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SBML Model Report

Model name: "Sluka2016 - Acetaminophen PBPK"

June 22, 2017

1 General Overview

This is a document in SBML Level 2 Version 4 format. The SBO concept of this model is a biochemical or transport reaction. Its SBO term is 0000167. See Section A for the definition. This model was created by the following three authors: Vijayalakshmi Chelliah[1], Xiao Fu[2] and James Sluka[3] at February fourth 2015 at 11:47 a. m. and last time modified at May 23rd 2017 at 10:32 a. m. Table 1 gives an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	3	compartments	9
species types	2	species	10
events	0	constraints	0
reactions	13	function definitions	0
global parameters	31	unit definitions	7
rules	0	initial assignments	16

Model Notes

Basic PBPK (Physiologically Based PharmacoKinetic) model of Acetaminophen.

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This is a basic model of Acetaminophen (APAP, Paracetamol) pharmacokinetics in humans. Many of the model parameters (compartment volumes, volumetric flow rates, etc.) are scaled allometrically based on the body weight (BW) raised to the3/4 power. Because of that, the assigned values of many of the parameters are recalculated at run time and are different than the default values for the particular entity (e.g., the volume of a compartment and the volumetric flow rate between compartments).

APAP dose is initially given in grams (APAP_Dose_gram), which is converted to moles via the APAP molecular weight (APAP_MW).APAP quantities throughout the rest of the models are given in moles.

The base parameters are for a 70Kg human and a pharmacological oral dose of 1.4 gram of APAP. Metabolism is modelled as a single ODE in the liver compartment and the metabolite does not leave that compartment.

This model is loosely based on the model of Wambaugh and Shaw (PLoS Comput Biol. 2010 Apr 22;6(4):e1000756. doi: 10.1371/journal.pcbi.1000756. Pubmed ID: PMID- 20421935) with the following changes:

1. The lung lumen compartment was omitted.
2. A kidney compartment was added.
3. Glomerular Filtration is from the kidney compartment.
4. The APAP dose was changed to 1.4g.
5. The gut adsorption rate constant (KGutabs), tissue partition coefficients and liver metabolism rate constant (CLmetabolism) were fit using the human *in vivo* data of Critchley (Critchley, J. A., Critchley, L. A. H., Anderson, P. J., and Tomlinson, B. 2005 Journal of clinical pharmacy and therapeutics, 30(2), 179-184).
6. **To model the extensive re-adsorption of APAP from the kidney tubules back into the blood the QGfr value is modified. This was done by changing the scaling parameter QGFR_ref value from 0.31 to 0.039, resulting in a decrease in the QGfr value of 8 fold (from 7.2 L/hr to 0.91 L/hr).**

The parameters in this file are the **REFSIM** parameters from our publication.

2 Unit Definitions

This is an overview of nine unit definitions of which two are predefined by SBML and not mentioned in the model.

2.1 Unit `time`

Name hour

Definition 3600 s

2.2 Unit first_order_rate_constant

Name first_order_rate_constant

Definition $(3600\ \mathrm{s})^{-1}$

2.3 Unit Volumetric_Flow

Name Volumetric_Flow

Definition $1 \cdot (3600\ \mathrm{s})^{-1}$

2.4 Unit volume

Name litre

Definition l

2.5 Unit substance

Name mole

Definition mol

2.6 Unit grams2mol

Name grams2mol

Notes Units of molecular weight: grams/mole

Definition $\mathrm{g} \cdot \mathrm{mol}^{-1}$

2.7 Unit BW_ref

Name BW_ref

Notes Reference body weight (Kg) for allometric scaling.

Definition kg

2.8 Unit area

Notes Square metre is the predefined SBML unit for `area` since SBML Level 2 Version 1.

Definition m^2

2.9 Unit `length`

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

3 Compartment types

This is an overview of three compartment types.

3.1 Compartment type `ORGAN`

SBO:0000290 physical compartment

Notes Compartments such as the liver, lungs, kidneys, ...

