* L. (Santalaceae). Due to its unique sweet, creamy and woody odour it is one of the oldest and widely used ingredients in fine perfumery (Buchbauer et al., 2004). The acute dermal LD50 value of sandalwood oil was determined to be greater than 5 g/k in rabbits (Shelanski, 1971 op.cit. Burdock&Carabin, 2008). There are only few reports about irritation or sensitisation reactions to sandalwood oil in humans.

At use levels below 0.001% (10 ppm), sandalwood oil is widely used to flavour food products such as beverages and sweets. The pale-yellow to yellow liquid has a slight bitter, resinous taste. "*Sandalwood oil is approved for food uses by the United States Food and Drug Administration (FDA), Flavor and Extract Manufacturers Association (FEMA) and Council of Europe (CoE)*" (Burdock&Carabin, 2008). The acute oral LD50 value of sandalwood oil was determined to be 5.58 g/kg in rats (Bar&Griepentrog, 1967 op.cit. Burdock&Carabin, 2008). Beside its use in perfumery and food industries, sandalwood oil is used medicinally to treat common colds, fever, bronchitis, infections of the urinary tract and other diseases (PDR Herbal, 2004 op.cit. Burdock&Carabin, 2008). During its long history of use, no reports about adverse effects have occurred. Concerning β-santalol in particular, there is no data available about the mutagenicity, gentoxicity or carcinogenicity (Paulpandia et al., 2012).

References:

Brocke C., Eh M., Finke A., 2008. Recent Developments in the Chemistry of Sandalwood Odorants. CHEMISTRY & BIODIVERSITY 5.

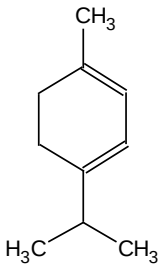
Buchbauer G., Stappen I., Pretterklieber C., Wolschann P., 2004. Structure-activity relationships of sandalwood odorants: synthesis and odor of tricyclo beta-santalol.. Eur J Med Chem. 39(12), 1039-46.

Burdock G.A., Carabin I.G., 2008. Safety assessment of sandalwood oil (Santalum album L.). Food and Chemical Toxicology 46, 421–432.

Paulpandia M., Kannana S., Thangamb R., Kaverib K., Gunasekaranb P., Rejeetha C., 2012. In vitro anti-viral effect of β-santalol against influenza viral replication. Phytomedicine 19, 231– 235.

Stappen I., Höfinghoff J., Friedl S., Pammer C., Wolschann P., Buchbauer G., 2008. Structureeactivity relationships of sandalwood odorants: Total synthesis and fragrance properties of cyclopropano-β-santalol. European Journal of Medicinal Chemistry 43, 1525-1529.

## α-Terpinene



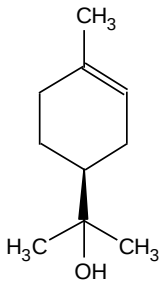

The cyclic monoterpene α-terpinene is a natural compound of various plants and is present in commonly used essential oils. For instance it is naturally occurring in tea tree oil (Brophy et al., 1989 op.cit. Rudbäck et al., 2012). There are many reports about contact allergy to tea tree oil. One of the components that are responsible for contact allergy to tea tree oil is supposed to be α-terpinene. The freshly distilled oil as well as the air exposed oil had sensitizing effects in guinea pigs (Rutherford et al., 2007). "*The sensitization potency of autoxidized α-terpinene was approximately 9 times higher compared to that of pure α-terpinene. Thus, α-terpinen. can be considered as a prehapten as well as a prohapten*" (Rudbäck et al., 2012).

References:

Rudbäck J., Bergström M.A., Börje A., Nilsson U., Karlberg A-T., 2012. α-Terpinene, an Antioxidant in Tea Tree Oil, Autoxidizes Rapidly to Skin Allergens on Air Exposure. Chem. Res. Toxicol. 25, 713−721.

