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”
Authors: Frans Jongeneelen & Wil ten Berge

Supplement 2. Mathematical description of absorption by dermal exposure to neat liquid

Description of absorption into the stratum corneum and evaporation from the skin surface of liquid by intermittent contact with the skin
The dermal exposure is assumed to occur by deposition of aerosol of the liquid up on the skin. The liquid will be removed from the dermal surface by evaporation and absorption. The program takes into account the following conditions:
1. skin absorption and evaporation are fast and the skin remains dry, that means there is no liquid left on the skin.
2. skin absorption and evaporation are slow and a thin liquid film is left on the skin surface.

\[ \frac{d\text{LiqFilm}_{\text{neat}}}{dt} = \text{Deposition rate} - \text{Absorption rate (into SC)} - \text{Evaporation rate (LF)} \]  \hspace{1cm} \text{eq. 1}

\[ \text{Absorption rate (into SC)} = \left[ \frac{\text{Dens} \cdot \text{Diff}_{\text{sc}} \cdot M_{\text{max}} - M_{\text{sc}}}{h_{\text{sc}} M_{\text{max}}} \right] \]  \hspace{1cm} \text{eq. 2}

\[ \text{Diff}_{\text{sc}} = \frac{Kp_{\text{aq}} \cdot h_{\text{sc}}}{P_{\text{sc/w}}} \] \hspace{1cm} \text{Kp}_{\text{aq}} = \frac{P_{\text{sc/w}} \cdot \text{Diff}_{\text{sc}}}{h_{\text{sc}}} \]  \hspace{1cm} \text{eq. 3}

\[ 10^{\log(Kp_{\text{lipids}})} = -2.59 + 0.732 \cdot 10^{\log(K_{\text{ow}})} - 0.0063 \cdot M_{\text{W}} \]  \hspace{1cm} \text{eq. 4}

\[ 10^{\log(Kp_{\text{corneocyte}})} = -1.37 - 1.36 \cdot 10^{\log(M_{\text{W}})} \]  \hspace{1cm} \text{eq. 5}

\[ Kp_{\text{aq}} = Kp_{\text{lipids}} + Kp_{\text{corneocyte}} \]  \hspace{1cm} \text{eq. 6}

\[ P_{\text{sc/w}} = 0.72 \cdot K_{\text{ow}}^{0.43} \]  \hspace{1cm} \text{eq. 7}

Deposition rate, absorption rate and evaporation rate are all expressed in mg/cm²/hour
SC = stratum corneum
Dens = density of liquid (mg/cm³)
\( \text{Diff}_{sc} = \) diffusivity of the liquid in the stratum corneum (cm\(^2\)/hour) \\
\( K_{P,aq} = \) overall aqueous dermal permeation coefficient through lipid and corneocyte part of stratum corneum (cm/hour) \\
\( K_{P,\text{lipids}} = \) aqueous permeation coefficient of lipid phase of the stratum corneum (QSAR, ten Berge 2009) \\
\( K_{P,\text{corneocytes}} = \) aqueous permeation coefficient of corneocyte phase of the stratum corneum (QSAR, ten Berge 2009) \\
\( P_{sc/w} = \) stratum corneum/water partition coefficient (QSAR, ten Berge 2009) \\
\( K_{ow} = \) octanol/water partition coefficient at the dermal pH=5.5 (pH adjustment needed for amines and acids) \\
\( M_w = \) molecular weight \\
\( h_{sc} = \) thickness stratum corneum (fixed to 0.002 cm) \\
\( M_{max} = 0.2 \times h_{sc} \times \text{Dens} \) (mg/cm\(^2\), maximum possible mass is 20% of volume of stratum corneum filled with liquid) \\
\( M_{sc} = \) mass actually present in stratum corneum (mg/cm\(^2\))

\[ \text{Evaporation rate}(LF) = \frac{\beta \times M_w \times V_p}{R \times T \times 10} \quad \text{eq. 8} \]

\[ \beta = \frac{0.0111 \times V^{0.96} \times D_g^{0.19}}{V^{0.15} \times X^{0.04}} \quad \text{eq. 9} \]

\[ D_g = 0.06 \times \frac{76}{\sqrt{M_w}} \quad \text{eq. 10} \]

Evaporation rate(LF), the evaporation from the liquid film (LF) is expressed in mg/cm\(^2\)/hour.

