Musks: The Choices

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Recently, the use of the musk odor in perfumery has been the subject of much lively discussion in the fragranced consumer goods industry. It is therefore, an appropriate topic for perfumers and the consumers of their creations. I would like to summarize the various possibilities, considerations and choices that are open to perfumers when they create fragrances that are safe for today's market, including a brief description of the versatility and functionality of the various musks, as well as the safety of these ingredients.

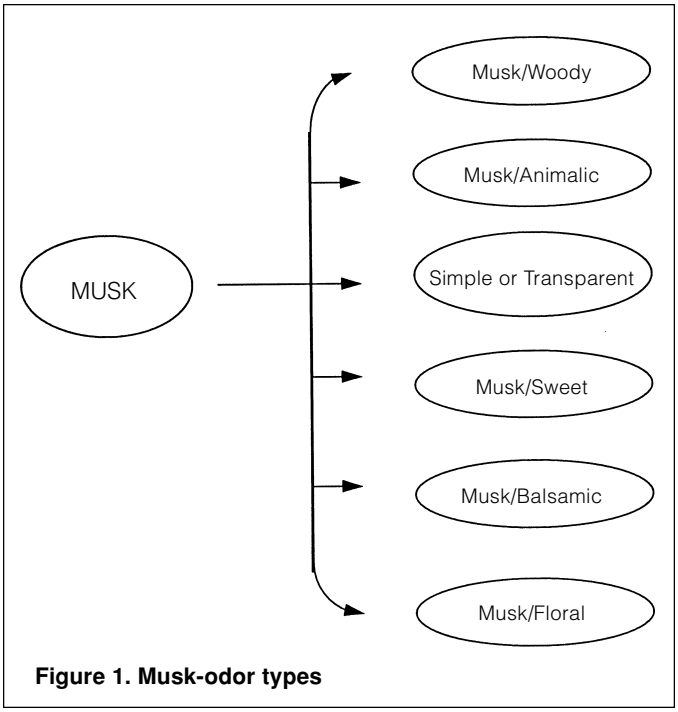

Figure 1. Musk-odor types

Musk-Odor Attributes

What is musk odor? Nature's own musks emanate from insects, vegetation and, primarily, animals, although not all musks have animalic odor. All musks share a rich enveloping smoothness of fragrance usually with modifying or secondary aspects. For some people, there is also a "pure" category, shown in Figure 1 as "simple" or "transparent" to which perhaps, could be added the descriptor, "cool". The "sweet" musks seem to have a powdery, vanilla character.

I will describe, briefly, the molecular shape of these substances that exhibit musk odor. Figure 2 shows the tremendous range and variety of chemical functionalities and structural shapes. Different as they clearly are, they share one common aspect, a primary odor, which we describe as musk. There are one, two, three and four-ringed structures. Functionally, we see ethers, ketones, chromans (otherwise known as internal ethers), lactones, alcohols and nitro groups. There are, of the order, twenty manufacturers of musk chemicals around the world. However, not all of the chemicals shown in Figure 2 are commercially available.

One very important factor shared by musks in widely varying degrees is the ability to act as "odor magnets", "fixatives", even synergists for other substances. They appear to cling to and extend the life of the more fleetingly odored materials. For example, nature-identical apple fragrance would primarily be comprised of lower molecular weight compounds (mostly esters) that are very volatile and hence not long-lasting. The presence of an appropriate musk (for example HHCB) will enable an apple fragrance to last for a much longer period of time as a single entity. Curiously, the musk note does not overpower the other components in the apple fragrance, even though the HHCB may be present at a higher percentage. Table 1 shows a list of attributes that are either exhibited collectively by the musks or aspects that musks strongly support and complement when skillfully incorporated into a fragrance. As can be seen, this list of attributes is very significant from a marketing viewpoint as it includes a high percentage of the benefits that we

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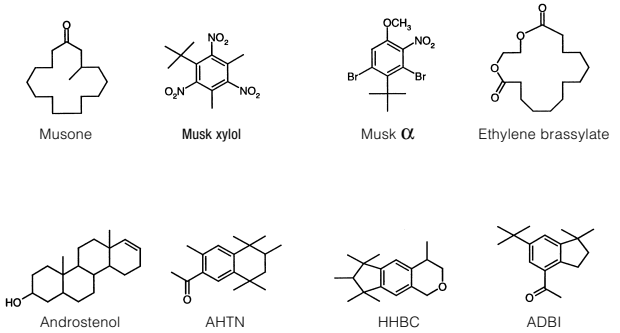

