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Perfume Materials

# Prediction of Fragrance Headspace Concentrations from Physico-Chemical Properties

Disposition of fragrance ingredients on skin

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Fragrance composition on and above the skin evolves continuously after topical application. Characterization of this process is valuable both for technical understanding of the perfume performance and for risk assessment of problematic ingredients. This report describes the application of a previously developed one-compartment, first-order kinetic model for disposition of fragrance ingredients on skin to analysis of recently reported headspace compositions associated with the application of five fine fragrance compositions to the human volar forearm.[4] The model, with no adjustment and no ingredient interactions, was able to account for an average of 65 percent (range: 32-76 percent) of the variance associated with measured headspace concentrations of the various components 1 h post-application. Significant negative departures from the model predictions were observed for the top notes limonene, benzyl acetate and ethyl acetoacetate, all of which evaporated more slowly than predicted. Interactions with the fixatives are implicated. Positive deviations were observed for a number of the less volatile ingredients including galaxolide, bacdanol and polysantol. Possibilities for extending the model to include ingredient interactions by means of thermodynamic activity calculations are discussed.

## Introduction

The amount of fragrance raw materials exposed to skin from fragranced products usually falls within the small dose limit in which nearly first-order absorption is anticipated.[1] On this basis, the authors have described a first-order kinetic model drawing on previous work in skin penetration and environmental engineering.[2] The model allows calculation of absorbed and evaporated fractions of topically applied chemicals based on three key physical properties — vapor pressure, molecular weight and lipid solubility — in combination with skin temperature and wind velocity. The evaporated fraction calculated from this model satisfactorily correlated experimental data on fragrance evaporation from human skin in vivo.[3]

However, additional tests are required to validate the first-order kinetic model and to optimize its predictive power. In the present report, the details of an analysis of skin evaporation data presented by Mookherjee and coworkers are given.[4] The study involved the application of different fragrance mixtures to the forearm of human subjects. The volatiles were collected using the SPME (solid-phase microextraction) technique.[5] The headspace samples were analyzed by GC/MS.

One of the underlying assumptions of the current model is that the behavior of each fragrance raw material is independent of other ingredients in the mixture.[2] In reality, ingredient interactions affecting both absorption and evaporation are possible, especially when applied doses are high. Each ingredient can modify the thermodynamic activity of other components according to well-known laws governing liquid-liquid and liquid-vapor mixtures.[6] Thus, in the present analysis, we have included calculations of the activity coefficients in order to determine whether this parameter may improve the accuracy of the model predictions.

## Data Analysis

***Theory:*** Based on a one-compartment, first-order kinetic model, the percentage evaporated of a topically applied compound at time $t$ following application

to skin at time zero can be calculated as follows:[2]

(1)
$$\left( \frac{k_1}{k_1 + k_2} \right)$$

In equation 1, and represent, respectively, the evaporation and absorption rate constants. They can be estimated from the following expressions:[2]

(2) $\quad k_1 = k_1^v * P_{vpr} / (K_{oct} S_w)_r$

and

(3) $\quad k_2 = k_2^\pi * MW_r^{-2.7}$

In equations 2 and 3, $P_{vp}$ = vapor pressure in torr, $K_{oct}$ = octanol/water partition coefficient, $S_w$ = water solubility in $gL^{-1}$, and $MW$ = molecular weight. The subscript '$r$' indicates the reduced or dimensionless form of each parameter. The properties $P_{vpr} = P_{vp} / 1$ torr, $(K_{oct} S_w)_r = (K_{oct} S_w) / 1000$ g $L^{-1}$ and $MW_r = MW / 100$ Da are chosen for computational convenience. Both $k_1^v$ and $k_2^\pi$ are constants, which must be determined experimentally. For the present analysis, we used $k_1^v$ and $k_2^\pi$ values determined by calibration with an earlier experimental study.[3,7] The product $K_{oct} S_w$ is used, for convenience, to represent octanol solubility, which is a measure of solubility in stratum corneum lipids.[2]

