# Multidimensional Visualization of Physical and Perceptual Data Leading to a Creative Approach in Fragrance Development

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Perfumers are being increasingly challenged to improve the performance of their formulations. As well as being pleasant, fragrances have to comply with growing requests for stability, biodegradability and uniqueness. Other factors render the work of the perfumers difficult, such as the specific smell of the non-perfumed substrate or the need to cover unpleasant odors. In addition, various applications have very different technical constraints. Whereas an eau de toilette is applied directly onto the skin, other fragrances are deposited onto a substrate after physical partitioning (e.g., in laundry detergents during the rinsing and drying phases). Thus, tools that take into account these constraints and help the perfumer create successful fragrances are in high demand.

It makes sense to measure relevant information concerning perfumery ingredients. Physical parameters, Odor Detection Thresholds (ODTs) and supraliminal intensity measurements contribute significantly to this knowledge, as they characterize important aspects of the perfumery ingredients. It would take perfumery a step forward if these measurements were organized in order to facilitate their access to perfumers.

Physicochemical data (e.g., volatility and partition coefficients) of perfumery ingredients still remains scarce. Herein we describe the recording of psychophysical data for a large set of ingredients and the organization of these data into a database. This database can be used to construct multidimensional visualizations of the perceptual and physical properties of fragrance raw materials. The perfumer can then use this information to decide on the choice of ingredients that may offer enhanced performance in a given application. To illustrate the process, we, the authors, show here a simplified eau de cologne-type fragrance case study.

## Physical Parameters of Perfumery Raw Materials

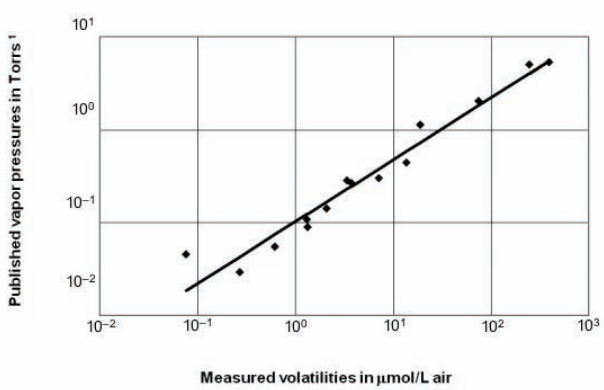
***Volatility:*** The liquid/vapor equilibrium of a chemical compound is usually characterized by its vapor pressure, and has been extensively measured for volatile chemicals such as solvents. The ebulliometers required for these measurements involve heating the compound in order to get a measurable variation in pressure; these measurements are then extrapolated to room temperature by the use of Antoine equation parameters. (For lists of vapor pressures, see references 1 and 2.) However, vapor pressures are difficult to work with, since most analytical measurements are expressed in gas phase concentrations. Moreover, the conversion of vapor pressures into concentrations is far from straightforward, as the gas law provides only approximations in real life systems.

For the case study, we have chosen to characterize the vapor/liquid partition at 22°C/730 mmHg (±30) by the concentration of the chemical in the air above the pure liquid or solid at equilibrium. We named this gas phase concentration "volatility," with units of µg or µmol per liter of air. The measurements were performed with standard quality perfumery ingredients. Detection thresholds were also expressed in the same units and thus enable direct comparisons with the volatility.

The graphical presentation of our set of volatilities and corresponding published vapor pressures[1] is given in **F-1**. These volatilities appear to be uniformly distributed around 10 µg/L air (**F-2**).

***n-Octanol/water partition coefficient:*** The logarithmic value of the n-octanol/water partition coefficient (Log P o/w) is often used in medicinal chemistry as an indicator of the lipophilicity of a chemical. In the nose, perfumery ingredients partition between an aqueous mucus layer and the cell membranes. Partition between aqueous and lipophilic phases also occurs in laundry, skin care or shampoo. Because the direct measurement of

**Measured volatilities versus published vapor pressures** **F-1**

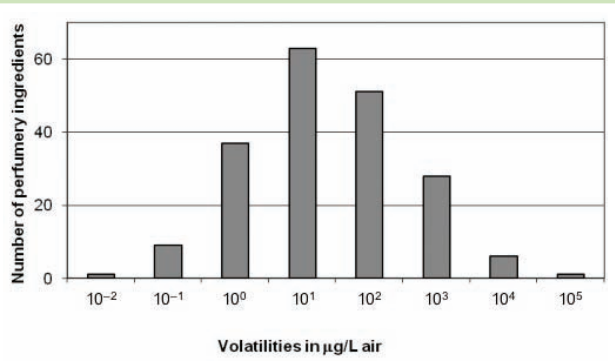



*The line represents the computed regression (the square value of the correlation coefficient ($R^2$) is 0.96).*