Figure 2. Structural varieties in musks

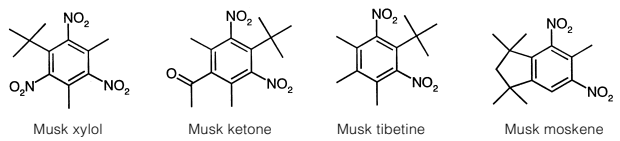

Figure 3. Nitromusks

need to convey to consumers regarding finished-fragrance products.

The table shows the attributes that could be selected by a marketing department when briefing an haute couture/up-market fragrance for women. The perfumer may decide to use more than one musk material, in order to incorporate qualities that the end user will associate with beauty, elegance, femininity and glamour.

In a man's sport soap, the marketing requirement would indicate a different selection of attributes. These include the musks which convey clean, fresh, masculine, natural and vigorous accents.

In a laundry detergent fragrance, a familiar odor based on clean, fresh notes with an overall impression of purity and floralcy would be appropriate.

Table 1 also shows musk attributes that encourage the use of skin-care products. These attributes include comforting aspects, emolliency, gentleness and relaxing qualities. Often there is an expensive air to these products, which ties into luxury and perhaps sensuous, soft and moisturizing qualities.

The above data displays why formulators employ such versatile materials as musks. They contribute a harmonizing capability to fragrances in which they are applied. Their attributes connote and reinforce many aspects of our daily lives, confirming their importance to us.

In the following discussion, we have subdivided the varied structures of musks into three basic categories; nitromusks, macrocyclic musks (MCM) and polycyclic musks (PCM).

Nitromusks

Nitromusks (Figure 3) was the first category discovered and has a 100-year history of safe usage. According to some evaluators, nitromusks have the strongest musk odor of the three groups and offer excellent economic value. They have some performance disadvantages from a perfumer's viewpoint. For instance, they are not very soluble in other fragrance materials and have a tendency to discolor on exposure to light. They are not as versatile in performance and utility as the PCMs. However, nitromusks have their place in perfumery with musk ketone having perhaps a more unique odor with an animalic aspect. It is useful in supporting the sensual aspects of fragrances. Currently, they are not the first choice for perfumers and usage of this category has declined. No nitromusks are made in Europe or the US. Production is limited to India and China.

Musk xylol and musk ketone are the most frequently used elements of this group. The Research Institute for Fragrance Materials (RIFM) and other authorities have conducted extensive testing on these ingredients.[1] Musk

Table 1. Musk attributes for selected product types

Attribute	A	B	C	D
beautiful	x			
classic				
clean		x	x	
comforting				x
creamy				
elegant	x			
emollient				x
expensive	x			x
familiar		x	x	
feminine	x			
floral		x	x	
fresh		x	x	
gentle				x
glamorous	x			
healthy		x		
long-lasting	x	x		
luxurious	x	x		x
masculine		x		
moisturizing				x
natural	x	x	x	x
pure		x	x	x
relaxing				x
romantic				
sensuous	x			x
sexy				
soft				x
sophisticated	x			
virogous		x		
warm				

Legend:
A = Women's up-market parfum
B = Men's sport soap
C = Laundry detergent
D = Skin care

xylol and musk ketone have been found to be safe for human health and the environment and have very wide margins of safety; well over 1,000 times the highest levels to which humans may have been exposed in consumer situations. A safety factor of 1,000 times is far in excess of the traditional 100-fold safety factor expected by regulators including the US FDA (US Food and Drug Administration) and the SCC (Scientific Committee on Cosmetic Products, the advisory body to the European Union).

