Essential oils: renewal of interest and toxicity

Essential oils are complex mixtures of substances from vegetable matter, the definition of which is based on their method of extraction. They are characterized by their ambivalence, their ambiguity and their disparity: plant families from which essential oils are extracted are numerous; the composition of each essential oil depends not only on the family but also on the part of the plant from which it is extracted, and sometimes on the soil where the plant grows, or even on the time of the harvest. Gas chromatography is therefore necessary to characterize an essential oil. Essential oils can be found in cosmetics, in drugs, and in food. They are natural substances, but natural is not synonymous with harmless. Evaluation of the toxicity of essential oils and European regulation are underway.

Key words: toxicity, allergy, essential oils, natural products, plant, regulation

In 2009, a search about essential oils on the Google France website retrieved 1,420,000 results, reflecting a renewal of interest in the general public. Physicians have to be able to answer their patients with precise information; they need to ask them about the use of essential oils to avoid missing diagnoses of contact allergy or pathologies linked to toxic phenomena. Since the beginning of the century, essential oils have been the subject of scientific and regulatory research aiming to clarify this complex issue, all the more so because serious undesirable effects have been reported by a “watchdog committee” in dermatology.

After reviewing the definition, method of extraction and composition of essential oils, this article will describe their history (to appreciate their comeback one must first understand why they fell out of favour), and finally their toxicity and its consequences (advice, recommendations and regulatory framework). Allergic reactions will only be mentioned briefly, as they were discussed by An Goossens [1].

Definition

The term “essential oil” is defined as follows [2]: “an odorous product, generally of complex composition, obtained from a botanically defined raw material, either by water vapour extraction (figure 1), by dry distillation, or by an appropriate mechanical process without heating. The essential oil is most often separated from the aqueous phase through a physical process, which does not involve a significant change in its composition”. Dry distillation, without addition of water vapour, is used for wood, bark and roots. The mechanical process is used exclusively for citrus fruit: their essential oils are contained in microvesicles located in the peel and extracted by pressure or friction (figure 2).

This type of definition excludes all other processes.

Essential oils are not produced by:
– Incision, except for pine resin, which, once distilled, gives essential oil of turpentine and colophony or rosin, a resinoid rich in diterpenes.
– Enfleurage: extraction of flower perfumes (jasmine, tuberose) through contact with fats, without immersion.
– Alcoholic maceration: natural vanilla extract is obtained from vanilla pods after soaking in alcohol, followed by distillation.
– The so-called “underground” industry may combine the different processes, which explains the need to ensure traceability.

Citrus fruits are always treated fresh, but for other plants essential oil can be extracted from fresh, wilted, dry, or whole vegetable matter ground or reduced to powder. Different plant parts can be used:
– rose petals,
– orange blossom, lavender blossom,
– leaves of lemon grass, eucalyptus, bay laurel,
– vetiver roots,
– turmeric, ginger rhizomes,
– nutmeg seed,
– cinnamon bark,
– mint secretory down.

After production, essential oils can be completely or partially freed of monoterpenic and/or sesquiterpenic hydrocarbons, rectified (some elements suppressed by fractional distillation), or deprived of X (complete or partial separation of one of their elements).

As a result, essential oils are a complex set of complex substances, unified by one method, water vapour extraction, and by one origin: vegetable matter. Essential oils are the volatile interactive part of the plant, i.e. the odorous part. Their composition can change after extraction depending on the storage conditions, they can quickly become oxidized, and this oxidation is responsible in some cases for their allergenic capacity [3]. Plant enzymes that produce odorous substances are not necessarily
present in all parts of the plant: the composition of the essential oil depends on the part of the plant that it comes from. Therefore essential oils have to be designated according to the scientific nomenclature developed by Linné: written in Latin, the name of the genus precedes the name of the species, which is then followed by the initials of the botanist who first described the plant and, if necessary, the subspecies or the variety type, then possibly the name of the part of the plant, and lastly the word “oil”, which takes into account the extraction process. Furthermore, for the same part of a plant, the composition of the oil can noticeably change depending on the soil, the harvest date, and even the season [4], leading to the biosynthesis of different metabolites, the toxicity of which may be different. Several different chemotypes exist for one and the same oil. This explains the creation in France, by a decree of Oct. 24th 1997, of an AOC (appellation d’origine contrôlée or guarantee of origin), for the essence of lavender in France. To qualify for this AOC, only the flowering heads of *Lavandula angustifolia* P. Miller are used. Production area and yield are limited; no additives are authorized.

