The Musk Dilemma

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Musk aroma chemicals represent a very important class of constituents of fragrance compounds. This family of aroma chemicals has been one of the most controversial from the safety concerns of some nitro-musks, to the biodegradation of polycyclic musks (PCMs). Macrocyclic musks (MCMs) currently have the best potential for replacement of PCMs. However, the low cost and performance of PCMs makes the large-scale replacement of PCMs by MCMs a formidable task.

The representative structures of the various musk families are shown in Figure 1, starting with one of the oldest, the nitro musks (musk ketone), the indane class (Galaxolide) of polycyclic musks (PCMs), the macrocyclic musks (MCMs), which are represented by the C-16 ketone (Ambretone), the mono-lactones, (Cyclopentadecanolide), as well as the di-lactones, (Musk T, also known as Ethylene Brassylate). The acyclic structure, R-Citronellyl Ethyl Oxalate is obviously completely unrelated to the other structures, yet has a musk odor.

Fragrance can stimulate a wide range of responses in humans from arousing to energizing (Figure 2). Musks can also have a wide range of secondary odors, such as animalic, to woody notes. Like other aroma chemicals, they also have other attributes such as impacting our moods. The challenge is to evaluate these attributes in a more objective manner and one of the methods used at Takasago is a technique that we call Soul Mapping (Figure 3). The objective is to provide mood profiling for commonly used aroma chemicals. Each aroma chemical is evaluated by a panel, based on the degree to which it evokes a response to feeling alert and energetic, or the opposite attributes, such as feeling tranquil and composed. This data, while in of itself is quite subjective for each individual, does provide a remarkably consistent response from a large panel of evaluators.

The Soul Map radar graph (Figures 3-5) of some randomly selected aroma chemicals shows the energizing attributes on the right-hand side and the calming attributes on the left side of the graph and the general responses to those attributes on a scale of 0-5.

Some aroma chemicals like *l*-Laurinal (levo-Hydroxycitronellal) give a generally stimulating response, while

Figure 1. Structural classes of musks

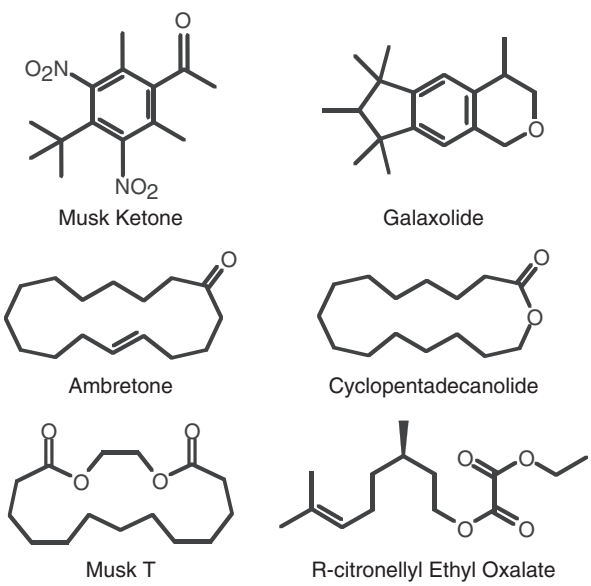

Figure 2. Capabilities of a Fragrance

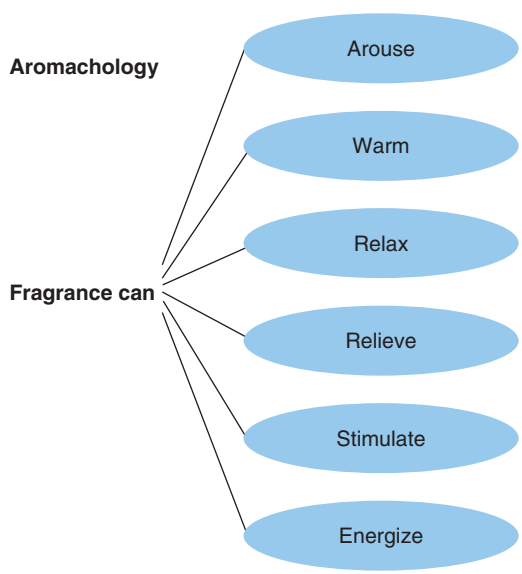

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Figure 3. Soul Map of individual aroma chemicals (randomly selected set of aroma chemicals)

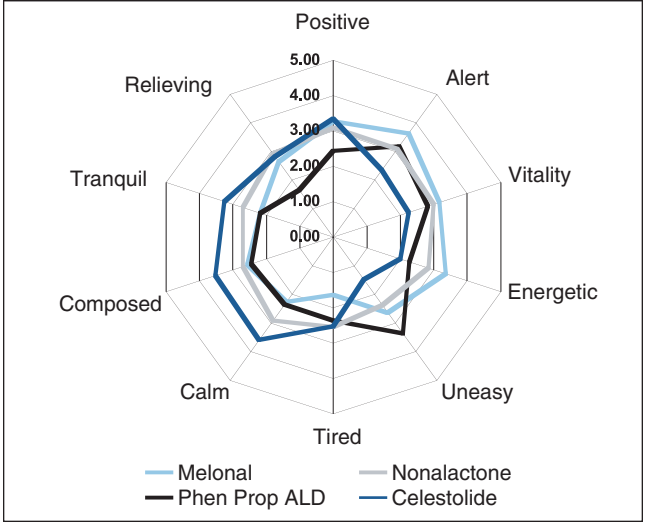


Figure 4. Soul Map of individual aroma chemicals (randomly selected set of aroma chemicals)