Rutherford T., Nixon R., Tam M., Tate B., 2007. Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years.
Australas J Dermatol. 48(2), 83-7.

**α-Terpineol**




α-Terpineol is a relatively non-toxic volatile terpenoid alcohol. It is one of the major constituents of essential oils of various plant species (Moreira et al., 2001), such as *Ravensara aromatica* Sonn. (Lauraceae), *Melaleuca quinquenervia* S.T.Blake (Myrtaceae), *Myrtus communis* L. (Myrtaceae), *Laurus nobilis* L. (Lauraceae), *Croton sanderianum* L. (Euphorbiaceae) and *Eucalyptus globulus* Labill. (Myrtaceae), which have a vast use in folk medicine and in aromatherapy. It has been reported that α-terpineol shows antimicrobial and immunostimulant qualities (Franchome P. & Penoel D., 1995 op.cit. Moreira et al., 2001). Therefore, it is also important to understand the physiological effects. Since the compound blocks the CAP (compound action potential) of rat sciatic nerves, it owns a local anaesthetic activity; but to characterise this substance as a local anaesthetic agent, there are more criteria, like direct drug interaction with voltage-gated Na channels that need to be analysed (Moreira et al., 2001).

As component of the therapeutic potential *Croton nepetaefolius* L. (Euphorbiaceae), α-terpineol assumes a role in its cardiovascular effects like bradycardia, hypotension, anti-spasmodic and myorelaxant effects. Further studies are necessary to arrange it in anti-spasmodic therapies in humans (Abdon et al., 2002).

In the development of new clinically relevant drugs for the treatment of painful and inflammatory disease, α-terpineol might play an important role with its antinociceptive and anti-inflammatory properties on mechanical hypernociception. The reason for these effect may be the

inhibition of the NO release as well as the decrease of the production of inflammatory mediators (De Oliveira et al., 2012).

α-Terpineol, as a main component of pine oil, is not only widely used in the perfumery industry as fragrance ingredient in decorative cosmetics, shampoos, soaps and other toiletries, but also in household cleaners and detergents because of its mild antiseptic properties. A dose of 0.0726 mg/kg of α-terpineol is the maximum daily exposure on the skin (IFRA, 2004). Therefore, the consumer has to notice that many commonly used products contain high concentration of pine oil, which may cause skin irritation, acute respiratory system irritation and central nervous system depression. Depending on the kind of application, there is large variation in the maximal doses of α-terpineol. The Material Safety Data Sheet of the Product (MSDS) indicate that the oral LD50 may be as high as 4300 mg/kg for humans, and 5750 mg/kg for rats. Those data confirm the assumption of a moderate oral acute toxicity (Martz, 2010). This low toxicity is also approved in other studies like Ellenhorn, which investigated the lethal dose of pine oil: the adult LD50 was supposed to be 60-120 g (Ellenhorn, 1997 op.cit. Martz, 2010).

In carcinogenesis assays the maximum tolerated dose (MTD) was 0.400 g/kg (Stoner et al., 1973 op.cit. Bahita et al., 2008).

The LD50 of intramuscular injections in mice was calculated to be 2 g/kg (Northover & Verghese, 1962 op.cit. Bahita et al., 2008). The ID50 (irritant dose in 50% individuals) on mice was observed to be 0.853 µg/5 µl (Saeed & Sabir, 1994 op.cit. Bahita et al., 2008).

The intravenous injection of 0.1 ml/kg of pine oil in horses lead to the animal's death within minutes because of massive pulmonary edema (Bahita et al., 2008).

References:

Abdon A.P., Leal-Cardoso J.H., Coelho-de-Souza A.N., Morais S.M., Santos C.F., 2002. Antinociceptive effects of the essential oil of Croton nepetaefolius on mice. Braz. J. Med. Biol. Res. 35, 1215–1219.

Bhatia S.P., Letizia C.S., Api A.M., 2008. Fragrance material review on (-)-a-terpineol. Food and Chemical Toxicology 46, S280–S285.

