Karl Unterkofler and Susanne Teschl

On the influence of inhaled volatile organic compounds (VOCs) on exhaled VOCs concentrations

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Abstract

In this paper we explore the influence of the inhaled concentration of a volatile organic compound (VOC) on its concentration with the help of two compartment models.
These models also connect the exhaled breath concentration of systemic VOCs with physiological parameters such as endogenous production rates and metabolic rates.

Keywords:

Breath gas analysis, Volatile organic compounds (VOCs), trace gases, room air concentrations, mathematical modeling

1. Introduction

Endogenous volatile organic compounds (VOCs) are released within the human organism either as a result of normal metabolic activity or due to pathological disorders. They enter the blood stream and are eventually metabolized or excreted via exhalation, skin emission, urine, etc.

Breath sampling presents a golden opportunity for a **non-invasive** means of extracting information on these topics. Other advantages lie in the possibility to extract breath samples as often as desired, and in the fact that exhalation can be measured in **real time**, even in breath-to-breath resolution.
All together, these factors render breath analysis to be an ideal choice for the purpose of obtaining ongoing information on the current metabolic and physiological state of an individual.

In that process, the identification and quantification of potential disease biomarkers serve as the driving force in that analysis of exhaled breath. Moreover, future applications for medical diagnosis and therapy control with dynamic assessments of normal physiological function or pharmacodynamics are intended. Exogenous VOCs, substances that penetrate the body as a result of environmental exposure, furthermore, can be ultimately utilized to quantify body burden. Finally, breath tests are often based on the ingestion of isotopically labeled precursors, producing isotopically labeled carbon

dioxide as well as the possibility of many other labeled metabolites.

Yet, due to a whole host of confounding factors biasing the concentrations of volatiles in the breath, breath sampling currently stands far-removed from the ranks of standardized procedure. These factors are related to both the breath sampling protocols as well as to the complex physiological mechanisms underlying pulmonary gas exchange. Even under resting conditions, exhaled breath concentrations of VOCs can strongly be influenced by specific physiological parameters such as cardiac output and breathing patterns, depending on the physico-chemical properties of the compound under study. Understanding the influence of all these factors and harnessing their control are therefore central to achieving an accurate standardization of breath sample collection and for the correct deduction of the corresponding blood concentration levels, and ultimately paving the way for the routinization of breath sampling.

In this text we investigate the influence of room air pollution on breath concentrations. The contribution of room air concentrations to breath concentrations is a long-standing unresolved issue in breath gas analysis. M. Phillips et al 1999 summarized the situation as follows:

Researchers have responded to the problem of room air concentrations with three different strategies:

1. Ignore the problem.
2. Provide the subject with VOC-free air to breathe prior to the collection of the breath sample. Unfortunately high quality, pristine breathing air from commercial sources is usually found to contain a large number of VOCs. In addition, it also contributes to the wash-in/wash-out effect.
3. Correct for the problem by subtracting the background VOCs in room air from the VOCs observed in the breath.

Phillips calls this difference of exhaled concentration and inhaled concentration the alveolar gradient, i.e. he assumed that the pollution free concentration $C_A(0)$ is given by $C_A(0) = C_A(C_I) - C_I$ where C_I denotes the inhaled concentration.

2. Compartmental modeling

To see if this subtraction is correct, we have developed two models based on mass balance equations:

(1) a two compartment model for VOCs with small partition coefficients (Henry constant) $\lambda_{b:air}$ which fulfill the Farhi equation (see Figure 1) and

(2) a three compartment model (see Figure 2) for VOCs where the influence of the upper airways contributions cannot be neglected.

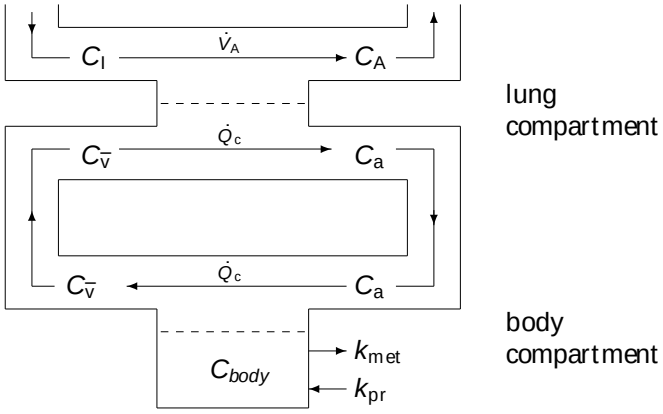

Figure 1: The two compartment model consists of a lung compartment (gas exchange) and a body compartment with production and metabolism. Dashed lines indicate equilibrium according to Henry's law. Notations: k_{met} ...metabolic rate [nmol/l], k_{pr} ... production rate [l/min], C_X... concentration in X [nmol/l] with A... Alveolar, a ... arterial, $\bar{v}$ .. mixed venous, I ... Inhaled, $\dot{Q}_c$ ... cardiac output [l/min], $\dot{V}_A$ ... ventilation [l/min]