\( M_w = \) Molecular weight \\
\( V_p = \) Vapour pressure of the liquid at skin temperature in Pascal \\
\( R = \) Gas constant in J/Mol/°K \\
\( T = \) Skin temperature in °K \\
\( \beta = \) Coefficient of mass transfer in the vapour phase in meter/hour \\
\( V = \) Velocity of air (1080 meter/hour) \\
\( D_g = \) Diffusivity of the liquid in the gas phase in m\(^2\)/hour \\
\( \nu = \) Kinematic viscosity of air (0.054 m\(^2\)/hour) \\
\( X = \) Length of the area of evaporation (0.1 meter)
The evaporation rate (LF) as described above is part of the REACH Guidance for chemical safety assessment (REACH Guidance 2008).

**Description of absorption in blood and evaporation from stratum corneum without liquid film**

The basic assumption is, that the dermal absorption rate will never exceed the absorption from a saturated aqueous solution of the liquid in case of an undamaged skin. Direct and prolonged contact with lipophilic liquids may harm the lipid phase of the stratum corneum and increase the permeability of the skin.

\[
\text{Evaporation (dry SC)} = K_{p_{evap}} \times Fr_{Aq} \times W_{solub} \quad \text{eq. 11}
\]

\[
\text{Absorption (blood)} = K_{p_{aq}} \times Fr_{Aq} \times W_{solub} \quad \text{eq. 12}
\]

\[
\frac{dM_{sc}}{dt} = (K_{p_{evap}} + K_{p_{aq}}) \times Fr_{Aq} \times W_{solub} \quad \text{eq. 13}
\]

\[
K_{p_{evap}} = \frac{1}{\frac{1}{K_{p_{aq}}} + \frac{1}{K_{air}}} \quad \text{eq. 14}
\]

\[
K_{air} = 120 \times \sqrt{\frac{76}{M_{w}}} \\
K_{wa} = \frac{R \times T \times W_{solub}}{M_{w} \times V_{p}} \quad \text{eq. 15}
\]

\[
Fr_{Aq} = \frac{2 \times M_{sc}}{M_{max_{aq}}} \quad (\text{If } Fr_{Aq} > 1 \text{ then } Fr_{Aq} = 1) \quad \text{eq. 16}
\]

\[
M_{max_{aq}} = P_{sc/w} \times h_{sc} \times W_{solub} \quad \text{eq. 17}
\]

\[
P_{sc/w} = 0.72 \times K_{ow}^{0.43} \quad \text{eq. 18}
\]

Evaporation (dry SC) = mg/cm²/hour
Absorption (dermis) = mg/cm²/hour
\(M_{sc}\) = mass actually present in stratum corneum (mg/cm²)
\( K_{p_{aq}} = \) overall aqueous dermal permeation coefficient through lipid and corneocyte part of stratum corneum (cm/hour) estimated from QSAR (ten Berge 2009)

\( K_{p_{evap}} = \) evaporation coefficient from the stratum corneum without a film of deposited liquid on the stratum corneum (cm/hour)

\( K_{air} = \) permeation coefficient through air layer around the skin of uncovered skin (cm/hour)

\( K_{wa} = \) partition coefficient water/air needed to adapt \( K_{air} \) to permeation from stratum corneum matrix.

\( M_{max_{aq}} = \) maximum mass (mg/cm\(^2\)), that can be absorbed into the stratum corneum from a saturated aqueous solution. This is the mass in the stratum corneum, at which the absorption rate in the blood is maximum.

\( P_{sc/w} = \) stratum corneum/water partition coefficient (QSAR, ten Berge 2009)

\( W_{solub} = \) water solubility (mg/cm\(^3\))

In the modelling it is needed to take into account, that deposition of aerosol will not hit the same tiny surface of the skin all the time. The deposition is so small that a liquid film on the skin surface is not formed. This means that the sum of the rate of evaporation and the rate of absorption is much larger than the deposition rate. In this case the rates of evaporation and absorption become:

\[
\text{Absorption rate}(\text{into SC}) = \frac{\text{Absorption rate}(\text{into SC})}{\text{Absorption rate}(\text{into SC}) + \text{Evaporation rate}(\text{LF})} \times \text{Deposition rate} \quad \text{eq. 19}
\]

\[
\text{Evaporation rate}(1) = \frac{\text{Evaporation rate}(\text{LF})}{\text{Absorption rate}(\text{into SC}) + \text{Evaporation rate}(\text{LF})} \times \text{Deposition rate} \quad \text{eq. 20}
\]

\[
\text{Evaporation rate}(2) = K_{evap} \times Fr_{Aq} \times W_{solub} \quad \text{eq. 21}
\]

If \( \text{Evaporation rate}(1) > \text{Evaporation rate}(2) \) then \( \text{Evaporation rate} = \text{Evaporation rate}(1) \)  \text{eq. 22}

If \( \text{Evaporation rate}(2) > \text{Evaporation rate}(1) \) then \( \text{Evaporation rate} = \text{Evaporation rate}(2) \) \text{eq. 23}

References