The current model assumes no interactions among ingredients in the fragrance mixture....in reality, ingredient interactions affecting both absorption and evaporation are possible.
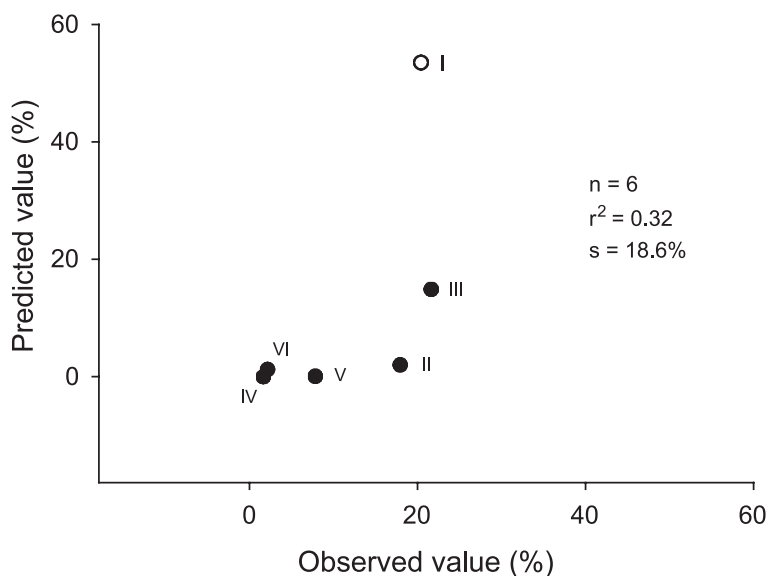
**Methods:** Five of the perfumes studied in reference 4 were analyzed — Shalimar, Amarige, unisex, feminine and women's fragrances. Predicted values of the percentage evaporated after 1 h were calculated using equation 1. These values were then corrected to represent the predicted concentrations in the headspace samples for direct comparisons with the published experimental values. In some cases, the concentrations of each ingredient were corrected in proportion to the activity coefficient parameter, and the predicted headspace concentration values were recalculated using the modified concentrations.

Vapor pressures at skin temperature (30°C) and octanol-water partition coefficients were estimated using commercially available computer programs.[8,9] Octanol solubility values were calculated using the formula suggested by Kasting et al.[10] Water solubilities were calculated from octanol solubility values and octanol-water partition coefficients according to the relationship $S_w \approx S_{oct} / K_{oct}$.

Activity coefficients were calculated using the UNIFAC model.[6] The calculations were performed using an Excel workbook.[11] This program allows the user to select mixtures of up to 15 components.

## Results

The physico-chemical properties and the predicted percentage evaporated values of each fragrance raw material in all five mixtures are summarized in Table I. The experimental and predicted values of headspace concentration along with the activity coefficients for each ingredient in the composition at time zero are reported in Tables II-VI. Comparisons between observed and predicted values are shown in Figures 1-6.

## Discussion

In all cases except Shalimar (Figure 1), the predicted headspace concentrations correlated reasonably well ($r^2 = 0.70$-$0.76$) with experimental values.[4] There was a weak correlation ($r^2 = 0.32$) between the observed and predicted percentage evaporated values in Shalimar. However, a stronger correlation ($r^2 = 0.57$) was obtained when limonene was removed from the analysis. Inter-

**Predicted and observed headspace concentrations for Shalimar fragrance; with limonene (I) excluded from the analysis, $r^2 = 0.57$ and s = 4.8 percent** **F-1**