Table 2: Compartments of this type

Id	Name
`VGut`	VGut
`VLung`	VLung
`VRest`	VRest
`VLiver`	VLiver
`VKidney`	VKidney

3.2 Compartment type `CIRCULATORY`

SBO:0000290 physical compartment

Notes Blood only compartments such as the arteries and veins.

Table 3: Compartments of this type

Id	Name
`VArt`	VArt
`VVen`	VVen

3.3 Compartment type `LUMEN`

SBO:0000290 physical compartment

Notes Lumen compartments such as in the lungs, gut and kidney.

Table 4: Compartments of this type

Id	Name
VGutLumen	VGutLumen
VKidneyTubules	VKidneyTubules

4 Compartments

This model contains nine compartments.

Table 5: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
VArt	VArt	0000290	3	1.4994	l	☑	
VGut	VGut	0000290	3	1.1046	l	☑	
VGutLumen	VGutLumen	0000290	3	1	litre	☑	VGut
VLung	VLung	0000290	3	0.5082	l	☑	
VVen	VVen	0000290	3	3.4104	l	☑	
VRest	VRest	0000290	3	33.4698	l	☑	
VLiver	VLiver	0000290	3	1.7136	l	☑	
VKidney	VKidney	0000290	3	0.294	l	☑	
VKidneyTubules	VKidneyTubules	0000290	3	1	litre	☑	VKidney

4.1 Compartment VArt

This is a three dimensional compartment of type CIRCULATORY with a constant size of 1.4994 litre.

Name VArt

SBO:0000290 physical compartment

Notes Volume of the arterial blood. Note that this value is modified by allometric scaling in an initial assignment or rule equation.

4.2 Compartment VGut

This is a three dimensional compartment of type ORGAN with a constant size of 1.1046 litre.

Name VGut

SBO:0000290 physical compartment

Notes Perfusable volume of the Gut (small intestine). The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.3 Compartment VGutLumen

This is a three dimensional compartment of type LUMEN with a constant size of one litre, which is surrounded by VGut (VGut).

Name VGutLumen

SBO:0000290 physical compartment

Notes Lumen of the Gut. Note that the volume is arbitrary.

4.4 Compartment VLung

This is a three dimensional compartment of type ORGAN with a constant size of 0.5082 litre.

Name VLung

SBO:0000290 physical compartment

Notes Perfusable volume of the Lungs.The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.5 Compartment VVen

This is a three dimensional compartment of type CIRCULATORY with a constant size of 3.4104 litre.

Name VVen

SBO:0000290 physical compartment

Notes Volume of the venous blood.The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.6 Compartment VRest

This is a three dimensional compartment of type ORGAN with a constant size of 33.4698 litre.

Name VRest

SBO:0000290 physical compartment

Notes Perfusable volume of the Rest of the body, that is, all tissues and blood volumes not explicitly described by other compartments.The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.7 Compartment VLiver

This is a three dimensional compartment of type ORGAN with a constant size of 1.7136 litre.

Name VLiver

SBO:0000290 physical compartment

Notes Perfusable volume of the Liver.The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.8 Compartment VKidney

This is a three dimensional compartment of type ORGAN with a constant size of 0.294 litre.

Name VKidney

SBO:0000290 physical compartment

Notes Perfusable volume of the Kidney. The compartment volume is allometrically scaled and is assigned in an initialAssignment.

4.9 Compartment VKidneyTubules

This is a three dimensional compartment of type LUMEN with a constant size of one litre, which is surrounded by VKidney (VKidney).

Name VKidneyTubules

SBO:0000290 physical compartment

Notes Kidney (renal) Tubules (lumen). This, like the gut lumen, is treated as a volumeless compartment.

5 Species types

This is an overview of two species types.

5.1 Species type APAP

SBO:0000247 simple chemical

Notes Acetaminophen in all locations.

