CHAPTER

18

Fragrance

S. Herman

Diffusion LLC, Totowa, NJ, United States

18.1 INTRODUCTION

Fragrance is a critical aesthetic component in most personal care and household products. Consumers shopping for a shampoo will invariably smell it, as this is the only assessment that can be made in a store. Thus fragrance is an essential product attribute at the point of sale and during use. The emotive effects of fragrance are such that it even contributes to the perception of a product's functionality, even if there is no factual basis for such a judgment.

Fragrance can also be viewed as an expensive ingredient that has no true functional value. Fragrance can create stability problems for the formulator, and some consumers have demonized fragrance as an unnecessary cause of irritation and allergic reactions. In fact our products would be much less appealing without an appropriate smell enhancing the product attributes and marketing profile. Formulators must know how to use fragrance as an integral part of their products, and consumers must continue to trust in their safety and beneficial properties.

18.2 NATURAL PRODUCTS

Until the end of the 19th century all fragrances were solely composed of natural products. Even now, after 150 years of aroma chemical development, natural products are still a vital component of most fragrances. There are nuances of natural products that have never been perfectly replicated by synthetic means. Even if a natural component can be synthesized, it may be too difficult or expensive a process to be a practical alternative. Many parts of a plant can be used, and many extraction methods applied.

Enfleurage is an historic extraction process rarely used today. It makes wonderful products and can be used successfully on heat-sensitive materials, but it is far too time and labor consuming and expensive. A large framed glass plate called a chassis is spread with animal fat. Flower petals are applied to it by hand, and the essential oil migrates from the petals to the plate. As the petals are depleted, usually in a few days, new ones are applied. Once the fat is totally saturated with the aromatic oils, it is called pomade. When the pomade is dissolved in alcohol, it is possible to separate the aromatic material from the fat. The alcohol is then driven off, leaving behind the absolute. The absolute, which is alcohol soluble, is the finest and most expensive aromatic product.

Expression or cold pressing of fruit oils originated in the citrus industry. Essential oil is contained in small pockets on the fruit's skin. Cold pressing involves puncturing the skins of the whole fruit or the fruit peel and mechanically pressing the oil out. The essential oil is then collected below the container. A small amount of juice is also extracted, which is separated from the oil with a centrifuge. Orange, grapefruit, lemon, lime, tangerine, mandarin, and bergamot can be extracted by this method. Since the fruits commonly used are high-volume flavor materials, it is usually very cost effective to make these oils unless there is a problem with a crop such as bad weather.

Products such as orange oil contain a very high level of limonene, a terpene that may be undesirable. Limonene has minimal olfactive value and easily oxidizes into sensitizing materials. The process of "folding" removes most of the limonene by distillation, leaving a more concentrated product. If 10 drums of orange oil are processed and nine drums of limonene removed, the resultant product is termed orange oil 10-fold or 10X. The folded oil has a much stronger odor value and its use can reduce stability issues in many applications. The limonene that is removed can be used in inexpensive flavors or fragrances or for institutional cleaning.

Cosmetic Science and Technology: Theoretical Principles and Applications
http://dx.doi.org/10.1016/B978-0-12-802005-0.00018-5

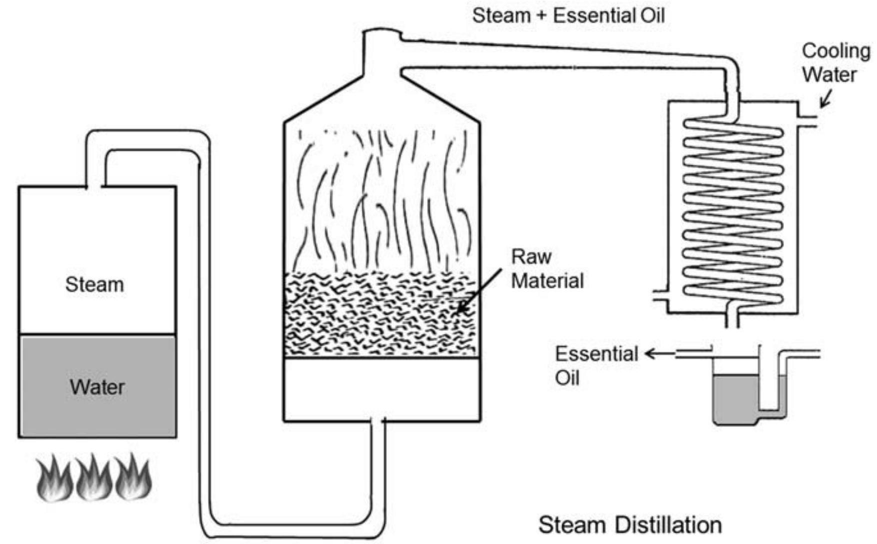


FIGURE 18.1 Steam distillation.

Steam distillation (Fig. 18 1) is a common extraction process for aroma compounds, working well for most heat-tolerant materials. Adding steam to the native material creates an azeotrope that lowers the boiling points of the compounds being extracted. Steam is injected into the material and vaporizes the essential oils present. A condenser cools the liquid, which will separate into oil and water phases. The oil can then be drawn off. For some materials too sensitive for steam distillation, solvent extraction can be used. The plant matter is placed in a static extractor on perforated trays. A benzene-free nonpolar solvent or solvent mix, 8 to 10 times the weight of the plant matter, is added. The extractor is closed and the solvent is passed through the material from 3 to 15 times. The solvent is transferred to a decanter to remove any water present. The water-free solvent is transferred to a concentrator. Heat is applied to remove the solvent, and the material left behind is referred to as a concrete.

The concrete can be gently heated and blended with ethyl alcohol. A rotative filter is then used to remove approximately 80% of the waxes and terpenes. The resultant solution is chilled and the remaining waxes precipitated. The ethyl alcohol is evaporated under a vacuum and the resulting product is termed the absolute. The absolutes of certain flowers such as jasmine, rose, and tuberose are among the most beautiful, potent, and expensive components of fine fragrances.

An even more delicate process uses CO_2 supercritical extraction. CO_2 is easily compressed to a supercritical liquid phase at ambient temperatures and has lipophilic solvent properties. The solubility of supercritical liquids changes with temperature and pressure, which allows the fine-tuning of the extraction. A second solvent can also be added to further refine the process. Dissolved waxes can be present in the product, similar to what results from standard solvent extraction. Many unique olfactive products can be achieved by this process.

Natural products are not necessarily safer than synthetics, a common misconception among consumers. They are complex mixtures that can include undesirable components, such as irritants or phototoxins, an example being the bergaptenes in bergamot oil. Low-color materials are also needed for some purposes, Rectification is a process of cleaning oils through fractional distillation. Materials with cleaner odor, low color, and low residue can result.

Individual components known as isolates can be separated from essential oils. For example, eugenol can be extracted from clove leaf oil, and eucalyptol from eucalyptus oil. Orange oil can yield many valuable components such as octanal, decanal, valencene, and sinensal. There can be technical difficulty in obtaining some of these products in high yield, as the boiling points can be too close to allow efficient separation. Nonetheless, constant progress continues to yield new products of technical and aesthetic value.

Many plants, particularly citrus species like orange and lemon, biochemically synthesize a family of chemicals called terpenes (Fig. 18.2). Large quantities of aroma chemicals can be extracted from this basic supply at low cost. Isoprene is the basic building block of terpenes, with head-to-tail unions forming the larger polymer structures.

