**PBPK model for acrylamide and glycinamide**

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**Abbreviations**

* AA – acrylamide
* GA - glycidamide
* c – concentration
* m – amount
* d - derivative (marks ODEs)
* k - reaction rate constant
  + e.g. k\_on\_B - reaction rate constant for binding to brain tissue
* p - partition coefficient
* V - compartment volume
* F - fraction of body weight/volume
* BW - body weight
* AB - arterial blood
* VB - venous blood
* Lu – lung
* B – blood
* T - tissue
* Ki – kidney
* Li - liver

**List of Parameters**

* Green values are checked
* Orange values need checking
* Yellow will be estimated later as in the other works

Units:

* AA and GA in mg
* GST in mmol

References:

1 Valentin, Jack. "Basic anatomical and physiological data for use in radiological protection: reference values: ICRP Publication 89." *Annals of the ICRP* 32.3-4 (2002): 1-277.

2 Walker, Katherine, et al. "Approaches to acrylamide physiologically based toxicokinetic modeling for exploring child–adult dosimetry differences." *Journal of Toxicology and Environmental Health, Part A* 70.24 (2007): 2033-2055.

NOTE: binding rate are very different between Sweeney et al. 2010 and Walker et al. 2007 -> in Sweeney K\_onAA > k\_onGA and vise versa in Walker … I would have expected that the values vary but the ratio would be preserved

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | | **Value** | **Unit** | **Reference** |
| Body weight | BW | 70 | kg |  |
| Blood fraction of BW | F\_B | 0.079 |  | Brown et al. 1997 |
| Fraction of arterial blood | F\_B\_AB | 0.35 |  |  |
| Fraction of venous blood | F\_B\_VB | 0.65 |  |  |
| Liver fraction of BW | F\_Li | 0.026 |  | Jack 2002 |
| Kidney fraction of BW | F\_Ki | 0.0044 |  | Jack 2002 |
| Tissues fraction of BW | F\_T | 1-sum(F\_otherTiss) |  |  |
| Arterial blood volume | V\_AB | BW \* F\_B \* F\_B\_AB | L |  |
| Venous blood volume | V\_VB | BW \* F\_B \* F\_B\_VB | L |  |
| Tissues volume | V\_T | BW \* F\_T | L |  |
| Kidney volume | V\_Ki | BW \* F\_Ki | L |  |
| Liver volume | V\_Li | BW \* F\_Li | L |  |
| **Cardiac output** | QCC | 16 | L/kg/h |  |
| **Cardiac output** | Q\_C | QCC\*BW0.75 | L/h | See Trine’s comments |
| Alveolar ventilation | Q\_P | 2.5/100 | L/h | Only use with lung |
| Blood flow to the liver as fraction of QCC | FQ\_Li | 0.255 |  | Jack 2002 |
| Blood flow to the kidney as fraction of QCC | FQ\_Ki | 0.19 |  | Jack 2002 |
| Blood flow to tissues | FQ\_T | 1-sum(FQ\_otherTissues) |  |  |
| Liver\_Blood partition coefficient | pAA\_LiB | 0.33 |  | Doerge et al. 2005b (average tissue/serum concentration) with data from Table 4 |
| pGA\_LiB | 0.63 | Doerge et al. 2005b  GA below detection level -> hence p\_LiB\_GA can not be calculated based on this work |
| Kidney\_Blood partition coefficient | pAA\_KiB | 0.8 |  | Calculated based on reed out from Miller et al. 1981 |
| pGA\_KiB | 1.0 |  |
| Tissue\_Blood\_partition coefficient. | pAA\_TB | 0.2 |  | calculate this from Doerge (2005) paper on acrylamide in rats |
| pGA\_TB | 1.35 |  | Also calculate this from Doerge (2005) paper on acrylamide in mice. |
| Rate constant for binding of AA in blood | k\_onAA\_B | 0.0036 | h-1 | Walker et al. 2007 2  red blood cells/hemoglobin not considered directly because, Walker et al. claims that Haem in human lacks a cysteine that prevents a significant binding reaction -> this might be a wrong assumption |
| k\_onGA\_B | 0.0108 |
| Rate constant for binding of AA in slowly perfused tissues | k\_onAA\_T | 0.028 | h-1 | Walker et al. 2007 2 |
| k\_onGA\_T | 0.089 |
| Rate constant for binding of AA in kidney tissue | k\_onAA\_Ki | 0.13 | h-1 | Sweeney et al. 2010 |
| K\_onGA\_Ki | K\_onAA\_Ki/2 |
| Rate constant for binding of AA in liver tissue | k\_onAA\_Li | 0.071 | h-1 | Walker et al. 2007 |
| k\_onGA\_Li | 0.215 |
| Uptake rate constant from diet | k\_uptake | 0.27  0.964-1.147 |  | Sweeney et al. 2010  Absorption cate can be calculated based on t\_max and k\_e from Kopp and Dekant |
| Synthesis rate constant of GSH | k\_turnover | 0.14 | h-1 | Sweeney et al. 2010 |
| Binding rate constant AA to GSH | k\_onAA\_GSH | 0.55 | L mmol-1 h-1 | Kirman et al. 2003 |
| Binding rate constant GA to GSH | k\_onGA\_GSH | 0.8 | L mmol-1 h-1 | Kirman et al. 2003  For the binding we could use a hill term. Maria found some publications that might give parameter values |
| Maximum velocity for enzymatic reaction with P450 | V\_max\_P450 | 0.235 | mg h-1 | Kinetic measurement of P456: <https://doi.org/10.3109/15376516.2012.759307>  Check calculation |
| Km for Michaelis Menten Kinetics of P450 | KM\_p450 | 241.672 | mg L-1 | <https://doi.org/10.3109/15376516.2012.759307> |
| Maximum velocity for enzymatic reaction with EH | V\_max\_EH | 20.0 | mg kg-0.7 h-1 | Sweeney et al. 2010 |
| Km for Michaelis Menten Kinetics of EH | KM\_EH | 100.0 | mg L-1 | Sweeney et al. 2010 |
| Urinary excretion of AAMA | k\_exc\_AAMA | 0.13 (Sweeney)  0.049 (Kopp) | h-1 | Toxicokinetics of acrylamide in rats and humans following single oral administration of low doses Kopp and Dekant 2009)  Tabel3 gives coefficients of elimination. That is the excretion rate, or? |
| Urinary excretion of GAMA | k\_exc\_GAMA | 0.077 (Sweeney)  0.027 (Kopp) | h-1 |  |
| Urinary excretion of GAOH | k\_exc\_GAOH | 0.077 | h-1 | Sweeney et al. 2010 |
| Urinary excretion of GA | k\_exc\_GA | 2.48 | h-1 | Sweeney et al. 2010 |
| KM for GSH conjugation | KMGG | 0.1 | mM |  |
| Km with respect to GA for GSH conjugation | KMG2 | 90 | mg |  |
| Km with respect to AA for GSH conjugation | KMG1 | 20 | mg |  |