Table 6: Species of this type

Id	Name
CArt	CArt
CGut	CGut
AGutlumen	AGutlumen
CLung	CLung
CVen	CVen
CRest	CRest
CLiver	CLiver
CKidney	CKidney
CTubules	CTubules

5.2 Species type METAB

SBO:0000247 simple chemical

Notes All metabolites of APAP in all locations.

Table 7: Species of this type

Id	Name
CMetabolized	CMetabolized

6 Species

This model contains ten species. Section 10 provides further details and the derived rates of change of each species.

Table 8: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
CArt	CArt	VArt	mol	⊟	⊟
CGut	CGut	VGut	mol	⊟	⊟
AGutlumen	AGutlumen	VGutLumen	mol	⊟	⊟
CLung	CLung	VLung	mol	⊟	⊟
CVen	CVen	VVen	mol	⊟	⊟
CRest	CRest	VRest	mol	⊟	⊟
CLiver	CLiver	VLiver	mol	⊟	⊟
CMetabolized	CMetabolized	VLiver	mol	⊟	⊟
CKidney	CKidney	VKidney	mol	⊟	⊟
CTubules	CTubules	VKidneyTubules	mol	⊟	⊟

7 Parameters

This model contains 31 global parameters.

Table 9: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
APAP_Dose_grams	APAP_Dose_grams	0000504	1.400	g	☑
APAP_MW	APAP_MW	0000002	151.200	$g \cdot mol^{-1}$	☑
APAP_Dose	APAP_Dose	0000002	1.000	mol	☑
BW	BW	0000002	70.000	kg	☑
BW_ref	BW_ref	0000381	1.000	kg	☑
Cardiac_flow_ref	Cardiac_flow_ref	0000380	15.000	$1 \cdot (3600\ s)^{-1}$	☑
QCardiac	QCardiac	0000016	363.000	$1 \cdot (3600\ s)^{-1}$	⊟
QGut_fraction_QCardiac	QGut_fraction_QCardiac	0000380	0.205	dimensionless	☑
QGut	QGut	0000016	74.420	$1 \cdot (3600\ s)^{-1}$	⊟
QLiver_fraction_QCardiac	QLiver_fraction_QCardiac	0000380	0.054	dimensionless	☑
QLiver	QLiver	0000016	19.420	$1 \cdot (3600\ s)^{-1}$	⊟
QKidney_fraction_QCardiac	QKidney_fraction_QCardiac	0000380	0.221	dimensionless	☑
QKidney	QKidney	0000016	80.370	$1 \cdot (3600\ s)^{-1}$	⊟
QRest	QRest	0000016	188.800	$1 \cdot (3600\ s)^{-1}$	⊟
QGFR_ref	QGFR_ref	0000380	0.039	$1 \cdot (3600\ s)^{-1}$	☑
Qgfr	Qgfr	0000016	0.944	$1 \cdot (3600\ s)^{-1}$	⊟
kGutabs	kGutabs	0000016	1.500	$(3600\ s)^{-1}$	☑
CLmetabolism	CLmetabolism	0000016	9.500	$(3600\ s)^{-1}$	☑
Fraction_unbound_plasma	Fraction_unbound_plasma	0000470	0.800	dimensionless	☑
Ratioblood2plasma	Ratioblood2plasma	0000470	1.090	dimensionless	☑
Kliver2plasma	Kliver2plasma	0000281	1.000	dimensionless	☑
Kkidney2plasma	Kkidney2plasma	0000281	1.000	dimensionless	☑
KRest2plasma	KRest2plasma	0000281	1.600	dimensionless	☑
VTotal_ref	VTotal_ref	0000380	0.600	l	☑
VTotal	VTotal	0000468	42.000	l	⊟

Id	Name	SBO	Value	Unit	Constant
VLiver_fraction_VTotal	VLiver_fraction_VTotal	0000380	0.041	dimensionless	☑
VArt_fraction_VTotal	VArt_fraction_VTotal	0000380	0.036	dimensionless	☑
VLung_fraction_VTotal	VLung_fraction_VTotal	0000380	0.012	dimensionless	☑
VVen_fraction_VTotal	VVen_fraction_VTotal	0000380	0.081	dimensionless	☑
VGut_fraction_VTotal	VGut_fraction_VTotal	0000380	0.026	dimensionless	☑
VKidney_fraction_VTotal	VKidney_fraction_VTotal	0000380	0.007	dimensionless	☑

8 Initialassignments

This is an overview of 16 initialassignments.

