Huber the Nose.

Musks in Perfumery

Passion for Scents
Musks in Perfumery

Natural musk is an intensely-smelling secretion from an abdominal “musk” gland of the rare musk deer, *Moschus moschiferus*, that lives in the Central and East Asian highlands (Tibet, Himalayas, etc.). The scent from the secretion entices fertile females to approach and mate.

For decades, the male deer was hunted and killed to garner the valuable musk, a viscous brown liquid that becomes grainy after drying. Later efforts to breed the animals on farms met with scant success. Others attempted to trap them in their natural habitat during the mating season and extract the costly secretion from the gland with a syringe. Shortly before complete extinction, protection programs were instituted and, as chemical synthesis of the musk composition became possible, hunting this endangered animal became obsolete. In the past 20 years, the use of natural musk for “medicinal” purposes or as an aphrodisiac in perfumery has decreased drastically. Today, use of genuine animal extracts (ambergris, civet, musk) is unpopular and no longer of commercial significance.

Musks have always played a significant role in perfumery. Substances from this group lend a fragrance composition sensual warmth, a velvety-fine essential note, and are long-lasting. Indeed, these scents are synthesized in large scale by the industry for many types of products, including shampoos, detergents, soaps, creams and, naturally, also for “haute parfumerie”, in other words, perfumes, eaux de parfum, eaux de toilette, etc.

Synthetic musks are generally divided in four subgroups: nitro-, polycyclic, macrocyclic and linear musk scents.
Nitromusks

Nitromusks are artificial compounds, i.e., they are not found in nature. The first product of this group was accidentally discovered in 1888 by A. Baur.\(^1\) While researching explosives (nitrating aromatic compounds), he perceived the sweet musky odor of one of his intermediate reaction products (1). He later also identified Musk Xylene (2), Musk Ketone (3) and Musk Ambrette (4), all nitration products of aromatic compounds that, likewise, exhibit the typical warm and sensual musk notes. Musk Tibetene (5) and Musk Moskene (6) are also members of this group, but are of little commercial significance. Due to its phototoxicity\(^2\) and neurotoxic\(^3\) effects, the use of Musk Ambrette (4) has been restricted for more than 30 years and is thus no longer industrially important. According to the European Union Regulation No. 1907/2006 REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), amended in 2008, the use of Musk Xylene (6) is of particular concern and can no longer be used to perfume products for everyday use. Musk Ketone (3) remains the only nitromusk still used in Europe.

![Chemical structures](images)

1. Baur Musk
2. Musk Xylene
3. Musk Ketone
4. Musk Ambrette
5. Musk Tibetene
6. Musk Moskene

Nevertheless, because of its poor biodegradability, its concentration is severely limited in new cosmetic products, and even prohibited by many commercial users of fragrance oils. Even though this nitromusk contributes essentially to the sensory perception of certain older, traditional fragrance oils and is difficult to substitute, it will most likely soon disappear from the market.

The nitroaromatics are rather dangerous to manufacture; indeed, several musk factories have experienced severe explosions. Safer options were sought and, in the 1960s, a newly-discovered substance group of polycyclic musk scents with distinctive musk character was found that could successfully compete with the older representatives of this fragrance group. But it was only after reports about the poor biological degradation and the increased presence of nitromusks in nature and in man (bioaccumulation), that ultimately led to the discontinued use of nitromusks.
Polycyclic Musks

In the middle of the 20th century, while investigating musk compounds without the aromatic nitro group, the polycyclic musks were discovered. They include representatives such as indane, tetraline or isochromane derivatives. The first commercially-available member of this group was Structure 7. Today only a few are still used in many different applications in the fragrance industry: Isochromane (8), Tetraline (9), and Indane (10) derivatives are the economically most significant compounds (in decreasing volume). Structures 7, 11, 12 and 13 are much rarer. Due to its neurotoxicity, Structure 14 has been banned for more than 40 years. Structure 15 is also considered part of this group even though its scent has a distinctive woody character. 16, a propylene glycol acetal of an otherwise non-commercialized polycyclic compound, has an intense ambergris note. Structures 17 – 19 depict the most important discoveries of the past 30 years in this musk category, though their volumes are in no way (yet) comparable to those of the above-mentioned stars of the group.

