Modeling-based determination of physiological parameters of systemic VOCs by breath gas analysis, part 2

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Abstract. In a recent paper [16] we presented a simple two compartment model which describes the influence of inhaled concentrations on exhaled breath concentrations for volatile organic compounds (VOCs) with small Henry constants.

In this paper we extend this investigation concerning the influence of inhaled concentrations on exhaled breath concentrations for VOCs with higher Henry constants.

To this end we extend our model with an additional compartment which takes into account the influence of the upper airways on exhaled breath VOC concentrations.

Keywords: Modeling, Breath gas analysis, Volatile organic compounds (VOCs), Metabolic rates, Production rates, Acetone

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1. Introduction

In their paper [12] Španěl et al. investigated the short-term effect of inhaled volatile organic compounds (VOCs) on exhaled breath concentrations. They showed for seven different VOCs with very different Henry constants (blood:air partition coefficients) that the exhaled breath concentration closely resembles an affine function (straight line) of the inhaled concentration.

This motivated our theoretical investigation [16] regarding the impact of inhaled concentrations for VOCs with low blood:air partition coefficients, i.e., compounds with exhalation kinetics that are described by the Farhi equation [3]. For these VOCs the exhaled end-tidal breath concentration resembles the alveolar concentration.

Here we extend this investigation to VOCs with higher blood:air partition coefficients where the influence of the upper airways cannot be neglected. For such VOCs the exhaled end-tidal breath concentration does not equal the alveolar concentration but the bronchial concentration.

Consider for example acetone with typical concentrations of 1 [μg/l] in breath. Assuming that the exhaled end-tidal breath concentration equals the alveolar concentration and using the Farhi equation‡ the blood:air partition coefficient (dimensionless Henry constant) of acetone $\lambda_{\mathrm{b:air}} \approx 340$ (from table 2 in [1]) would lead to a concentration of 0.341 [mg/l] in blood which differs considerably from typically measured values in blood of 1 [mg/l].

Hence one can not neglect the influence of the upper airways when investigating VOCs with higher partition coefficients, see e.g., [1].

2. A three compartment model

To incorporate the influence of the upper airways on exhaled VOC concentrations we choose the simplest possible model. It consists of three compartments as sketched in Figure 1: a two compartment lung (bronchioles and alveoli) as used in [7] and one body compartment.

We consider the bronchial compartment separated into a gas phase and a mucus membrane, which is assumed to inherit the physical properties of water and acts as a reservoir. The part of a VOC dissolved in this layer is transferred to the bronchial circulation, whereby the major fraction of the associated venous drainage is postulated to join the pulmonary veins via the post capillary anastomoses [8].

The amount of a VOC transported at time t via exhalation and inhalation to the bronchial compartment equals therefore

$$\dot{V}_{\mathrm{A}}\big(C_{\mathrm{I}} - C_{\mathrm{bro}}\big),$$

where $\dot{V}_{\mathrm{A}}$ denotes the ventilation, C_{I} denotes the concentration in the inhaled air (normally assumed to be zero), and C_{bro} the bronchial air concentration§. Moreover,

‡ The Farhi equation [3] relates the mixed venous concentration $C_{\bar{\mathrm{v}}}$ with the alveolar concentration C_{A} by

$$C_{\mathrm{A}} = \frac{C_{\bar{\mathrm{v}}}}{\lambda_{\mathrm{b:air}} + r}.$$

Here $\lambda_{\mathrm{b:air}}$ is the blood:air partition coefficient and r is the ventilation-perfusion ratio which is approximately 1 at rest.

§ Note: we have suppressed the time variable t, i.e., we write $\dot{V}_{\mathrm{A}}$ instead of $\dot{V}_{\mathrm{A}}(t)$, and so on.

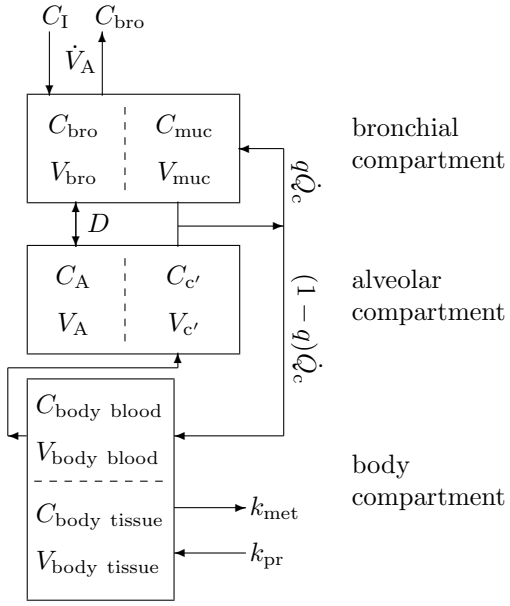

Figure 1. Sketch of the model structure. The body is divided into three distinct functional units: bronchial/mucosal compartment (gas exchange), alveolar/end-capillary compartment (gas exchange) and body compartment (metabolism and production). Dashed boundaries indicate a diffusion equilibrium. Thus in each case two compartments can be combined into one compartment with an effective volume $\tilde{V}$, e.g., the body blood compartment and the body tissue compartment are assumed to be in an equilibrium and therefore can be combined into one single body compartment with an effective volume, $\tilde{V}_B = V_{\text{body blood}} + \lambda_{B:b} V_{\text{body tissue}}$. For more details about effective volumes compare appendix A.2 in [7]. The conductance parameter D has units of volume divided by time and quantifies an effective diffusion barrier between the bronchial and the alveolar tract.

we state that the measured (exhaled) end-tidal breath concentration equals the bronchial level, i.e.,

$$C_\mathrm{measured} = C_\mathrm{bro}.$$

The contribution of the blood flow through the pulmonary veins via the post capillary anastomoses is

$$q\,\dot{Q}_\mathrm{c}\left(C_\mathrm{a} - \frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} C_\mathrm{bro}\right),$$

where q denotes the fractional blood flow through the bronchioles, $\dot{Q}_\mathrm{c}$ the cardiac output, C_a the arterial blood concentration, $\lambda_\mathrm{muc:b}$ the mucus:blood partition coefficient, and $\lambda_\mathrm{muc:air}$ the temperature dependent mucus:air partition coefficient (see Appendix B for details).