Driven by water vapour, essential oils float at the surface of the liquid in the still. Essential oils are hydrophobic and lipophilic, they interact with fat and organs rich in fat content, which may explain their pharmacological and toxic effects. They are essences and not oils (figure 3). Their composition is determined by gas chromatography and by mass spectrometry. They are made of 3 types of constituents: terpenes, aromatic compounds and others of diverse origins.

**Terpenes of formula** (C5H8)n. The most volatile terpenes in essential oils are monoterpenes and sesquiterpenic terpenes. As their functions can display a variable degree of oxidation, numerous substances are possible: Monoterpenes [5] C10H16 (n = 2) can be acyclic (myrcene for instance), monocyclic (such as thymol), or bicyclic. They can represent 90 percent of the essential oil (i.e. turpentine). They are the principal constituents of essential oils; as they form the first link in biosynthesis, they are found in many plants. Simple terpenes are not very allergenic, but quickly become so, due to oxidation into hydroperoxide derivatives. Oxidation can be prevented by storage in conditions of obscurity and low temperature. Once applied to the skin, terpenes are able to interact, and this can change their penetration [6]. Sesquiterpenes (n = 3) are the subject of many cyclizations, reorganizations, and oxidation that generate a great number of structures. They can present as lactone rings that are readily allergenic.

**Aromatic compounds**

Biosynthesized from shikimic acid (first isolated from shikimi or *Illicium anisatum*, also called Japanese anise
Other compounds

During distillation some aliphatic compounds such as carbides, acids, alcohols, and esters are also extracted. Undesirable compounds, pesticides and similar products used during plant growth, can sometimes be found in the essential oil.

Uses of essential oils

They are used in pharmacology, either as the active principle or as the vehicle of medicines, and also in cosmetics, in food, during leisure activities and in industry.

The main plant families from which essential oils can be extracted include: the abietaceae (the best known member is Pinus pinaster Ait which produces turpentine), the cupressaceae (thuja, cypress, juniper), the lamiaceae, one of the most important families for essential oils (basil, true or hybrid lavender, marjoram, lemon balm, mint, oregano, patchouli, rosemary, sage), the myrtaceae (eucalyptus, clove tree, myrtle, niaouli), the lauraceae (cinnamon, laurel, rosewood, clove nutmeg, sassafras), the rutaceae (lemon, lime, mandarin, sweet and bitter orange, grapefruit), the ericaceae (wintergreen, Labrador tea), the asteraceae (camomile, tarragon, sweet inula, gray santolina), the poaceae (lemon grass), and the rosaceae (rose).

Essential oils should be distinguished from

- Herbal tea: a potable aqueous preparation obtained by decoction, infusion or maceration of one or several drug plants [8].
- Vegetable oils obtained by pressure (olive oil, seed oil, etc). They are not very interactive, dry slowly and leave greasy residues, whereas essential oils quickly vanish without any trace, like gasoline.
- Oils of mineral origin, which are greasy like oils obtained through extraction.
- Aromatic water or distilled flower water: the aqueous residue of water vapour distillation, once the essential oil is removed.
- Concretes: plant essences obtained from fresh raw material by extraction with a non aqueous solvent. Their composition, olfactory qualities and effects are different from those of essential oil of the same plant, because the solvent does not act on the same molecules as water vapour.
- Absolute concretes: these extracts are obtained by washing concretes with alcohol which removes the aromatic compounds from the greasy phase, followed by icing and filtering.
- Resinoids: concretes obtained from seeds, roots or mosses.

