Supplement to manuscript AnnHyg-10-232.R2 entitled: “A generic, cross-chemical predictive PBTK-model with multiple entry routes running as application in MS-Excel; Design of the model and comparison of predictions with experimental results”
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Supplement 1. Mathematical description of the generic PBTK-model IndusChemFate.

Generic mass flow described for all organs

The equations below describe the generic mass change of the parent compound (i=0) in time and of its succeeding metabolites (i=1 to 4) in all organs considered. These mass changes apply to all organs considered and relate to the fraction of the cardiac output to the specific organ $Q_{org}$ and to the metabolic removal and formation of the parent and its metabolites.

\[
\frac{dA_{org}[0]}{dt} = Q_{org} \left( C_{art}[0] - \frac{C_{org}[0]}{R_{org/ven}[0]} \right) - \frac{V_{max_{rem}[0]}*C_{org}[0]}{K_{m_{rem}[0]} + C_{org}[0]} \quad \text{(parent substance } i = 0) \quad \text{eq. 1}
\]

\[
\frac{dA_{org}[i]}{dt} = Q_{org} \left( C_{art}[i] - \frac{C_{org}[i]}{R_{org/ven}[i]} \right) - \frac{V_{max_{rem}[i]}*C_{org}[i]}{K_{m_{rem}[i]} + C_{org}[i]} + \frac{V_{max_{form}[i-1]}*C_{org}[i-1]}{K_{m_{form}[i-1]} + C_{org}[i-1]} \quad \text{(metabolites } i = 1 \text{ to } 4) \quad \text{eq. 2}
\]

$A_{org}[i]$ = Mass of substance $i$ in organ (µMol)

$Q_{org}$ = Arterial blood flow to organ (fraction of cardiac output) in litres/hour

$C_{art}[i]$ = Conc subst[i] µMol/litre in arterial blood.

$C_{org}[i]$ = Conc subst[i] µMol/kg in organ tissue (density tissue is 1 kg/per litre)

$R_{org/ven}[i]$ = Organ tissue/blood partiton coefficient of substance $[i]$, estimated by QSAR (DeJongh et al. 1997)

$V_{max_{rem}[i]}$ = Maximum biotransformation in µMol/kg tissue/hour in subst[i+1] from subst[i]
\[ \text{Km}_{\text{rem}[i]} = \text{Conc subst}[i] \, \mu\text{Mol/kg tissue}, \text{at which the biotransformation rate into subst}[i+1] \text{ from subst}[i] \text{ is half maximum} \]

\[ \text{Vmax}_{\text{form}[i-1]} = \text{Maximum biotransformation in } \mu\text{Mol/kg tissue/hour in subst}[i] \text{ from subst}[i-1] \]

\[ \text{Km}_{\text{form}[i-1]} = \text{Conc subst}[i] \, \mu\text{Mol/kg tissue}, \text{at which the biotransformation rate into subst}[i] \text{ from subst}[i-1] \text{ is half maximum} \]

However, there are some organs that deserve special attention and additional source and removal contributing to mass changes have to be formulated.

**Mass change in the liver, added to the generic mass change description**

\[
\frac{dA_m_{\text{liver}[i]}}{dt} = \frac{dA_m_{\text{liver}[i]}}{dt} + Q_{\text{intestines}} \frac{C_{\text{intestines}[i]}}{R_{\text{intestines/ven}[i]}} - Q_{\text{intestines}} \frac{C_{\text{liver}[i]}}{R_{\text{liver/ven}[i]}} - \text{Removal}_{\text{Bile}} \times A_M_{\text{liver}[i]} \quad \text{eq. 3}
\]

The removal from the liver into the bile (Removal\text{ Bile}) is expressed as the fraction of the mass[i] in the liver per hour, discharged via the bile in the intestinal lumen. In the input information for running the program, this removal via the bile has to be indicated relative to the removal of the mass in the liver via the venous blood flow out of the liver. The software assigns the proper value to the removal from the liver into bile as the fraction of the mass[i] in the liver per hour.