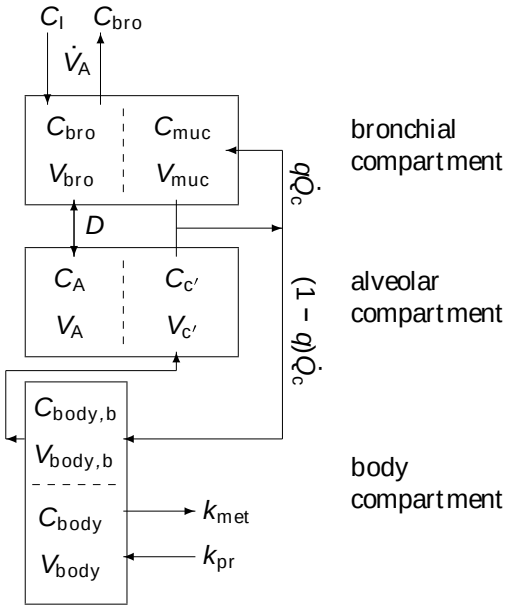

Figure 2: Sketch of the model structure. The body is divided into three distinct functional units: bronchial/mucosal compartment (gas exchange), alveolar/end-capillary compartment (gas exchange) and body compartment (metabolism and production). Dashed boundaries indicate a diffusion equilibrium. The conductance parameter D quantifies an effective diffusion barrier between the bronchial and the alveolar tract. Notations: q... fractional blood flow, k_{met} ...metabolic rate [nmol/l], k_{pr} ... production rate [l/min], V_X... volume of X [l], C_X... concentration in X [nmol/l] with muc... mucus, bro ... bronchial, c' .. mixed venous, I ... Inhaled, $\dot{Q}_c$ ... cardiac output [l/min], $\dot{V}_A$ ... ventilation [l/min]

Both models show that the **exhaled concentration** (in case (1) this is $C_A(C_I)$ and in case (2) this is $C_{bro}(C_I)$) is an affine function (as recently measured by P. Spanel et al 2013) of the inhaled concentration C_I when cardiac output $\dot{Q}_c$ and ventilation $\dot{V}_A$ are kept constant, i.e.

$$C_A(C_I) = aC_I + b, \quad C_{bro}(C_I) = aC_I + b,$$

C_I being the variable here. In case (1) we get for the parameters a and b

$$a = \left(1 + \frac{\lambda_{b:air}}{\frac{\dot{V}_A}{\dot{Q}_c} + \frac{\dot{V}_A}{k_{met}}}\right)^{-1}, \qquad b = C_A(0) = \frac{\frac{k_{prod}}{k_{met}}}{\frac{\dot{V}_A}{\dot{Q}_c} + \frac{\dot{V}_A}{k_{met}} + \lambda_{b:air}}$$

and in case (2), when $D = 0$,

$$a = \frac{1}{1 + \frac{\lambda_{muc:air}}{\lambda_{muc:b}} \frac{\dot{Q}_c}{\dot{V}_A} \frac{q(1-q)}{1+q(1-q)\frac{\dot{Q}_c}{k_{met}}}},$$

$$b = C_{bro}(0) = \frac{k_{pr}}{\dot{V}_A + k_{met}\left(\frac{\lambda_{muc:air}}{\lambda_{muc:b}} + \frac{\dot{V}_A}{\dot{Q}_c}\frac{1}{q(1-q)}\right)}.$$

3. Conclusions

Hence, to calculate the correct concentration (for a clean room air) $C_A(0)$, one has to take

$$C_A(0) = C_A(C_I) - aC_I, \quad C_{bro}(0) = C_{bro}(C_I) - aC_I.$$

We obtain the following values for the most frequently occurring VOCs in breath (equilibrium at rest):

Methane ($\lambda_{b:air} = 0.066$): $C_A(0) = C_A(C_I) - 1.0\,C_I$
Pentane ($\lambda_{b:air} = 0.42$): $C_A(0) = C_A(C_I) - 0.81\,C_I$
Isoprene ($\lambda_{b:air} = 0.95$): $C_A(0) = C_A(C_I) - 0.66\,C_I$
Acetone ($\lambda_{b:air} = 340$): $C_{bro}(0) = C_{bro}(C_I) - 0.38\,C_I$
Ethanol ($\lambda_{b:air} = 1200$): $C_{bro}(0) = C_{bro}(C_I) - 0.07\,C_I$.

This shows that the amount which should be subtracted in order to get the concentration of a VOC ultimately corresponding to a clean environment strongly depends on the metabolic rate and the Henry constant $\lambda_{b:air}$ of a substance! As a result, in order for the use of breath VOCs as biomarkers of cancer in a clinical setting to be applied, it is essential to first take proper consideration of the clinics' background air. Otherwise, erroneous diagnoses may occur. Hence it is important to measure the parameters a, b, D and $\lambda_{b:air}$ for a wide range of VOCs.

4. References

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