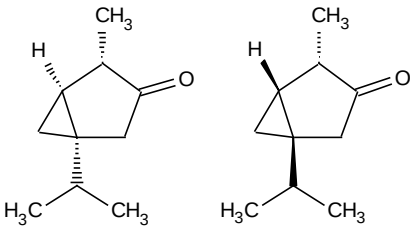
De Oliveira M.G.B., Marques R.B., De Santana M.F., Santos A.B.D., Brito F. A., Barreto E.O., De Sousa D.P., Almeida F.R.C., Badauê-Passos Jr. D., Antoniolli A.R., Quintans-Júnior L.J., 2012. Alpha-Terpineol Reduces Mechanical Hypernociception and Inflammatory Response. Basic & Clinical Pharmacology & Toxicology 111, 120–125.

IFRA (International Fragrance Association), 2004. Use Level Survey

Martz W., 2010. A Lethal Ingestion of a Household Cleaner Containing Pine Oil and Isopropanol. Journal of Analytical Toxicology Vol. 34.

M.R., Cruz G.M.P., Lopes M.S., Albuquerque A.A.C., Leal-Cardoso J.H., 2001. Effects of terpineol on the compound action potential of the rat sciatic nerve Brazilian. Journal of Medical and Biological Research 34, 1337-1340.

**Thujone**




(+)-α (+)-β

The monoterpene thujone is a main constituent of the essential oils of *Artemisia absinthium* L. (Asteraceae), *Salvia officinalis* L. (Lamiaceae), *Thuja occidentalis* L. (Cupresseceae) and other plants. It occurs naturally as a mixture of alpha and beta diasteroisomers. Thujone is widely used to flavour foodstuff and beverages (Höld et al., 2000), especially for alcoholic beverages such as absinthe. "*The maximum level in the final product ready for consumption is 100 mg/l*". At high concentrations of thujone the attention performance could be decreased (Dettling et al., 2004). There have been reports about intoxications after exposure to herbal products containing thujone (Stafstrom, 2007). For instance doses higher than 200 nl/ml of the essential oil of *Salvia officinalis* cause hepatotoxic effects. At that, thujone contributes with its neurotoxicity (Lima et al., 2004). "*The European Medicines Agency (EMA) has recently implemented an acceptable daily intake (ADI) of 5.0 mg/person for a maximum duration of use of 2 weeks in their Salvia officinalis monograph*" (EMEA, 2009 op.cit. Walch et al., 2011). Due to its toxicity, the use of thujone is only allowed in determined concentrations. The oral LD50 in rats has been reported to be 192 mg/kg (EC, 2003 op.cit. Al-Haj Baddar et al., 2011).

The LD50 value after subcutaneous administration in mice was reported to be 87.5 mg/kg. After intraperitoneal administration to rats, the LD50 value was determined to be 240 mg/kg (EMEA, 1999 op.cit. Naser et al., 2005). "*Up to a single daily dose of 75 mg is reported to be safe in humans*". The maximum permitted level of thujone in alcoholic beverages is 5 mg/l in 25% alcohol (EC, 2002 op.cit. Naser et al., 2005). Mentionable is that β-thujone is generally of lower toxicity than the α-diastereomer (Höld et al., 2000).

Concerning food stuff, thujone as such is not allowed to be added; "*it may only be indirectly introduced into foods by use of thujone-containing plants*" (EC, 2008 op.cit. Walch et al., 2011).

References:


Al-Haj Baddar N.W. , Aburjai T.A., Taha M.A. Disi A.M., 2011. Thujone corrects cholesterol and triglyceride profiles in diabetic rat model Natural Product Research 25(12), 1180–1184.

Dettling A., Grass H., Schuff A., Skopp G., Strohbeck-Kuehner P., Haffner H.T., 2004. Absinthe: Attention Performance and Mood under the Influence of Thujone. J. Stud. Alcohol 65, 573-581.