**Mass change in the lumen of the intestines**

\[
\frac{dA_m_{\text{intest-lumen}[i]}}{dt} = \text{Removal}_{\text{Bile}} \times A_M_{\text{liver}[i]} - 0.3 \times A_m_{\text{intest-lumen}[i]} \quad \text{eq. 4}
\]

It is assumed that the mass[i] in the intestinal lumen, released via the bile, is re-absorbed in the intestinal tissue with a rate of 0.3 per hour.
Mass change in the intestinal tissue, added to the generic mass change description

\[
\frac{dAm_{intestines[i]}}{dt} = \frac{dAm_{intestines[i]}}{dt} + \text{AbsRate} \cdot \text{Bolus[i]} + 0.3 \cdot Am_{lumen[i]} \quad \text{eq. 5}
\]

It is assumed, that the mass in the intestinal tissue is increased by an oral dose (\(\text{Bolus[i]} \ \mu\text{Moles}\)), which is absorbed form the intestinal lumen in the intestinal tissue with the rate \(\text{AbsRate} \ (1/\text{hour})\) and by the re-absorption of the mass\([i]\) from the intestinal lumen, released via the bile, with a rate of 0.3 per hour.

Mass change in dermal tissue, added to the generic mass change description

Dermal absorption is generally assumed to occur for the parent compound \((i=0)\) and is dependent on:

The dermal absorption flux consists of two parts:

- Intermittent dermal exposure to liquid.
- Dermal exposure from the ambient air.
\[
\frac{dAm_{\text{skin}}[i]}{dt} = \frac{dAm_{\text{skin}}[i]}{dt} + \text{[Intermittent Liquid Exposure]} + \text{[Rate}_{\text{Skin-Air}}[i]
\]

\textit{Intermittent Liquid Exposure} (see Appendix 2)

\text{Rate}_{\text{Skin-Air}}[i] = Kp_{\text{air-x}}[i] * \text{Surface}_{\text{Body}} * C_{\text{air}}[i] / 1000

\[K_{\text{air-rex}}[i] = 36 \sqrt[12]{\frac{76}{\text{Mw}[i]}} \quad K_{\text{air-light-activity}}[i] = 120 \sqrt[12]{\frac{76}{\text{Mw}[i]}} \quad K_{\text{wa}}[i] = \frac{R * T * W_{\text{solub}}[i]}{\text{Mw}[i]*Vp[i]}
\]

\[Kp_{\text{air-x}}[i] = \frac{1}{Kp_{\text{aq}}[i]*K_{\text{wa}}[i] + \frac{1}{K_{\text{air-x}}[i]}}
\]

\begin{align*}
Am_{\text{skin}}[i] & = \text{Mass of substance } [i] \text{ in skin (µMol)} \\
\text{Rate}_{\text{Skin-Air}}[i] & = \text{Dermal absorption rate of substance } [i] \text{ from air into the skin [dermis] (mg/cm}^2\text{/hour)} \\
Kp_{\text{air-x}}[i] & = \text{Dermal permeation coefficient of substance } [i] \text{ through the skin from air as vehicle} \\
K_{\text{air-x}}[i] & = \text{Permeation coefficient of substance } [i] \text{ through air layer around the skin, dependent on } K_{\text{air-x}}[i] \text{, related to worker activity (cm/hour)} \\
K_{\text{wa}}[i] & = \text{Water/air partition coefficient of substance } [i] \text{ to adapt } Kp_{\text{aq}}[i] \text{ to absorption from air} \\
Kp_{\text{aq}}[i] & = \text{Aqueous permeation coefficient of substance } [i] \text{ in cm/hour, estimated by QSAR (ten Berge 2009)} \\
C_{\text{air}}[i] & = \text{Concentration of substance } [i] \text{ in air (µMol/litre)} \\
\text{Surface}_{\text{body}} & = \text{Surface area of the body of an adult (18000 cm}^2\text{)} \\
R & = \text{Gas constant (8.314 Joule/Mol/°K)} \\
T & = \text{Skin surface temperature (°K)} \\
W_{\text{solub}}[i] & = \text{Water solubility of substance } [i] \text{ (gram/litre)} \\
\text{Mw}[i] & = \text{Molecular weight of substance } [i]. \\
Vp[i] & = \text{Vapour pressure of substance } [i] \text{ at skin surface temperature (Pascal)}
\end{align*}
Mass change in kidney tissue, added to the generic mass change description

\[
\frac{d\text{Am}_{\text{kidney}}[i]}{dt} = \frac{d\text{Am}_{\text{kidney}}[i]}{dt} - 0.3 \times \text{Fr}_{\text{watersoluble}}[i] \times \text{Remov}_{\text{kidney}}[i] \times Q_{\text{kidney}} \times C_{\text{art}}[i]
\]  
** eq. 10

\text{Fr}_{\text{watersoluble}}[i] = \text{Fraction of substance}[i] \text{ in arterial blood, that is dissolved in water}