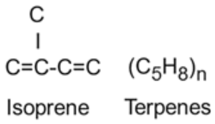

$$\overset{\overset{\textstyle C}{|}}{C}{=}C{-}C{=}C \qquad (C_5H_8)_n$$

FIGURE 18.2 Isoprene rule.

Because terpenes have had commercial importance for many years, common historical names have endured:

n	Name	Formula
2	Monoterpene	$C_{10}H_{16}$
3	Sesquiterpene	$C_{15}H_{24}$
4	Diterpene	$C_{20}H_{32}$
6	Triterpene	$C_{30}H_{48}$

Terpenes can have open or closed rings, double bonds, and readily accept hydroxy or carboxy groups. Many of the transitions between these forms occur easily, so it is easy to synthesize numerous derivatives with an interesting olfactory range. The structures in Fig. 18.3 illustrate some of the major types of natural terpenes. The flat depiction of terpenes, particularly a puckered bicyclic terpene like pinene, does not do justice to the complexity of its three-dimensional structure, which is illustrated in greater detail in Fig. 18.4.

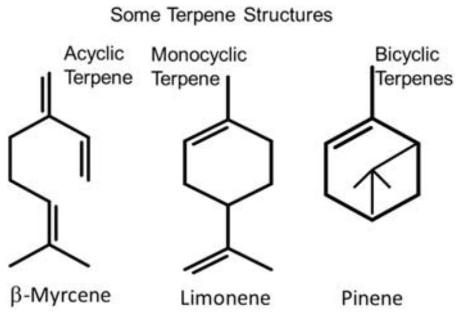


FIGURE 18.3 Examples of terpene structures.

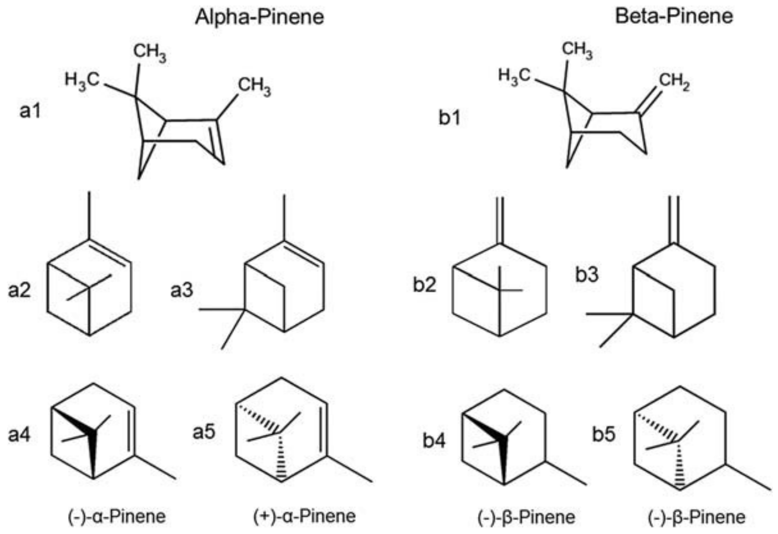


FIGURE 18.4 Stereochemistry of pinenes.

TABLE 18.1 Landmarks in the History of Fragrance-Related Science

1834	Cinnamic aldehyde isolated from cinnamon oil
1837	Benzaldehyde isolated from bitter almond oil
1844	Methyl salicylate identified in wintergreen oil
1856	Cinnamic aldehyde synthesized
1863	Benzaldehyde synthesized
1868	Coumarin synthesized
1876	Vanillin synthesized
1888	Discovery of nitro musks
1919	Linalool synthesized
1923	Amyl cinnamaldehyde discovered
1934	Muscone synthesized
1939	Leopold Ruzicka wins Nobel Prize for Chemistry
1971	Synthesis of α and β damascone

18.3 AROMA CHEMICALS

Starting in the 1850s, advances in organic chemistry made possible an explosive expansion of the perfumer's palette. First, individual odorous materials from natural products were isolated and later synthesized. Next, new chemicals were created that did not exist in nature, making possible a revolution in fragrance design. Table 18.1 shows a few highlights in aroma chemistry history. One scientist, Leopold Ruzicka deserves special mention. He won the 1939 Nobel Prize in Chemistry[1] for work he did for the fragrance industry, especially in synthesizing large ring compounds and exploiting the isoprene rule.

Aroma raw materials are characterized by great chemical diversity. They are all organic compounds, so their chemistry is based on the properties of carbon. The size of aroma molecules ranges from C5 to C17, with Helvetolide, molecular weight 284, the largest current example. Nitrogen and oxygen are common heteroatoms, with sulfur appearing occasionally. These elements are also known as osmophores, a broad term for groups that, when present in a molecule, are responsible for its odor. Aroma molecules have olfactive thresholds from 10^{-6} to 10^{-2} g/L. Some minimal polarity is necessary to interact with the odor receptors.

Esters are the largest family of aroma chemicals. They can be easily produced by the reaction product of a carboxylic acid with an alcohol in the presence of an acid catalyst. At high pH and elevated temperature, the reverse of the esterification reaction occurs, which is termed hydrolysis, and results in a total change in odor quality. Hydrolysis also occurs, but at a reduced rate, at low pH. Low-molecular-weight esters have a fruity odor, examples being the odors of apples (methyl butyrate) or bananas (3-methylbutyl acetate).

Alcohols contain a hydroxyl (OH) group and can be aliphatic or aromatic. If the hydroxyl group is directly attached to an aromatic ring it is a phenol and has much different properties. Phenols can be very unstable and can create severe color changes. Phenols are very sensitive to oxidation and can undergo autoxidation. An example is vanillin (Fig. 18.5), a major component of vanilla. Other examples of phenolics are methyl salicylate, eugenol, and thymol. Even though there are other functional groups attached to the ring, the phenol group still exerts its influence as an independent reactive factor.

Glycols are similar to alcohols, having two or more hydroxyl groups (Fig. 18.6). They are common diluents in perfumery, especially dipropylene glycol (DPG). Propylene glycol, butylene glycol, and hexylene glycol are other examples. Nonpolar diluents are also useful. The polarity of the diluent affects the polarity and thus the solubility properties of the fragrance oil. Thus, DPG is better in a shampoo, and DEP or benzyl benzoate is better in a candle.

Aldehydes and ketones are closely related. Aldehydes can be aromatic or aliphatic. Aldehydes are easy to oxidize or reduce. Even under the mildest conditions, some aldehydes can be oxidized in air. Benzaldehyde is particularly reactive because the functional group is attached directly to the aromatic ring and there are no other reactive sites on the molecule. Benzaldehyde readily exhibits autoxidation to benzoic acid, an odorless white powder.

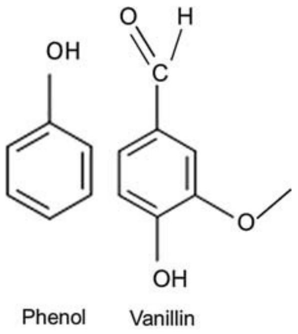


FIGURE 18.5 Phenolic structures.