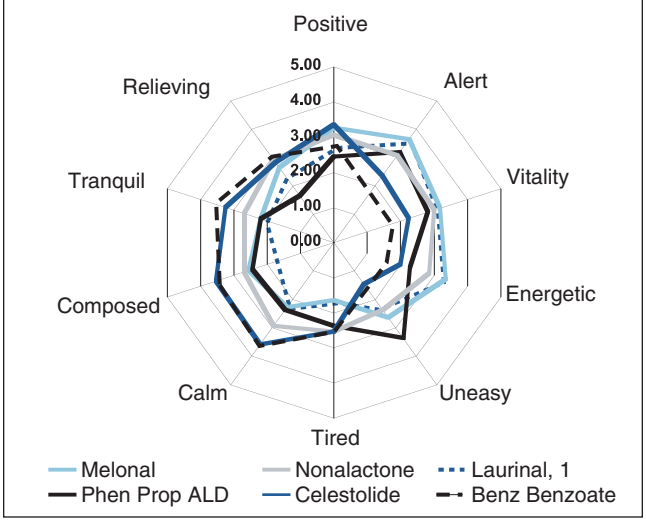


Figure 5. Soul Map of individual aroma chemicals

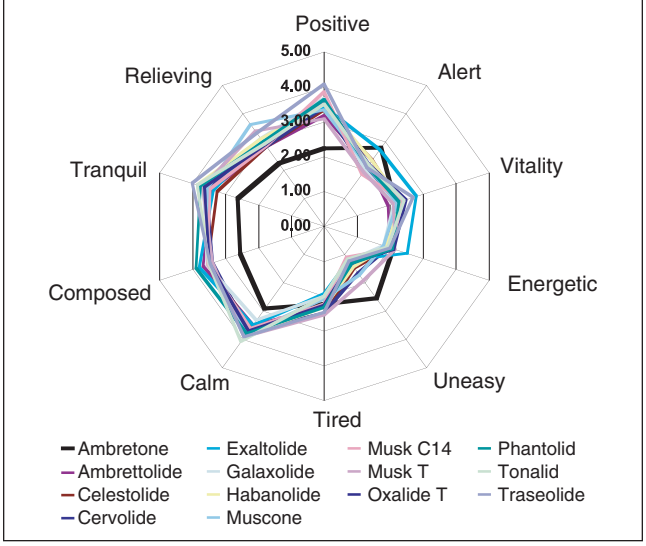
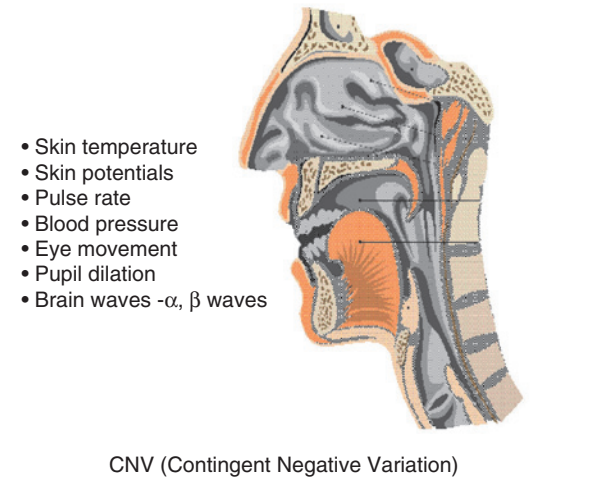


Figure 6. Scientific evidence for human response to odor



CNV (Contingent Negative Variation)

Figure 7. CNV test paradigm

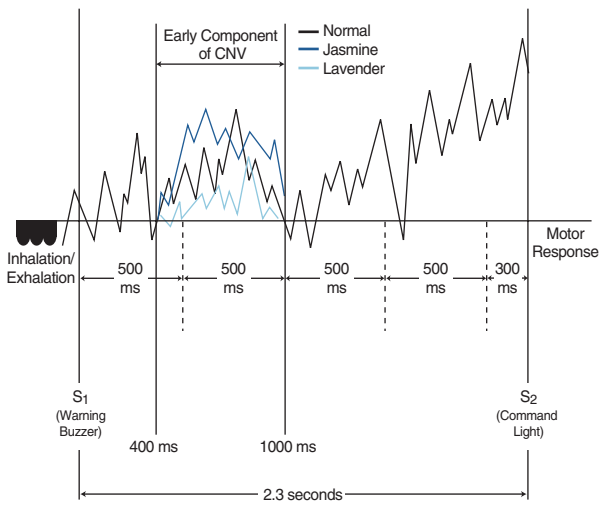
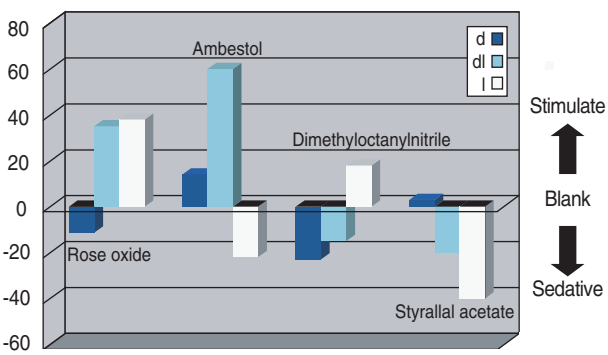