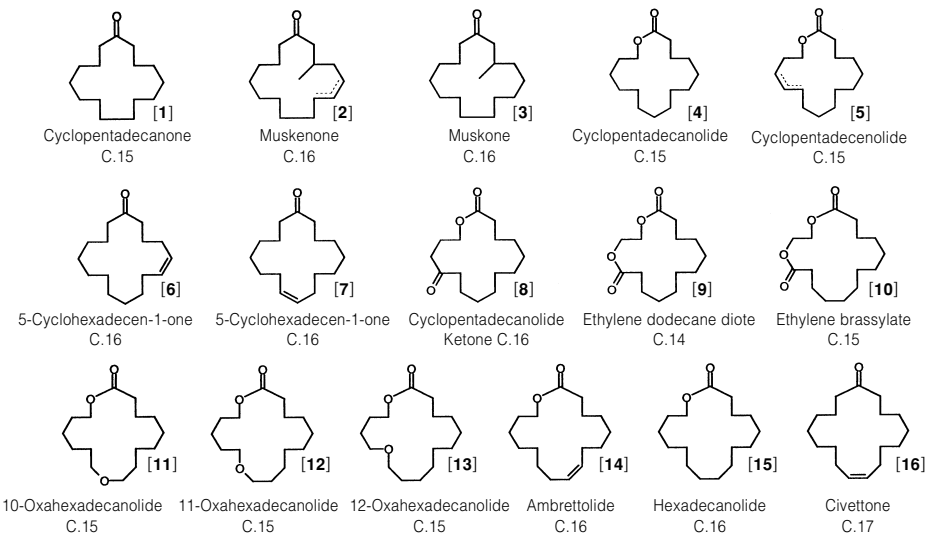

Figure 4. Macrocyclic musk compounds

Macrocyclic Musks

The next group, and perhaps the most populated in terms of related elements, is the macrocyclic musks (Figure 4). During the 1920s, two of them were isolated from the natural air oxidized exudates from two mammals (small musk deer from Asia, *Moschus moschiferus*, and the civet cat) and various other species from the Middle East and Africa. The products identified from these animals are commonly known as muscone **[3]** and civettone **[16]**, respectively. Muscone has 15 carbons of the large ring while civettone has 17. The discovery and subsequent synthesis of these two products in the late 1920s defied previous theories of organic chemistry that argued against a single ring having so many elements to it. In the 1940s an ambrettolide isomer was identified in ambrette seed oil (*Abelmoschus moschatus*).

The lengths of the MCM chains vary widely as illustrated by **[1]**, **[4]** and **[14]** having rings containing 15, 16 and 17 links, respectively. MCMs may also contain one, two, three or four oxygen atoms of which one or more may be links in the ring, as shown in **[1]**, **[4]**, **[13]** and **[10]**, respectively.

The amount of oxygen contained in the molecule also has a bearing on its diffusivity and substantivity. The penalty for increased substantivity is often a reduction in initial odor impact. The expert perfumer will be familiar with these aspects.

Functionally, the MCMs may be ketones, lactones, or dilactones and internal ethers as shown in Figure 4. They can be saturated or unsaturated and this feature seems to have a large bearing on whether or not the macrocyclic musk will be a good choice for conveying long-lasting properties. Certain unsaturated MCMs develop a rancidity; a fatty acid, hot wax or metallic odor upon aging. These should not be used where residual fragrance is desirable on the end product (as, for example, on laundry, facial tissues or toilet paper).

The chemist's ingenuity has resulted in experimentation with various positionings of oxygen in the ring, as shown in