In summary, essential oils are defined by a physical method of extraction without addition of chemical compounds; however, they exhibit great disparity from one another, and the same oil can present with multiple different chemotypes. Their precise composition can only be determined by chemical analysis.

History [9]

It is not easy to determine when the extraction of essential oils first appeared; in fact ancient writings that reported on medicinal distilled waters do not accurately describe the process used. The first documents describing distillation date back to the 9th century. Imported into Europe by the Arabs, the products were not at that time what we now define as essential oils: plants were prepared with alcohol, and the substances produced were distilled aromatic waters. In the 16th century the notions of fatty oils and essential oils, as well as the methods for separating essences from aromatic waters, became established. Essential oils were at this time commercialized with cosmetic, industrial and therapeutic objectives. At the end of the 19th century, chemistry made it possible to isolate and reproduce molecules active in therapy and perfumery, and used in industry. The development of chemistry in the 20th century made it possible to produce numerous, cheap and stable molecules that ensured standardized production, security of formulation and efficiency, and that slowly replaced essential oils, which then came to be considered as alchemy. In fact their production depended on a high number of workers whose wages and social taxes reduced the profitability of manufacturers. Furthermore, these workers, often not well paid, preferred urban migration and the dream of better conditions. At the same time, many publications demonstrated the allergenic potential of essential oils used for wound healing. Medical progress, universal access to health care systems, as well as published reports of fatalities from the use of Chinese herbs [10] did not motivate people to look beyond conventional medicine, even if René Maurice Gattefossé created the word aromatherapy in the 1920s in France (this engineer had observed the healing power of lavender essential oil in curing burns) and, in the seventies, Dr. Jean Valnet had devoted his career to promoting phyto-aromatherapy and in 1981 founded the institute for phyto-aromatherapy (Journal Officiel de la République Française 02/04/1981).

Beginning in the 1990s, and increasingly so since the beginning of the 21st century, it has become apparent that essential oils are enjoying a renewal of popularity. This can be attributed to a number of factors: the ecological trend that calls for a return to nature and preservation of the environment; economic considerations that promote self-medication; improved social and cultural conditions with greater leisure time; increased access to unfiltered information from the internet, such as postings about the risk of cancer from hair dyes, the effects of chemicals on human fertility, or awareness of the toxicity of chemical pesticides for the planet; scandals involving public health (such as tainted transfusion blood, asbestos, growth hormones); the implementation of the REACH system (Registration, Evaluation, Authorisation and restriction of CHemicals) that targets substances produced in amounts of more than one ton per year and to which it seems that essential oils will not be submitted because of a lack of patents applicable to plant extracts; increasing suspicion of entirely synthetic odorous molecules, gradual harmonization of the legal framework throughout the European Union (in some European countries essential oils are considered as medicaments and may be registered
for traditional use) [11]; globalization, which makes available essential oils produced in countries where the workforce is cheap, etc. Essential oils have thus emerged from oblivion and dominate the market among organic products (even allopathy has come up with its own organic or bio-therapies). This renewal is partly based on dissatisfaction with synthetic chemistry and partly on aggressive marketing that emphasizes that natural products are harmless. This explains the more than one million results found on a Google search.

**Toxicity of essential oils**

Essential oils certainly play an important role in plants: they are secreted as a reaction to the environment, as a means of protection (inhibition of germination in winter for instance, triggering of flowering, or protection against parasites, insects or herbivores) [12], or to assist pollination by attracting certain insects. For the sake of comprehensiveness, toxicity should be considered from all angles for each essential oil: acute toxicity, irritation and corrosiveness, sensitization, percutaneous absorption, effects of repeated exposure, phototoxicity, carcinogenicity, reprotoxicity, and teratogenicity. In practice, only a few publications tackle this complex question. A toxicity report should be based on findings of percutaneous or mucous membrane penetration for each essential oil, but this kind of research is difficult to carry out.