8.1 Initialassignment VArt

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Arterial (Art) compartment after allometric scaling.

Derived unit l

Math $\mathrm{VTotal} \cdot \mathrm{VArt\_fraction\_VTotal}$

8.2 Initialassignment VGut

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Gut compartment after allometric scaling.

Derived unit l

Math $\mathrm{VTotal} \cdot \mathrm{VGut\_fraction\_VTotal}$

8.3 Initialassignment VLung

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Lung compartment after allometric scaling.

Derived unit l

Math VTotal · VLung_fraction_VTotal

8.4 Initialassignment VVen

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Venous (Ven) compartment after allometric scaling.

Derived unit l

Math VTotal · VVen_fraction_VTotal

8.5 Initialassignment VLiver

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Liver compartment after allometric scaling.

Derived unit l

Math VTotal · VLiver_fraction_VTotal

8.6 Initialassignment VKidney

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Kidney compartment after allometric scaling.

Derived unit l

Math VTotal · VKidney_fraction_VTotal

8.7 Initialassignment VRest

SBO:0000064 mathematical expression

Notes Assignment of the perfusable volume (L) of the Rest (of the body) compartment after allometric scaling.

Derived unit l

Math $\mathrm{VTotal} - \mathrm{vol}(\mathrm{VArt}) - \mathrm{vol}(\mathrm{VGut}) - \mathrm{vol}(\mathrm{VKidney}) - \mathrm{vol}(\mathrm{VLiver}) - \mathrm{vol}(\mathrm{VLung}) - \mathrm{vol}(\mathrm{VVen})$

8.8 Initialassignment APAP_Dose

SBO:0000064 mathematical expression

Notes Calculate APAP dose in moles based on the dose in grams (APAP_Dose_grams) and APAP moleuclar weight (APAP_MW).

Derived unit mol

Math $\frac{\mathrm{APAP\_Dose\_grams}}{\mathrm{APAP\_MW}}$

8.9 Initialassignment AGutlumen

SBO:0000064 mathematical expression

Notes Starting compartment for the APAP dose (moles) is the lumen of the gut/stomach/small intestine.

Derived unit mol

Math APAP_Dose

8.10 Initialassignment QCardiac

SBO:0000064 mathematical expression

Notes Allometric calculation of the total cardiac output inL/hour (QCardiac) based on the body weight ((BW/BW_ref)^(3/4)).

Derived unit contains undeclared units

Math $\mathrm{Cardiac\_flow\_ref} \cdot \left(\frac{\mathrm{BW}}{\mathrm{BW\_ref}}\right)^{0.75}$

8.11 Initialassignment QGut

SBO:0000064 mathematical expression

Notes Allometric calculation of the Gut blood flow rate (QGut) in L/hour based on the body weight (BW^(3/4)).

Derived unit $1 \cdot (3600\ \mathrm{s})^{-1}$

Math QCardiac · QGut_fraction_QCardiac

8.12 Initialassignment QLiver

SBO:0000064 mathematical expression

Notes Allometric calculation of the Liver blood flow rate (QLiver) in L/hour based on the body weight (BW^(3/4)).

Derived unit $1 \cdot (3600\ \mathrm{s})^{-1}$

Math QCardiac · QLiver_fraction_QCardiac

8.13 Initialassignment QKidney

SBO:0000064 mathematical expression

Notes Allometric calculation of the Kidney blood flow rate (QKidney) in L/hour based on the body weight (BW^(3/4)).