Figure 8. Effects of optically active materials



others such as benzyl benzoate have a generally relaxing response.

Remarkably, the whole musk family of products, from the PCMs to the MCMs, regardless of chemical structure, uniformly exhibits a calming or relaxing response from the evaluators. There is, however, one musk that falls outside of this tight range of responses and that is the C16 unsaturated MCM ketone, Ambretone. This gets scores that are slightly less in the calming response and slightly higher in the energizing responses.

This methodology, while providing reasonably reproducible data from a large panel, is nonetheless, a subjective evaluation. Thus, more quantitative techniques would be desirable. There are a number of well-documented human physiological responses to odors ranging from changes in skin temperature to blood pressure. Interestingly, it has been shown that the response of the human brain to odors can be observed by measuring the alpha and beta brainwaves (Figure 6). This observation has led to the development of a technique called Contingent Negative Variation (CNV).

The CNV chart (Figure 7) shows how the normal brain wave behaves after a stimulus, such as a light, has been turned on and in the absence of a specific odor. The top line is the energizing response to the stimulus, generated after 1000 microseconds, when the subject is in the presence of a jasmine fragrance. The bottom line shows the calming response generated by a lavender fragrance under the same conditions.

When chiral aroma chemicals are evaluated using the CNV method, it is found that the *d* and *l* enantiomers can have completely opposite physiological effects. For example, *d*-Rose Oxide is relaxing while *l*-Rose Oxide exhibits a significantly higher simulative effect. Not surprisingly, the racemic mixture shows a response that is approximately the sum of the two responses. Figure 8 illustrates the evaluations for several other chiral aroma chemicals.

The musk aroma chemicals shown in Figure 9 were evaluated using CNV techniques. These included members of the common MCM families as well as the *d* and *l* enantiomers of Muscone.

The synthesis of the *d*- and *l*-Muscones was achieved in high optical purity and was carried out using the Takasago's chiral BINAP hydrogenation methodology.

The right hand side of the CNV graph (Figure 11) shows that both Musk T and Galaxolide gave relaxing CNV brainwaves in both men and women while the data in the center shows that Exaltolide and Musk Ketone had stimulating effects, again in both men and women.

The most interesting finding was that the two enantiomers of Muscone, shown on the left, had completely different gender responses. *d*-Muscone was found to be relaxing to both men and women, while *l*-Muscone was found to be relaxing to women, but stimulating to men. The CNV data shows that while each of these products are in the same odor family, our physiological responses differ for each one and

Figure 9. CNV evaluation of musks

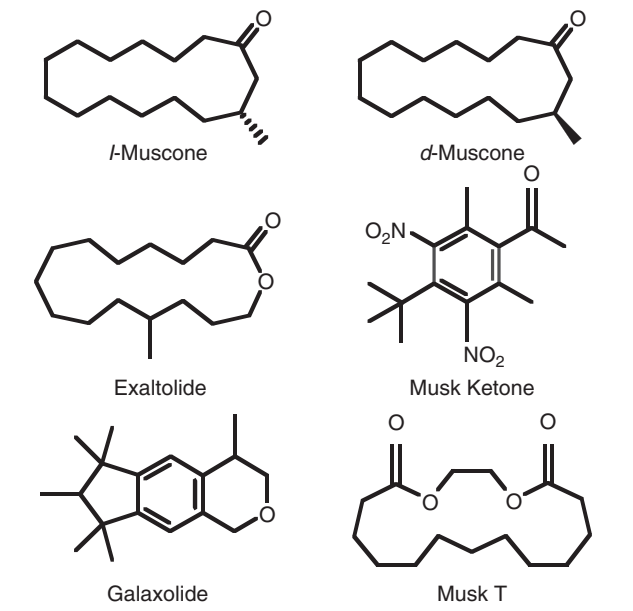
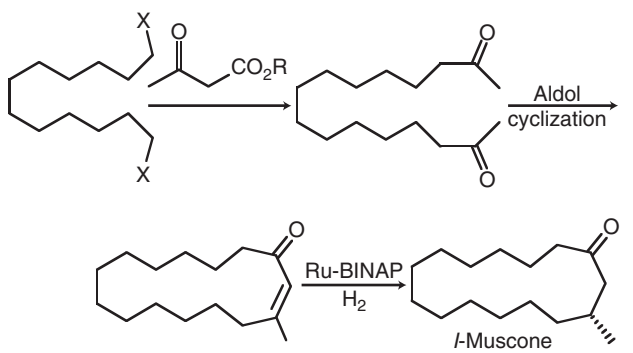