Then the arterial blood concentration C_a is given by

$$C_\mathrm{a} = (1-q)\lambda_\mathrm{b:air} C_\mathrm{A} + q\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} C_\mathrm{bro} \tag{1}$$

with $\lambda_\mathrm{b:air}$ denoting the blood:air partition coefficient and C_A the alveolar concentration.

The exchange between the bronchial compartment and the alveolar compartment is modeled as a diffusion process

$$D\,(C_{\mathrm{A}} - C_{\mathrm{bro}})$$

with a diffusion constant D which takes values between zero and infinity.

Thus the total mass balance for the bronchial compartment reads

$$\tilde{V}_{\mathrm{bro}}\frac{\mathrm{d}C_{\mathrm{bro}}}{\mathrm{d}t} = \dot{V}_{\mathrm{A}}(C_{\mathrm{I}} - C_{\mathrm{bro}}) + D(C_{\mathrm{A}} - C_{\mathrm{bro}}) + q\,\dot{Q}_{\mathrm{c}}\left(C_{\mathrm{a}} - \frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}C_{\mathrm{bro}}\right). \tag{2}$$

Analogously we derive the mass balance equations from Figure 1 for the alveolar compartment

$$\tilde{V}_{\mathrm{A}}\frac{\mathrm{d}C_{\mathrm{A}}}{\mathrm{d}t} = D(C_{\mathrm{bro}} - C_{\mathrm{A}}) + (1-q)\dot{Q}_{\mathrm{c}}\big(C_{\bar{\mathrm{v}}} - \lambda_{\mathrm{b:air}}C_{\mathrm{A}}\big), \tag{3}$$

and the body compartment

$$\tilde{V}_B\frac{dC_B}{dt} = (1-q)\dot{Q}_c(C_a - C_{\bar{\mathrm{v}}}) - k_{\mathrm{met}}\lambda_{b:B}C_B + k_{\mathrm{pr}}, \tag{4}$$

where k_{met} denotes the total metabolic rate‖ of the body and k_{pr} the production rate. $\tilde{V}_{\mathrm{bro}}$, $\tilde{V}_{\mathrm{A}}$, and $\tilde{V}_B$ denote the effective volume of the bronchiols, alveoli, and the body, respectively. C_B is the concentration in the body which is connected to the mixed venous concentration $C_{\bar{\mathrm{v}}}$ by Henry's law $C_{\bar{\mathrm{v}}} = \lambda_{b:B}\,C_B$ where $\lambda_{b:B}$ denotes the blood:body tissue partition coefficient.

Remark: A single body compartment can be derived from the combination of the liver and tissue compartment of the model in [7].

Thus the three compartment model for VOCs with higher Henry constant consists of the system of the three linear differential equations (2) – (4)

$$\begin{aligned}
\tilde{V}_{\mathrm{bro}}\frac{\mathrm{d}C_{\mathrm{bro}}}{\mathrm{d}t} &= \dot{V}_{\mathrm{A}}(C_{\mathrm{I}} - C_{\mathrm{bro}}) + D(C_{\mathrm{A}} - C_{\mathrm{bro}}) + q\dot{Q}_{\mathrm{c}}\left(C_{\mathrm{a}} - \frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}C_{\mathrm{bro}}\right),\\
\tilde{V}_{\mathrm{A}}\frac{\mathrm{d}C_{\mathrm{A}}}{\mathrm{d}t} &= D(C_{\mathrm{bro}} - C_{\mathrm{A}}) + (1-q)\dot{Q}_{\mathrm{c}}\big(C_{\bar{\mathrm{v}}} - \lambda_{\mathrm{b:air}}C_{\mathrm{A}}\big),\\
\tilde{V}_B\frac{dC_B}{dt} &= (1-q)\dot{Q}_c(C_a - C_{\bar{\mathrm{v}}}) - k_{\mathrm{met}}C_{\bar{\mathrm{v}}} + k_{\mathrm{pr}}.
\end{aligned} \tag{5}$$

Remarks: (i) Summing up these three linear differential equations yields the total change of mass m_{tot} of a VOC, i.e.,

$$\tilde{V}_{\mathrm{bro}}\frac{\mathrm{d}C_{\mathrm{bro}}}{\mathrm{d}t} + \tilde{V}_{\mathrm{A}}\frac{\mathrm{d}C_{\mathrm{A}}}{\mathrm{d}t} + \tilde{V}_B\frac{dC_B}{dt} = \frac{dm_{tot}}{dt} = \dot{V}_{\mathrm{A}}C_{\mathrm{I}} - \dot{V}_{\mathrm{A}}C_{\mathrm{bro}} + k_{\mathrm{pr}} - k_{\mathrm{met}}C_{\bar{\mathrm{v}}}. \tag{6}$$

Equation (6) shows that the total change of mass of a VOC is given by what is inhaled minus what is exhaled plus what is produced by the body minus what is eliminated by metabolism (metabolism includes all losses, e.g., by liver, urine, skin, etc.), so that the total mass balance is fulfilled.

(ii) In general, ventilation $\dot{V}_{\mathrm{A}}$ and cardiac output $\dot{Q}_{\mathrm{c}}$ are non-constant functions of time. Nevertheless one can show that all solutions of the system (5) starting in $\mathbb{R}^3_{>0}$ remain bounded (see appendix B, proposition 1 in [7]).

