, director of new technology at , offers a brief overview of the science behind fragrance, including the olfaction mechanism, fragrance chemistry, perfume creation, applications and the role of the brain

he world is awash in smells, from fine fragrance to laundry detergent to the spray of a skunk. Smell is an inherent property of many chemicals, a property that is given little attention by most chemists. Show a chemist a molecular structure and ask him what it would smell like, and the response would likely be incredulity. Try it yourself: what are the characteristic odours of the molecules in Figure 1?

Our nose has a remarkable ability, chemoreception, which allows us to detect airborne molecules. The mechanism of odour reception has proven the most difficult of all our senses to decode. As recently as 2004, the Nobel Prize in Physiology or Medicine went to Linda Buck and Richard Axel for the identification of the olfactory gene family.[1]

The odour receptor neuron is a 7-transmembrane domain protein coupled to a G-protein. Figure 2 shows the broad outline of the olfactory process. Each receptor is connected to the olfactory bulb, where it is bundled with similar receptors in a ball of nerves called a glumeruli.

There are, to the best of our knowledge, 347 odour receptor genes that encode working receptor types. Since we smell thousands of different odours, the process is clearly combinatorial. One odour molecule can trigger multiple receptors, creating a complex pattern that the brain must decode.

Whether the odour receptor responds to shape and undergoes a configurational change (the stereochemical theory) or responds to molecular vibrations (the vibrational theory) is still open to debate. The stereochemical theory was championed by John Amoore and has long been accepted, at least partly because many similar receptors are known to work that way. The current leader of the vibrational theory is Luca Turin, who has demonstrated how a functioning spectroscope can exist in the receptor protein.

At stake is the holy grail of olfaction, Quantitative Structure-Odour Relationships (QSORs). This promises the ability to predict smell by molecular structure and consequently being capable of designing new aromas through rational design. Whilst we have not reached that goal, Turin's company, Flexitral, is successfully producing new fragrance molecules based on his theories.

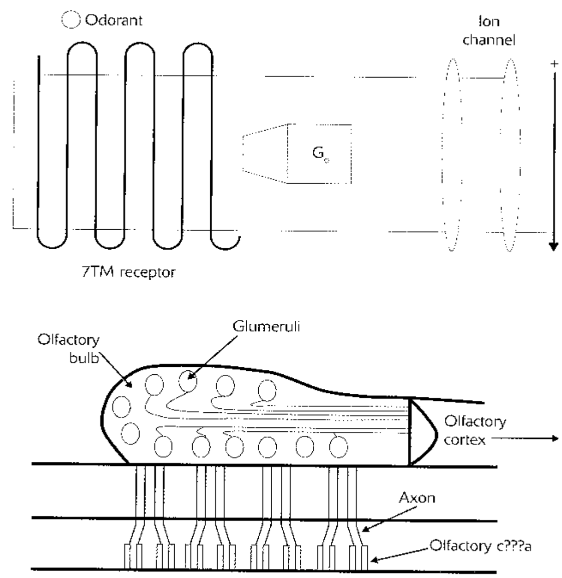


Figure 2 - Initial response to odour (top) **& odour response in the brain** (above)

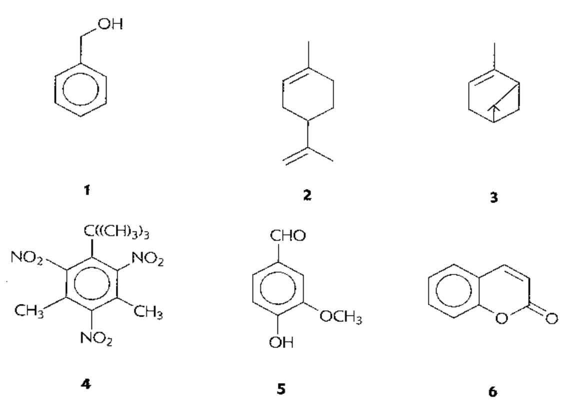


Figure 1 - Selected aroma chemicals

Commercial fragrances are complex mixtures of chemicals, embracing an extraordinary diversity of families and functional groups. A typical fragrance can contain aliphatic and aromatic alcohols, esters, aldehydes and ketones, lactones, heterocyclics, sulphur compounds, nitriles, Schiff bases and so on. The commercial consumption of chemical families is shown in Figure 3.

Many aroma molecules have more than one functional group, each of which contributes to its properties. Reactions can take place in the isolated fragrance mixture, in the products that are fragranced, with packaging, on the skin, from UV, heat or oxidation and with reactive species in the air - all making the challenges for bringing a perfumed product to market daunting

The first fragrance materials were natural products: woods and roots, flowers and leaves. They still play an essential role in fragrance creation. No man-made mixture has ever totally replicated the scent of a pure rose or jasmine oil. Natural products are processed by a variety of processes, most commonly distillation, solvent extraction and expression, each best suited to a specific material.