Figure 10. Asymmetric synthesis of *l*-Muscone



Japanese Patent: JP6192161

Figure 11. CNV evaluation of musks

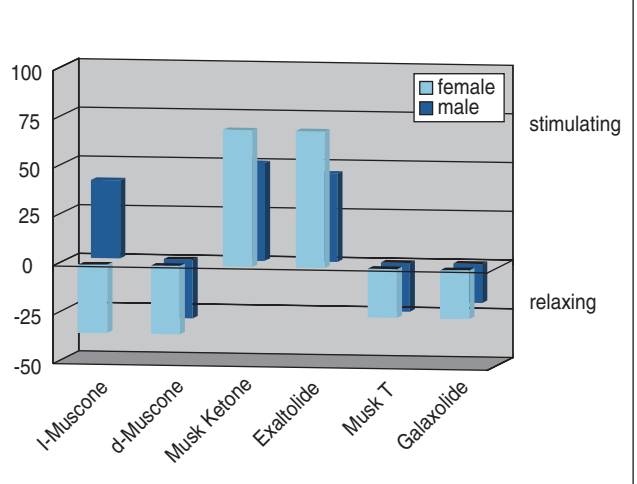


Figure 12. Approximate detection sensitivity

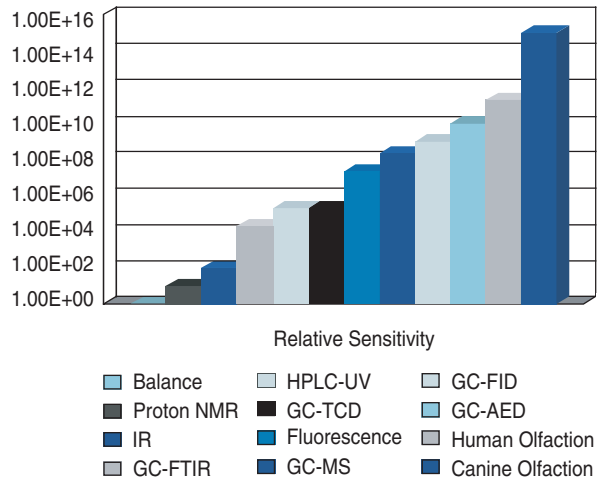


Figure 13. Odor detection threshold of musks

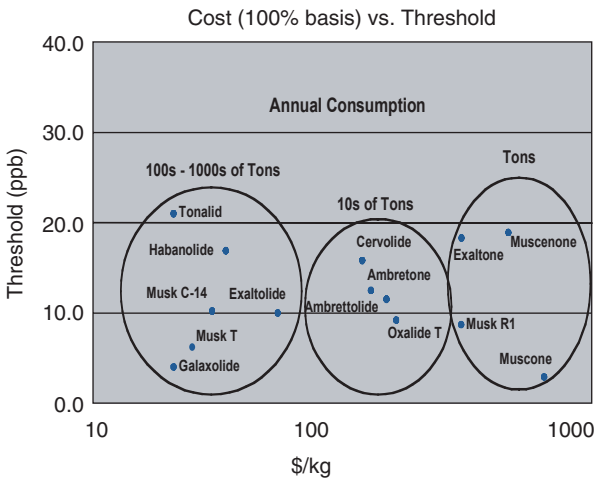


Figure 14. Relative cost of detection (Galaxolide = 1)

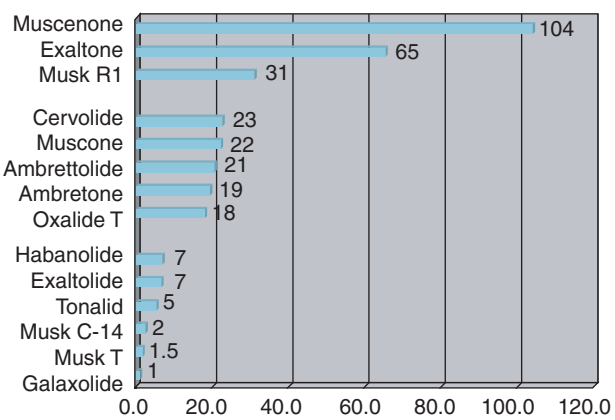
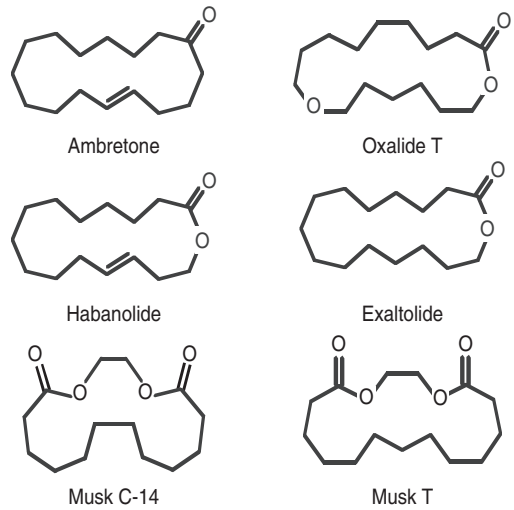


Figure 15. Macrocyclic musks



indeed can even differ between men and women. Thus, this approach actually helps to reveal some additional subtleties that might not be apparent simply using Soul Mapping. While that might appear very academic, it does have real world application and has resulted in the recent Energizing and Relaxing fragrances from Shiseido. If, we turn our attention to the analysis of odors, Figure 12 shows that there is difference of 14 orders of magnitude in detection ability between the simple balance and the human nose. The human nose is obviously a very sensitive and ideal instrument to detect musk odors.