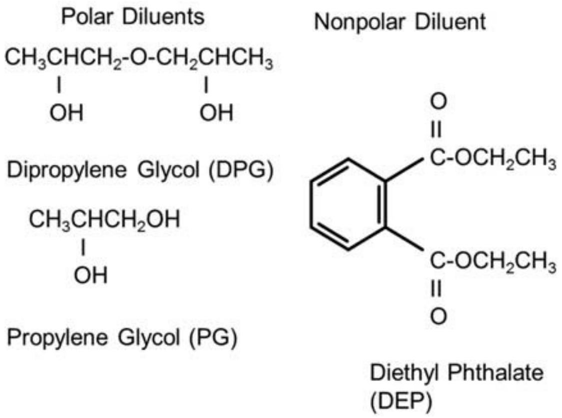


FIGURE 18.6 Fragrance diluents.

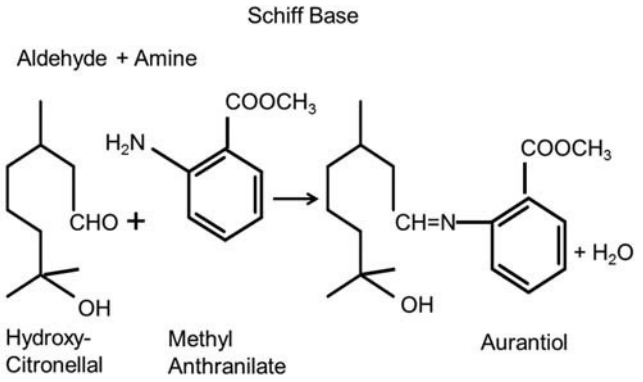


FIGURE 18.7 Schiff base.

Aldehydes can condense with primary amine to form Schiff bases. An important example is hydroxycitronellal and methyl anthranilate, which yields Aurantiol (Fig. 18.7). The reaction can take place slowly if both components are present in a fragrance, contributing to the natural aging of the oil. Alternatively, the Schiff base can be intentionally created by a reflux reaction with the water drawn off and the resultant product used as an ingredient. Ketones are much less reactive than aldehydes but are easily reduced to secondary alcohols.

Heterocyclics are cyclic compounds that contain one or more heteroatoms: oxygen, nitrogen, or sulfur. They are identified by the prefixes Aza- for nitrogen, Oxa- for oxygen, and Thia- for sulfur. They are typically five- or six-member rings, and rings can be fused. Ring sizes are denoted by suffixes: -irane for a 3-membered ring, -etane for 4, -olane for 5, -ane for 6, and -epam for 7. The rings can be aromatic or nonaromatic. Some common heterocyclic structures are shown in Fig. 18.8.

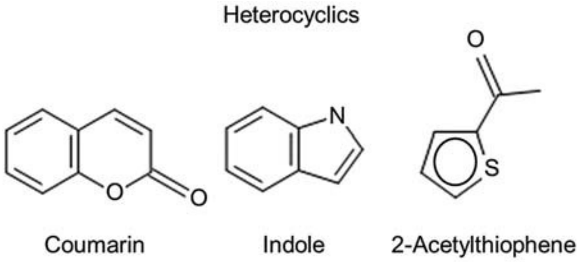


FIGURE 18.8 Heterocyclics.

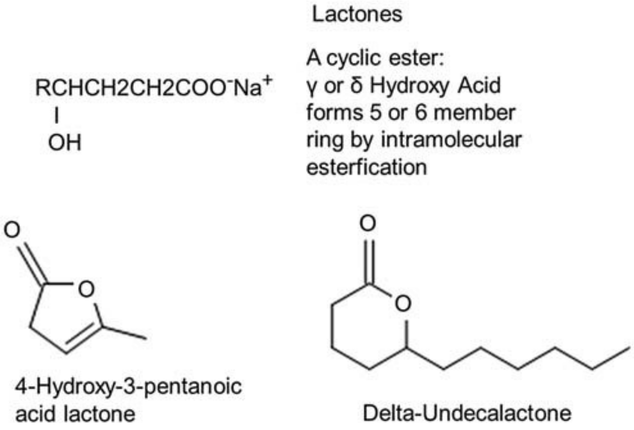


FIGURE 18.9 Lactones.

Nitriles contain triple-bonded nitrogen, $-C\equiv N$. Nitriles occur naturally in plant and animal sources. Over 120 naturally occurring nitriles have been isolated from terrestrial and marine sources. Nitriles are commonly encountered in fruit pits, especially almonds, and during the cooking of cabbage, Brussels sprouts, and cauliflower, which release nitriles through hydrolysis. A nitrile sometimes has an odor similar to its corresponding aldehyde. Nitriles are more stable than aldehydes to oxidation and extremes of pH.

Lactones are cyclic esters. Common examples are γ or ô hydroxy acids forming 5- or 6-member rings by intramolecular esterification as shown in Fig. 18.9 with some examples of lactones used in perfumery. Lactones react under the same conditions as noncyclic esters.

There is a specialized nomenclature for sulfur-containing molecules. For example, thioethers, thioesters, and thioacetals are characterized by C—S—C bonds. Thiol groups contain the structure R—SH. Disulfides have an R—S—S—R with a covalent sulfur-to-sulfur bond.

Originally, musk came from the male musk deer. Real, naturally derived musk is rare and expensive, and many synthetic compounds are made to satisfy the demands of perfumery. The first successful synthetics were nitro musks. The nitro musks—musk xylene, musk ketone, and musk ambrette—were historically important but experienced regulatory problems. More recent molecules have been polycyclic musks, macrocyclic musks, and acyclic musks. Examples of each are shown in Fig. 18.10.

Nonionic surfactants may be used as a fragrance ingredient when extra polarity is needed to make a "water-soluble" version. A surfactant such as polysorbate 20 at a 3:1 ratio is a common solution. This does not make fragrances truly water soluble, but creates a microemulsion that is visibly clear. The mechanism is hydrogen bonding, so a clear solution can reversibly become hazy when heated, as the thermal energy becomes greater than the hydrogen bonding.

18.4 FRAGRANCE CREATION AND DUPLICATION

Historically, fragrance creation was a slow and haphazard process, working with a limited range of materials and producing a limited spectrum of aromas, mostly floral, citrus, and woody. The introduction of synthetic chemicals at the end of the 19th century vastly increased the size and complexity of the perfumer's palette. Perfumers were able to work primarily by trial and error in the early period, slowly accumulating a library of acceptable blends. The number and diversity of the new materials required a method to give logic to the perfumer's art.

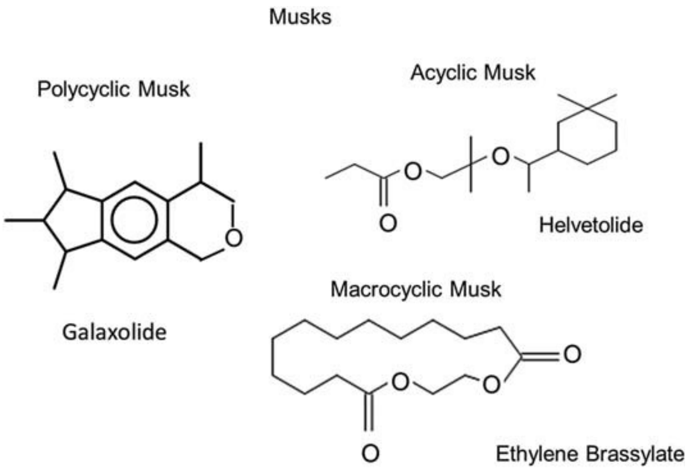


FIGURE 18.10 Musks.