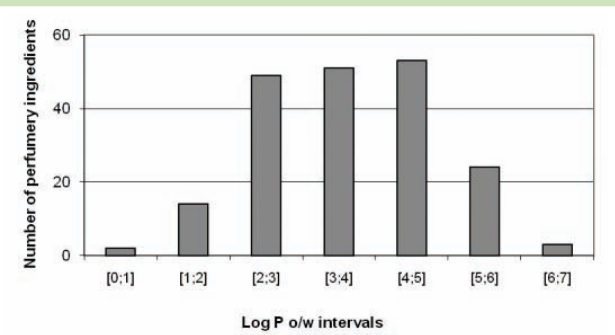
Log P o/w can be difficult to perform above values of 3, we decided to determine a correlated value by measuring the HPLC retention indices.[3] The affinity of perfumery ingredients for cotton and polyacrylonitrile was thus measured in fabric softener and detergent solutions.[5] Log P o/w appears to be linearly correlated with the fabrics affinity. The distribution of a set of our Log P o/w measurements is presented in **F-3**. The majority of the ingredients have values between 2 and 5.

***Partition phenomena of perfumery ingredients in application:*** References 5 and 6 discuss the perfume transfer of fragrance ingredients to and from substrates. In particular, the performance of an ingredient on a piece of fabric is dependent on several partitions: detergent to water, water to clothes and clothes to air.

**Distribution of measured volatilities for a set of perfumery ingredients** **F-2**




**Distribution of n-octanol/water partition coefficients for a set of perfumery ingredients** **F-3**




Knowledge of the physical behavior of these fragrance ingredients would allow the perfumer to formulate the fragrance for optimum delivery for a targeted application.

## Odor Detection Threshold (ODT) and Supraliminal Intensity Measurements

Physical parameters alone are insufficient to help perfumers create successful formulations. In his famous series of articles, Louis Appell was one of the first authors to specify the interest in the measurement of vapor pressures and odor intensity.[7] Appell highlighted the need to relate physical data with sensory information. Accordingly, in this example we set up an efficient sensory methodology combining robustness and measurement throughput, and used it to characterize a large and representative selection of fragrance ingredients.

***The relation between concentration and perceived intensity:*** The relation between perceived intensity and stimulus concentration is an important characteristic of perfumery ingredients, and S.S. Stevens and G.T. Fechner related the perceived intensity to concentration by using power functions.[8,9] On the other hand, Beidler proposed a sigmoïdal logarithmic relationship between taste response and stimulus concentration.[10]

***The group Odor Detection Threshold:*** The group ODT is the lowest detectable odor level expressed in liquid or gaseous concentration units. It reflects the olfactive impact of a chemical. Power law exponents can be found in which we apply correction factors to the data to obtain "standardized" values.[11,12] In this example, however, we decided to generate our own datasets.