$n = 6$
$r^2 = 0.32$
$s = 18.6\%$

**Physical properties and predicted percentage evaporated values of fragrance raw materials studied in reference 4** — **T-1**

| Component | MW (Da) | $P_{vp}$ (mm Hg) | log $K_{oct}$ | $S_w$ (mg/ml) | $k_1^a$ (h$^{-1}$) | $k_2^b$ (h$^{-1}$) | Total %evap | After 1h %evap |
|---|---|---|---|---|---|---|---|---|
| aldehyde AA | | | | NA$^c$ | | | | |
| ambrox | 236 | 0.0069 | 5.40 | 0.0017 | 0.15 | 0.15 | 50.4 | 12.9 |
| bacdanol | 208 | 0.00015 | 4.54 | 0.015 | 0.003 | 0.21 | 1.2 | 0.2 |
| benzyl acetate | 150 | 0.28 | 1.96 | 8.9 | 3.10 | 0.50 | 86.1 | 83.8 |
| benzyl salicylate | 226 | 3.7E-05 | 3.76 | 0.024 | 0.002 | 0.17 | 1.4 | 0.2 |
| cashmeran | 206 | 0.0071 | 4.62 | 0.010 | 0.15 | 0.21 | 42.0 | 12.9 |
| cedramber | 236 | 0.016 | 6.16 | 0.00036 | 0.28 | 0.15 | 65.6 | 22.8 |
| coumarin | 146 | 0.0012 | 1.39 | 14.1 | 0.03 | 0.54 | 5.6 | 2.4 |
| cyclogalbaniff | 198 | 0.033 | 2.86 | 1.1 | 0.37 | 0.24 | 60.8 | 27.6 |
| cyclopentadecanolide | 240 | 0.0085 | 5.35 | 0.0035 | 0.10 | 0.14 | 41.0 | 8.7 |
| α-damascone | 192 | 0.032 | 3.62 | 0.16 | 0.43 | 0.26 | 62.8 | 31.3 |
| β-damascone | 192 | 0.022 | 3.77 | 0.10 | 0.35 | 0.26 | 57.8 | 26.4 |
| dihydro myrcenol | 156 | 0.19 | 2.99 | 0.83 | 2.16 | 0.45 | 82.8 | 76.7 |
| diphenyl ether | 170 | 0.029 | 4.21 | 0.050 | 0.32 | 0.36 | 47.6 | 23.5 |
| ethyl acetoacetate | 130 | 1.3 | 0.24 | 468 | 14.78 | 0.74 | 95.3 | 95.3 |
| ethyl linalool | 168 | 0.029 | 3.08 | 0.68 | 0.32 | 0.37 | 46.7 | 23.3 |
| ethyl vanillin | 166 | 0.00056 | 1.58 | 8.6 | 0.02 | 0.38 | 3.9 | 1.3 |
| floralozone | 190 | 0.0088 | 3.60 | 0.16 | 0.13 | 0.26 | 32.7 | 10.6 |
| galaxolide | 258 | 0.00017 | 6.06 | 0.00023 | 0.006 | 0.12 | 4.8 | |

estingly, the correlation in unisex fragrance was also improved when limonene was excluded ($r^2 = 0.87$). In both cases, the model overestimated the headspace concentration of limonene, which is a relatively low molecular weight fragrance raw material with high vapor pressure. A similar result was found with benzyl acetate and ethyl acetoacetate, which have physical properties comparable to limonene.

We noted that each perfume in the study contained one or more fragrance fixative(s) such as galaxolide and musk xylol. The mechanism for the fixative activity of these materials is depression of the volatility of the low-to-moderate boiling point components of the final perfume. This extends the duration of the fragrance intensity by reducing the rate at which the fragrance components evaporate from the skin. In general, the fragrance fixative should have an affinity for the more volatile fragrance molecules (top notes), so that the odor of the perfume is more consistent throughout its life. The fixative