Some of these products, like the best rose and jasmine oils, exist in relatively limited supply and are very expensive. Others, such as citrus derivatives, are based on commodity products and are usually economical, although a hurricane in Florida can wreak havoc on short-term supply.

Dry distillation involves high temperatures from direct heat, frequently a flame. This is used for the highest boiling oils, usually from wood. Pyrolysis gives these materials a characteristic smoky or burnt note. In steam distillation, water or steam is added to the plant material, co-distilled and separated in a Florentine flask. Expression involves simply pressing the oil mechanically out of the fruit.

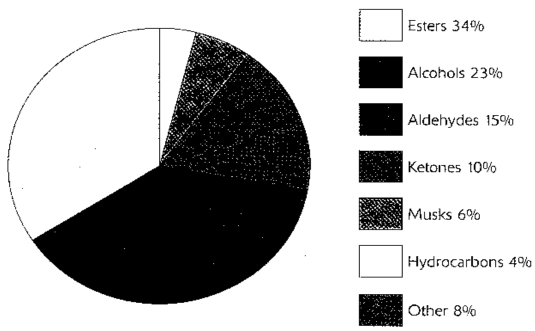


Figure 3 - Fragrances by chemical type

Solvent extraction once used benzene, but now hexane, petroleum ether and other solvents are used, in addition to more advanced techniques like the use of supercritical CO_2. The product extracted is termed a concrete and contains waxy and resinous components. Dissolving the concrete in ethanol, then chilling and filtering results in the absolute, which is alcohol-soluble and is the most precious form of natural oil.

Roughly 3,000 chemicals are available to the perfume industry and even a cursory overview cannot do it justice. Aroma chemistry is intimately entwined with the growth of organic chemistry from about 1860 onwards, and synthetic materials began to enter fragrance compositions by 1883 (Houbigant's *Fougère Royal*).

We can learn about two important classes of materials through the work of two pioneers in the field: Albert Baur (sometimes spelled Bauer) and Leopold Ruzicka. Baur entered the scene in 1888 - by mistake! He was experimenting with new explosives, when he found that the reaction product of TNT and tert-butyl halides was a poor explosive but had an unusually pleasant odour.

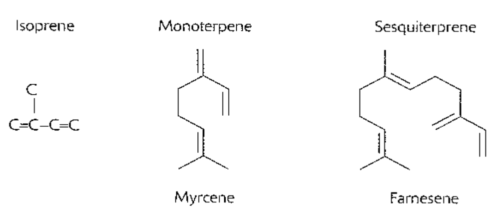
From this, he created Musk Baur, the first synthetic musk, then in 1894 he went on to produce Musk Ketone. This was an excellent substitute for natural musk from the gland of the musk deer, a uniquely effective fragrance fixative for which a synthetic substitute had long been sought. Safety issues have pushed nitromusks into the background, but they were important components of classic fragrances, like Chanel No. 5.

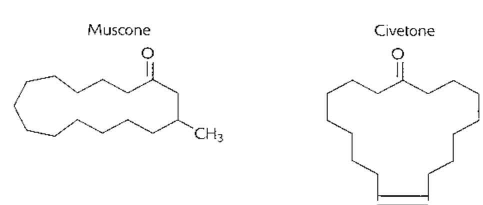
Ruzicka was the most prominent chemist to ever work in the field of aroma chemistry. He was always interested in natural products and his study of Dalmatian insect powder introduced him to the chemistry of terpenes, an essential family of natural products, which are mainly derived from citrus products or pine trees.

Isoprene is the building block of the terpene family, the conjugated double bonds allowing ready head-to-tail polymerisation. Terpene nomenclature was established long before modern systems. 'Mono' denotes two isoprenes, 'di' means four and 'sesqui' is 1.5 or three (Figure 4). Since humans cannot smell molecules with a molecular weight beyond 300, anything beyond a sesquiterpene is too large to smell.

Figure 4 - (left) **Terpenes**

Figure 5 - (right) **Macrocyclic musks**





Orange oil, abundantly available, is a key feedstock. Roughly 90% is limonene, which is virtually odourless, as are most other purely hydrocarbon components. Limonene can be driven off by distillation, resulting in 'folded oils'. If ten drums of initial product have nine drums of terpenes removed, it is termed a '10X' oil. After the oil is folded, other chemicals ('addbacks') can be used to create value-added flavour and fragrance raw materials.

In 1916-1917, Ruzicka received the support of Haarman & Reimer and later Ciba, leading to the synthesis of fenchone and linalool and the partial synthesis of pinene. With the Geneva-based perfume manufacturers Chuit, Naef & Firmenich, he synthesised civetone and muscone, with 17 and 15 carbons respectively (Figure 5).

Adolf von Baeyer had claimed that 15 to 17 carbon rings could not be stable because of bond strain. Ruzicka was then able to prepare a series of alicyclic ketones with nine to over 30 carbon atoms. Before this discovery, rings with more than eight atoms had been unknown and, indeed, had been believed to be too unstable to exist.