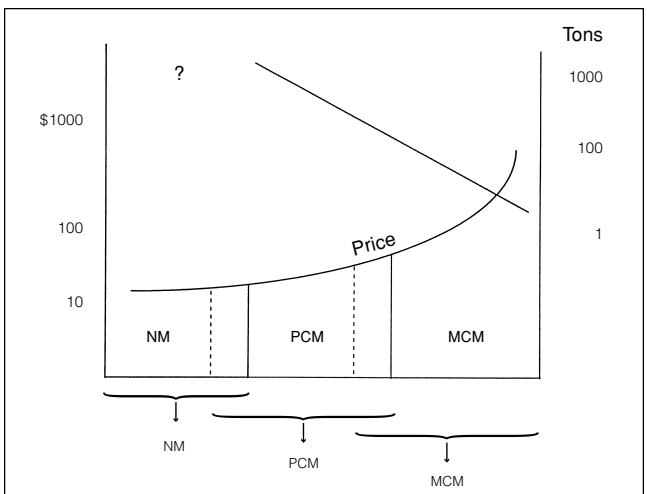

Figure 5. Price/volume ratios for several musk categories

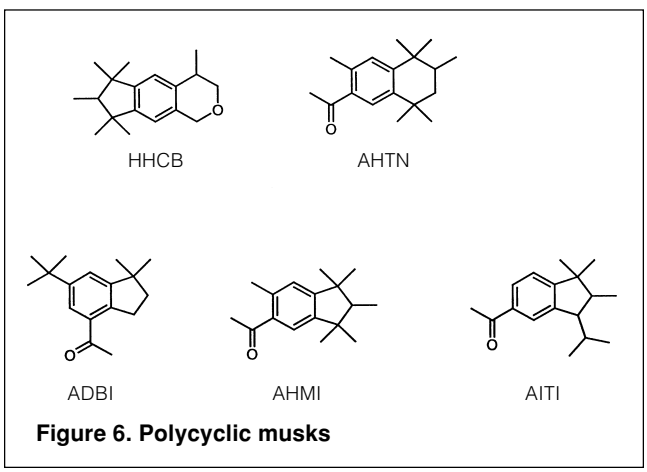

Figure 6. Polycyclic musks

Table 2. Biodegradation of HHCB in soil microcosms incubated for 12 months and tracked by radiolabeled tracer following US FDA protocol

	A	B	C	D
Starting HHCB added to microcosms	500 µg	350 µg	500 µg	500 µg
Final HHCB measured in microcosms	44 µg	25 µg	173 µg	18 µg
% HHCB remaining	9%	7%	35%	4%

Legend:
A = sludge-amended soil
B = forest soil
C = agricultural soil
D = river sediment

[11], **[12]** and **[13]**. Even though these structures look and are similar, they differ widely in the cost of synthesis due to the chemistry involved.

The virtues of the MCMs encompass all of the secondary odor descriptors that modify the basic musk odor. As a group, they biodegrade more rapidly than nitromusks or PCMs. They have widely varying performance results that are much appreciated in fine fragrance, but for consumer products with active bases, they are generally inferior to the PCMs.

MCM disadvantages would include higher costs (Figure 5) than the other two categories, ranging from approximately US$25/kg to several hundred dollars per kilo, dependent on the molecular structure involved. Their syntheses, generally speaking, involve multiple-stage reactions, many of which are at fairly high dilutions. As a result, they are equipment-intensive. The need for multiple-stage reactions contributes greatly to the higher cost of production. They are not as readily available as many would wish. However, there are efforts being made by a few major producers of aroma chemicals to reduce cost and increase availability.

One aspect of all musks is that the elements have varying levels of anosmia or parosmia in one or more of the known structures. The difference in people's perceptions of scent can be quite startling. Some people will not smell a musk odor at all while others will find it very powerful. In some cases, evaluators will perceive the secondary descriptor of a musk only, such as woodiness. Many people find secondary descriptors moderately strong, but not strong enough to be described as musk. This has implications for fragrance marketers in that the general public perceives the odor of products differently through the variations of the musk used. An inspection of the constituents of many recently introduced fragranced products shows that perfumers have employed more than one musk. It is not unusual to find four or five different musks present in a fragrance formulation that reinforce all necessary attributes. The logic is that consumers will respond to at least some of the musks if not to all.

HHCB and the Environment: Recent Findings from Procter & Gamble[7]

Recent laboratory studies show HHCB is biotransformed to polar metabolites, which are predicted to be less bioaccumulative than HHCB itself.

Strongest evidence from recent sewage conditions: HHCB halflife of less than 35 hours. This reduction has resulted from biologically mediated oxidation to polar metabolites which increase as time progresses.

Biotransformation greatly decreases the potential for HHCB to bioaccumulate or cause harm to the environment.

These findings are consistent with the lower-than-expected concentrations of HHCB measured in the environment.