## Oil and headspace composition for Shalimar fragrance — T-2

| | Component | Oil conc. (%) | Headspace conc. (%) | | | Activity coefficient | Ratio (Pred/Obs) | Ratio (Pred[a]/Obs) |
|---|---|---|---|---|---|---|---|---|
| | | | Obs | Pred | Pred[a] | | | |
| I | limonene | 30 | 20.4 | 53.5 | 50.8 | 1.0480 | 2.6 | 2.5 |
| II | linalool | 1.7 | 17.9 | 2.0 | 4.4 | 2.4141 | 0.1 | 0.2 |
| III | linalyl acetate | 9.9 | 21.6 | 14.9 | 15.1 | 1.1209 | 0.7 | 0.7 |
| IV | ethyl vanillin | 0.2 | 1.6 | 0.005 | 0.03 | 7.9705 | 0.003 | 0.02 |
| V | coumarin | 1.7 | 7.8 | 0.1 | 0.2 | 2.6334 | 0.01 | 0.02 |
| VI | methyl ionone | 1.1 | 2.1 | 1.2 | 1.2 | 1.0469 | 0.6 | 0.6 |
| VII | musk xylol | trace | 0.3 | NA | NA | NA | | |
| | Total | 44.6 | | | | | | |

[a]corrected with activity coefficient parameter at time zero

## Oil and headspace composition for Amarige fragrance — T-3

| | Component | Oil conc. (%) | Headspace conc. (%) | | | Activity coefficient | Ratio (Pred/Obs) | Ratio (Pred[a]/Obs) |
|---|---|---|---|---|---|---|---|---|
| | | | Obs | Pred | Pred[a] | | | |
| I | linalool | 1.7 | 17.9 | 10.9 | 12.2 | 1.4154 | 0.6 | 0.7 |
| II | benzyl acetate | 4.9 | 22.7 | 40.6 | 29.9 | 0.9274 | 1.8 | 1.3 |
| III | styrallyl acetate | 1.2 | 9.7 | 9.7 | 7.1 | 0.9209 | 1.0 | 0.7 |
| IV | cashmeran | NA | 0.5 | NA | NA | NA | NA | NA |
| V | bacdanol | 0.2 | 0.5 | 0.005 | 0.006 | 1.5900 | 0.01 | 0.01 |
| VI | hedione | 29.9 | 4.9 | 4.5 | 2.9 | 0.7954 | 0.9 | 0.6 |
| VII | cedramber | 1.5 | 4.9 | 3.4 | 15.1 | 5.6342 | 0.7 | 3.1 |
| VIII | iso E super | 7.1 | 12.1 | 3.4 | 4.3 | 1.6187 | 0.3 | 0.4 |
| IX | ambrox | 0.2 | 0.1 | 0.3 | 0.8 | 3.7889 | 2.6 | 7.7 |
| X | benzyl salicylate | 32.5 | 1.1 | 0.7 | 0.6 | 0.9726 | 0.7 | 0.5 |
| XI | muskalactone | 0.9 | 0.4 | 0.8 | 1.3 | 2.1764 | 1.9 | 3.3 |
| | Total | 80.1 | | | | | | |