The challenge of systematizing fragrance creation was accepted by a generation of perfumers in the early 20th century led by Jean Carles (1892–1966). Fortunately for posterity, Carles wrote an invaluable series of papers entitled "A Method of Creation in Perfumery."[2] The raw materials Carles used are not always available to the modern perfumer, but the principles used by Carles are of permanent value, and his examples of accords will be discussed.

Jean Carles did not believe that perfumers necessarily have an exceptional sense of smell but rather that they must develop a refined olfactory memory through practice. First, the student learns to identify contrasting odors, then various members within an odor family. Examples of contrasting notes are indole, linalool, menthol, phenylethyl alcohol, and vanillin. An odor family of balsam notes includes cinnamyl acetate, cinnamic alcohol, ethyl cinnamate, and amyl salicylate.

After the olfactory memory is developed, the volatility of various perfume materials is studied. Very volatile materials comprise the "top note" of a finished perfume, those of intermediate volatility and tenacity become the "modifiers" or "middle notes," and the low volatility, tenacious products constitute the "base notes." When smelling a fragrance out of the bottle all these notes are present, but during use the fragrance evolves continuously as materials evaporate in order of volatility.

The characteristic odor of a single material is called a *note*. Mixtures of two or more materials, having a unified olfactory theme, are called *accords*. Jean Carles develops a chypre note based on oakmoss, beginning by evaluating a series of ratios with ambergris:

Oakmoss	9	8	7	6	5
Ambergris	1	2	3	4	5

The perfumer's choice was the 6:4 ratio, which needed additional musk character, resulting in this chypre accord:

Oakmoss	5
Ambergris	4
Musk ketone	1

Materials of medium volatility are used to modify the base accord. Middle notes are often florals, and in this example, an animal note is included, resulting in the following blend:

Absolute rose	3
Absolute civet 10%	1
Oakmoss	6
Ambergris	4
Musk ketone	1

Some pleasant, highly volatile notes are added to create the top note, which is the sparkle that creates the immediate impression of the fragrance. The result becomes:

Sweet orange oil	4
Bergamot	1
Absolute rose	3
Absolute civet 10%	1
Oakmoss	6
Ambergris	4
Musk ketone	1

The ratio of 25% top notes, 20% modifiers, and 55% base notes is characteristic of a well-balanced blend. This formula demonstrates how notes combine into accords, and how materials of different volatilities combine to make a fragrance that evolves in an acceptable way over its lifetime. Many more materials can be added to round out the fragrance and provide interest and complexity, but the overall composition is maintained.

Another important component of a fragrance is a fixative, a material that reduces the volatility of another fragrance ingredient. These materials extend the life of the fragrance, a very important property for consumer satisfaction. Fixitives typically have lower volatility than the other materials in the formula. Some common fixatives are musks, benzyl benzoate, terpinoid gums like Hercolyn D (methyl hydrogenated rosinate), and olibanum (frankincense).

The Jean Carles example was designed for hydroalcoholic use. Perfumes for functional products are balanced differently, emphasizing either the top notes (for impact) or the base notes (for substantivity). Since cost is a factor, inexpensive odorless solvents such as dipropylene glycol or diethyl phthalate are included to reduce the price. Linear fragrances, which maintain their character through the evaporative cycle, can be used for fine fragrances (e.g., Trésor) or even air fresheners.

Fragrance houses have the capability of duplicating fragrance products with great accuracy. A fragrance is almost always a complex mixture of chemicals. The gas chromatograph (GC) separates these components by passing the mixture through a column packed with a material that interacts with the components in varying degrees. Fig. 18.11 shows an example output. The separate portions can then be placed in a mass spectrometer (MS) for the identification of the chemical structure. The GC−MS chromatogram alone is not sufficient in identifying the composition of a fragrance. A database of values of aroma chemicals is required to convert the raw data into the information needed to reconstruct the target oil.

The vapors over a fragranced object or in the air can be identified by the addition of head space analysis. Solid phase microextraction is a sophisticated version of this technology. A glass globe is placed over the object being analyzed, and a porous material absorbs the aroma chemicals. The quantity extracted can then be analyzed and is proportional to the concentration in the sample, so the odor can be quantitatively replicated. This has been used by fragrance companies to replicate many odors in the environment, from flowers and exotic woods to the canopy of the Amazon rain forest.

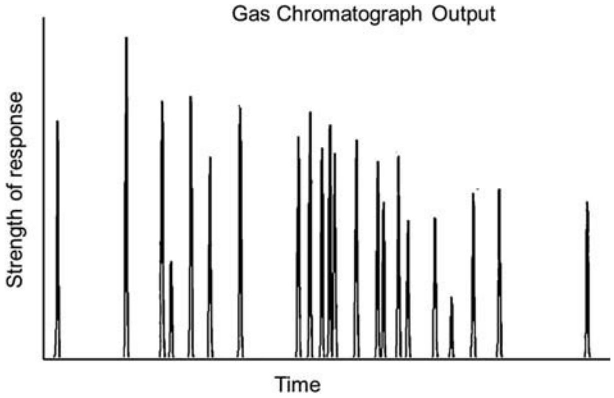


FIGURE 18.11 Gas chromatograph output.

The electronic nose (e-nose) is different from a GC and also does not take the place of the human nose. It is a quality control device capable of responding to chemicals in the air. An e-nose consists of three major parts: (1) a sample delivery system generates headspace and injects sample into detection system; (2) the detection system reacts to the presence of specific molecules, making it undergo a chemical change and produce a useable electronic signal; and (3) a computing system combines the responses of individual sensor elements and generates sample information.

An e-nose can use metal oxides or conducting polymers that change conductivity when bound to airborne molecules. Possible transducer sensors include quartz crystal microbalances, surface acoustic wave sensors (SAWs), and metal oxide semiconductor sensors. The quartz microbalance uses piezoelectric crystals that increase in mass as odorants are absorbed, altering the oscillation frequency. SAW devices consist of two electrodes (source and receptor) over a sandwich of a piezoelectric thin film. Metal oxides employ oxidation/reduction reactions on the surface that is in contact with the gas.

18.5 POLARITY

A key property for understanding the behavior of fragrances with products such as emulsions and surfactant systems is the polarity of the individual fragrance components. This is created by slight concentrations of charge in parts of the molecule and is a guide to where in a complex system a specific molecule is most likely to be.

Chemistry is usually concerned with strong forces: covalent or polar bonds. Solubility depends on weak forces. The Van der Waals force is loosely used to describe all weak intermolecular forces, including London dispersion, Keesom, and Debye forces. A common measure of polarity is the solubility parameter (SP). Two versions are common, the Hildebrand solubility parameter from the early 20th century, and more recently the Hansen solubility parameter (HSP).

Hildebrand developed an equation to calculate the SP of a small molecule based on the fact that cohesive energy is overcome when liquids boil. The following equation is used to determine the Hildebrand solubility parameter as the square root of the cohesive energy density: $\sigma = ((\Delta H\text{-}RT)/V)^{1/2}$. The cohesive energy density is the energy required to completely remove a unit volume of molecules from their neighbors to infinite separation. It is equal to the heat of vaporization divided by molar volume. Hildebrand determined that the square root is a good indicator of solvency.

Charles Hansen developed the Hansen solubility parameters in 1967 and has refined the system over the years. This concept took the Hildebrand solubility parameter concept, which was based on a one-dimensional or free-energy parameter, and expanded it to a three-dimensional cohesive energy parameter. HSP utilizes components of the cohesive energies derived respectively from polarity, dispersion, and hydrogen bonding.