(iii) Rearranging Equation (5) yields a system of the form

$$\frac{\mathrm{d}\mathbf{c}(t)}{\mathrm{d}t} = N\mathbf{c}(t) + \mathbf{h} \tag{7}$$

‖ We assume that the ambient air is not severely contaminated and hence metabolism can be modeled with a linear kinetics.

for the vector $\mathbf{c}$ of the three concentrations $(C_{\text{bro}}, C_{\text{A}}, C_{\bar{\text{v}}})$, i.e.,

$$\mathbf{c} = (c_1, c_2, c_3) = (C_{\text{bro}}, C_{\text{A}}, C_{\bar{\text{v}}})\,.$$

If ventilation $\dot{V}_{\text{A}}$ and cardiac output $\dot{Q}_{\text{c}}$ are kept constant and assuming that the production k_{pr} is constant, too, the solution of this system can be given explicitly (see, e.g., chapter 3.2 in [15]¶). All eigenvalues of the constant matrix N are negative and the concentrations approach exponentially (the eigenvalues of N are the exponential constants) the equilibrium state $\mathbf{c}(\infty) = -N^{-1}\mathbf{h}$.

When in a stationary state, namely where all quantities and concentrations are constant, the left hand sides of the system (5) are zero and the system of differential equations reduces to a linear algebraic system of the form

$$M\mathbf{c} = \mathbf{b} \tag{8}$$

where the matrix M and the vector $\mathbf{b}$ are given by

$$M = \begin{pmatrix} \dot{V}_{\text{A}} + D + q(1-q)\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}\dot{Q}_{\text{c}} & -D - q(1-q)\lambda_{\text{b:air}}\,\dot{Q}_{\text{c}} & 0 \\ -D & D + q(1-q)\lambda_{\text{b:air}}\,\dot{Q}_{\text{c}} & -(1-q)\dot{Q}_{\text{c}} \\ -q(1-q)\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}\dot{Q}_{\text{c}} & -(1-q)^2\lambda_{\text{b:air}}\,\dot{Q}_{\text{c}} & k_{\text{met}} + (1-q)\dot{Q}_{\text{c}} \end{pmatrix},$$

$$\mathbf{b} = \begin{pmatrix} \dot{V}_{\text{A}}\,C_{\text{I}} \\ 0 \\ k_{\text{pr}} \end{pmatrix}. \tag{9}$$

Trivial linear algebra lets us write the solution of the system (8) with the help of Cramer's rule

$$C_{\text{bro}} = c_1 = \frac{\det(M_1)}{\det(M)}, \quad C_{\text{A}} = c_2 = \frac{\det(M_2)}{\det(M)}, \quad C_{\bar{\text{v}}} = c_3 = \frac{\det(M_3)}{\det(M)} \tag{10}$$

where M_j denotes the matrix M where the j-th column, $j = 1, 2, 3$, is replaced by the vector $\mathbf{b}$ and $\det(M)$ denotes the determinant of a matrix M.

From equation (10) we conclude that all concentrations are indeed affine functions (straight lines) of the inhaled concentration C_{I}. C_{I} appears in the first component of the vector $\mathbf{b}$ only. Hence $\det(M)$ is independent of C_{I}. The multilinearity of the determinant of the matrix M_j implies the affine dependence on C_{I}, i.e.,

$$c_j(C_{\text{I}}) = a_j\,C_{\text{I}} + b_j, \tag{11}$$

where a_j and $b_j, j = 1, 2, 3$ are dependent on $D, \dot{V}_{\text{A}}$, etc.

For the special case $D = 0$ (this is the case for very high partition coefficients $\lambda_{\text{b:air}} > 100$)$^+$ we get $C_{\text{A}} = 1/\lambda_{\text{b:air}}\,C_{\bar{\text{v}}}$ and furthermore

$$\begin{aligned} C_{\text{bro}}(C_{\text{I}}) &= a_1\,C_{\text{I}} + b_1, \\ C_{\text{A}}(C_{\text{I}}) &= a_2\,C_{\text{I}} + b_2, \\ C_{\bar{\text{v}}}(C_{\text{I}}) &= a_3\,C_{\text{I}} + b_3 \end{aligned} \tag{12}$$

¶ A pdf version of this book is available from
`http://www.mat.univie.ac.at/~gerald/ftp/book-ode/index.html`

$^+$ The decoupled case $D = q = 0$ will be excluded from now on as it lacks physiological relevance.

with

$$
\begin{aligned}
a_1 &= \frac{1}{1+\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}\frac{\dot{Q}_\text{c}}{\dot{V}_\text{A}}\frac{q(1-q)}{1+q(1-q)\frac{\dot{Q}_\text{c}}{k_\text{met}}}},\\
b_1 &= C_\text{bro}(0) = \frac{k_\text{pr}}{\dot{V}_\text{A}+k_\text{met}\big(\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}+\frac{\dot{V}_\text{A}}{\dot{Q}_\text{c}}\frac{1}{q(1-q)}\big)},\\
a_2 &= \frac{a_3}{\lambda_{\text{b:air}}}, \quad b_2 = C_\text{A}(0) = \frac{b_3}{\lambda_{\text{b:air}}},\\
a_3 &= \frac{1}{\frac{\lambda_{\text{muc:b}}}{\lambda_{\text{muc:air}}}+k_\text{met}\big(\frac{1}{\dot{V}_\text{A}}+\frac{1}{\dot{Q}_\text{c}}\frac{1}{q(1-q)}\frac{\lambda_{\text{muc:b}}}{\lambda_{\text{muc:air}}}\big)},\\
b_3 &= C_{\bar{\text{v}}}(0) = \frac{k_\text{pr}}{k_\text{met}+\frac{\dot{V}_\text{A}}{\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}+\frac{\dot{V}_\text{A}}{\dot{Q}_\text{c}}\frac{1}{q(1-q)}}}.
\end{aligned}
\tag{13}
$$

Furthermore, the connection between the mixed venous blood concentration and the measured exhaled concentration is given by

$$
C_{\bar{\text{v}}}(0) = \big(\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}+\frac{1}{q(1-q)}\frac{\dot{V}_\text{A}}{\dot{Q}_\text{c}}\big)\,C_\text{bro}(0). \tag{14}
$$