Höld K.M., Sirisoma N.S., Ikeda T., Narahashi T., Casida J.E., 2000. α-thujone (the active component of absinthe): γ-aminobutyric acid type A receptor modulation and metabolic detoxification. Proc Natl Acad Sci USA. 97(8), 3826-31.

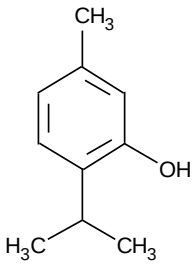
Lima C.F., Carvalho F., Fernandes E., Bastos M.L., Santos-Gomes P.C., Fernandes-Ferreira M., Pereira-Wilson C., 2004. Evaluation of toxic/protective effects of the essential oil of Salvia officinalis on freshly isolated rat hepatocytes. Toxicology in Vitro 18, 457–465.

Naser1 B., Bodinet C., Tegtmeier M., Lindequist U., 2005. Thuja occidentalis (Arbor vitae): A Review of its Pharmaceutical, Pharmacological and Clinical Properties eCAM 2(1), 69–78.

Stafstrom C.E., 2007. Seizures in a 7-month-old child after exposure to the essential plant oil thuja. Pediatr Neurol 37,446e8.

Walch S.G., Kuballa T., Stühlinger W., Lachenmeier D.W., 2011. Determination of the biologically active flavour substances thujone and camphor in foods and medicines containing sage (Salvia officinalis L.). Chemistry Central Journal 5, 44.

**Thymol**




"*Thymol is a naturally occurring phenolic monoterpene which is found as a component of many essential oils used extensively in fragrances, flavour additives, or scenting products*" (Burt, 2004). It is the major compound of the essential oils of many aromatic plants, for instance *Thymus vulgaris* L. (Lamiaceae), *Origanium compactum* Benth. (Lamiaceae), *Acalypha phleoides* Cav. (Euphorbiaceae), *Lippia sidoides* Cham. (Verbenaceae) and others. Those plants are widely used in folk medicine as well as in aromatherapy (Lemos et al., 1990 op.cit. Peixoto-Neves et al., 2010).

Thymol is generally recognised as safe by the United States Food and Drug Administration FDA (Rivas et al., 2010). Studies about the acute toxicity of thymol in mice reported that all tested animals died at a dose of 1800 mg/kg. The LD50 was determined to be 1134.03 mg/kg (Archana et al., 2011).

Furthermore thymol was found to possess clastogenic effects. Therefore, it could be concluded that thymol may have a genotoxic risk (Azirak&Rencuzogullari, 2008). Despite to its toxicity, thymol is still widely used to prepare food items, drinks and household materials (Nibret&Wink, 2010).

References:

Archana P.R., Raoa B.N., Raoa B.S.S., 2011. In vivo radioprotective potential of thymol, a monoterpene phenol derivative of cymene Mutat Res. 726(2), 136-45.

Azirak S.&Rencuzogullari E., 2008. The In Vivo Genotoxic Effects of Carvacrol and Thymol in Rat Bone Marrow Cells. Inc. Environ Toxicol 23, 728–735.

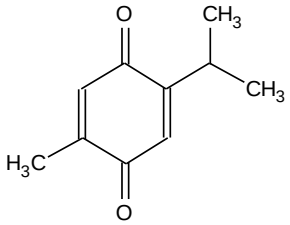
Burt S., 2004. Essential oils: their antibacterial properties and potential applications in foods - a review. Int. J. Food Microbiol. 94, 223e253.

Nibret E.,& Wink M., 2010. Trypanocidal and antileukaemic effects of the essential oils of Hagenia abyssinica, Leonotis ocymifolia, Moringa stenopetala, and their main individual constituents. Phytomedicine 17, 911–920.