Hansen solubility parameter in practice (HSPiP) is a computer program that creates 3D images of solubility regions.[3] It was designed originally to optimize solvents for polymers, which in itself is useful for personal care applications. A green ball in the HSPiP graphical image is the compatible volume in three dimensions. Databases have been added for cosmetic and fragrance materials, further enhancing its value in our industry. The basic formula used to compute the HSP is:

$$\delta^2_{\text{Total}} = 4\delta^2_{\text{P}} + \delta^2_{\text{D}} + \delta^2_{\text{H}}$$

where δ_{Total} is the distance from the target HSP, δ_{P} is the contribution from dipolar intermolecular forces, δ_{D} is the contribution from dispersion forces, and δ_{H} comes from hydrogen bonds between molecules.

Clog P is an alternate way to look at polarity. P is the partition coefficient, the ratio of a molecule's partitioning between water and oil. The data is more linear as a logarithm. If it is done by a computer program rather than wet chemistry, it is calculated. Thus Clog P is a computer calculation of the logarithm of the water/oil partition coefficient. Clog P values are available for most fragrance materials.

Both Clog P and HSP are valuable for determining where fragrance ingredients will partition between the different phases of a base, or if a solution will be clear. A change of solvents can often adjust the values to solve clarity or viscosity problems.

The HSPiP program computes several functions that are valuable in fragrance and flavor chemistry. Some of these functions include solvent optimization, skin permeation, diffusion and volatility calculations, and, of course, solubility parameter calculations. The permeation of molecules in skin is looked upon as a hydrophobic—lipophilic interaction due to the hydrophobic nature of human skin. Relative to fragrance, determining the amount of material that can permeate the skin cannot only determine the efficacy of the product but also indicate its likely safety to the consumer.

By their fundamental nature, fragrances are small molecules with low polarity. This makes them likely to be skin irritants, to penetrate the skin, and get into the blood. There is nothing intrinsically unsafe about that, it's just simple chemistry and biology in action. It does not mean that fragrances are not safe as typically used. But it does mean that the guidelines set by the industry must be followed without exception.

18.6 FRAGRANCE APPLICATIONS

Hydroalcoholics are a common fragrance application, typically in the form of perfume, cologne, and aftershave. The basic components are fragrance oil, alcohol, and water. Common additives are color, chelating agents like EDTA, antioxidants such as BHT, and ultraviolet (UV) absorbers. In manufacturing, the fragrance oil is added into the alcohol and then the water added. Commercial alcohol contains ethanol, water, and a denaturant. To discourage drinking the alcohol, it is poisoned with a denaturant. The denaturant is selected from materials that cannot readily be distilled out. Denaturing exempts the alcohol from the taxes normally imposed on the ingestible version.

When the perfume oil is placed in solution the aging process begins. The container is important: stainless steel and glass-lined vats are best. Iron should never be in contact with the solution. All hoses, gaskets, and stirrers should be carefully chosen to ensure compatibility. The solution should be aged in a covered container at room temperature for at least a week. Fine fragrances should be aged as long as six months, but this is often impractical. Mass-market fragrances are frequently not aged at all, with chilling and filtering done in a continuous process. Continuous processing is only practical for very large production.

Aftershaves are an economical delivery system for male fragrances. The alcohol content is limited to 60—65% to avoid stinging, since minor cuts and abrasions often occur during shaving. Emollient oils such as glycerin and propylene glycol are frequently added for feel, as are healing agents for cuts.

When a fragrance compound is incorporated into an emulsion system a variety of processes can occur. An emulsion has water, oil, and interfaces where individual fragrance materials can partition based on chemical and physical properties. The aqueous phase also usually contains areas of liquid crystal structures, loosely organized regions of fatty acids. Many fragrance materials can discolor an emulsion system—indole and vanillin are classic examples. High levels of fragrance can break an emulsion. It is important to conduct a full battery of stability tests including elevated temperatures, freeze-thaw, and UV radiation exposure comparing unfragranced to fragranced samples to ensure product integrity. Testing in the final packaging is also necessary.

Another process occurs when the emulsion is applied to the skin. When applying external shear, the emulsion breaks, and the water and other volatiles will evaporate quickly. What is left on the skin after application is the oil phase, most of the fragrance, and the emulsifiers. This will re-emulsify the fragrance, retarding its evaporation and thus muting its character and impact.

The viscosity of a surfactant system can be built by the judicious selection of surface-active materials. Many formulators build viscosity solely with the addition of salt, which is a less-expensive approach. Fragrance is easily solubilized by surfactants, but a low active formula with a high level of salt may become hazy when fragrance is added. In these cases, fragrances mixed with nonionic surfactants such as polysorbates may be needed to achieve clarity.

In addition, many surfactant systems such as bath gels are colored, creating light-stability problems when fragrances are present. Cosmetic colors contain molecules that are chromophores, structures that emit light in the visible spectra thereby becoming visible colors. Examples of chromophores are conjugated double bonds and the azo group. A standard stability test involves exposure to UV light. Some aroma chemicals, such as benzaldehyde, create free radicals when exposed to UV. In the free radical state, they can react with the color-generating structures and cause pronounced discoloration.

18.7 PHYSICAL CHEMISTRY OF AROMA CHEMICALS

The evaporation properties of a fragrance can best be understood by applying the laws of the physical chemistry of mixtures. Many characteristics of fragrances are based on their cohesive properties. Evaporation rate, boiling point, vapor pressure, diffusivity, and molar mass are important examples. The thermodynamics of cohesion is well understood for simple systems, but harder to apply to complex mixtures such as fragrances.

A fragrance material must be volatile, have an acceptable odor threshold, and consist primarily of C, H, and O atoms with occasional N and S. Volatility demands a range of C5 to C17. Olfactive thresholds range from 10^{-6} to 10^{-2} g/L. Raoult's law explains the properties of vapor pressure over a complex solution. The vapor pressure of component A, P_A, is given by its vapor pressure as a pure solution times its mole fraction in the solution, X_A. For a simple mixture of A and B, $P_{total} = P_A X_A + P_B X_B$. For complex perfume mixtures, the process is expanded to include each component.

A solution that obeys Raoult's law is called an ideal solution. Nonideal behavior can result in higher or lower pressures, and this is one reason why fragrance mixtures sometimes produce unexpected properties.

Henry's law states that at a constant temperature, the amount of a given gas that dissolves in a liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid. The activity coefficient is defined by a combination of Henry's and Raoult's laws, and can provide the scientific basis for understanding how fixatives can prolong fragrance life and affect the top note impact.

18.8 ENCAPSULATION AND CONTROLLED RELEASE

Encapsulation of fragrance allows novel delivery systems, can release fragrance under specific triggers, and can protect fragrance in a hostile chemical environment. The history of encapsulation started in 1927 when capsules were spray-dried with an oil and gum acacia coating. In 1955 the National Cash Register Company received a patent for encapsulation, using the technology to make carbon paper. The first major fragrance use was the "scratch and sniff" sampling of Giorgio fragrance in 1983.

Controlled release can provide fragrance when and where it is needed. It can also counteract loss of intensity during use. A practical use of encapsulation is to protect a fragrance chemical from a hostile environment. Common triggers of release are water, heat, or pH. Mechanical action can also function as a release mechanism.