For exogenous VOCs (i.e., $k_\text{pr}=0$) we have $b_1=b_2=b_3=0$ and $C_\text{bro}(C_\text{I}) = a_1\,C_\text{I}$, $C_{\bar{\text{v}}}(C_\text{I}) = a_3\,C_\text{I}$ which yields

$$
C_{\bar{\text{v}}}(C_\text{I}) = \frac{\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}}{1+\frac{1}{q(1-q)}\frac{k_\text{met}}{\dot{Q}_\text{c}}}\,C_\text{bro}(C_\text{I}). \tag{15}
$$

Since the fractional blood flow of the bronchial circulation q is very small ($q\approx 0.01$ [8]) we have $q(1-q)\approx q$ and the following approximations are valid

$$
\begin{aligned}
a_1 &\approx \frac{1}{1+\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}\frac{\dot{Q}_\text{c}}{\dot{V}_\text{A}}\frac{q}{1+q\frac{\dot{Q}_\text{c}}{k_\text{met}}}},\\
b_1 &\approx \frac{k_\text{pr}}{\dot{V}_\text{A}+k_\text{met}\big(\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}+\frac{\dot{V}_\text{A}}{\dot{Q}_\text{c}}\frac{1}{q}\big)},\\
a_3 &\approx \frac{1}{\frac{\lambda_{\text{muc:b}}}{\lambda_{\text{muc:air}}}+k_\text{met}\big(\frac{1}{\dot{V}_\text{A}}+\frac{1}{\dot{Q}_\text{c}}\frac{1}{q}\frac{\lambda_{\text{muc:b}}}{\lambda_{\text{muc:air}}}\big)},\\
b_3 &\approx \frac{k_\text{pr}}{k_\text{met}+\frac{\dot{V}_\text{A}}{\frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}+\frac{\dot{V}_\text{A}}{\dot{Q}_\text{c}}\frac{1}{q}}}.
\end{aligned}
\tag{16}
$$

Further simplifications are possible under further assumptions, e.g., $k_\text{met}\to 0$ leads to $a_1=1$ or $k_\text{met}\approx\dot{Q}_\text{c}$ leads to $b_3\approx\frac{k_\text{pr}}{k_\text{met}}$.

Remarks: (i) Looking at the equation $C_\text{bro}(C_\text{I}) = a_1\,C_\text{I}+b_1$ we see that b_1 is the contribution to the exhaled breath by the endogenous production when no room concentration is present and $(1-a_1)$ is the proportion of the room concentration which is taken up by the body.

(ii) For $D \neq 0$ the calculation is straight forward but the expressions are quite lengthy. However, these calculation can be easily done with a computer algebra system, e.g., using *Mathematica*. The results are supplied in Appendix E.

2.1. Correction method in order to account for inhaled VOC concentrations

From Equation (11) we conclude that to correct the measured exhaled concentration for the inhaled one, one has simply to subtract the inhaled concentration multiplied by the gradient a_1, i.e.,

$$C_{\text{exhaled}}(0) = C_{\text{bro}}(0) = b_1 = C_{\text{bro}}(C_{\text{I}}) - a_1 C_{\text{I}}. \tag{17}$$

Example 1: With the data from Section 2.3 we therefore get for acetone

$$C_{\text{bro}}(0) = C_{\text{bro}}(C_{\text{I}}) - 0.384\, C_{\text{I}} = C_{\text{measured}} - 0.384\, C_{\text{I}}. \tag{18}$$

Example 2: To estimate a_1 for ethanol we use the following nominal values: $q = 0.01$, $\dot{V}_{\text{A}} = 5.2$ [l/min], $\dot{Q}_{\text{c}} = 6$ [l/min] (from table 1 and 2 in [7]), $k_{\text{met}} = 0.15$ [l/min] (= 7 [g/h] from [2]), $\lambda_{\text{b:air}} = 1756$ (from [6]), $\lambda_{\text{muc:air}} = 2876.7$ at 32° C, $\lambda_{\text{muc:b}} = 1.17$ (from [13]). This yields

$$C_{\text{bro}}(0) = C_{\text{bro}}(C_{\text{I}}) - 0.047\, C_{\text{I}} = C_{\text{measured}} - 0.047\, C_{\text{I}}. \tag{19}$$

This shows that in contrast to methane [14] where one must subtract the total inhaled concentration, for ethanol the inhaled concentration is nearly neglectable.

2.2. Endogenous production and metabolic rates

The question remains how to determine the endogenous production rate and the total metabolic rate of the body using the theoretical framework introduced above? When in a stationary state, the averaged values of ventilation and perfusion are constant, then Equation (11) resembles an affine function (straight line) of the form

$$C_{\text{bro}}(C_{\text{I}}) = a_1\, C_{\text{I}} + b_1, \tag{20}$$

C_{I} being the variable here. The constants a_1 and b_1 are given for $D = 0$ by Equation (13).

However, for all cases of D the constants a_j and b_j, $j = 1, 2, 3$ are completely determined by the physiological quantities $\dot{V}_A, \dot{Q}_c, k_{\text{pr}}, k_{\text{met}}, q$, and partition coefficients. The gradient a_1 is independent of k_{pr}, fulfills $0 < a_1 \leq 1$, and depends on the metabolic rate k_{met} but not the production rate k_{pr}. The quantity $b_1 = C_{\text{bro}}(0)$ is proportional to the production rate k_{pr}.

Varying C_{I}, one can measure $C_{\text{bro}}(C_{\text{I}})$ experimentally and thus determine a_1 and b_1. Measuring in addition ventilation and perfusion allows for calculating the total production rate and the total metabolic rate of the body from these two equations. For $D = 0$ this yields

$$k_{\text{met}} = \frac{q(1-q)(1-a_1)\,\dot{Q}_{\text{c}}}{(1 + \frac{\lambda_{\text{muc:air}}}{\lambda_{\text{muc:b}}}\, q(1-q)\, \frac{\dot{Q}_{\text{c}}}{\dot{V}_{\text{A}}})\, a_1 - 1}, \tag{21}$$

$$k_{\text{pr}} = \frac{b_1\, \dot{Q}_{\text{c}}}{a_1 \frac{\dot{Q}_{\text{c}}}{\dot{V}_{\text{A}}} + \frac{\lambda_{\text{muc:b}}}{\lambda_{\text{muc:air}}} \frac{1}{q(1-q)}(a_1 - 1)}, \tag{22}$$

or

$$k_{\rm pr} = b_1\big(\dot V_{\rm A} + k_{\rm met}(\frac{\lambda_{\rm muc:air}}{\lambda_{\rm muc:b}} + \frac{\dot V_{\rm A}}{\dot Q_{\rm c}}\frac{1}{q(1-q)})\big) \tag{23}$$

if $k_{\rm met}$ is already known.