![Musk Structures](image-url)
Environmental Concerns

Proof of the current omnipresence of nitromusks in the environment, specifically in water and in fish, date back to the early eighties. And in the 1990s, research on the contamination of surface water, purification plants, water supply and wells intensified. The nitromusk, Musk Xylene (2), has been detected in human milk, fat and blood. Likewise, polycyclic musks were later also found in the environment, in human fat and breast milk.

In these studies, both nitromusks and polycyclic musks were present at easily detectable concentrations; indeed, their abundance in the environment, in animal or human fat, milk and blood correlated with the quantities manufactured at that time throughout the world. As both nitro- and polycyclic musk scents are highly lipophilic, they are readily absorbed by fat tissue where they are present at higher levels than elsewhere in the body. In the eel, known for its comparatively high fat content, concentrations per kg body weight were 5 - 10 times higher than those found in the bream.

The most widely-used nitromusk and polycyclic compounds have been examined intensively in recent years. Toxicological and dermatological data show no harmful effects on humans, animals or the environment. However, their extreme chemical stability and very low biodegradability make polycyclic and nitromusks potential long-term environmental contaminants because of bioaccumulation.

Whereas chemical stability, i.e., resistance to chemical or biological degradation, used to be a highly desired property among fragrance manufacturers, for modern ecological perfumery, a scent has to be stable enough not to change during a product’s lifetime, but biodegradable enough to disappear swiftly once the product has been used. In recent years, ever more companies demand fragrances without nitromusks or polycyclic musks; a development that seems ecologically sound and far-sighted.

Macrocyclic Musks

This third subgroup consists of both nature-identical and artificial substances. The macrocyclic musk scent era was initiated with the structural elucidation of Muscone (20) in 1926 by the Nobel laureate, L. Ruzicka.

Macrocyclic musks are found not only in the animal kingdom, but also in plants. For example, Structure 21 is found in angelica root oil. Together with Structures 22 and 23, it belongs to the most commonly-used macrocyclic musk scents. Isoambrettolide (24), Civetone (25), and Normuscone (26) are rarely encountered due to their high cost. Structures 27 to 32 are additional compounds of this group. Structures 33 to 35 are the most important discoveries of the past 20 years in this group. The chemical structure of macrocyclic musks indicates that one can expect a good biodegradability, and indeed, this has been confirmed in individual cases (internal studies by certain manufacturers).
Muscone Exaltolide™, Cyclopentadecanolid™ Macrolide™, Pentalide™, Thibetolide™ Astratone™, Musk T™

Globalide™, Habanolide™ Isoambrettolide, Ambrettolide™ Zibeton, Civetone™

Normuscone, Exaltone™ Globanone™ Ambretone™, Velvione™

Musk R1™ Arova N™, Musk 144™, Zenolide™

Exaltenone™ Nirvanolide™ Cosmone™

Muscenone™
Problems with the Substitution of Nitro- and Polycyclic Musks

Several problems arise with the substitution of nitro- or polycyclic musks. First, the odor profiles (intensity, tonality, odor threshold, tenacity, etc.) are often different. As a matter of fact, it is quite difficult to adequately substitute Musk Ketone (3) with its powdery sweet, strong almost overpowering musk scent, even using a mixture of musk compounds. For this reason, certain cosmetic products still contain nitro- and polycyclic musks, even some newer creations. Further complicating the situation is that some of the macrocyclic substitutes show different stability profiles, depending on the medium used (e.g., acidic or alkaline milieu). And thirdly, the high price of many of the macrocyclic musk scents makes their use prohibitively expensive. The fragrance industry and perfumers are challenged to overcome the above problems; easy solutions that solve all the problems are not yet in sight.

Linear Musks

In the past 10 to 20 years, the alicyclic and aliphatic musk scents - often shortened to “linear” musk scents - have emerged. In addition to their musk notes, they often have a fruity, pear-like nuance, and are even capable of influencing the top note of a scent. The first representative of this group, Rosamusk (Structure 36), has an intense foreground scent of geranium; the other important members of this group that were discovered later can clearly be described as true musk scents (Structures 37-42).
References


Review Article: