# Implementation and validation of in vitro equilibrium distribution model for neutral molecules

(According to Fisher et al., 2019)

## Material and methods

### Universal model parameters

Table 1: Universal parameters.

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Parameter** | **Value** | **Units** |
| R | Universal gas constant | 8.314 | JK-1mol-1 |
| ΔUaw |  | 60000 | Jmol-1 |
| ΔUow |  | -20000 | Jmol-1 |
| fiw | Fraction intracellular water | 0.568 |  |
| fmito | Fraction mitochondria | 0.1 |  |
| flyso | Fraction lysosomes | 0.01 |  |
| fnl | Fraction neutral lipids | 0.0348 |  |
| fnp | Fraction neutral phospholipids | 0.0252 |  |
| fSerum | Fraction in serum | 0.1 |  |

### System specific parameters

Table 2: System specific parameters.

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | **Parameter** | **Value** | **Units** |
| mass TAG | Concentration of triacylglycerides (TAG) | 0.46 | g/L |
| mass albumin | Concentration of proteins | 24 | g/L |
| PSVTAG | Partial specific volume | 1.093 | mL/g |
| PSValbumin | Partial specific volume | 0.73 | mL/g |
| TSys | System temperature | 310.15 | K |
| TRef | Reference temperature | 298.15 | K |
| Vwell | Volume in culture well | 0.025 | L |
| Vcell | Volume of cells | 3e-6 | L |
| Vmedium | Volume in medium | 0.005 | L |
| Vair | Volume of headspace | Vwell – Vmedium – Vcell | L |
| SAplastic | Surface area of culture vessel | 0.000354 | m2 |

### Miscellaneous abbreviations

Table 3: Abbreviations describing partition coefficients and compartment related parameters.

|  |  |
| --- | --- |
| **Abbreviation** | **Parameter description** |
| **C/Mair** | Concentration/ Mass of a chemical in headspace |
| **C/Mcell** | Concentration/ Mass of a chemical in cells |
| **C/Mlyso** | Concentration/ Mass of a chemical in lysosomes |
| **C/Mmedium(free)** | (Free) Concentration/ Mass of a chemical in medium |
| **C/Mmito** | Concentration/ Mass of a chemical in mitochondria |
| **C/Mnom** | Nominal concentration/ mass of a chemical |
| **C/Mplastic** | Concentration/ Mass of a chemical in plastic/ culture vessel |
| **fprotein** | Fraction of proteins |
| **fui** | Fraction unionized in the headspace |
| **fuFBS(dilu)** | Fraction unbound in fetal bovine serum (in dilution) |
| **logPow,TSys** | Octanol-water partition coefficient corrected by system temperature |
| **Kcell** | Partition coefficient between cells and water phase |
| **Kiw** | Partition coefficient between intracellular water and water phase |
| **Klyso** | Partition coefficient between lysosomes and water phase |
| **Kmito** | Partition coefficient between mitochondria and water phase |
| **Kplastic** | Partition coefficient between plastic vessel and water phase |
| **Kprotein** | Partition coefficient between proteins and water phase |
| **Pnl** | Partition coefficient between neutral lipids and water phase |
| **Pnp** | Partition coefficient between neutral phospholipids and water phase |
| **Pvow** | Olive oil-water partition coefficient |

## Structure of the model implemented in R

### Initializations

, for oxygen containing compounds

, for others

### Binding to serum

,

, otherwise:

Defining,

### Partitioning to plastic

### Partitioning to headspace

### Partitioning to cell

Note,

### Mass Balance / Medium concentration

### Concentration in compartments

### Mass balance calculations

## Results

### Validation of the model with published data (Armitage et al., 2014)

As previously performed by Fisher et al. (2019), the outcome of the distribution model was compared against published predicted data extracted from Armitage et al.,2014. A data set of 1194 chemicals was considered as well as the system parameters of the in vitro system.

In figure 1, concentrations in culture medium predicted by the above-described model (Fisher et al., 2019) were correlated against concentrations in culture medium predicted by the published model by Armitage et al., 2014. In figure 2, predicted concentrations in cells were compared.



Figure 1: Predicted concentrations in medium derived from the in vitro distribution model correlated against predicted concentrations in medium derived from Armitage et al., 2014.

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Automatisch generierte Beschreibung

Figure 2: Predicted concentrations in cells derived from the in vitro distribution model correlated against predicted concentrations in medium derived from Armitage et al., 2014.

In order to validate the implemented model from Fisher et al., 2019 and evaluate the findings, figure 1 from Fisher et al., 2019 was reproduced (See Figure 3) where the predicted concentrations in cells were plotted against the octanol-water partition coefficient.



Figure 3: Simulated data of cellular concentrations from Armitage et al., 2014 (black/ white dots) and the implemented in vitro distribution model (green dots).