Remarks: (i) Note that the numerators in Equations (21) and (22) are small which will cause large errors when there are no good data available.

(ii) For $D \neq 0$ the calculation is straightforward, too, but the expressions are also quite lengthy. The results are supplied in Appendix E.

2.3. Test of the theory with data available from literature

Since Španěl et al. did not provide any data for blood flow (cardiac output $\dot Q_{\rm c}$) and breath flow (alveolar ventilation $\dot V_{\rm A}$) we took the data for *acetone* provided by Wigaeus [17] (i.e., series 1). This data which we have already used in [7] are listed in Table 1. Note that D equals zero at rest for acetone.

Table 1. List of data and determined parameters values from [17] and [7].

Parameter	Symbol	value
inhaled air concentration	$C_{\rm I}$	1.309 [mg/l]
exhaled concentration	$C_{\rm exhaled}$	0.504 [mg/l]
Diffusion	D	0 [l/min]
alveolar ventilation	$\dot V_{\rm A}$	6 [l/min]
cardiac output	$\dot Q_{\rm c}$	5.8 [l/min]
fractional bronchial blood flow	q	0.0043
blood:air partition coefficient	$\lambda_{\rm b:air}$	340
mucus:air partition coefficient (32° C)	$\lambda_{\rm muc:air}$	498
mucus:blood partition coefficient (37° C)	$\lambda_{\rm muc:b}$	1.15
mean bronichal concentration	$C_{\rm bro}(0)$	0.0016 [mg/l]

This data determine $a_1 = 0.384$ ($\approx C_{\rm exhaled}/C_{\rm I}$ for $C_{\rm I} >> C_{\rm bro}(0)$) and $b_1 = 0.0016$ in Equation (13). Then the following values can be calculated from Equation (13). They are listed in Table 2.

Table 2. List of calculated values

Parameter	Symbol	value	value in [7]
metabolic rate	$k_{\rm met}$	0.21 [l/min]	0.18 [l/min]
production rate	$k_{\rm pr}$	0.24 [mg/min]	0.19 [mg/min]
mixed venous concentration	$C_{\bar{\rm v}}(0)$	1.079 [mg/l]	1.0 [mg/l]
alveolar air concentration	$C_{\rm A}(0)$	0.0032 [mg/l]	0.0029 [mg/l]
arterial concentration	$C_{\rm a}(0)$	1.077 [mg/l]	0.98 [mg/l]

These values are in good agreement with the values from the more detailed model developed in [7].

3. Discussion

In this paper we extended our investigation of the short-term effect* of inhaled volatile organic compounds (VOCs) on exhaled breath concentrations to VOCs with higher Henry constants. For such VOCs the exhaled end-tidal breath concentration does not equal the alveolar concentration but equals the bronchial concentration and hence it is essential to take the influence of the upper airways into account.

In particular, a special focus is given to the case when the inhaled (e.g., ambient air) concentration is significantly different from zero. The model elucidates a novel approach for computing metabolic/production rates of systemic VOCs with high blood:air partition coefficients from the respective breath concentrations. Moreover, it clarifies how breath concentration of such VOCS should be corrected (see Equation 17) when the inhaled concentration cannot be neglected. The model predicts an affine relationship (straight line) between exhaled breath concentrations and inhaled concentrations as shown by measurements by Spanel et al. [12] and are in good agreement with data available from Wigaeus [17].

The gradient of this line is completely determined by the physiological quantities $\dot{V}_A, \dot{Q}_c, k_{\mathrm{pr}}, k_{\mathrm{met}}, q$, and partition coefficients. However, for practical use it might be easier to determine this gradient directly by experiments for the VOC one is interested in. Note that the gradient a_1 is approximately $C_{\mathrm{exhaled}}/C_{\mathrm{I}}$ if $C_{\mathrm{I}} >> C_{\mathrm{bro}}(0)$. Even labeled♯ inhaled VOCs might be used to exclude effects from endogenous production.

Nevertheless, a number of limitations should be mentioned here. Firstly, in order to apply this model for the estimation of metabolic/production rates, further studies with a representative number of patients will be necessary. In particular, the individual and population ranges of these quantities will have to be determined. In addition, it should be investigated how these parameters vary with age, body mass, sex, etc.. To circumvent the intricate measurements of ventilation and perfusion, one could measure heart frequency and breath frequency and deduce ventilation and perfusion from these parameters.

In order to account for long-term exposure, the model should be extended to incorporate a storage compartment which fills up and depletes according to its partition coefficient. This yields then at least a 4-compartment model. However, for short-term exposure experiments the influence of such a storage compartment will merely be reflected by a slightly different metabolic rate.

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* This is the typical situation in a clinical examination.

♯ ^{13}C labeling is preferred to avoid D-H-exchanges (article in preparation) when labeling with D-atoms.

Appendix A. List of symbols

Table A1 summarizes the list of symbols used in the text.