The toxicity of essential oils varies according to their composition, which itself varies with the plant, which itself may vary with the soil where it grows (chemotype). Their composition may be ascertained with precision by gas chromatography. For example, the essential oil of the *Salvia officinalis* L leaf is richer in toxic thujone in Estonia than in other parts of Europe [13]. Toxicity varies according to the period of the year where the plant is harvested [14, 15]. It varies with the route of administration (oral, cutaneous or airborne), with the general health of the exposed person (penetration and toxicity are maximized by damaged skin) and with eventual additives associated with the oil (surface active potpourris for instance) [16]. It varies according to the species of the recipient and its level of development. The toxicity of essential oils is more desirable on insects than on infants. Certain publications are not easy to interpret, because the described essential oil is not characterized by gas chromatography and mass spectrometry or is referred only to by its vernacular name.

However, some international public health groups are working to evaluate the toxicity of some components of essential oils and establish their NO Adverse Effect Level (NOAEL). They aim to set standards to ensure the safe use of these products. Research is handicapped by the complexity of essential oils. Some reports have examined only a single terpene isolated from the product, or even produced by synthesis. Publications about the toxicity of essential oils are heterogeneous: simple case reports, animal studies of specific essential oils including calculation of LD 50, or animal studies of a particular element of essential oils that can be produced by synthesis and used in industry, such as dipentene.

**Toxicity on germs** [17, 18]

Numerous publications show the anti-infectious effect of essential oils over an extremely wide spectrum. A kind of aromagram (the equivalent for essential oil of the antibiogram for antibiotics) has been developed [19]. The risk of allergic reactions and irritation of mucous membranes and the respiratory tract currently limit their use [20, 21]. This risk can be difficult to detect, because current tracers of contact allergy to odorous substances cannot reveal all allergies to essential oils [22].

**Toxicity in animals**

**Against insects**

Numerous recent publications, which cannot all be quoted herein, [23, 24] describe the insecticidal effect of different oils on different parasites, sometimes in larval state, and even on pyrethrum- or malathion-resistant lice [25].

**Toxicity in mammals**

House cats and dogs [26] treated with tea tree oil (melaleuca) for dermatoses have developed depression, weakness and muscle tremors that disappeared three days after stopping the application. A dog intoxicated with the essential oil of *Mentha pulegium* L died. Its owner applied the oil to eliminate fleas and when he noticed vomiting in the dog he gave it a shampoo. The shampoo was certainly not appropriate, given its contents of active surface agents and the lipophilicity of essential oils. The autopsy demonstrated widespread internal bleeding and hyaline membranes in the lungs [27]. Other essential oils have poisoned dogs. Cats were in most cases poisoned by potpourris.

Experiments with mice were carried out to determine seasonal changes in toxicity of the essential oil of *Salvia officinalis* L leaf by calculating its LD 50 when administered by intraperitoneal injection. Springtime extracts proved to be the least toxic and winter extracts the most, causing convulsions. Gas chromatography indicated that toxicity depended on the level of camphor and α-thujone. This corroborates the results of Millet and Jouglard [28]. In 1981, these scientists demonstrated in rats the toxic, convulsant and lethal properties of camphor and α-thujone, monoterpenic ketone in salvia oil, of thujone in thuja and cedar oils, and also of terpeneic pinocamphone ketone in hyssop oil. The toxicity of terpeneic ketones has been known since the beginning of the 20th century; its effect is cumulative and its role has been demonstrated in the toxicity of absinth. The carcinogenicity with DNA damage of estragol (1-methoxy-4-(3-propenyl)-benzene) and of its metabolites, present in the essential oils of several plants (tarragon, star anise, green anise, some basils and fennels, etc.), has also been demonstrated in mice through ingestion or intraperitoneal injection. This effect is dose-dependent and the toxic level is much higher than that which is predictable for man. There is not enough data about topical exposure [29]. Studies of force-feeding, first with rats, then with mice, have shown similar results for methyl iso-eugenol [30].