Derived unit $1 \cdot (3600\ \mathrm{s})^{-1}$

Math QCardiac · QKidney_fraction_QCardiac

8.14 Initialassignment QRest

SBO:0000064 mathematical expression

Notes Allometric calculation of the Rest of the body's blood flow rate (QRest) in L/hour based on the body weight (BW^(3/4)).

Derived unit $1 \cdot (3600\ \mathrm{s})^{-1}$

Math QCardiac − QGut − QKidney − QLiver

8.15 Initialassignment Qgfr

SBO:0000064 mathematical expression

Notes Allometric calculation of the Qgfr inL/hour based on the body weight ((BW/BW_ref)^(3/4)).

Derived unit contains undeclared units

Math $\mathrm{QGFR\_ref} \cdot \left(\frac{\mathrm{BW}}{\mathrm{BW\_ref}}\right)^{0.75}$

8.16 Initialassignment VTotal

SBO:0000064 mathematical expression

Notes Allometric calculation of the total perfusable volume of the body in litres (VTotal) based on the body weight.

Derived unit $1 \cdot \mathrm{kg} \cdot \mathrm{kg}^{-1}$

Math $\mathrm{VTotal\_ref} \cdot \frac{\mathrm{BW}}{\mathrm{BW\_ref}}$

9 Reactions

This model contains 13 reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by a modifier, the identifier of this species is written above the reaction arrow.

Table 10: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	J1	J01	CArt ⟶ CGut	0000185
2	J2	J02	AGutlumen ⟶ CGut	0000185
3	J3	J03	CLung ⟶ CArt	0000185
4	J4	J04	CVen ⟶ CLung	0000185
5	J5	J05	CArt ⟶ CRest	0000185
6	J6	J06	CRest ⟶ CVen	0000185
7	J7	J07	CArt ⟶ CLiver	0000185
8	J8	J08	CLiver ⟶ CMetabolized	0000182
9	J9	J09	CGut ⟶ CLiver	0000185
10	J10	J10	CLiver ⟶ CVen	0000185
11	J11	J11	CArt ⟶ CKidney	0000185
12	J12	J12	CKidney ⟶ CTubules	0000185
13	J13	J13	CKidney ⟶ CVen	0000185

9.1 Reaction J1

This is an irreversible reaction of one reactant forming one product.

Name J01

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Arterial compartment (CArt) to the Gut (CGut) in moles/hour.

Reaction equation

$$\mathrm{CArt} \longrightarrow \mathrm{CGut} \tag{1}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
CArt	CArt	

Product

Table 12: Properties of each product.

Id	Name	SBO
CGut	CGut	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_1 = \frac{\mathrm{QGut}}{\mathrm{vol}\left(\mathrm{VArt}\right)} \cdot \mathrm{CArt} \tag{2}$$

9.2 Reaction J2

This is an irreversible reaction of one reactant forming one product.

Name J02

SBO:0000185 transport reaction

Notes First order adsorption of compound from the lumen of the gut (AGutlumen) to the gut compartment (CGut) in mole/hour.

Reaction equation

$$\text{AGutlumen} \longrightarrow \text{CGut} \tag{3}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
AGutlumen	AGutlumen	

Product

Table 14: Properties of each product.

Id	Name	SBO
CGut	CGut	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_2 = \text{kGutabs} \cdot \text{AGutlumen} \tag{4}$$

9.3 Reaction J3

This is an irreversible reaction of one reactant forming one product.

Name J03

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Lung compartment (CLung) to the Arterial blood compartment (CArt) in moles/hour.

Reaction equation

$$\text{CLung} \longrightarrow \text{CArt} \tag{5}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
CLung	CLung	

Product

Table 16: Properties of each product.

Id	Name	SBO
CArt	CArt	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_3 = \frac{\mathrm{QCardiac}}{\mathrm{vol}\,(\mathrm{VLung})} \cdot \mathrm{CLung} \tag{6}$$

9.4 Reaction J4

This is an irreversible reaction of one reactant forming one product.