[a]corrected with activity coefficient parameter at time zero

## Oil and headspace composition for unisex fragrance — T-4

| | Component | Oil conc. (%) | Headspace conc. (%) | | | Activity coefficient | Ratio (Pred/Obs) | Ratio (Pred[a]/Obs) |
|---|---|---|---|---|---|---|---|---|
| | | | Obs | Pred | Pred[a] | | | |
| I | ethyl linalool | 0.7 | 2.8 | 0.5 | 0.5 | 1.3087 | 0.2 | 0.2 |
| II | linalyl acetate | 10.4 | 36 | 26.6 | 23.7 | 1.1220 | 0.7 | 0.7 |
| III | floralozone | 0.1 | 0.3 | 0.03 | 0.01 | 0.4703 | 0.1 | 0.0 |
| IV | cyclogalbaniff | 0.2 | 0.7 | 0.2 | 0.2 | 1.0986 | 0.2 | 0.2 |
| V | dihydromyrcenol | 5.8 | 10.6 | 13.9 | 15.6 | 1.4127 | 1.3 | 1.5 |
| VI | linalool | 7.7 | 11.5 | 15.5 | 16.8 | 1.3633 | 1.3 | 1.5 |
| VII | limonene | 4.5 | 1.4 | 13.6 | 14.9 | 1.3715 | 9.7 | 10.6 |
| VIII | β-ionone | 2.5 | 6.2 | 4.7 | 3.9 | 1.0359 | 0.8 | 0.6 |
| IX | polysantol | 0.2 | 0.4 | 0.003 | 0.003 | 1.3042 | 0.01 | 0.01 |
| X | iso E super | 4.8 | 4.8 | 0.7 | 0.6 | 1.0393 | 0.1 | 0.1 |
| XI | ambrox | 0.7 | 0.4 | 0.3 | 0.4 | 1.6991 | 0.7 | 1.0 |
| XII | hedione | 25.9 | 5 | 1.2 | 1.0 | 1.0366 | 0.2 | 0.2 |
| XIII | galaxolide | 5.5 | 0.6 | 0.1 | 0.1 | 1.2741 | 0.2 | 0.2 |
| XIV | tonalid | 3.3 | 0.1 | 3.5 | 3.1 | 1.1163 | 34.8 | 30.9 |
| | Total | 72.3 | | | | | | |

[a]corrected with activity coefficient parameter at time zero

| | Oil and headspace composition for feminine fragrance | | | | T-5 |
|---|---|---|---|---|---|
| | **Component** | **Oil conc. (%)** | **Headspace conc. (%)** | | **Ratio (Pred/Obs)** |
| | | | **Obs** | **Pred** | |
| I | aldehyde AA | 0.1 | 0.8 | NA | NA |
| II | methyl phenyl acetate | 0.02 | 0.2 | 0.5 | 2.4 |
| III | ethyl linalool | 5.0 | 30 | 21.2 | 0.7 |
| IV | diphenyl ether | 0.01 | 0.04 | 0.03 | 0.7 |
| V | cyclogalbaniff | 0.2 | 0.9 | 0.8 | 0.8 |
| VI | methyl ionone | 2.5 | 9.5 | 17.7 | 1.9 |
| VII | ethyl acetoacetate | 1.8 | 3.4 | 9.8 | 2.9 |
| VIII | iso E super | 2.6 | 2.1 | 0.3 | 0.1 |
| IX | ambrox | 0.2 | 0.1 | 0.04 | 0.4 |
| X | hedione | 18.0 | 2.4 | 0.1 | 0.05 |
| XI | cyclopentadecanolide | 4.8 | 1.2 | 0.3 | 0.3 |
| XII | galaxolide | 14.0 | 0.9 | 0.01 | 0.02 |
| | Total | 49.2 | | | |

| | Oil and headspace composition for women's fragrance | | | | T-6 |
|---|---|---|---|---|---|
| | **Component** | **Oil conc. (%)** | **Headspace conc. (%)** | | **Ratio (Pred/Obs)** |
| | | | **Obs** | **Pred** | |
| I | lolitol | NA | 0.1 | NA | NA |
| II | passion fruit compound | NA | 0.01 | NA | NA |
| III | methyl octin carbonate | NA | 0.1 | NA | NA |
| IV | givescone | 0.10 | 1.2 | 0.3 | 0.2 |
| V | floralazone | 0.01 | 0.1 | 0.01 | 0.1 |
| VI | $\alpha$-damascone | 0.1 | 0.5 | 0.3 | 0.6 |
| VII | $\beta$-damascone | 0.04 | 0.2 | 0.1 | 0.5 |
| VIII | ethyl linalool | 1.4 | 6 | 2.9 | 0.5 |
| IX | undecavertol | 0.3 | 1.0 | 0.3 | 0.3 |
| X | linalyl acetate | 2.0 | 7.8 | 8.0 | 1.0 |
| XI | cis-jasmone | 0.1 | 0.2 | 0.2 | 1.2 |
| XII | methyl ionone | 2.0 | 4.6 | 7.4 | 1.6 |
| XIII | cyclopentadecanolide | 0.9 | 0.2 | 1.6 | 8.2 |
| XIV | galaxolide | 8.0 | 1 | 1.7 | 1.7 |
| | Total | 15.0 | | | |