Microencapsulation is the process by which individual particles or droplets of solid or liquid material are surrounded or coated with a continuous film of polymeric material to produce capsules in the micrometer to millimeter range. Capsules can have a liquid inside a shell, multiple liquid areas in a shell, or the liquid spread through a matrix (Fig. 18.12).

Common shell materials are gums (gum arabic, sodium alginate, carrageenan), carbohydrates (starch, dextran, sucrose), celluloses (carboxymethylcellulose, methylcellulose), lipids (beeswax, stearic acid, phospholipids), and proteins (gelatin, albumin). Microencapsulation methods include physicochemical processes, such as coacervation and solvent evaporation, and physicomechanical processes, such as spray-drying.

Contemporary formulation may use nanotechnology, where the first generation technologies such as liposomes are being replaced by newer structures such as solid lipid nanoparticles and nanostructured lipid carriers. Nanosized particles that have a shell and an interior space that can be used to load perfume are called nanocapsules. Polymers have been widely used to create nanocapsules, which are then functionalized for various applications. Application of nanoencapsulation in fragrance products enables more efficient, prolonged, and time-controlled release of the scent. Using this approach, materials can be engineered to be stable in aqueous solution, nontoxic, and biodegradable.

18.9 ANTIBACTERIAL EFFECTS OF ESSENTIAL OILS

It has long been known that many essential oils possess the ability to inhibit bacterial growth. Martindale in 1910[4] used the phenol coefficient to characterize the effectiveness of essential oils, work that is still the basis of many

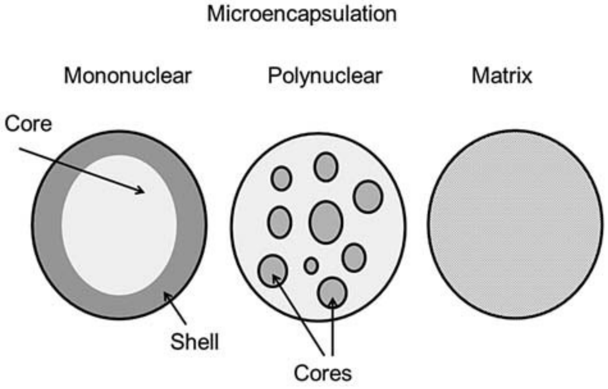
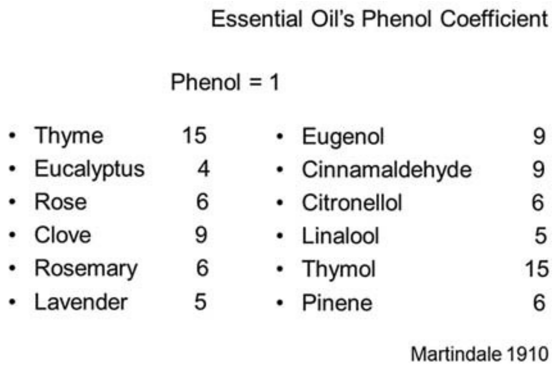


FIGURE 18.12 Microencapsulation.



Essential Oil's Phenol Coefficient

Phenol = 1

Thyme	15	Eugenol	9
Eucalyptus	4	Cinnamaldehyde	9
Rose	6	Citronellol	6
Clove	9	Linalool	5
Rosemary	6	Thymol	15
Lavender	5	Pinene	6

Martindale 1910

FIGURE 18.13 Essential oil's phenol coefficient.

claims. The phenol coefficient itself is now only of historical interest. It is the concentration of phenol at which the compound kills the test organism divided by the concentration of the test compound that kills the organism under the same conditions. Materials that are more effective than phenol have a coefficient greater than 1; those that are less effective have a coefficient less than 1. The phenol coefficients of some essential oils are shown in Fig. 18.13.

Because of the demand for novel preservative systems, essential oils are still valuable for their activity. There are limits to their application since they can be irritants, they have strong odors, and their efficacy is not enough to provide preservation without the assistance of more conventional solutions.

18.10 MALODOR

The chemistry of malodor molecules is fundamentally different from most fragrance molecules. Malodor molecules frequently contain nitrogen or sulfur. Sulfur imparts the skunk excretion in its distinctive aroma, and nitrogen creates the smell of a rotten egg or cigarette smoke. Because they have unique chemistry, it is possible to destroy a malodor without destroying a fragrance at the same time.

Most compounds are susceptible to oxidation. In many materials, this can lead to a decomposition of the malodor creating substance, removing the odor. Chlorine dioxide is a commercial example. While commercially useful, this approach is not compatible with the use of fragrance as a solution.

Zwaardemaker pairs are conjugates of odorants that neutralize each other's respective odors. Examples are butyric acid and oil of juniper, ethyl mercaptan and eucalyptol, skatole and cedarwood, and tobacco and wintergreen oil. Their usefulness in malodor is increased as an appropriate fragrance can be built around the aromatic component of the pair.

To some extent all fragrances may assist in masking malodor, but some materials are much more effective than others. Aldehydes, orange oil, minty, fruity, and green notes are often useful. Fragrance companies have also designed nonaroma chemicals targeting malodor. A classic example is Veilex 1 (1-cyclohexylethyl butyrate), patented in 1980 by Bush Boake Allen (now part of IFF). Veilix molecules may bind to the same receptors in the nose as malodor molecules, eliminating the perception of the malodor. Other commercial malodor counteracting molecules are Meelium and Metazene.

Two of the most pervasive materials used in malodor products are zinc ricinoleate (Fig. 18.14) and cyclodextrin (Fig. 18.15). They both capture malodor molecules but use very different mechanisms.

Zinc binds very strongly to nitrogen and sulfur, both characteristically found in malodor molecules. When a malodor molecule can bind to the zinc, the chains of zinc ricinoleate can fold to totally encapsulate it. Zinc ricinoleate can also bind to many fragrance molecules, which is one limit on its use. It is also very hard to solubilize in many applications. Since ricinoleic acid comes from castor oil, this material has been positioned as a naturally derived product.

Cyclodextrin comes in three different forms (alpha, beta, gamma) and is shaped like a truncated cone. Cyclodextrin is relatively polar on the outside and nonpolar on the inside, so it can capture aroma chemicals or malodor molecules in its interior and be compatible with water-based delivery systems. This material is used extensively in P&G's Febreze line and is covered by many patents. In addition to cyclodextrin as an active material, this patent also specifies a preferred Clog P of three or less for fragrances. It is unclear which has the most malodor effect in the finished consumer products, the cyclodextrin or the fragrances.

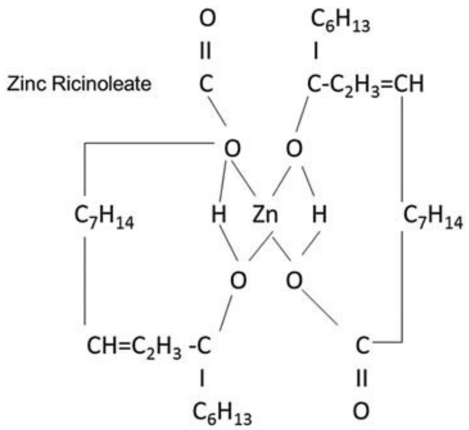
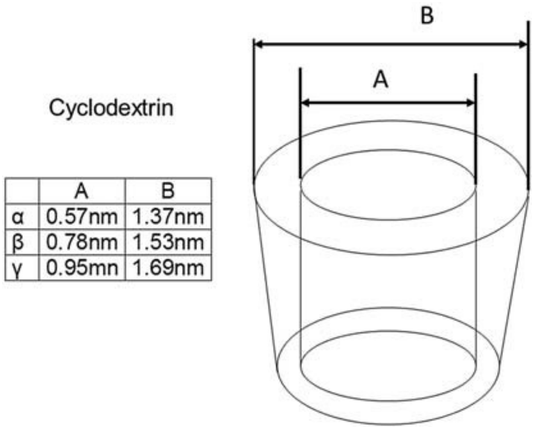


FIGURE 18.14 Zinc ricinoleate.