In mice the essential oil *Mentha pulegium* L, rich in R- (+) pulegone, is hepatotoxic due to the ketone function of this terpene, as well as to its metabolite, menthofuran, which has a different structure [31]. Pulegone has been limited in mint candies to a maximal dose of 250 ppm, and 20 ppm in mint drinks.
Different animal species have been used to evaluate the toxicity of dipentene, a mixture of two optic isomers of limonene present in the essential oils of citrus fruits [32]. It is hepatotoxic after acute exposure from oral and peritoneal administration. It has a sedative muscular relaxing effect in mice and is nephrotoxic only in male rats, through the irreversible binding of its metabolite to the protein alpha 2 u globuline. During prolonged exposure, no NOAEL could be calculated for the male rat because of its nephrotoxicity, whereas the NOAEL israther high in female rats (1,200 mg/kg). Dipentene has little irritating effect on rabbit skin and induces tearing and redness in rabbit conjunctiva. In mice, inhalation can induce sensory irritation with a RD 50 of more than 1,000 ppm. Guinea pigs can regularly become sensitized to dipentene, when exposed in open air for at least two months, doubtless due to the formation of dipentene and carvone hydroperoxide through self-oxidation. It is not genotoxic, but carcino- genic in male rats and anti-tumoral in mice and female rats (it shrinks induced tumors but not implanted ones). As such, it is an unclassifiable carcinogenic agent. It is foetotoxic in rats and rabbits, and teratogenic for rabbit and mouse. These different reports attest to the complexity of the problem. Essential oils are natural products, but display toxicity in animals. Natural is not synonymous with harmless. Toxicity may vary according to the species, sometimes according to sex in the same species, thus making it difficult to transpose the result of these studies to humans. Toxicity on bacteria and insects could be used, but the side effects on humans and the environment are not easy to evaluate.

**Toxicity in humans**

It has been observed in 5 main situations: application to freshly excised human skin, accidental ingestion, clinical studies of industrial products, inadequate or improper use, and clinical observations of cutaneous toxicity. On freshly excised human skin, the essential oil of *Backhousia citriodora* creates histological cell necrosis and vacuolation, whereas only citral is found in the entire skin through gas chromatography and mass spectrometry [33].

**Accidental or intentional ingestions:** accidental ingestion casualties often occur among young children. Ingestion of anti-mosquito citronella does not seem significantly toxic [34].

**Reports about industry** deal with turpentine and iso-eugenol.
- With turpentine, the administration to 8 healthy volun- teers of 450 mg/m3 in an inhalation chamber caused throat irritation during exposure, and increased airway resistance post exposure [35].
- Limonene [32] caused diarrhoea and transient proteinuria in healthy volunteers after ingestion of 20 g of d-limonene. Vapour inhalation caused respiratory disorders coupled with a decrease in vital capacity. No neurological disorders occurred. Limonene is a skin irritant when applied for 4 hours. Splashing may cause ocular irritation. Chronic exposure to dipentene can induce irritation and allergy.

**Inadequate use:** As registered by the committee for cosmetic safety in 2003-4, a balm containing camphor, eucalyptol and menthol given with free cosmetic gifts in a maternity hospital and used to treat respiratory tract ailments, caused convulsions in children aged between 21/2 months and 4 years. Similar cases have been described with camphor [36-38]. The most important essential oil-producing plants that contain toxic substances for humans are listed in table 1.

**Clinical observations of cutaneous toxicity**

Phototoxic dermatoses caused by essential oils have been well known for a long time and include meadow dermatitis and berloque dermatitis. They are sometimes due to in vivo distillation phenomena. The essential oils can be produced close to the skin by heat and humidity. The substances involved are furocoumarins among others. Allergic contact dermatitis caused by essential oils is common enough that many essential oil components have been added to the list of fragrance allergens (table 2). Some allergens are found in standard series (fragrance mix and fragrance mix 2, sesquiterpene lactone mix), while others are present in specialized series (d-limonene, geraniol, citronella, linalool, citral, coumarin, cinnamic alcohol, iso-eugenol. 