The detection threshold of a variety of musks has been determined using an air dilution instrument. It is particularly difficult to obtain threshold data for musks, since many people are anosmic to one or more musks. Therefore, the panel selection process is more critical. The data obtained by a particular method, or instrument, are thus best viewed as relative, rather than as an absolute value because the published data is wide ranging.

Nonetheless, most common musks show a relatively tight band of detection in the 3-20 ppb range, as shown in Figure 13. One of the exceptions is musk ketone that can be detected at 0.1ppb and is not included in the graph. The musk products on the market can be broken down into three distinct families that are clearly differentiated by cost and demand. Note that the bottom scale of Figure 13 is a log scale. The graph shows that the musks in the left circle with costs typically below $40/kg have annual consumption in the hundreds of tons. With the low cost PCMs, the demand is in the thousands of tons.

Those musks with costs above $150/kg have annual demands only in the tens of tons range, while the more costly products shown on the right side have annual merchant sales measured only in ton quantities. Certainly all musks do not have the same odor or performance but it is clear from Figure 13 that there are differences in cost, demand and thresholds of detection.

Figure 16A. Musk stability in product bases

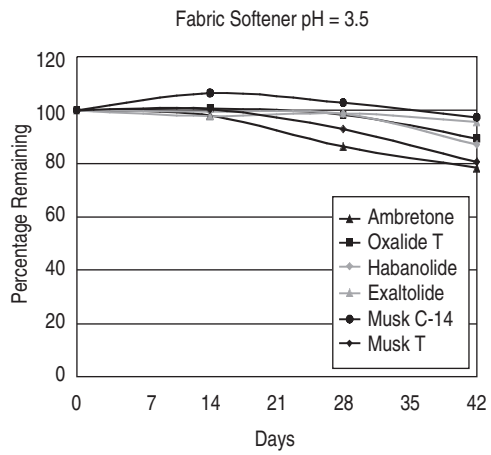
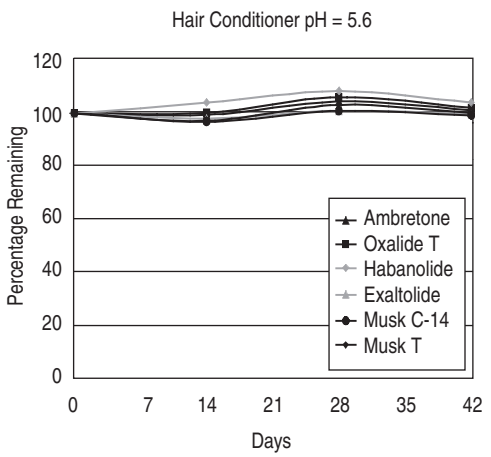


Figure 16B. Musk stability in product bases



If we look at the data as a ranking of the "cost to detect" there is indeed a wide range in performance of the common musks.

The data shown in Figure 14 is listed relative to Galaxolide and shows the relative cost to detect each musk (100% basis) at its limit. The products generally fall into three groups, much like that seen in earlier figures. (There are no significant statistical differences between the products, beyond the broad groupings). While these products are generally used in most fragrances in concentrations far above the threshold of detection, it is a valid comparison of a product's performance at its limit of detection. This is a common occurrence in the application of a fragrance in detergent, for example, where the fragrance is deposited on a fabric in low concentrations. However, the actual cost-performance ranking cannot be simply taken from this data as the real value of a particular musk. Under normal use conditions, it is quite different and is a complex function of deposition and vaporization rates as well as perceived intensities from substrates such as skin and fabric. For example, Muscenone, which does poorly in the ranking of Figure 14, solely because of its market price, actually improves the performance of other musks, when it is used at low concentrations.

This ranking is clearly a bit too simplistic because the performance of the various musk aroma chemicals is, in fact, not uniform in every application. There are other important factors, such as functionality as shown below that can change their performance.

The MCMs can be divided into three categories (Figure 15):

- the ketones - such as Ambretone;
- the mono-lactones - such as Oxalide, Exaltolide and Habanolide; and
- the di-lactones, such as Musk T and Musk C-14.

This functionality imparts differing stabilities to these products in functional products.