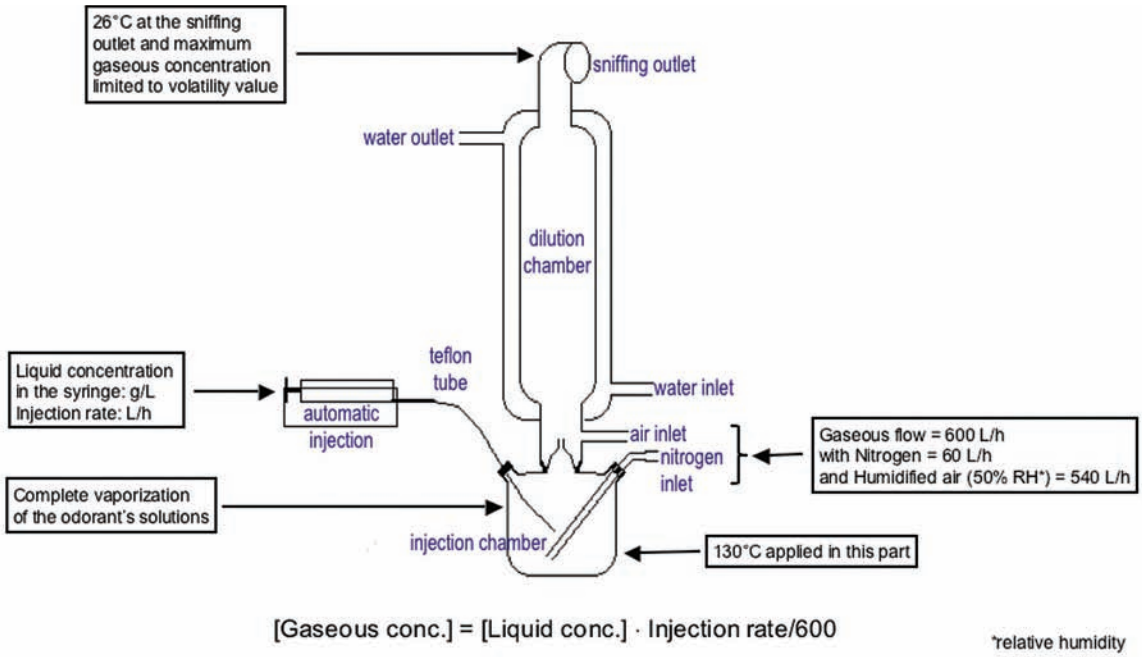
***A simplified measurement of Dose-Response curves and group ODTs:*** We improved the methodology to measure the ODT and also the relation between the perceived intensity (response) and the gas phase concentration (dose). We called the plot of this relation the Dose-Response curve. By the use of our air dilution olfactometers, the perfumery ingredients were first diluted in propylene glycol or mixtures of propylene glycol and dipropylene glycol. These solutions were then injected continuously into a chamber at 130°C, where they vaporize instantaneously at the end of the tube. Nitrogen carrier gas was used to avoid oxidative processes in the concentrated odor flow. This flow was then diluted with humidified air to obtain the final gas phase concentration. The sniffing outlet delivers a continuous and constant odorized air flow. The upper working limit was determined by the volatility of the odorant at a temperature of 26°C, close to the temperature within the nose (**F-4**). This apparatus has already been described.[13–15]

We established our methodology using an iterative process to obtain valid results with a minimum number of experiments.[16] The Dose-Response plot and the ODT determinations were combined in the process, illustrated in **F-5**. We used a panel of 35 subjects, all Firmenich employees, aged between 17 and 65 years.

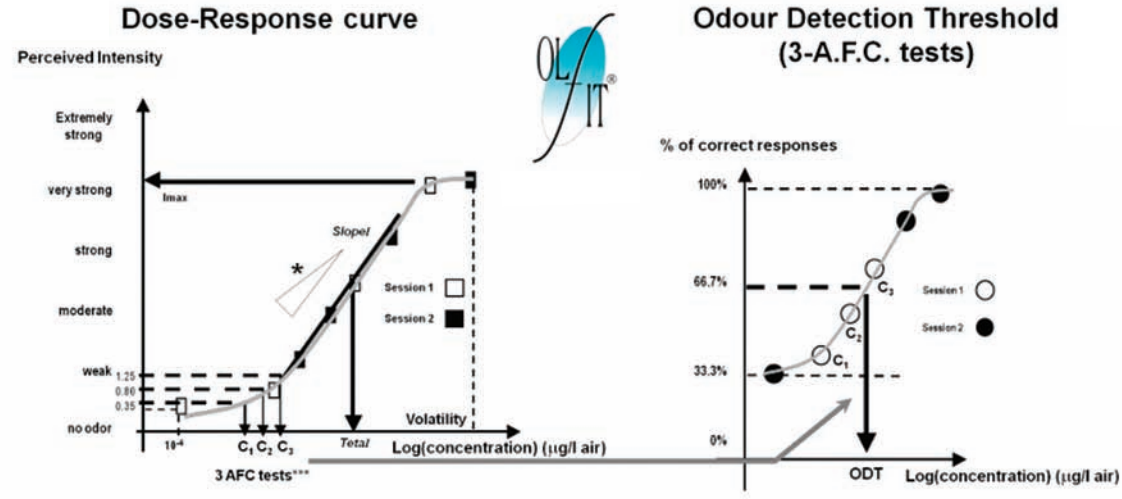
The measurement process starts with the determination of the Dose-Response curve. This is done in two consecutive sessions. First, the panelists rate the intensity of the studied ingredient at four different concentrations chosen between its volatility value and $10^{-6}$ µg/L air, which corresponds to a low threshold value. The ratings for these four initial concentration steps serve as the basis for the choice of the next four concentration levels used in a second experiment, and thus span the supraliminal concentration domain where intensity changes noticeably with concentration. We then fit the experimental points to a sigmoïdal curve using a nonlinear regression of the following form:[10]