**Table 1. Essential oils and toxic substances**

<table>
<thead>
<tr>
<th>Plant generally toxic for humans</th>
<th>Incriminated compound/composite</th>
<th>A Woolf C toxicology 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Eucalyptus globulus</em> Labill</td>
<td>1.8 cineol</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Foeniculum vulgare</em> Mill</td>
<td>Fenchone</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Hyssopus officinalis</em> L</td>
<td>Pinocamphone, 1.8 cineol</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Mentha pulegium</em> Labill</td>
<td>Pulegone</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Hedeoma pulegioides</em> L</td>
<td></td>
<td>Hepatic necrosis, DIC*</td>
</tr>
<tr>
<td><em>Rosmarinus officinalis</em> L</td>
<td>1.8 cineol, camphor</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Salvia officinalis</em> L</td>
<td>Thujone, camphor, 1.8 cineol</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Juniperus sabina</em> L</td>
<td>Sabinalacetate, camphor, thuzone</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Tanacetum vulgare</em> L</td>
<td>Thujone, camphor, 1.8 cineol</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Thuya occidentalis</em> L</td>
<td>Thujone, fenchone, camphor</td>
<td>Convulsions</td>
</tr>
<tr>
<td><em>Artemisia absinthium</em> L</td>
<td>@Thujone</td>
<td>Epilepsy, dementia</td>
</tr>
<tr>
<td>Mentha sp</td>
<td>Menthol, menthone</td>
<td>Ataxia, myalgia</td>
</tr>
<tr>
<td>Nutmeg</td>
<td>Myristicine, eugenol</td>
<td>Hallucination</td>
</tr>
</tbody>
</table>

*Disseminated Intravascular Coagulation.*
benzyl alcohol, anisic alcohol, eugenol, isoeugenol, benzyl salicylate benzyl cinnamate, cinnamaldehyde, menthol, atranorin, turpentine, tea tree oil, etc.), but others are not available for tests (β pinenes, etc.) [22]. It is therefore necessary to test essential oils that are in actual use. They are toxic and should not be applied at full strength under occlusion; they should be open tested or diluted at 2 percent. Petrolatum is not always the best vehicle. Alcohol, or acetone, is to be preferred [2]. As soon as the allergen is determined, avoidance of cosmetics and detergents that contain it is mandatory, provided it can be identified by an INCI label. This cannot always be done; indeed, some ingredients are not noted, because they are part of the plant raw material and are not among the 26 allergens listed in table 2, for example sesquiterpene lactones. The allergen need not always be included in the list of “ingredients”, because it is below the required registration level, or is a contaminant of an ingredient. Allergic contact dermatitis caused by essential oils has important implications for the occupational future of affected individuals. The sensitizing capacity of essential oils increases after exposure to open air, a phenomenon that has been proven for the essential oil of Lavandula officinalis, L [39]. Because of the complexity of these compounds, Elispot detection of allergy from essential oils can be very difficult. [40]

Consequences of toxicity: regulatory structure [2] and advice

Advice on the internet

Many internet sites marketing essential oils give the following warnings:

“Always keep essential oils out of reach of children. Some oils can irritate sensitive skin. Some oils are phototoxic (angelica, orange, bergamot orange, lemon, etc.) After application of these oils, sun exposure can cause the appearance of marks on the skin. Use of essential oils is definitely not recommended during pregnancy and breastfeeding, except if medically prescribed. Essential oils should not be used on infants and children under 3 years of age. Pure essential oils should never be applied to ocular, auricular, nasal, and ano-genital mucous membranes. Do not touch your eyes with essential oils on your fingers. Essential oils should be diluted with vegetable oils. In case of respiratory or cutaneous allergies, consult your doctor. Avoid mixing essential oils with medications. Do not swallow essential oils. Do not decide on your own to use essential oils. Avoid intravenous and intramuscular injections of essential oils. Seek the advice of your attending physician. Your family doctor, if not an aromatherapist, will probably refer to a reliable publication [41]”. As a consequence, each medical examination should not only find out if the patient uses drugs, herbal medicine and diet food, but also, owing to their potential reactivity, essential oils [42].