Figure 16C. Musk stability in product bases

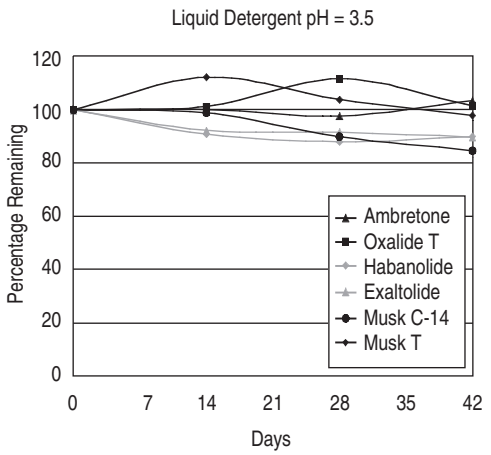
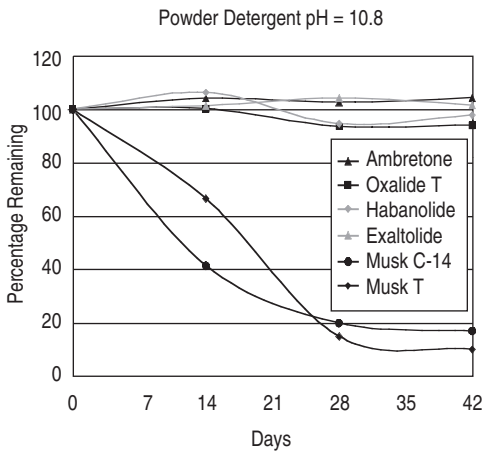


Figure 16D. Musk stability in product bases



A study of the chemical stability of a number of these MCMs was done in a variety of functional products from hair conditioners to detergents in accelerated stability tests at 40°C for six weeks. The results are displayed in Figure 16.

All of the products performed well in a hair conditioner of pH=5.6 and, also, in a more acidic antiperspirant base at pH=4.1. Even in fabric softener at pH=3.5, all of the MCMs showed relatively good stability.

In alkaline conditions of liquid detergents (pH=8), chemical stabilities were quite good. But with higher pH products, such as a powder detergent of pH=10.8, the mono lactone MCMs begin to show some instability while the di-lactones are not stable. Under all of these conditions, the PCMs show excellent stability. Di-Lactone MCMs, such as Musk T, have long been widely used by perfumers in personal care, fine fragrance and toiletries because of their excellent substantivity and long-lasting character, and despite reduced stability in high pH's functional products, they nonetheless contribute these characteristics to fragrances used in these products because of their low odor threshold.

Looking at the relative chemical stabilities of these families, however, does not show the whole story. Relative to the PCMs, the MCMs show considerably better biodegradability, which is of growing concern in some areas (Figure 17). In the search for new musk products, the graphs suggest that the ketone family of MCMs represents the best compromise between good stability and a low potential for bioaccumulation in the environment.

Takasago has taken a pro-active approach towards the design of new fragrances, called Aromaconscience (Figure 18), that strives to use aroma chemical components with consumer-orientated and nature-friendly properties. This philosophy also applies to the search for new aroma chemicals, including new musks.

The traditional approach to the hunt for new aroma chemicals is the synthesis and evaluation of hundreds of new products. If any pass the initial sensory evaluation, they proceed next down the costly safety and regulatory testing phase before seeing the possibility of commercial introduction. This method is both costly and inefficient. The challenge is to try to increase the success rate for new product synthesis (Figure 19).

One such approach involves a QSAR—Quantitative Structure Activity Relationship (Figure 20)—approach in which attempts are made to model a particular attribute, for example, vapor pressure. How can we apply such techniques to the search for new musk smelling aroma chemicals?

Figure 17. Relative stability and biodegradability of musk families

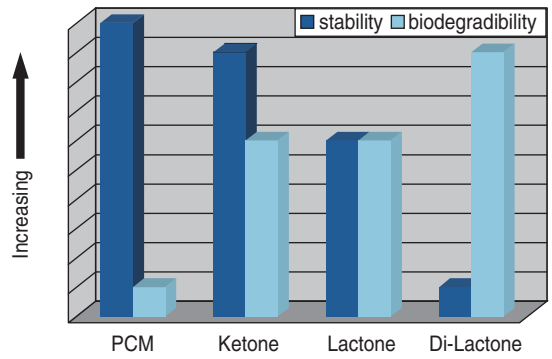


Figure 18. Aromaconscience Philosophy

A Philosophy for Fragrance Creation

- Concern for the consumer's well-being
- Respect for the environment
- Using only nature-friendly materials

Naturals	Natural mimics
Natural derivatives	Biodegradable materials
Nature identicals	

Figure 19. New Aroma Chemical Commercialization Funnel

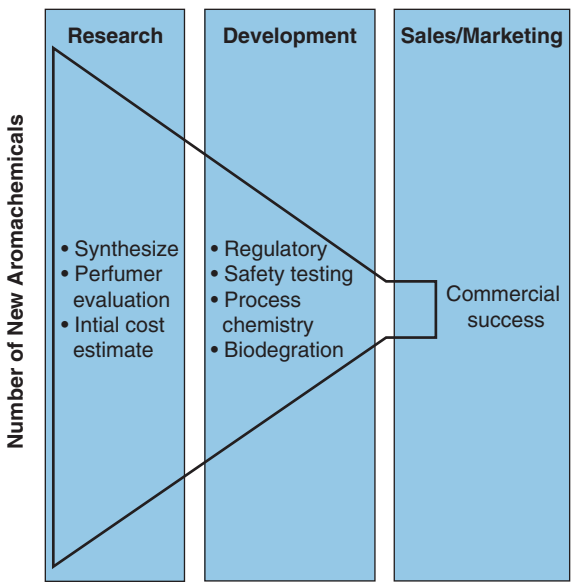


Figure 20. Computer-assisted fragrance molecule research

- Quantitive Structure - "Activity" Relationships (QSAR):
  Prediction of fragrance molecule properties e.g. V.P.
  Predicition of Structure Odor Relationships (SOR)
- Conformational Analysis:
  Prediction of fragrance molecule properties
  New molecule design