Peixoto-Nevesa D., Silva-Alvesa K.S., Gomesa M.D.M., Limaa F.C., Lahloua S., Magalha˜esb P.J.C., Ceccattoa V.M., Coelho-de-Souzaa A.N., Leal-Cardosoa J.H., 2010. Vasorelaxant effects of the monoterpenic phenol isomers, carvacrol and thymol, on rat isolated aorta. Fundamental & Clinical Pharmacology 24, 341–350.

Rivas L., McDonnell M.J., Burgess C.M., O'Brien M., Navarro-Villa A., Fanning S., Duffy G., 2010. Inhibition of verocytotoxigenic Escherichia coli in model broth and rumen systems by carvacrol and thymol. International Journal of Food Microbiology 139, 70-78.

**Thymoquinone**




The monoterpenoid hydrocarbon thymoquinone is a compound of the essential oil of *Nigella sativa* L. (Ranunculaceae) (Nickavar et al., 2003 op.cit. Akhondian et al., 2011). The essential oil is used therapeutically because of its carminative, diuretic and lactagogue properties. It is also widely used as spice in foods. The oil is known to have a very low degree of toxicity (Ali&Blunden, 2003). "*The seeds of the black seeds, or Nigella sativa, have long been used in folk medicine for a wide range of illnesses including allergy, bronchial asthma, headache, dysentery, infections, obesity, back pain, hypertension and gastrointestinal problems*" (Al-Ghamdi et al., 2001). There have been only few cases of allergic contact dermatitis after the topical use of pure oil of *N. sativa* (Zedlitz et al., 2002).

Studies show that thymoquinone owns hepatoprotective properties, especially in low doses. It has been reported that the oral LD50 value of thymoquinone in rats and mice was ten times higher than the intraperitoneal LD50. The estimated LD50 level in mice was
104.7 mg/kg.

It is suggested to be a relatively safe compound (Al-Ali et al., 2008). "*The adverse effects most commonly attributed to thymoquinone treatment involved CNS (somnolence) and gastrointestinal tract (nausea) effects*". Investigations about the effect of thymoquinone on intractable pediatric seizures demonstrated that a dose of 1 mg/kg/day was generally well tolerated (Akhondian et al., 2011).

References:

Akhondian J., Kianifar H., Raoofziaee M., Moayedpour A., Toosi M.B., Khajedaluee M., 2011. The effect of thymoquinone on intractable pediatric seizures (pilot study). Epilepsy Research 93, 39—43.

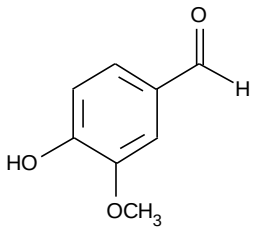
Al-Ali A., Alkhawajah A.A., Randhawa M.A., Shaikh N.A., 2008. Oral and intraperitoneal LD50 of thymoquinone, an active principle of Nigella sativa, in mice and rats. J Ayub Med Coll Abbottabad 20, 25–27.

Al-Ghamdi M.S., 2001. The anti-inflammatory, analgesic and antipyretic activity of Nigella sativa. J Ethnopharmacol 76, 45–48.

Ali B. H.& Blunden G., 2003. Pharmacological and Toxicological Properties of Nigella sativa. Phytother. Res. 17, 299–305.

Zedlitz S., Kaufmann R., Bochncke W.H., 2002. Allergic contact dermatitis from black cumin (Nigella sativa) oil-containing ointment. Contact Derm 46, 188.