Essential oils and drugs

When essential oils are mixed in remedies, there is no specific regulation: plant-based medicines are medicines, and their active ingredients are exclusively plant drugs and/or plant drug-based preparations. They can be included in the list of traditional plant-based medicines, if they have been marketed in a European Union Member State for ten years, or for 30 years in other countries, insofar as their safety has been proven and their efficiency plausible, considering the time they have been in use (European directive 2004/24 CE). Since 2004, within the EMEA (European MEdicine Agency), a committee (Herbal Medicinal Products Committee) has established monographs of lists recording traditional plant based medicines. But there is neither an INCI code, nor a stringent nomenclature. In France (CSP art. 1.42.11,6th) there is a list of essential oils sold only in drug stores; decree Nr 2007-1221 of 2007.8.3 lists the essential oils involved: great and little absinth, common hyssop, medicinal sage, tansy, thuja, sassafras, sabine, rue, vermituge and antihelminticum chenopodium, rush-shaped mustard. In France, these essential oils are not allowed in food or cosmetics.

Essential oils and cosmetics

When essential oils are used in “any substance or preparation intended to be placed in contact with the various external parts of the human body (…) or with the teeth

### Table 2. List of 26 allergens of odorous substances which must be mentioned in the list of “ingredients” of cosmetics. Bold face for substances of possible vegetable origin

<table>
<thead>
<tr>
<th>2 benzylidene heptanal/amyl cinnamal*</th>
<th>Benzyl cinnamate*/Cinnamate of Benzyle xBP</th>
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<tbody>
<tr>
<td>Benzyl alcohol*</td>
<td>Farnesol*/**</td>
</tr>
<tr>
<td>Cinnamic alcohol*</td>
<td>2-(4-ter-butylbenzyl)propionaldehyde/lilial*</td>
</tr>
<tr>
<td>Citral*/**</td>
<td>Linalol*</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Benzyl Benzoate*</td>
</tr>
<tr>
<td>Hydroxycitronellal*</td>
<td>Citronellol*/**</td>
</tr>
<tr>
<td>Isoeugenol*</td>
<td>Hexyl cinnamal*/**/Alpha-hexylcinnamaldehyde</td>
</tr>
<tr>
<td>2 pentyl 3 phenylprop-2ene-1-ol, amylcinnamyl alcohol*</td>
<td>D-limonene/R-p-mentha-1,8-diene*</td>
</tr>
<tr>
<td>Benzyal salicylate*/benzyl α hydroxybenzoate</td>
<td>Methyl 2-octynoate*</td>
</tr>
<tr>
<td>Cinnamal*/cinnamaldehyde</td>
<td>alpha-isomethyl ionone*</td>
</tr>
<tr>
<td>Coumarin**</td>
<td>Evernia prunastri</td>
</tr>
<tr>
<td>Geraniol*</td>
<td>Evernia furfuracea</td>
</tr>
<tr>
<td>Lyral**/4-(4-hydroxy-4-methylpentyl)3 cyclohexene-1-carboxaldehyde</td>
<td>Anisyl alcohol/ Alcohol 4 methoxybenzylcine*</td>
</tr>
</tbody>
</table>

* Name in INCI. ** Ingredients of fragrance mix II.
and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours”, they are subject to cosmetic regulations and recommendations for perfumes. The International Fragrances Association regularly publishes on its site [43] recommendations for the use of odorous substances, which its members must follow, as well as data supplied by the Research Institute for Fragrance Material (RIFM).

The names of the ingredients of cosmetics must be listed on the product packaging using the INCI (International Nomenclature of Cosmetic Ingredients) code. Each essential oil has an extremely precise INCI code name, due to the variability of the essential oils depending on the plant or even the part of it that is used. However, this name may not clearly appear on the packaging label when essential oils are named as “perfume” or as “fragrance”, as “solvent or vector of a perfuming compound”, or as “contaminant of raw material” as well [44]. Note the ambiguity of the word “oil”, which designates essential oils as well as stone or seed oils.