Ruzicka also showed that the carbon skeletons of terpenes and many other large organic molecules are constructed from multiple units of isoprene. This work lead to the synthesis of a vast array of aromatic terpene derivatives. In the mid-1930s, Ruzicka discovered the molecular structure of several male sex hormones, notably testosterone and androsterone, and subsequently synthesised them. His work in aroma chemistry was rewarded with the 1939 Nobel Prize.

Mention the word 'perfume' and the mind may conjure an expensive elixir in an elegant bottle, worn by the fashionable elite. Of course, most fragrances have become a much less expensive commodity within everyone's means.

Over the last few decades, personal products and home environments have become increasingly fragrant. The creation of these odours is the domain of a highly trained group of practitioners, the perfumers.

The life of a fragrance usually begins in a hydro alcoholic solution, but a successful odour soon morphs into a variety of more mundane applications. The greatest quantities of fragrances are used in functional products for skin and hair, laundry and indoor air.

The process of 'translation' from a cologne form to a functional product hinges on price, stability and aesthetics. Price is the easiest to grasp: as the uses become more utilitarian, the acceptable cost of goods drops. Stability often hinges on chemical interactions with base materials, pH, temperature sensitivity and so on. It is simple chemistry but is applied to a complex system with innumerable variables.

It is the composition of aroma chemicals from a bottle of pure perfume oil or fragranced shampoo in the air that makes the olfactive impression - the headspace. Interaction with a substrate will change the odour quality when placed in different carriers, such as a lotion, soap or antiperspirant. Most perfumers in large companies spend a great part of their time making the adjustments necessary for these mundane applications, a process called fragrance translation.

This might be a good time to go back to Figure 1 and identify those molecules. **1** is phenylethyl alcohol, a rose note. **2** is limonene, a monoterpene with a faint lemon odour, which is the main component of orange oil. **3** is pinene, a bicyclic terpene that smells like a pine tree, which is where it may come from.

4 is musk xylene, which bears a close chemical resemblance to TNT and was an early discovery of Baur. **5** is vanillin, a main component of vanilla. **6** is coumarin, a lactone with a sweet smell. Lactones are cyclic esters resulting from intramolecular esterification.

How many chemists would identify them as rose, lemon, pine, musk, vanilla or sweet? What in their structure determines the odour? What other structures would have the same or similar odours? How would adding a methyl group change the odour?

The fragrance industry has been traditionally self-regulating, but external forces have increasingly dictated the allowable raw material palette. Since 1966, the Research Institute for Fragrance Materials (RIFM) has tested our products. The results are turned into policy by the International Fragrance Association (IFRA).

As the industry becomes more global, numerous pressures have been placed on common fragrance materials. The EU, first by establishing a list of fragrance allergens and now with the new REACH legislation, has been a major factor.

Other counties, especially Japan, have separate requirements. Large companies such as P&G have additional restrictions of their own. The impact of these cumulative forces on the perfumer's palette is profound.

Aroma science studies temporary effects on emotions via olfactory pathways and has been the focus of numerous researchers. Many aromas are known to be stimulating or tranquilising. Lemon is an example of a stimulant; it can influence mental and physical performance and vigilance.

The phenomena known as the 'lingering effect' is used to make shoppers spend more time in stores or keep gamblers at slot machines. Odours have also been closely linked to sexual desires. Dr Alan Hirsh established the increase in sexual activity in men caused by the smell of doughnuts and pumpkin pie and in women by the smell of Good & Plenty (a licorice candy) and cucumber.

Pheromones are well known in the insect and animal world, and commercial pheromones are sold to influence their behavior. The impact of pheromones on humans is more controversial. The seminal study,[2] McClintock's findings that women living together tend to synchronise their menstrual cycles, proves that chemical signally among humans exist. It is much less sure that pheromones influence human sexual behaviour, as vision is so much more important in humans.

Pheromones are usually assumed to be recognised by a separate organ, the volmeronasal organ. There have been many indications that olfactory receptors can also respond to pheromones. Recent research[3] by Linda Buck has uncovered a new family of receptors, trace amine-associated receptors (TAARs), that are present in humans, mice and fish. Some TAARs can recognise volatile amines in urine, which are richer in the male and may be a pheromone.

Chemistry is the technical heart of fragrance and regulatory forces are determining the possibilities of the industry, but the power of smells over our minds and emotions are what make it special. We have seen how much science, from the olfactory cilia to aroma chemistry to brain response, is integral to the process. Yet, to the consumer, a bottle of perfume will never be a mixture of aldehydes, indoles and nitriles, but a mysterious liquid that adds something intangibly beautiful to our lives.

L. Buck & R. Axel, A Novel Multigene Family May Encode Odourant Receptors: A Molecular Basis for Odour Recognition, *Cell* 1991, *65*, 175-187

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