Table A1. Abbreviations

Parameter	Symbol
cardiac output	$\dot{Q}_{\mathrm{c}}$
alveolar ventilation	$\dot{V}_{\mathrm{A}}$
ventilation-perfusion ratio	$r = \dot{V}_{\mathrm{A}}/\dot{Q}_{\mathrm{c}}$
effective volume of alveoli	$\tilde{V}_{\mathrm{A}}$
effective volume of the body	$\tilde{V}_B$
effective volume of the bronchioles	$\tilde{V}_{\mathrm{bro}}$
inhaled air concentration	C_{I}
bronchial concentration	C_{bro}
arterial concentration	C_{a}
alveolar air concentration	C_{A}
averaged mixed venous concentration	$C_{\bar{\mathrm{v}}}$
exhaled (measured) concentration	$C_{\mathrm{exhaled}} = C_{\mathrm{measured}}$
body concentration	C_B
metabolic rate	k_{met}
production rate	k_{pr}
blood:air partition coefficient	$\lambda_{\mathrm{b:air}}$
blood:body partition coefficient	$\lambda_{b:B}$
mucus:blood partition coefficient	$\lambda_{\mathrm{muc:b}}$
mucus:air partition coefficient	$\lambda_{\mathrm{muc:air}}$
fractional blood flow through bronchioles	q

Appendix B. Temperature dependence of $\lambda_{\mathrm{muc:air}}$ $(= \lambda_{water:air})$

There is strong experimental evidence that airway temperature constitutes a major determinant for the pulmonary exchange of highly soluble VOCs, cf. [5]. How this influences the $\lambda_{\mathrm{muc:air}}(T)$ partition coefficient was described in detail for acetone in [7]. However, this can immediately be adapted to other highly soluble VOCs.

The decrease of solubility in the mucosa – expressed as the water:air partition coefficient $\lambda_{\mathrm{muc:air}}$ – with increasing temperature can be described in the ambient temperature range by a van't Hoff-type equation [13]

$$\log_{10} \lambda_{\mathrm{muc:air}}(T) = -A + \frac{B}{T + 273.15}, \tag{B.1}$$

where A and B (in Kelvin) are proportional to the entropy and enthalpy of volatilization, respectively.

$\lambda_{\mathrm{b:air}}$ will always refer to 37°C. Similarly, the partition coefficient between mucosa and blood $\lambda_{\mathrm{muc:b}}$ is treated as a constant defined by

$$\lambda_{\mathrm{muc:b}} := \lambda_{\mathrm{muc:air}}(37^{\circ}\mathrm{C})/\lambda_{\mathrm{b:air}}. \tag{B.2}$$

Note, that if the airway temperature is below 37°C we always have that

$$\lambda_{\text{muc:air}}/\lambda_{\text{muc:b}} \geq \lambda_{\text{b:air}}. \tag{B.3}$$

as $\lambda_{\text{muc:air}}$ is monotonically decreasing with increasing temperature. In a typical situation the absolute sample humidity at the mouth is 4.7% (corresponding to a temperature of $T \approx 32$°C and ambient pressure at sea level, cf. [9, 4]). Thus the local solubility of a VOC in the mucus layer increases considerably from the lower respiratory tract up to the mouth, thereby predicting a drastic reduction of air stream VOC concentrations along the airways.

Remark: A comprehensive compilation of water:air partition coefficients including their temperature dependence is given in [11]. Moreover, this reference also discusses the various forms of units used for Henry constants in different fields and the corresponding conversion factors.

Appendix C. Estimation of the blood-air partition coefficient

The blood-air partition coefficient can be estimated using the method of Poulin & Krishnan [10]

$$\lambda_{\text{b:air}} = \lambda_{o:w}\lambda_{w:a}(a + 0.3\,b) + \lambda_{w:a}(c + 0.7\,b) \tag{C.1}$$

where, $a = 0.0033$ is the fraction of neutral lipids in blood, $b = 0.0024$ is the fraction of phospholipids in blood, $c = 0.82$ is the fraction of water in blood, $\lambda_{o:w}$ is the octanol:water partition coefficient and $\lambda_{w:a}$ is the water:air partition coefficient. Equation (C.1) shows the close correlation between $\lambda_{\text{b:air}}$ and $\lambda_{w:a} =: \lambda_{\text{muc:air}}$.

Appendix D. Converting breath VOC concentrations to different conditions

When we measure a room concentration of a breath VOC, we measure the temperature t [C], the air pressure p [kPa], the relative humidity h_r [%], and the VOC concentration C_{room} in, e.g., parts per billion [ppb]= [nmol/mol]†.

Since we use conservation laws for modeling we have to convert relative concentrations into [mol/l] (counting number of particles) or [g/l] (mass balance).

To convert relative concentrations into [mol/l] we must divide this concentration by the volume of one mole V_m. The volume of one mole can be calculated using the ideal gas law which is sufficiently accurate for trace gases

$$p\,V = n\,R\,T.$$

Here n denotes the number of moles, $R = 8.3144598$‡ the gas constant, and $T = (273.15 + t)$ the absolute temperature. Hence as can be seen from

$$V_m = \frac{R\,T}{p}$$

the volume of one mole depends on pressure and temperature.

To convert relative concentrations further into [g/l] we must in addition multiply with the molar mass m_m of the VOC.

In addition we have to take into account the humidity of the room air. Humidity is the amount of water in gas form in air. It can be measured as relative humidity

† The advantage of [ppb] is that is independent of p and V.
‡ see `http://physics.nist.gov/cgi-bin/cuu/Value?r`

h_r (unit [%]) defined as ratio of the partial pressure of water vapor $p_{H_2O}(t)$ (absolute humidity) to the equilibrium vapor pressure of water $p^*_{H_2O}(t)$ at a given temperature

$$h_r = 100\ \frac{p_{H_2O}(t)}{p^*_{H_2O}(t)}.$$

The vapor equilibrium pressure of water is the pressure at which water vapor is in thermodynamic equilibrium with its condensed state. It depends solely on the temperature t and can be computed accurately enough by the Buck equation§

$$p^*_{H_2O}(t) = 0.61121 \exp\left(\left(18.678 - \frac{t}{234.5}\right)\left(\frac{t}{257.14+t}\right)\right).$$

Here t is measured in [C] and p in [kPa].