Table 3. Risk characterization ratios (RCR) of AHTN and HHCB[6]

	AHTN	HHCB
Aquatic organisms	0.057	0.074
Sediment organisms	0.44	0.064
Soil organisms	0.81	1.2[a]
Fish-eating predators	0.015	0.0013
Worm-eating predators	0.078	0.017

[a] Recent soil data is expected to bring this value down to less than 0.1

Polycyclic Musks

Polycyclic musks (Figure 6) are called polycyclic because they contain two or three rings in their molecular structures. This also includes six or seven methyl groups. Their molecular weight is not less than 244. Functionally, they are all ketones, with the exception of HHCB, which is an isochroman and the only three-ringed structure.

The major products of this group are AHTN and HHCB. The others are used in significantly lower amounts. Due to their great versatility, these materials have found broad-range usage in perfumery and are the musks of choice of most perfumers, particularly for fragrances intended for household cleaning products and also for cosmetic and fine-fragrance purposes. They are very economical in use due to their comparatively low costs of production from abundant raw material feed stocks (Figure 5).

RIFM has conducted extensive testing and risk assessments[2] to demonstrate the high safety factors that prevail when AHTN and HHCB are used at the prescribed levels. From a human-health perspective, you could use 25 gallons (approximately 100 liters) of fragrance every day[3] and still not have a safety problem. Nevertheless, there have been concerns over the detection of these PCMs in the environment. Recently completed studies[4,5] demonstrate that the environment is able to satisfactorily degrade such products. Table 2 shows results of work recently reported

to RIFM concerning the fate of HHCB in soil microcosms. As demonstrated in all the soil samples tested (sludge-amended soil, forest soil, agricultural soil and river sediment), the results support the conclusion that HHCB has a halflife, in soil and sediments, significantly less than one year.

The detection of trace quantities of AHTN and HHCB in river water ultimately stimulated the Dutch government to request its National Institute of Public Health and the Environment (RIVM) to prepare an environmental risk assessment.[6] The report strongly supports the conclusion that the usage of AHTN and HHCB is safe for the environment. Scientific evidence is presented that indicates AHTN and HHCB biotransform under actual environmental conditions. RIVM estimates the risks using risk characterization ratios (RCR). If the RCR is less than 1, then the material in question is considered acceptable in terms of its impact on the environment. The summary shown in Table 3 demonstrates that an RCR less than 1 was achieved in all cases except the soil compartment for HHCB. However, this assessment was released before the results of the RIFM soil study were known. Addition of the RIFM results are expected to reduce the RCR value from 1.2 to less than 0.1. In addition, the RIVM has concluded that no additional environmental studies are warranted.

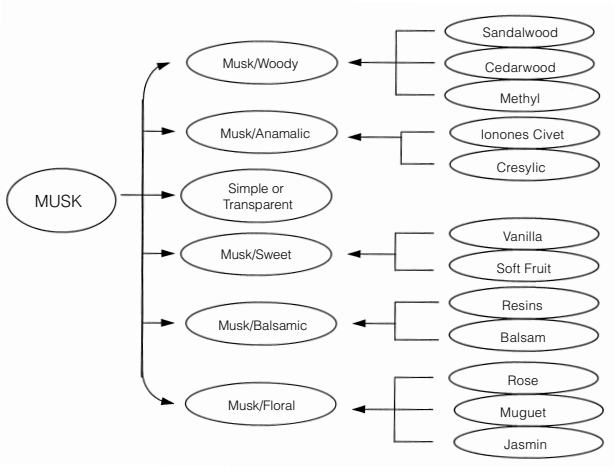

Figure 7. Up-market parfum qualities for women

Bear in mind that the science of environmental risk assessment with its underlying theories and assumptions is

The Safety of Musks

Due to the ever increasing capability and skill in the science of analytical analysis and developing technology, we are now able to detect the presence of a large number of chemical substances. This includes nitro and polycyclic musks in infintesimally low traces (parts per billion or even parts per trillion) in both the environment and in living creatures. In the future we must come to understand the real significance of our ability to detect all manner of chemicals in lower and lower concentrations.

We all easily relate to percentage parts of 100; for example, 1 out of 100 is 1%. But what is one part per billion? One part per billion is a distance of 4 centimeters compared to the earth's total circumference (40,000 km). One part per billion would be one second within a span of 31.7 years. One part per trillion is one second within a span of 31,700 years. As technology develops, and as more substances are searched for, there will be no end to the number of materials that can be found in incredibly low trace amounts in virtually every part of the environment and the creatures that inhabit it.