$$Intensity = IMax \frac{1}{1+(Exp(-CurveParamterI\ (LOG(Conc.)-Tetal)))}$$

## Scheme of an olfactometer F-4




## Process of the ODT and supraliminal intensity measurements F-5



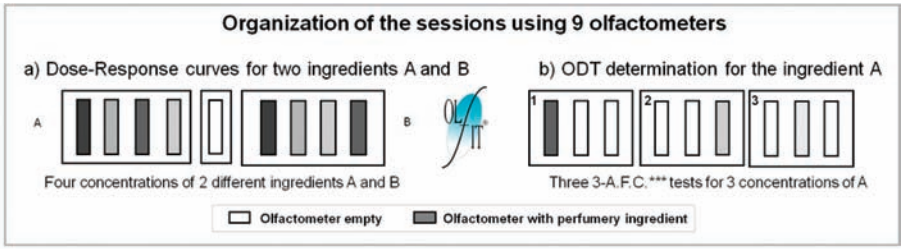

Rating in 2 sessions of 8 gas phase concentrations of one chemical

The panel evaluates the 4 first concentrations of the compound (Session 1), then according to the results, 4 other concentrations are proposed in order to complete the psychophysical curve (Session 2)

6 Discriminative tests in 2 sessions

The first 3 concentrations are calculated from the Dose-Response curve model (corresponding to low intensities: 1.25, 0.80, 0.35) for the 3 "3-A.F.C.***" tests. Using panel results, 3 other concentrations close to the ODT are evaluated

* The white arrow in the Figure indicates the slope (expressed by *Slope I*) of the Dose-Response curve
** Volatility is the maximum gazeous concentration for a pure chemical at room temperature
*** A.F.C.: Alternative Forced-Choice procedure



A sigmoidal curve is defined by three parameters. These are *Imax* (the asymptotic value for the perceived intensity), *TetaI* (the logarithmic value of gaseous concentration corresponding to the inflexion point of the curve) and the *Curve ParameterI*. This last one is related to the tangent value (we named it *SlopeI*) at the *TetaI* concentration by the following equation:

$$SlopeI = \frac{CurveParameterI \quad IMax}{4}$$

A steep slope may suggest that the perfumery ingredient is more sensitive to the applied dosage in a fragrance, which leads to a rapid decrease of intensity if the concentration falls. A decrease in concentration is typically the situation for fragrance loss during washing, rinsing and drying operations for laundry or body care products. The Dose-Response curves are useful for the prediction of a perceived intensity based on a gas phase concentration.

The second step of the process is the determination of the ODT by three Alternative Forced Choice (3-AFC) tests. Panelists are first submitted to concentrations corresponding to predefined levels of intensity (close to 0) determined from the Dose-Response curve regression and then to additional calculated concentrations. The ODT, expressed as a gas phase concentration, is calculated at the concentration corresponding to two-thirds of the correct answers.

The distribution of individual ODTs can be simple or multimodal for each chemical. The mathematical treatment of such results is similar to that of the Dose-Response curve with a sigmoïdal fit and the following equations:

$$\%... \frac{100}{3} + \frac{2}{3}\%Max \frac{1}{1+(Exp(-CurveParamter\% \ (LOG(Conc.)-Teta\%)))}$$

$$Slope\% = \frac{2}{3}\%Max\frac{CurveParameter\%}{4}$$

at *Teta%* concentration.

The *Teta%* and *CurveParameter%* play the same role as the similar parameters within the Dose-Response curve mathematical equation.

The amplitude of this distribution is reflected by the *Slope%* of this psychometric function, giving the percentage of correct answers from our panelists versus concentration.[10] This is observed by the results we obtained by submitting our panelists to 3-AFC tests. In this case, this *Slope%* characterized the agreement of the panelists in the ODT concentration range. The higher the *Slope%,* the more our panelists were in agreement.

We named our method as described above *OLFIT*.