activity is not accounted for in the current model, although the parameters used for the calculation were developed for a fixed fragrance mixture. Based on the present analysis, we found that the current model generally over predicted the evaporation of the top note ingredients while it often under predicted the evaporation of the fragrance fixatives, which are the least volatile compounds in the mixture. Compounds having intermediate volatilities were, in general, better predicted.

The linear regression statistics show that, on average, the model predicted the experimental data to within a factor of 1 to 4. However, examination of the data in Tables II-IV shows that about half of the ingredients in the list were not accurately predicted by the model. In the worst case, ethyl vanillin, the observed value deviated from the predicted value by a factor of 340. The discrepancies could be related to a number of factors. First, the constants used for estimating evaporation and absorption rate constants were obtained from experiments conducted under different conditions. Second, the values of vapor pressure used in the analysis were estimates only, as we could not find well-documented experimental values. These estimations may introduce significant error. Third, there may be experimental error associated with the data, e.g., the sampling efficiency may differ between compounds. More documentation of the SPME method would be helpful in addressing this question.[4]
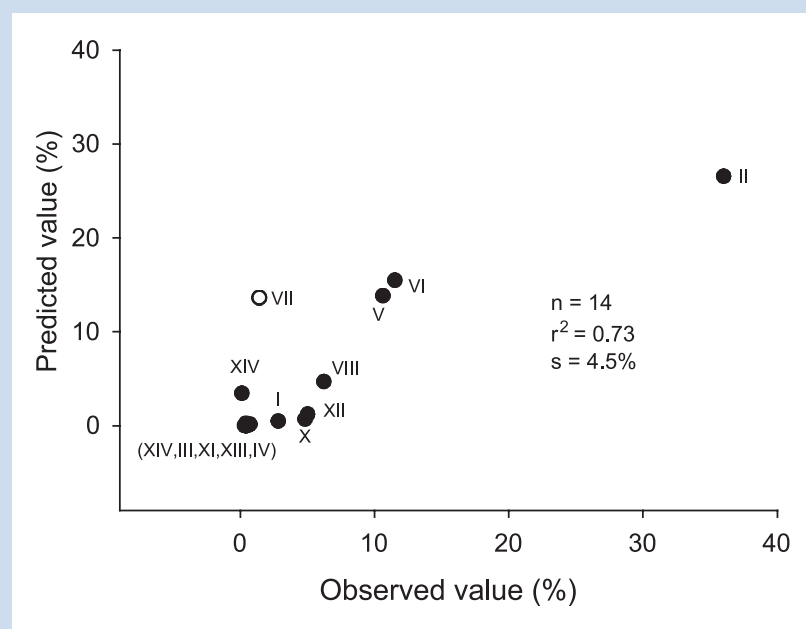
**Predicted and observed headspace concentrations for Amarige fragrance; with benzyl acetate (II) excluded from the analysis, $r^2 = 0.75$ and s = 2.2 percent**