This relates to the case of the much-debated polycyclic musks. A European Flavor and Fragrance Association (EFFA) manual[8] states that these valuable substances are safe for human health and the environment and that there are no identical in-use replacements for them. Here's a summary EFFA's position.

Our association and the industry are dedicated to providing customers and consumers with safe products.
Science demonstrates musks, as currently used, are safe for human health and the environment.
There are no regulatory restrictions on polycyclic musks (PCMs) approved for use anywhere in the world.
PCMs are ingredients in many personal fragrances, soap, detergents, and other household and cosmetic products.
PCMs have many important benefits, adding greatly to a product's fragrance performance and meeting consumer expectations.
Substitute ingredients will alter the fragrance substantially; there is no identical replacement.
The industry is willing to cooperate with any government and/or stakeholder that would wish to discuss questions related to the science of musks.
It is absolutely necessary that, in all ways possible, we assist our consumers to understand these safety concepts and thus allay their suspicions and fear of the unknown. We are all consumers. We all want to use products that are safe for us and the environment. All of us have to better communicate the safety of our products to our consumers.

relatively young and in the past could not be conducted as it is today due to non-existent, or inadequate equipment and testing methods. This science is being refined by improved test procedures, such as biodegradation, which allow us to have a better understanding of the true fate and distribution of a material in the environment.

We are also learning that some materials in the environment do not directly mineralize rapidly but nevertheless are indeed biotransformed. They then transform into CO_2 in the presence of common fungi and soil bacteria. This is an important aspect which cannot be determined by the specified "official' tests.

Many materials which occur naturally in the environment will fail the current Organization for Economic Cooperation and Development (OECD) test for ready biodegradability. Most experts today agree that this official test is inappropriate, artificial and superficial. It in no way represents what actually occurs in nature when materials enter the environment. What we have already learned is that the mineralization process (the conversion of an organic material into simpler elements such as carbon dioxide and water) is the end of the story. However, there are intermediate stages that of themselves indicate that a process of biotransformation is taking place without harm to the environment. Some recent data[7] from Procter & Gamble illustrates this point (see sidebar).

In view of the overwhelmingly favorable safety and environmental data, it is not surprising that no governmental or other regulations presently exist to control the use of these PCMs. These products offer the best overall value. Industry supports them (see EFFA position in sidebar). Perfumers should continue to use them.

Formulating Without Musks

A fourth option has to be considered: making a fragrance without using any musk at all. After all, there is no 11th Commandment that states "Thou shalt use musks in every fragrance." When musk is used in a fragrance, it is very often in the presence of floral, woody, balsamic odors. The resulting fragrance is required to be a harmonious blend that satisfies the consumers' requirements.

On examination of the different subsections of the musk odor (Figure 7), we can approach or simulate some of these desirable musk aspects by the use of various of these other fragrance types. Sandalwood chemicals or cedarwood derivatives may be used for the woody connotation. Animal notes can be derived from the various animalic civet-type materials or cresylic notes. The sweet notes of some musks can partially be approximated or simulated by vanilla-type odors or from certain elements of exotic fruits. This does not include citrus, but rather the soft-berry or guava-type odors such as rosamusk. Similarly, for the balsamic aspect of some musks, the various resinoids and can be helpful, as can heliotropine and various coumarin derivatives. Finally, and for perhaps the most important of the musk notes, the various floral moieties, we can look to rose notes such as phenoxanol, muguet notes such as lyral, and jasmin notes such as methyl dihydrojasmonate.

While some of these approaches help, it is virtually impossible to find an exact replacement for musks used in significant percentages in a fragrance that is not, itself, also a musk.

Conclusion

The key objective with any fragrance is to achieve high consumer acceptability while supporting the various themes designated by the marketing requirements without compromising consumer safety. In today's world, virtually all companies are looking for better fragrances at lower prices. No customer wants to be at a competitive disadvantage. This is a tough requirement but one that can be achieved by continuing to use PCMs with their superior combination of value, good all-around performance and high margins of consumer and environmental safety at the intended use levels.

No one should tell you what to do, or which musks to use, but I do suggest, in fact request, that whatever you decide, you base your decision on sound facts and not on emotion or perceptions; as that road has no ending.

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