Thus the fractional pressure $f_{p,w}$ of the absolute humidity is given by

$$f_{p,w}(t, h_r) = \frac{p_{H_2O}(t)}{p} = \frac{1}{100}\ h_r \frac{p^*_{H_2O}(t)}{p}.$$

This lets us convert the measured concentration $C_{room}(t)$ of a VOC to dry conditions by

$$C_{room,dry}(t) = C_{room}(t)\ \frac{1}{1 - f_{p,w}(t, h_r)}.$$

When we breathe air into the lungs it is warmed up to body temperature $t_{body} = 37$ [C] and moisturized to 100% humidity. However, the pressure is immediately balanced. Using the ideal gas equation for constant pressure we arrive at

$$C_{lung,dry}(t_{body}) = C_{room,dry}(t)\ \frac{T}{T_{body}}.$$

In addition when we take 100% humidity into account we end up with

$$\begin{aligned} C_{lung}(t_{body}) &= C_{lung,dry}(t_{body})(1 - f_{p,w}(t_{body}, 100)) \\ &= C_{room}(t)\ \frac{(273.15+t)}{(273.15+t_{body})} \frac{(p - p^*_{H_2O}(t_{body}))}{(p - p^*_{H_2O}(t)\ h_r/100)}. \end{aligned}$$

Examples: For $t = 22$ [C] the influence of the temperature on the concentration is about 5%.

$$\frac{T_{22}}{T_{body}} = \frac{295.15}{310.15} = 0.95.$$

For a pressure of $p = 100$ [kPa] and a relative humidity of 50 % the influence of moistening on the concentration is also about 5%.

$$\frac{(p - p^*_{H_2O}(37))}{(p - 0.5\ p^*_{H_2O}(22))} = \frac{(100 - 6.27988)}{(100 - 1.3221)} = 0.95.$$

Together this gives a correction factor of about 0.9.

What we denote by C_{I} is hence $C_{lung}(t_{body})$, which is $C_{room}(t)$ converted to body conditions.

§ `https://en.wikipedia.org/wiki/Arden_Buck_equation`

Remark: For $t = 34$ [C] we get $\frac{T_{34}}{T_{body}} = \frac{307.15}{310.15} = 0.99$ or for $t = 32$ [C] we get $\frac{T_{32}}{T_{body}} = \frac{305.15}{310.15} = 0.98$.

Hence a temperature difference between body or lung compartment and the bronchial compartment can safely be ignored since there is no measurable effect on concentrations.

Appendix E. The general case where $D \neq 0$.

Here we present the general form of the coefficients $a_j, b_j, j = 1, 2, 3$ where the diffusion constant D is not zero, i.e.,

$$c_j(C_\mathrm{I}) = a_j(D)\, C_\mathrm{I} + b_j(D), \tag{E.1}$$

and a_j, $b_j, j = 1, 2, 3$ are dependent on $D, \dot{V}_\mathrm{A}$, etc.

In addition we did not introduce dimensionless quantities (e.g., $r := \frac{\dot{V}_\mathrm{A}}{\dot{Q}_\mathrm{c}}$, etc.) to get a more compact form for these coefficients since we did not want to introduce a batch of new symbols. However, we rearranged the coefficients in such a way that the limit $D \to 0$ ($\lambda_{\mathrm{b:air}} > 100$ large enough) or $D \to \infty$ (upper airways have no influence) can be read off directly.

$$\begin{aligned} C_\mathrm{bro}(C_\mathrm{I}) &= a_1(D)\, C_\mathrm{I} + b_1(D), \\ C_\mathrm{A}(C_\mathrm{I}) &= a_2(D)\, C_\mathrm{I} + b_2(D), \\ C_{\bar{\mathrm{v}}}(C_\mathrm{I}) &= a_3(D)\, C_\mathrm{I} + b_3(D) \end{aligned} \tag{E.2}$$

with

$$a_1 = \frac{1 + D\left(\frac{1+(1-q)\frac{\dot{Q}_\mathrm{c}}{k_\mathrm{met}}}{(1-q)\lambda_{\mathrm{b:air}}\dot{Q}_\mathrm{c}(1+(1-q)q\frac{\dot{Q}_\mathrm{c}}{k_\mathrm{met}})}\right)}{1 + \frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\frac{\dot{Q}_\mathrm{c}}{\dot{V}_\mathrm{A}}\frac{q(1-q)}{1+q(1-q)\frac{\dot{Q}_\mathrm{c}}{k_\mathrm{met}}} + D\left(\frac{1+(1-q)\frac{\dot{Q}_\mathrm{c}}{k_\mathrm{met}}+(1-q)^2\lambda_{\mathrm{b:air}}\frac{\dot{Q}_\mathrm{c}}{\dot{V}_\mathrm{A}}+q(1-q)\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\frac{\dot{Q}_\mathrm{c}}{\dot{V}_\mathrm{A}}}{(1-q)\lambda_{\mathrm{b:air}}\dot{Q}_\mathrm{c}(1+(1-q)q\frac{\dot{Q}_\mathrm{c}}{k_\mathrm{met}})}\right)},$$

$$b_1 = \frac{k_\mathrm{pr}\left(1 + \frac{D}{(1-q)q\lambda_{\mathrm{b:air}}\dot{Q}_\mathrm{c}}\right)}{\dot{V}_\mathrm{A} + k_\mathrm{met}(\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}} + \frac{\dot{V}_\mathrm{A}}{\dot{Q}_\mathrm{c}}\frac{1}{q(1-q)}) + D\left(\frac{\dot{V}_\mathrm{A}}{\dot{Q}_\mathrm{c}}\frac{1}{q(1-q)\lambda_{\mathrm{b:air}}} + \frac{k_\mathrm{met}}{\dot{Q}_\mathrm{c}}\left(\frac{1}{q} + \frac{\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}}{(1-q)\lambda_{\mathrm{b:air}}} + \frac{\dot{V}_\mathrm{A}}{(1-q)^2q\lambda_{\mathrm{b:air}}\dot{Q}_\mathrm{c}}\right)\right)},$$