**F-2**



n = 10
$r^2 = 0.70$
s = 7.1%
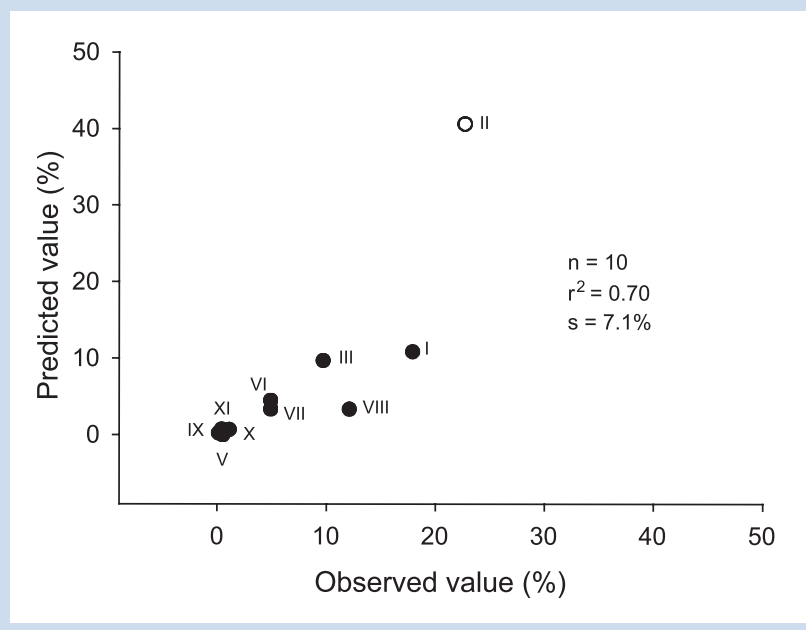
**Predicted and observed headspace concentrations for unisex fragrance; with limonene (VII) excluded from the analysis, $r^2 = 0.87$ and s = 3.1 percent**

**F-3**



n = 14
$r^2 = 0.73$
s = 4.5%

There are several underlying assumptions in the model as discussed in reference 2. One of these assumptions is related to the ingredient interactions. The current model assumes no interactions among ingredients in the fragrance mixture. If this is really the case, one would expect an ingredient to behave identically in each product, regardless of the mixture in which it is applied. The present analysis shows that relative headspace concentrations of some materials (e.g., cyclopentadecanolide, galaxolide and
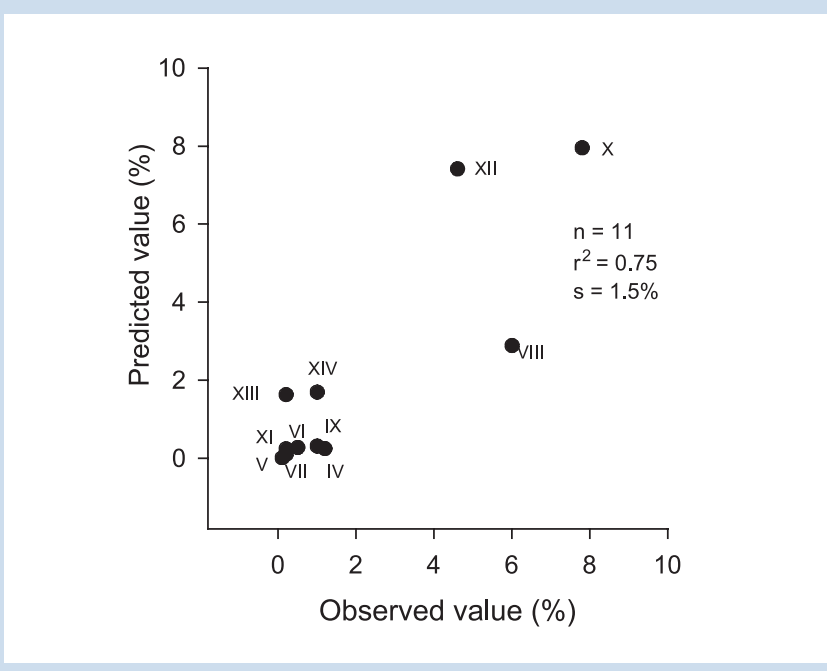
## F-4

**Predicted and observed headspace concentrations for feminine fragrance; with ethyl acetoacetate (VII) excluded from the analysis $r^2 = 0.81$ and s = 3.7 percent**