	A	B
α	0.57nm	1.37nm
β	0.78nm	1.53nm
γ	0.95mn	1.69nm

FIGURE 18.15 Cyclodextrin.

18.11 SAFETY AND REGULATORY CONCERNS

No aspect of fragrance is more important than its safety and regulatory compliance. No fragrance, no matter how beautiful it may smell, can be marketed without complete compliance. Consumers assume the products they use are safe and effective, and that the manufacturers take their responsibilities as a top priority. There are two broad classes of regulation: mandatory requirements from official agencies, and those specifically self-imposed by the fragrance industry with voluntary compliance.

Mandatory requirements apply when fragrances are simply considered a mixture of chemicals, and all the chemical safety rules apply. Safety data sheets, certificates of analysis, the Toxic Substances Control Act, and the European Union's Registration, Evaluation, Authorization, and Restriction of Chemicals registrations are examples. The Volatile Organic Compound regulations of the California Air Resources Board, which can be narrowly viewed as just a state regulation, are equally important. The European regulation requiring labeling of a specific list of alleged allergens, while geographically limited, is also of great importance in the global marketplace.

The fragrance industry established self-regulation when the Research Institute for Fragrance Materials[5] (RIFM) was established in 1966. RIFM is financially supported by the fragrance industry but functions independently. RIFM generates a safety dossier that is reviewed by the RIFM Expert Panel (REXPAN) and the results are published in peer-reviewed journals. RIFM itself does not publish or enforce specific industry guidelines based on its findings.

The International Fragrance Association[6] (IFRA) was created in 1973. The fragrance organizations of individual countries such as IFRA North America, formerly the Fragrance Materials Association, are members. IFRA evaluates the RIFM publications and, based on the best possible scientific appraisal, issues industry guidelines, which are freely available online. All responsible fragrance suppliers follow these guidelines, and global conformance is excellent.

From the inception of RIFM to the mid-1990s, the emphasis of testing focused on the individual use of fragrance on the skin. The reason was simple—the most intimate and prolonged exposure to humans from fragranced products came via personal care products. Fragrance use was divided into two broad categories: “skin contact” and non-skin contact.” “Skin contact” was further divided into “leave on” and “rinse off.” Rinse-off products were deemed less of a safety issue—until one addressed the fate of chemicals going down the drain!

In the 1990s the use of fragrance changed in ways significant for safety assessment. Personal use moved away from perfumes and colognes to bath and skin products. Environmental fragrance delivery through scented candles and plug-in air fresheners created much more respiratory exposure. Finally, the environmental movement focused attention on the fate of fragrance in water, its consequences for aquatic life, and from there back into the food chain, finally ending in our bodies. Four guidance papers elucidated the scientific basis for all RIFM activities.

Determining environmental safety may be even more complicated than determining dermal or respiratory safety. The RIFM guidance paper uses data and models to estimate the effects of fragrance materials on the aquatic environment. More than 2100 aroma molecules were assessed, with 92.3% having negligible effect on the environment at current volumes of use. The evaluation used KOW, molecular weight and usage volume. The “predicted environmental concentration” (PEC) was compared to the “predicted no effect concentration” (PNEC), ascertained by a quantitative structure-activity relationship. If $PEC/PNEC < 1$, the material passed the initial screen. For questionable materials, “ecological structure-activity relationships” was applied. This approach was a highly conservative risk-based screening without requiring experimental ecotoxicological or fate data.

Quantitative risk assessment (QRA) has the goal of minimizing, or ideally eliminating completely, skin sensitization caused by fragrance. It is a refinement of all the dermal safety data accumulated over many years. The method involves the determination of a benchmark (no expected sensitization induction level, or NESIL), application of sensitization assessment factors (SAF), and the calculation of consumer exposure through product use. It reduces to a simple relationship:

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{SAF}}$$

where NESIL = No-Expected-Sensitization Induction Level; WoE = Weight of Evidence; SAF = Sensitization Assessment Factor.

The “weight of evidence” is the conclusion reached by the REXPAN after evaluation all the available literature and data on a material.

After many years of evolving methodology, RIFM updated and combined all its methods in a new guidance document available to the industry at the end of 2015.[7] A basic, extremely simplified, version of the RIFM algorithm (Fig. 18.16) describes the essential steps, with different endpoints for skin safety, respiratory effects, or environmental impact. Innovations introduced by RIFM included increased reliance on computer programs (in silico), and the introduction of the threshold of toxicological concern (TCC). The TCC was created for the food industry with the cooperation of the US Food and Drug Administration (FDA) to deal with the numerous chemicals present at extremely low levels that are extremely unlikely to have any negative effects.

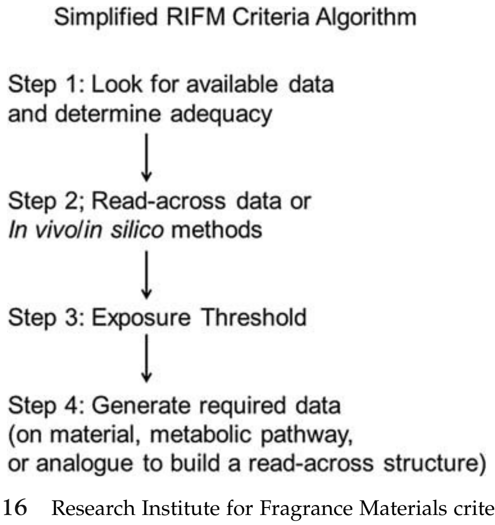


FIGURE 18.16 Research Institute for Fragrance Materials criteria algorithm.

The goal of the new guidance document and algorithm is to apply the best possible science for the foreseeable future and to have a single flow path for a material entering the evaluation process to be assessed. RIFM is now in the process of putting all known fragrance materials through this screening. Even though safety testing has been done for many years, it is still necessary to reevaluate every material due to the changing requirements for dermal, respiratory, and environmental concerns.

18.12 THE REGULATION OF FRAGRANCE

Fragrance formulas are almost always kept confidential by the suppliers who create them. The formulas are considered intellectual property and the name "Fragrance" on the product, plus an allergen report for EU labels, satisfies the legal requirements for disclosure. The fragrance house necessarily provides a large number of supporting documents such as safety data sheets, product data sheets, IFRA conformance certificates, and EU allergen statements. The formulator is usually not privy to the details of the process whereby these documents are generated.

IFRA has several ways of classifying fragrance materials. Most have no restrictions. Some are banned outright and cannot be used under any circumstances. Some have restricted levels in different applications. Some have quality standards limiting trace components of concern. Some are fine themselves but can oxidize to produce sensitizers, and must only be used in conjunction with an antioxidant.

The most necessary fragrance-specific document for every user to have on file is the IFRA Certificate. It usually specifies limits on the use of the fragrance in a number of application categories. For some products there is a separate specification for leave-on products and nonskin contact products. Every two years RIFM publishes an amendment containing updated regulations and it is necessary to review all the regulatory documents on every fragrance to make changes if necessary.

