**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.  This is correct for the rats, but the values are measurable in the Doerge (2005) paper on acrylamide in mice.  In mice  Male 1h 0.36/0.8=0.45  Male 2h 0.32/0.5=0.64  Female 1h 0.34/0.63=0.54  Female 2h 0.36/0.39=0.92  The average is 0.63 |
| Kidney\_Blood partition coefficient | pAA\_KiB | 0.8 |  | Calculated based on reed out from Miller et al. 1981  Calculation from Miller et al  pAA\_KidneyBlood:  Blood at 24 h: approx 10% of the dose 10 mg/kg = 1 mg/kg  If plasma 24 h: approx. 0.12 of the dose 10 mg/kg = 0.012  Kidney at 24 h: approx. 0.13 of the dose 10 mg/kg = 0.013  pAA\_KB = 0.013/1 = 0.013 (using blood values)  pAA\_KB = 0.013/0.012 = 1,08  Calculations from tissue blod using the analysed values for muscle.  Male 2h 0.51/0.64= 0.9  Male 4h 0.22/0.33=0.67  Female 2h 0.45/0.69=0.65  Female 4h 0.20/0.32=0.63  The average would be 0.71 |
| pGA\_KiB | 1.0 | There is no data on GA in Miller. |
| 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.  Calculations from tissue blod using the analysed values for muscle.  Male 1h 1.0/0.8=1.25  Male 2h 00.63/0.5=1.26  Female 1h 0.87/0.63=1.38  Female 2h 0.58/0.39=1.49  The average would be 1.35 |
| 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 |