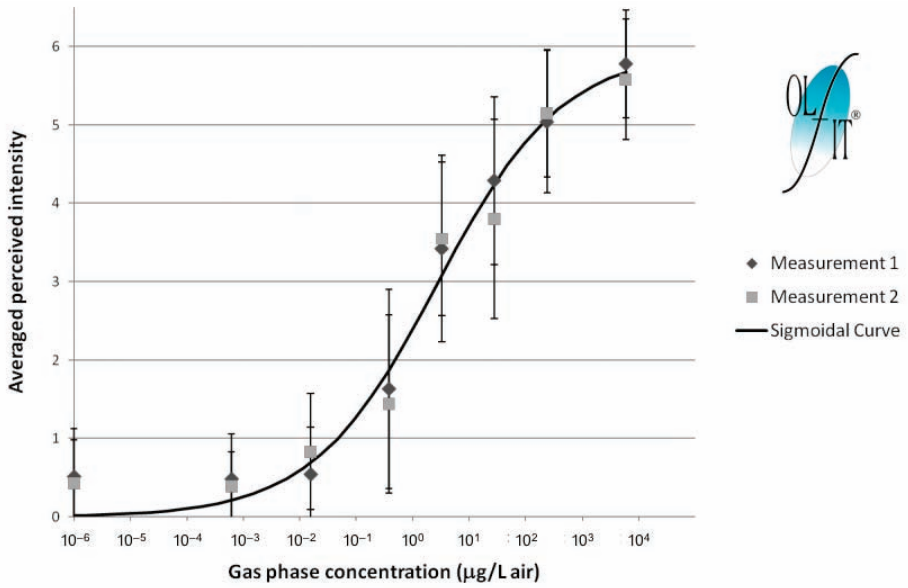
In order to demonstrate that our method leads to reproducible results, we have replicated the Dose-Response curve for a chemical ((Z)-3-hexenyl acetate, CAS# 368-71-8). **F-6** illustrates the results. It appears that for the two replicated measurements, the averaged perceived intensities are similar within the studied range of concentrations. Statistical analysis was performed by Student's t test for the two sets of data at each concentration. It showed that there are no significant differences between these two series.

As an example, **F-7** shows the Dose-Response curves for two classical perfumery ingredients: methyl atrarate and PADMA (phenylacetaldehyde dimethyl acetal, CAS# 101-48-4). We observed that an intensity of one corresponds to very different concentrations for these two raw materials, whereas similar concentrations are needed to get a medium intensity level. This is a consequence of their well differentiated *SlopeI*. In addition, they also behave differently in terms of individual dispersion: methyl atrarate shows a large standard deviation for its higher studied concentrations range compared to PADMA, which is more or less invariable within the whole range of concentrations. **F-8** illustrates results from AFC tests showing that the two chemicals have a similar fast increase of the percentage of right answers versus concentration. This could be interpreted as a result of a narrow sensitivity distribution range in the ODT area. These two graphs are a good illustration of the complementary features from Dose-Response curves and Odor Detection Threshold determinations. It appears evident that we cannot extrapolate an Odor Detection Threshold study to any of the Dose-Response curve parameters. Reference 17 illustrates partial results for other ingredients.

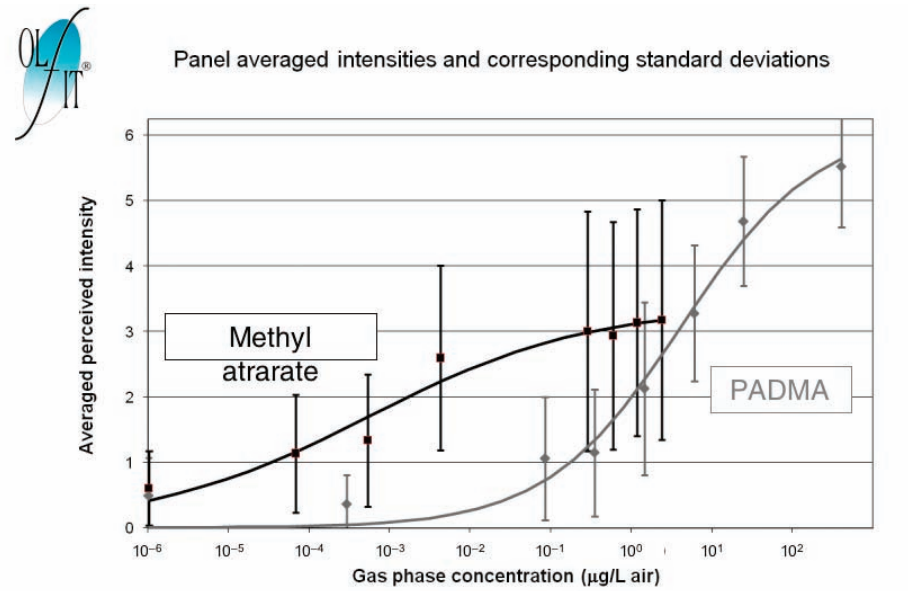
## The Multidimensional Visualization Interface: the See a Scent Concept