\text{Remov}_{\text{kidney}}[i] = \text{Fraction removed from the glomerulus filtrate and excreted with urine (input parameter).}

\begin{align*}
0.01 & \text{ in case of tubular re-absorption into the blood (assumption } \log(Kow) \text{ at } pH 7.4 > -1.5). \\
0.99 & \text{ in the absence of tubular re-absorption into the blood (assumption } \log(Kow) \text{ at } pH 7.4 \leq -1.5). 
\end{align*}

\text{Q}_{\text{kidney}} = \text{Fraction of cardiac ouput to the kidney (litres/hour)}

\text{C}_{\text{art}}[i] = \text{Conc subst}[i] \mu\text{Mol/litre in arterial blood}

Absorption by inhalation

\[
\text{C}_{\text{Lung,art}}[i] = \frac{Q_{\text{flow}} \times C_{\text{LungVen}}[i] + \text{AlvVent} \times C_{\text{inh}}[i]}{Q_{\text{flow}} + \text{AlvVent} / R_{\text{blood/air}}[i]} 
\]  
** eq. 11

\[
\text{C}_{\text{Alv,air}}[i] = \frac{C_{\text{LungArt}}[i]}{R_{\text{blood/air}}[i]} 
\]  
** eq. 12

\text{C}_{\text{LungArt}}[i] = \text{Concentration of substance}[i] \text{ in arterial blood flowing from lung (} \mu\text{Mol/litre)}

\text{C}_{\text{LungVen}}[i] = \text{Concentration of substance}[i] \text{ in venous blood entering lung (} \mu\text{Mol/litre)}

\text{Q}_{\text{flow}} = \text{Cardiac output (litres/hour)}

\text{AlvVent} = \text{Alveolar ventilation (litres/hour)}


\[ C_{\text{inh}[i]} = \text{Concentration of substance } [i] \text{ in inhaled air (µMol/litre)} \]
\[ R_{\text{blood/air}[i]} = \text{Blood/air partition ratio of substance } [i], \text{ estimated by QSAR (Meulenberg & Vijverberg 2000)} \]
\[ C_{\text{alv.air}[i]} = \text{Conc substance } [i] \text{ in alveolar air} \]

Concentration in arterial blood entering the organs

\[
\frac{dA_{\text{art.vol}[i]}}{dt} = Q_{\text{flow}} \times (C_{\text{lung.art}[i]} - C_{\text{art}[i]}) \quad \text{eq. 13}
\]
\[
C_{\text{art}[i]} = \frac{A_{\text{art.vol}[i]}}{\text{ArtVol}} \quad \text{eq. 14}
\]

\[ A_{\text{art.vol}[i]} = \text{Mass of substance } [i] \text{ in arterial blood volume} \]
\[ C_{\text{lung.art}[i]} = \text{Conc substance[i] in arterial blood flowing from lung (µMol/litre)} \]
\[ C_{\text{art}[i]} = \text{Conc subst[i] in arterial blood flowing to organs (µMol/litre)} \]
\[ Q_{\text{flow}} = \text{Cardiac output ( litres/hour)} \]
\[ \text{ArtVol} = \text{Volume of arterial blood.} \]
Concentration in venous blood entering the lung

\[
Am_{OrgVen}[i] = \sum_{\text{all organs}} Q_{org} \cdot C_{org}[i] / R_{org/Ven}[i] + (Q_{\text{intestines}} + Q_{\text{liver}}) \cdot C_{\text{liver}}[i] / R_{\text{liver/Ven}}[i] \quad \text{eq. 15}
\]

\[
C_{\text{ven}}[i] = Am_{OrgVen}[i] / Q_{\text{flow}} \quad \text{eq. 16}
\]

\[
\frac{dAm_{\text{LungVen}}[i]}{dt} = Q_{\text{flow}} \cdot (C_{\text{ven}}[i] - C_{\text{LungVen}}[i]) \quad \text{eq. 17}
\]

\[
C_{\text{LungVen}}[i] = Am_{\text{LungVen}}[i] / \text{VenVol} \quad \text{eq. 18}
\]

\[\begin{align*}
Am_{\text{OrgVen}}[i] &= \text{Mass of substance [i] in blood flowing out of all organs} \\
C_{\text{Ven}}[i] &= \text{Concentration of substance [i] in mixed venous blood from all organs} \\
Am_{\text{LungVen}}[i] &= \text{Mass of substance [i] in venous blood volume entering the lung} \\
C_{\text{LungVen}}[i] &= \text{Concentration of substance [i] in venous blood entering the lung} \\
\text{VenVol} &= \text{Volume of venous blood in the body}
\end{align*}\]

References