$$a_2 = \frac{1 + D\left(\frac{k_\mathrm{met}+(1-q)\dot{Q}_\mathrm{c}}{(1-q)^2q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\dot{Q}_\mathrm{c}^2}\right)}{\lambda_{\mathrm{b:air}}\left(\frac{\lambda_{\mathrm{muc:b}}}{\lambda_{\mathrm{muc:air}}} + k_\mathrm{met}\left(\frac{1}{\dot{V}_\mathrm{A}} + \frac{1}{(1-q)q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\dot{Q}_\mathrm{c}}\right)\right) + D\left(\frac{k_\mathrm{met}\lambda_{\mathrm{b:air}}+\frac{\dot{V}_\mathrm{A}}{(1-q)}+k_\mathrm{met}\left(\frac{q}{(1-q)}\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}+\frac{\dot{V}_\mathrm{A}}{(1-q)^2\dot{Q}_\mathrm{c}}\right)}{q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\dot{Q}_\mathrm{c}\dot{V}_\mathrm{A}}\right)},$$

$$b_2 = \frac{k_\mathrm{pr}\left(1 + D\frac{1}{(1-q)q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\dot{Q}_\mathrm{c}+\dot{V}_\mathrm{A}}\right)}{\lambda_{\mathrm{b:air}}\left(k_\mathrm{met} + \frac{\dot{V}_\mathrm{A}}{\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}+\frac{\dot{V}_\mathrm{A}}{(1-q)q\dot{Q}_\mathrm{c}}}\right) + D\left(\frac{\dot{V}_\mathrm{A}+k_\mathrm{met}\left((1-q)\lambda_{\mathrm{b:air}}+q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}+\frac{\dot{V}_\mathrm{A}}{(1-q)\dot{V}_\mathrm{A}}\right)}{(1-q)q\frac{\lambda_{\mathrm{muc:air}}}{\lambda_{\mathrm{muc:b}}}\dot{Q}_\mathrm{c}+\dot{V}_\mathrm{A}}\right)}$$

$$a_3 = \frac{1 + D\frac{1}{\dot{Q}_\mathrm{c}}\left(\frac{1}{(1-q)\lambda_\mathrm{b:air}} + \frac{1}{q}\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}}\right)}{\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}} + k_\mathrm{met}\left(\frac{1}{\dot{V}_\mathrm{A}} + \frac{1}{\dot{Q}_\mathrm{c}}\frac{1}{q(1-q)}\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}}\right) + D\left(\frac{\dot{V}_\mathrm{A} + k_\mathrm{met}\left((1-q)\lambda_\mathrm{b:air} + q\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} + \frac{\dot{V}_\mathrm{A}}{(1-q)\dot{Q}_\mathrm{c}}\right)}{(1-q)q\lambda_\mathrm{b:air}\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}}\dot{Q}_\mathrm{c}\dot{V}_\mathrm{A}}\right)},$$

$$b_3 = \frac{k_\mathrm{pr}\left(1 + D\left(\frac{(1-q) + \frac{q}{\lambda_\mathrm{b:air}}\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} + \frac{\dot{V}_\mathrm{A}}{(1-q)\lambda_\mathrm{b:air}\dot{Q}_\mathrm{c}}}{(1-q)q\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}}\dot{Q}_\mathrm{c} + \dot{V}_\mathrm{A}}\right)\right)}{k_\mathrm{met} + \frac{\dot{V}_\mathrm{A}}{\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} + \frac{\dot{V}_\mathrm{A}}{\dot{Q}_\mathrm{c}}\frac{1}{q(1-q)}}} + D\left(\frac{\frac{\dot{V}_\mathrm{A}}{\lambda_\mathrm{b:air}} + k_\mathrm{met}\left((1-q) + \frac{q}{\lambda_\mathrm{b:air}}\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} + \frac{\dot{V}_\mathrm{A}}{(1-q)\lambda_\mathrm{b:air}\dot{Q}_\mathrm{c}}\right)}{(1-q)q\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}}\dot{Q}_\mathrm{c} + \dot{V}_\mathrm{A}}\right)}. \tag{E.3}$$

Taking the limit $D \to 0$ we immediately recover the results in Equation (13).

Taking the limit $D \to \infty$ and $q \to 0$ we recover the results of the 2-compartment model of [16].

For the metabolic rate and the production rate we get in the general case where D is not zero

$$k_\mathrm{met} = \frac{q(1-q)(1-a_1)\,\dot{Q}_\mathrm{c} + D\frac{(1-a_1)}{\lambda_\mathrm{b:air}}}{\left(1 + \frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}}\,q(1-q)\,\frac{\dot{Q}_\mathrm{c}}{\dot{V}_\mathrm{A}}\right)\,a_1 - 1 + D\left(\frac{a_1(1-q)}{\dot{V}_\mathrm{A}} + \frac{qa-1}{\lambda_\mathrm{b:air}\dot{V}_\mathrm{A}}\frac{\lambda_\mathrm{muc:air}}{\lambda_\mathrm{muc:b}} - \frac{1-a_1}{(1-q)\lambda_\mathrm{b:air}\dot{V}_\mathrm{A}}\right)}, \tag{E.4}$$

$$k_\mathrm{pr} = \frac{b_1\left(\dot{Q}_\mathrm{c} + D\left(\frac{1}{\lambda_\mathrm{b:air}(1-q)} + \frac{1}{q}\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}}\right)\right)}{a_1\frac{\dot{Q}_\mathrm{c}}{\dot{V}_\mathrm{A}} - \frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}}\frac{(1-a_1)}{q(1-q)} + D\left(\frac{a_1}{a\dot{V}_\mathrm{A}}\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}} + \frac{a_1}{(1-q)\lambda_\mathrm{b:air}\dot{V}_\mathrm{A}} - \frac{1-a_1}{(1-q)^2q\lambda_\mathrm{b:air}\dot{V}_\mathrm{A}}\frac{\lambda_\mathrm{muc:b}}{\lambda_\mathrm{muc:air}}\right)}. \tag{E.5}$$

Again taking the limit $D \to 0$ we immediately recover the results in Equation (21) and Equation (22).

And taking the limit $D \to \infty$ and $q \to 0$ we recover the results of the 2-compartment model of [16].

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