To make our data useful for our perfumers and research

**Reproducibility in the determination of the Dose-Response curve for (Z)-3-hexenyl acetate** **F-6**



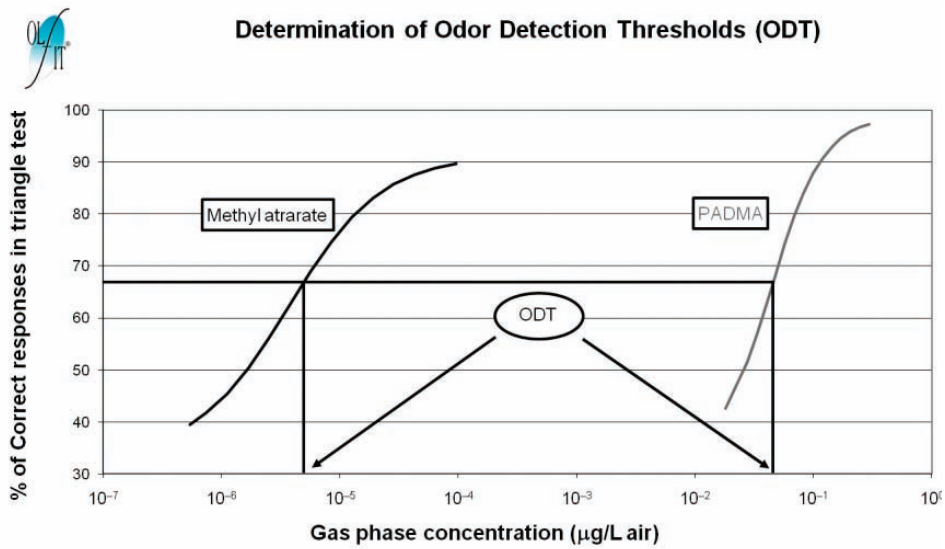

**Dose-Response curves of two perfumery ingredients** **F-7**




scientists, we incorporated them into a database. However, the collected data filled numerous tables and spreadsheets that would be unattractive and difficult to use. Thus, the use of a visualization tool based on adequate software is necessary. Our concept called See a Scent allows the construction of multidimensional representations of selected features and access to salient information. In order to illustrate this concept, a simple demonstration accord is provided by an eau de cologne-type composition (see **F-9**). This harmony is a simplified interpretation using key perfumery ingredients (citral and limonene for lemon oil, linalool and methyl anthranilate for neroli oil).

In **F-10**, the volatility change is visualized on the vertical axis, corresponding to top, middle, and base notes, traditionally used to create and describe a fragrance. The Odor Detection Threshold on the horizontal axis gives an additional dimension. The lower the ODT, the more detectable a perfumery ingredient is. With time, the low volatility and low Odor Detection Threshold ingredients will have an increasing contribution to the overall odor. They will actively participate in the application, even if

**ODT determinations of two perfumery ingredients** **F-8**






they are present in small amounts. On the other hand, the majority of the limonene in the mixture will rapidly disappear. Historically, this was illustrated in the J. Carles method.[18] The presence of "heavier," less volatile perfumery ingredients (vanillin for benzoin, coumarin for tonka and methyl atrarate for oak moss) is common in an eau de cologne, complementing the light, volatile citrus part (petitgrain, lemon, bergamot, mandarin oils, etc.). It is a valuable tool to find perfumery ingredients that are long-lasting, as indicated by the direction of the arrow. The triangular shapes indicate the intensity slopes of the various perfumery ingredients, which are related to the dosage range for an ingredient within a formula.

A second graph (**F-11**) involves an additional parameter, the n-octanol/water partition coefficient (Log P o/w). In a rinsed-off application, after washing and rinsing, the more substantive perfumery ingredients will be located following the general rule: low Odor Detection Thresholds and volatilities combined with high Log P o/w. The more hydrophilic molecules will be lost during the rinsing process and will probably not contribute to the long-term performance of the fragrance.

It is also worth mentioning that the relatively small amount (< 2%) of low volatile perfumery ingredients in this accord (see formula, **F-9**) exerts an impressive influence on the odor profile, in terms of hedonics and long-lastingness. These ingredients bring a remarkable contrast and depth to the transparent fresh citrus notes. This hydrophobic character is also considered to obtain long-lastingness for fabric care applications and is a contribution to the selection of perfumery ingredients.