## F-5
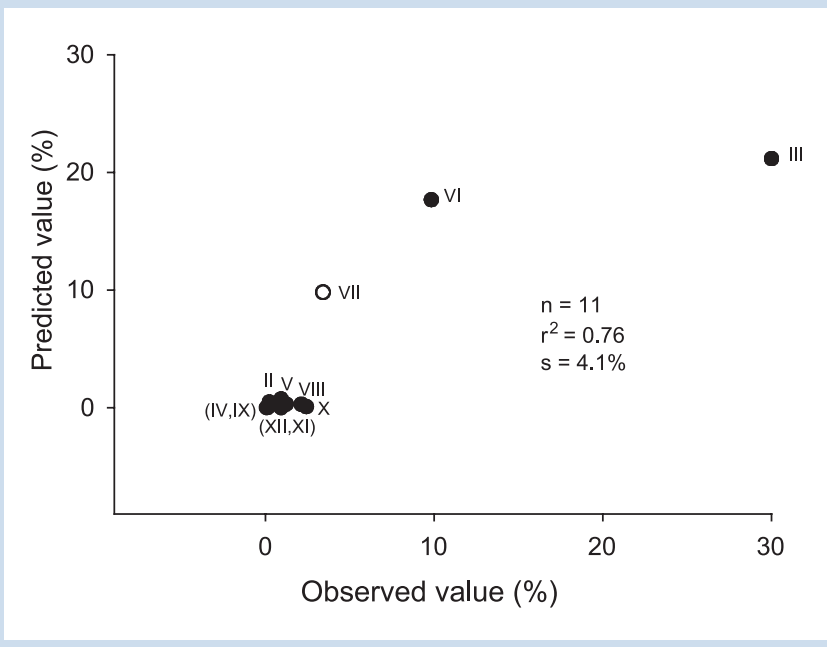
**Predicted and observed headspace concentrations for women's fragrance**



methyl ionone) varied from one mixture to another. These findings imply a significant effect of ingredient interactions in perfume mixtures. An additional parameter, the activity coefficient, may need to be incorporated into the calculation to account for these effects. The activity coefficient is a fractional number that, when multiplied by the mole fraction of a substance in solution, yields the thermodynamic activity. It is a measure of deviation from the ideal state.

The activity coefficients reported in Tables II-IV were calculated for the fragrance compositions prior to application on skin using the UNIFAC method, one of the best methods currently available.[6] The concept of this method is that a liquid mixture may be considered as a solution of the structural units (subgroups) from which the molecules are formed, rather than a solution of the molecules themselves. The fact that not all the components in the mixtures were reported (or even known) could lead to some errors in the calculations. Hence, the calculated activity coefficients are subject to this uncertainty. We could not obtain the activity coefficients of ingredients in feminine and women's fragrances, as parameters for the carbonyl subgroup present in $\alpha$- and $\beta$-damascone and the phenoxyl subgroup present in diphenyl ether are not yet available.

No significant improvements were observed in any of the three perfumes when rate constants were multiplied by initial activity coefficients. It must be noted that these calculations were performed using activity coefficients calculated for the initial mixtures only. A more accurate calculation would require that activity coefficients be re-evaluated regularly as the composition of the mixture remaining on the skin evolves over time. Our experience has not supported the use of activity coefficients in this manner, as add-ons to a kinetic model.[7,12] However, this does not rule out their possible value when incorporated into an appropriate diffusion/evaporation model based on solution of the diffusion equation rather than a compartmental approximation.

## Conclusions

In most cases, headspace concentrations predicted using a previously developed first-order kinetic model correlated reasonably well with experimental values from reference 4. The model employed in the analysis assumed independent absorption and evaporation of each fragrance ingredient. Further work is required to mechanistically understand the retention activity of the fragrance fixative, especially on top note chemicals. Development of a

diffusion model incorporating thermodynamic activity coefficients to represent the ingredient interactions appears to be warranted.

## Acknowledgements

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