Figure 21. Molecular modeling—conformational analysis

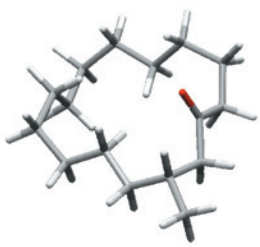
- Flexible molecules can exist in many conformations. Only structurally appropriate conformations can interact with an olfactive receptor resulting in an organoleptic characteristic.

Conformations Receptor

- A new molecule that has similiar functionality and shape that mimics these appropriate conformations can, in theory, have similiar olfactive characteristics.

Figure 22. Macrocyclic constrained musks

- Approach based on conformational analysis of Muscone and other macrocyclic musks
- Conformational analysis



Global minimum energy conformation of l-muscone

Kcal/mole above global minimum	# of Conformations
0 - 1	23
1 - 2	129
2 - 3	444

There are several methods now used in the industry which have their origins in the computational chemistry developed for the pharmaceutical industry. One of these being used at Takasago involves conformational analysis comparison for Structure Odor Relationships.

In a very simplistic view, the action of a fragrance molecule in the nasal membrane is analogous to enzyme-substrate binding. Aroma chemicals of the appropriate functionality and shape can fit into the corresponding nasal receptors and generate a neurological response that we perceive as odor. A new molecule that has similar functionality and shape and mimics the critical conformations of a target molecule can in theory generate similar olfactive characteristics (Figure 21).

A conformational analysis study of Muscone (Figure 22) shows that a total of almost 600 unique conformations can exist in energy states as little as 1-3 kcal from the minimum energy configuration.

A cluster analysis of the three most populated clusters of conformations in Muscone, in which the ketone function remains relatively stable and the other conformations are drawn superimposed on one another, is shown in Figure 23. We learn that the top three clusters represent less than 60% of the population but consist of over 300 conformations. Obviously, not all of these conformations are contributing to the odor since there is a fair degree in change of the molecular shape. One approach that has been studied at Takasago is the impact of reducing the conformational flexibility of these MCM structures through the introduction of *trans* double bonds into the rings.

Some of the potential targets that have been studied include the C-15 ring ketone di-dehydro-Exaltone and the C-16 ring ketone dehydro-ambretone.

What happens to the number of conformations when *trans* double bonds are introduced into these rings? The calculations show that these new rings significantly reduce the number of possible conformations (hopefully to ones that are odor contributors), and now the count has been reduced from about 600 to less than 200 in the case of the C-15 ring diene and to less than 100 in the C-16 ring diene (Figures 24, 25).

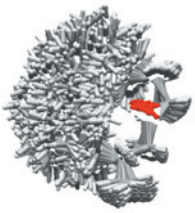
Looking at a cluster analysis where the conformations are superimposed one on the other, it is evident that the number of clusters of conformations have been substantially lowered where the ketone is facing outward (compare structures A) and where the ketone is facing inward (compare structures B) (Figure 26).

The synthesis of these potential targets was accomplished via a Claisen Rearrangement and a classic cyclization as shown in Figure 27. A patent has recently been granted for this new family of molecules (Figure 28). They are indeed musky in odor and are currently being evaluated for safety, stability as well as the likelihood to be synthesized at sufficiently low cost so as to make them attractive commercial candidates.

This is only one approach and, in fact, several other

Figure 23. Cluster analysis of conformations of *l*-Muscone

Three largest clusters of conformations



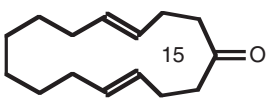
Cluster A
169 members
35.7% population

Cluster B
68 members
18.1% population

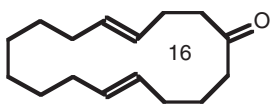
Cluster C
75 members
13.4% population

Figure 24. An approach to developing new macrocyclic musks

- Reduce conformational flexibility in large rings by incorporating *trans* double bonds
- Some potential targets:

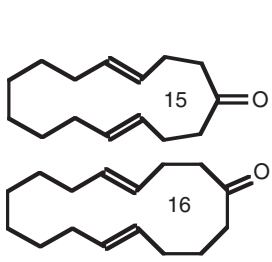


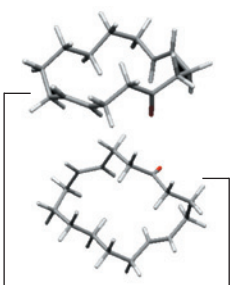
Didehydroexaltone



Dehydroambretone

Figure 25. Conformations of *trans*-olefin macrocyclic ketones



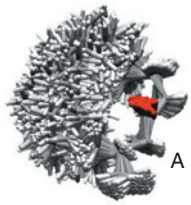


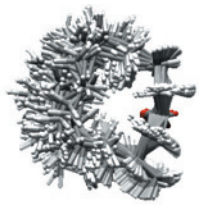
Kcal/mole above global minimum	15-membered ring # of conformations	16-membered ring # of conformations
0 - 1	22	6
1 - 2	92	16
2 - 3	178	55

Figure 26. Conformation cluster comparisons

The challenge is how to make these materials—
the *trans* double bond can be incorporated conveniently
via Claisen Rearrangement.

l-Muscone





C16 *trans*
Dioelfin

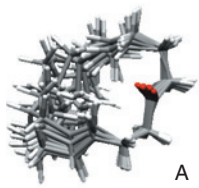
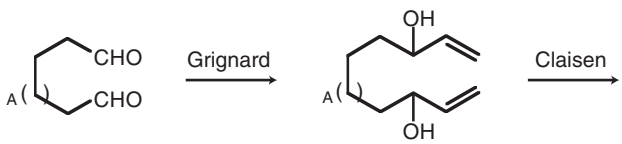
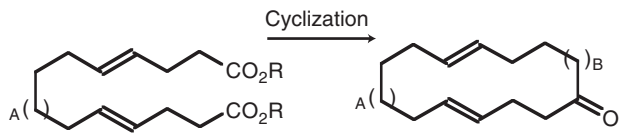


Figure 27. The synthesis of these potential targets via a Claisen Rearrangement and a classic cyclization





A = 1-5, B = 0,1

Figure 28. Aromaconscience musks

- **US Patent applications granted: 10/2000**
- Patents cover:
  - a new class of macrocycles (related to Ambretone)
  - processes to prepare this class of compounds
- Structures are a direct result of conformational analysis of other macrocyclic musks (Muscone, Ambretone, etc.)
- Lead compounds have shown good biodegradability
- Currently under perfumery evaluation

Table 1. Relative musk performance

Product	Type	pH Stability	Biodegrad.	Substantivity	Detection Threshold ppb
Galaxolide	PCM	+++	+	+++	4
Tonalid	PCM	+++	+	+++	21
Musk T	MCM	+	+++	+++	6
Musk C14	MCM	+	+++	++	10
Exaltolide	MCM	++	++	++	10
Habanolide	MCM	++	++	++	17
Oxalide	MCM	++	++	++	9
Ambrettolide	MCM	++	++	++	12
Muscone	MCM	++	++	++	3
Ambretone	MCM	+++	++	+++	12
Musk ketone	NM	+++	+	+++	0.1

MCM products have been produced at Takasago and are being evaluated as viable future products. Figure 29 outlines one such approach, which addresses the problem of ring closure to form 1,6-dioxa-MCMs using an internal metathesis reaction.

The 'Musk Dilemma' is summarized in Table 1.

The PCMs, which typically sell on a 100% basis for less than $20/kg, show excellent cost performance compared to the MCMs shown above, which typically sell from $25-500/kg.

The challenge for MCMs to provide the same cost benefits as PCMs is formidable, but one which is being addressed through cost reduction and new molecule development.

Conclusion

- Political toxicology is catalyzing a search for PCM substitutes.
- PCMs are a hard act to follow.
- The best alternatives to PCMs are MCMs which have excellent performance and substantivity, but not all are as stable as PCMs in aggressive media.
- Currently, mixtures of MCMs give the best performance.

- Ambretone is one of the best performing MCM products for stability and substantivity and is being cost reduced.
- The costs of MCMs are falling while demand and production is increasing as a result of greater use in functional products. Thus, Musk T has become one of the most cost effective alternatives to PCMs.
- The future outlook for MCMs is excellent.

These conclusions have led Takasago to expand its Musk T capacity by an additional 500 tons/year with a new plant in Chicago.

Acknowledgements

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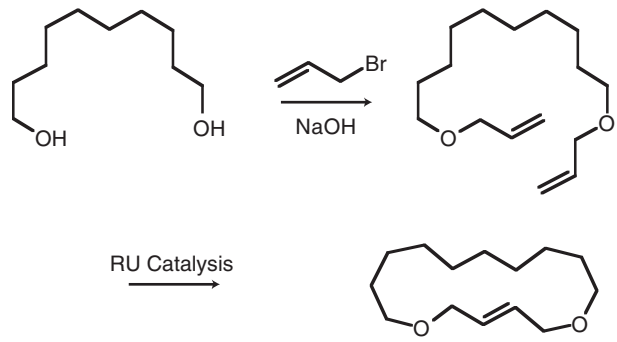
Proceedings of the IFEAT International Conference "Aroma Chemicals 2000—and Beyond," Amelia Island, FL, may be obtained from the organization via ifeatadministrator @fdf.org.uk or www.ifeat.org. ■

Figure 29. Synthesis of 1,6-dioxa-macrocyclic rings



Japanese patent: JP11124378

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