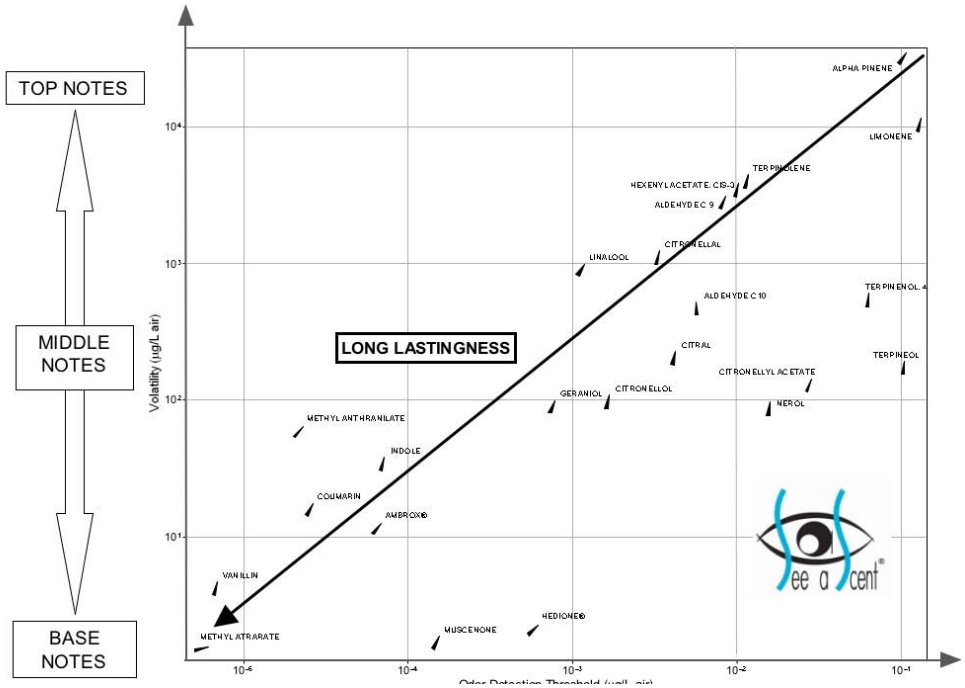
For a long-lasting effect in a non-rinsed application, the best ingredients are vanillin and coumarin. If a perfumer adapts such a formula to a fabric care product, the dosages will be adapted to increase the substantivity. For example, Ambrox and muscenone contribute to achieve this goal of substantivity (**F-11**). Some additional parameters will be taken into account, such as stability or safety, and may lead to possible substitutions of ingredients.

The various parameters mentioned above can of course be completed with additional ones such as price, aesthetic descriptors or any other qualitative or quantitative feature. Depending on the objective of the application, the parameters of interest will be selected and visualized with other physical and psychophysical measurements.

**Eau de cologne-type composition** **F-9**

| Parts | Name | CAS Number |
|---|---|---|
| 800 | aldehyde C 10 | 0000112-31-2 |
| 500 | aldehyde C 9 | 0000124-19-6 |
| 5000 | alpha-pinene | 0000080-56-8 |
| 5 | Ambrox | 0003738-00-9 |
| 5000 | citral | 0005392-40-5 |
| 500 | citronellal | 0000106-23-0 |
| 500 | citronellol | 0000106-22-9 |
| 500 | citronellyl acetate | 0000150-84-5 |
| 100 | coumarin | 0000091-64-5 |
| 1000 | geraniol | 0000106-24-1 |
| 1000 | Hedione | 0024851-98-7 |
| 10 | hexenyl acetate, *cis*-3 | 0003681-71-8 |
| 30 | indole | 0000120-72-9 |
| 73300 | limonene | 0068647-72-3 |
| 1000 | linalool | 0000078-70-6 |
| 100 | methyl anthranilate | 0000134-20-3 |
| 5 | methyl atrarate | 0004707-47-5 |
| 500 | muscenone | 0082356-51-2 |
| 2500 | nerol | 0000106-25-2 |
| 100 | terpinenol, 4 | 0000562-74-3 |
| 2500 | terpineol | 0008000-41-7 |
| 5000 | terpinolene | 0000586-62-9 |
| 50 | vanillin | 0000121-33-5 |
| **Total** 100000 | | |

**Visualization of various parameters for the raw materials involved in the eau de cologne-type perfume (the triangular shapes give a representation of the Dose-Response curve slopes)** **F-10**




## Conclusion

Perfumery is an art. The creative perfumer blends and harmonizes scents to evoke positive emotions based on creativity, learning and personal experience. But creative perfumery formulation also involves a technical dimension for issues such as malodor masking, diffusion, and chemical and olfactory stability. Here we have described an experimental approach to collect the physical and psychophysical characterizations of a large set of perfumery ingredients. The measurements are then used in a novel, validated process and provide a coherent and pertinent dataset for the perfumery palette. This dataset may be subsequently used to predict the behavior of perfumery ingredients in application. With the use of appropriate visualization software, choices of ingredients based on performance, solubility, volatility, etc., can lead more rapidly to fragrance formulations satisfying high technical requirements. This is illustrated by a simplified eau de cologne-type fragrance, by plotting the major constituents for top, middle and base notes. To the organic chemist responsible for synthesizing new ingredients and to the perfumer evaluating them, such a complementary tool can be successfully used to compare the performance of new candidate molecules with existing ingredients. Additionally, it may be used as a learning tool for beginning perfumers.