## Vanillin




"*Vanillin is the major component of natural vanilla, which is one of the most widely used and important flavouring materials worldwide*" (Walton et al., 2003). It could be obtained through extraction of the seedpods of the orchid *Vanilla planifolia* Jacks. ex Andrews (Orchidaceae) (Sinha et al., 2007 op.cit. Beaudry et al., 2010). "*Traditionally, vanillin was used as flavoring agent, sleep prevention agent, and aphrodisiac*" (Bythrow, 2005 op.cit. Ho et al., 2011). The Flavor and Extract Manufactures' Association FEMA gave Vanillin the GRAS status and the Food and Drug Administration FDA recognised it as suitable for food use. The oral LD50 value of vanillin has been determined between 1.58 and 2.8 g/kg in rats (Opdyke, 1977 op.cit. Lirdprapamongkol et al., 2009). "*The concentrations of vanillin used in food and beverage products cover a broad range of 0.3-33 mM*" (Kamat et al., 2000 op.cit Lirdprapamongkol et al., 2009). Studies reported about the anti-inflammatory property of vanillin. "*Therefore, due to its safety, vanillin seems to be a potent drug candidate for the treatment of inflammatory bowel disease*" (Wu et al., 2009).

References:

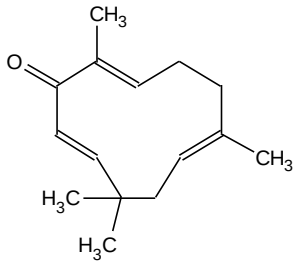
Beaudry F., Ross A., Lema P.P., Vachon P., 2010. Pharmacokinetics of Vanillin and its Effects on Mechanical Hypersensitivity in a Rat Model of Neuropathic Pain. Phytother. Res. 24, 525–530.

Lirdprapamongkol K., Kramb J.P., Suthiphongchai T., Surarit R. et al, 2009. Vanillin suppresses metastatic potential of human cancer cells through PI3K inhibition and decreases angiogenesis in vivo. J. Agric. Food Chem. 57, 3055–3063.

Walton N.J, Mayer M.J., Narbad A., 2003. Vanillin. Phytochemistry 63, 505–515.

Wu S-L., Chen J-C., Li C-C., Lo H-Y., Ho T-Y., et al., 2009. Vanillin Improves and Prevents Trinitrobenzene Sulfonic Acid- Induced Colitis in Mice. JPET 330, 370–376.

**Zerumbone**




The cyclic sesquiterpene zerumbone occurs naturally as main bioactive compound in the rhizome of *Zingiber zerumbet* Smith (Zingiberaceae) (Sulaiman et al., 2009). "*In Malaysia, the rhizome of the plant is commonly used as a condiment for flavoring food and have antispasmodic, analgesic, antirheumatic and carminative effects in folk medicine*" (Habsah et al., 2000).

Zerumbone has been reported to be little cytotoxic and genotoxic. The intraperitoneal administration of doses as high as 2000 mg/kg, were reported to be lethal in rats (Al-Zubairi et al., 2010). "*Toxicity tests of zerumbone showed no occurrence of death in mice over a period of seven days at a dose of 1 g/kg in the literature*" (Sulaiman et al., 2010). "*It has been shown to be one of the most promising chemopreventive agents against colon and skin cancer*" (Nakamura et al., 2004). Due to its low toxicity it could be safely used for various treatments (Tada et al., 2005)

References:

Al-Zubairi A.S., Abdul A.B., Syam M.M., 2010. Evaluation of the genotoxicity of zerumbone in cultured human peripheral blood lymphocytes. Toxicol In Vitro 24, 707–12.

Habsah M., Amran M., Mackeen M.M., Lajis N.H., Kikuzaki H., Nakatani H., et al., 2000. Screening of Zingiberaceae extracts for antimicrobial and antioxidant activities. J Ethnopharmacol 72, 403–10.

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Sulaiman M.R., Tengku Mohamad T.A., Shaik Mossadeq W.M., Moin S., Yusof M., Mokhtar A.F., et al., 2009. Antinociceptive activity of the essential oil of Zingiber zerumbet. Planta Med. 76, 107–12.

Tada T., Jimi E., Okamoto M., Ozeki S., Okabe K., 2005. Oral squamous cell carcinoma cells induce osteoclast differentiation by suppression of osteoprotegerin expression in osteoblasts. Int J Cancer 116, 253–62.

## Curriculum Vitae

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