18.13 NATURAL, GREEN, ORGANIC, AND SUSTAINABLE FRAGRANCES

The pervasive use of synthetic chemicals in modern perfumery has opened the door for a counter movement, the promotion of natural and organic fragrances. The exact definition of *natural* is hazy, as some type of manipulation is necessary to make almost every product useable in a fragrance composition. Natural compounds can be defined as products derived from plants via extraction, expression, or distillation without intentional chemical reaction or modification. Solvents have traditionally been used in many processes, but some groups limit their use exclusively to heat and water.

An issue arises in the difference between "natural" and "nature identical." Phenyl ethyl alcohol exists in rose oil. It can also be synthesized. It is virtually impossible to distinguish by chemical analysis between the naturally extracted and synthetic molecules, and the synthetic compound can be added to a naturally derived rose oil to "extend it." Recent technology utilizing isotopes identification has made it possible to identify the source of some compounds, but this is not in common use.

Creating fragrances exclusively with natural materials may pose challenges. They tend to be more expensive and despite the common perception linking "natural" with "safe," these may often cause skin irritation and sensitization reactions. In addition, the components of many natural products are prone to oxidation and decomposition and they frequently discolor and change odor. In addition to technical drawbacks, on the creative side being deprived of synthetics severely restricts the perfumer's palette.

To be certified as organic the composition must comply with specific regulatory guidelines and create a precise paper trail. Organic certification is a legal process in the United States created and monitored for food products by the United States Department of Agriculture that was extended to personal care products and fragrances. An organic fragrance is restricted to natural product compositions that are certified, which further reduces the raw material palette, elevates the price, and can create raw material shortages.

The FDA, in an alliance with stakeholders from the industry, created Design for the Environment guidelines for fragrances. This has been revised and rebranded as Safer Choice.[8] The fragrance criteria apply to household products such as laundry detergent and all-purpose cleaners, but not air fresheners or personal care products. It was intended to include the evaluation of very small quantities often excluded in environmental analysis and to move the industry to more environmentally friendly alternatives.

An attempt to make more stringent requirements in a document known as version 2.1 of the Criteria for Fragrances proved impractical to implement and the program reverted to the original Interim Fragrance Criteria. These documents are very long, technical, and detailed, and for those with a strong interest can be easily accessed online.

18.14 FRAGRANCE AND THE MIND

The chemical properties of fragrance are important, but there are also emotional and psychological aspects that are a major reason that smells are so important to people. Aspects that the formulator should be familiar with are aromatherapy, aromascience, and pheromones.

Aromatherapy is an ancient discipline involving the therapeutic effects of essential oils. Many fragranced products claim aromatherapy effects, usually based on folkloric information. The fragrance industry prefers to position itself with aromascience, defined as physical and psychological effects of fragrance backed by scientific testing. Much of the fragrance industry's research in aromascience is conducted by the Monell institute in Philadelphia.

The physiological basis of the effects of fragrance on the emotions concerns the basic anatomy of the olfactory system The odor receptors transmit a signal through the olfactory bulb to the limbic system of the brain, the location of human emotions. The sense of smell is ancient, its decoding is direct, and it helps explain the tangible impact scent has on most people.

Many tests have been conducted to identify aromas that are stimulating, relaxing, increase physical or mental performance, or effect emotions. Combining a relaxing smell with a relaxing delivery system such a candle or bubble bath in a serene environment can have an effective total effect.

Claims have been made for certain chemicals having pheromonal effects on humans, particularly androstenone, androstenal, and copulans (short-chain fatty acids). The most widely cited proof of pheromonal behavior is McClintock's 1971 paper on menstrual synchrony and suppression.[9] A recent book by Doty[10] has assigned human pheromones to the realm of myth. In fact, hard science on human pheromonal behavior is hard if not impossible to find, especially by Doty's standards, and the fragrance scientist should deal with pheromones with extreme skepticism.

18.15 THE FRAGRANCE BRIEF

Fragrance marketers like Coty and Estee Lauder do not make their own fragrances, nor do celebrities like Britney Spears labor in a lab. It is much more efficient to leave the creation of fragrances to companies deep in the appropriate expertise. Fragrance suppliers with names unfamiliar to the public make the scented juice, and the process is directed by a fragrance brief.

Fragrance briefs set all the key parameters for a new fragrance or a set of line extensions like bath gels or candles. Sometimes the initial request is highly imaginative, wanted to match a series of romantic pictures or the sensation of walking through a rain forest after a thunderstorm. Others can be very precise—a complex floral with a strong rose/jasmine core and haunting amber dry down.

The required information starts with the product type, including chemical or physical characteristics. The intended market, packaging, and price are key inputs. There must be a time frame for development and testing. Fragrance suppliers are well staffed with specialists in all phases of the commercial development process: perfumers, evaluators, expert panels, marketing departments, and analytical and application chemists who all play important roles in creating a successful submission.

The closer the customer works with the fragrance house, the greater the chance of success. Exact knowledge of the finished applications, packaging, pricing, target audience, and competitive products are all critical. A project that begins "just give us something that smells nice and don't worry what it costs" is doomed from the beginning.

18.16 CONCLUSIONS

Fragrance is an important aspect of our lives and a key component of many product types from designer perfumes to all-purpose cleaners. The creativity of the perfumers, the chemical expertise of the applications lab, regulatory diligence, and intelligent use of marketing are some necessary ingredients for success. Many pieces must fit together to make the ideal fragrance for each application, but the result will be a superior product and a satisfied consumer.

18.17 A BASIC FRAGRANCE LIBRARY

Classics:

Guenther, Ernest. *The essential oils*, six volumes, Van Nostrand Co. 1948–52 (republished Jepson Press 2007).

Arctander, Steffen. *Perfume and flavor materials of natural origin*, published by the author 1960 (republished by Allured Publishing 2003).

Arctander, Steffen. *Perfume and flavor chemicals*, two volumes, published by the author 1969 (republished by Allured Publishing 2000).

General works:

Muller PM, Lamparsky D, editors. *Perfumes: Art science & technology*: Elsevier Science; 1991.

Sell CS, Pybus DH, editors. *The chemistry of fragrances*: RSC; 1999.

Herman S. *Fragrance applications: A survival guide*: Allured Publishing; 2001.

Rowe D, editor. *Chemistry and technology of flavors and fragrances*: Blackwell; 2005.

Sell C. *Understanding fragrance chemistry*: Allured Publishing; 2008.

References

1. www.nobelprize.org/nobel_prizes/chemistry/laureates/1939/ruzicka-facts.html.
2. Carles J. *A method of creation in perfumery* [Researches #December 11, 1961, #December 12, 1962, #December 13, 1963].
3. http://hansen-solubility.com.
4. Martindale W. *Perf Essent Oil Rec* 1910;**1**(11):266.
5. www.rifm.org.
6. www.ifraorg.org.
7. Api AM, et al. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem Toxicol* August 2015;**82**(Suppl. S1–S19). http://dx.doi.org/10.1016/j.fct.2014.11.014.
8. www.epa.gov/saferchoice/standard.
9. McClintock MK. Menstrual synchrony and suppression. *Nature* January 21, 1971;**229**:244–5.
10. Doty R. *The great pheromone myth*. Johns Hopkins University Press; 2010.