**Acknowledgments**

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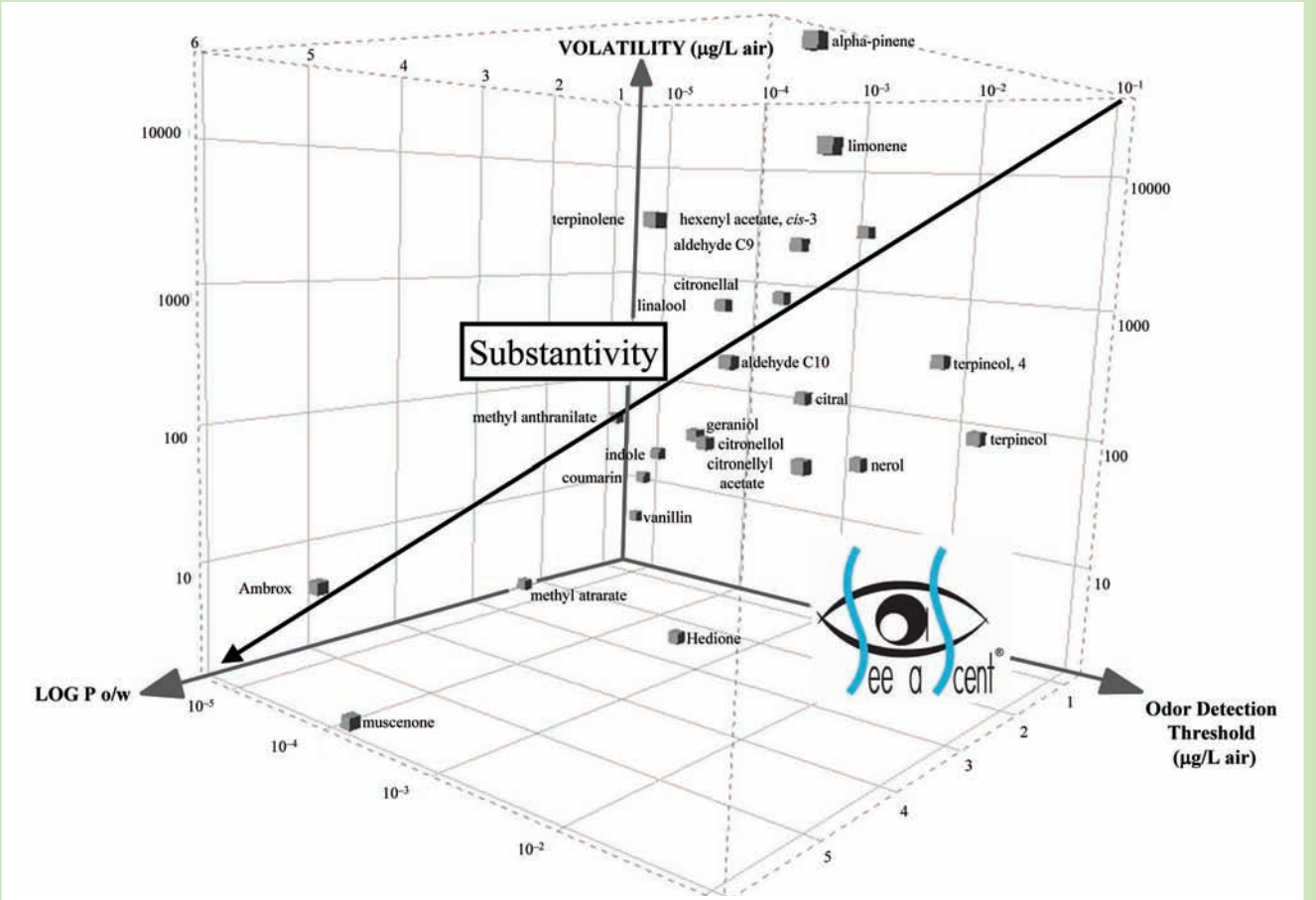
**Visualization of various parameters for the ingredients in the eau de cologne-type perfume for a rinsed application**

**F-11**

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