The seventh amendment of directive 76/768 CEE (directive 2003/15/CE) specifies a list of 26 odorous substances that have to be indicated on cosmetic packaging if they are present at more than 10 ppm in leave-on products, and at more than 100 ppm in rinse-off products. Some of these substances are of natural origin, most often derived from essential oils (table 1). As a result of the cases of convulsions reported by cosmeto-alert, the AFSSAPS (French Health and Safety Agency) has published recommendations for perfumes. The International "fragrance" as well [44]. Note the ambiguity of the word “oil”, which designates essential oils as well as stone or seed oils.

Essential oils and food
The use of essential oils in food is regulated by the directive relating to flavourings for use in foodstuffs and to source materials for their production (directive 88/388/CEE). Annexes 1 and 2 of this directive list substances forbidden for direct use but allowed with restriction in foodstuffs on account of the use, among other ingredients, of essential oils: beta asarone, coumarin, cyanhydric acid, pulegone, safrole, alpha and beta thuyone. The European regulations on fragrance and essential oils are constantly evolving, thanks to the deliberations of the European Parliament and the Council of Europe. The Parliament has targeted methyl eugenol and estragol: Considered to be genotoxic, these substances were removed from the list of directly usable flavourings (decision 2002/113/CE). They can be present in limited amounts from the use of natural flavours. Regulation 2232/96/CE establishes a procedure requiring Member States to publish a list of flavouring substances that are authorized to the exclusion of all others. The Council of Europe has published 3 volumes on the limitation of active ingredients in food, the natural sources of these active compounds, and the toxicologically unacceptable sources, while underlining the fact that nature supplies very active substances that consequently can also be harmful. Each member of the EU is allowed to take all necessary measures when a flavouring substance represents a potential danger to public health.

Quality criteria of essential oils
Whatever their use may be, in France, essential oils have to meet quality criteria for cosmetics that have been published on the AFSSAPS website [2]. Essential oils must come from raw materials clearly identified in the ISO 4720 (International Standardization Organization) nomenclature, to avoid potential confusion, be controlled according to distinct processes, possess precise physical and chemical characteristics, and be carefully stored. Conditions of production (natural, use of pesticides) and of harvesting are essential for the quality of the plants, and subsequently of their oil. In order to avoid damage and bacterial proliferation, distillation must take place immediately or after meticulous drying. Identification of the raw material is necessary to guarantee its traceability. It can be certified by the supplier and checked by the consumer, from the macroscopic aspects of the plant or the microscopic characteristics of the drug, or by thin layer or gas chromatography compared with a reference solution. The chemotype of the plant will be established after identification of the majority of its constituents. Controls of pesticide content and microbiological quality complete the operation.

Essential oils need to be evaluated for their physical and chemical properties, and their constituents identified at least by gas chromatography coupled with mass spectrometry. Other analyses verify the absence of fraud, or detect supposedly allergenic molecules.

Degradation, measured by the peroxide or acid index, by changes in physical properties, or by chromatography, can occur and can modify the properties or the safety of essential oils, thus, appropriate methods of conservation are mandatory: clean, leak-proof flasks made of glazed aluminium, stainless steel or anti UV glass, almost completely filled, sealed with an inert gas filling the empty space, and stored away from heat or sunlight. Such are the regulations established by AFNOR (French Industrial Standards Authority = British Standards Institution in Great Britain) on packaging, labelling of containers, and storage of essential oils.

Conclusion

Essential oils are characterized by their ambivalence, their ambiguity and their disparity. They are complex mixtures of substances of vegetable origin, defined by their method of extraction. They are reactive substances that can affect living organisms. Some are useful as plant-based medicaments, while others are harmful and particularly toxic. Some unwanted effects can be evaluated by the cosmeto-alert network: reports of adverse neurological effects on infants from camphor-based balm led to its withdrawal in 2004, and then to the publication of recommendations to manufacturers and distributors of terpenoid-based cosmetics such as camphor, eucalyptol and menthol. The evaluation of the toxicity of specific essential oils is under way. The AFSSAPS has already published recommendations in relation to the quality criteria of essential oils. Advice on toxicological risk management should follow soon. These actions should relieve some of the confusion about the use of products whose complexity favours confusion.
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References