Name J04

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Venous compartment (CVen) to the Lung compartment (CLung) in moles/hour.

Reaction equation

$$\mathrm{CVen} \longrightarrow \mathrm{CLung} \tag{7}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
CVen	CVen	

Product

Table 18: Properties of each product.

Id	Name	SBO
CLung	CLung	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_4 = \frac{\mathrm{QCardiac}}{\mathrm{vol}\,(\mathrm{VVen})} \cdot \mathrm{CVen} \tag{8}$$

9.5 Reaction J5

This is an irreversible reaction of one reactant forming one product.

Name J05

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Arterial compartment (CArt) to the Rest of the body compartment (CRest) in moles/hour.

Reaction equation

$$\mathrm{CArt} \longrightarrow \mathrm{CRest} \tag{9}$$

Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
CArt	CArt	

Product

Table 20: Properties of each product.

Id	Name	SBO
CRest	CRest	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_5 = \mathrm{QRest} \cdot \frac{\mathrm{CArt}}{\mathrm{vol}\,(\mathrm{VArt})} \tag{10}$$

9.6 Reaction J6

This is an irreversible reaction of one reactant forming one product.

Name J06

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Rest compartment (CRest) to the Venous compartment (CVen) in moles/hour.

Reaction equation

$$\mathrm{CRest} \longrightarrow \mathrm{CVen} \tag{11}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
CRest	CRest	

Product

Table 22: Properties of each product.

Id	Name	SBO
CVen	CVen	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_6 = \frac{\frac{\mathrm{QRest}}{\mathrm{vol}(\mathrm{VRest})} \cdot \mathrm{CRest} \cdot \mathrm{Ratioblood2plasma}}{\mathrm{KRest2plasma} \cdot \mathrm{Fraction\_unbound\_plasma}} \tag{12}$$

9.7 Reaction J7

This is an irreversible reaction of one reactant forming one product.

Name J07

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Arterial compartment (CArt) to the Liver compartment (CLiver) in moles/hour.

Reaction equation

$$\mathrm{CArt} \longrightarrow \mathrm{CLiver} \tag{13}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
CArt	CArt	

Product

Table 24: Properties of each product.

Id	Name	SBO
CLiver	CLiver	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_7 = \frac{\mathrm{QLiver}}{\mathrm{vol}\,(\mathrm{VArt})} \cdot \mathrm{CArt} \tag{14}$$

9.8 Reaction J8

This is an irreversible reaction of one reactant forming one product.

Name J08

SBO:0000182 conversion

Notes Metabolism of compound in the Liver compartment (CLiver) to metabolites (CMetabolized) in moles/hour. The metabolites stay in the liver compartment. This single first order ODE represents both Phase I (Cyp-P450 2E1, 1A2) and Phase II (glucuronidation and sulfation) reactions.

Reaction equation

$$\text{CLiver} \longrightarrow \text{CMetabolized} \tag{15}$$

Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
`CLiver`	CLiver	

Product

Table 26: Properties of each product.

Id	Name	SBO
`CMetabolized`	CMetabolized	

Kinetic Law

Derived unit $(3600\ \text{s})^{-1} \cdot \text{mol}$

$$v_8 = \frac{\text{CLmetabolism} \cdot \text{CLiver}}{\text{Kliver2plasma} \cdot \text{Fraction\_unbound\_plasma}} \tag{16}$$

9.9 Reaction J9

This is an irreversible reaction of one reactant forming one product.

Name J09

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Gut compartment (CGut) to the Liver compartment (CLiver) in moles/hour.

Reaction equation

$$\text{CGut} \longrightarrow \text{CLiver} \tag{17}$$

Reactant

Table 27: Properties of each reactant.

Id	Name	SBO
CGut	CGut	

Product

Table 28: Properties of each product.

Id	Name	SBO
CLiver	CLiver	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_9 = \frac{\mathrm{QGut}}{\mathrm{vol}\,(\mathrm{VGut})} \cdot \mathrm{CGut} \tag{18}$$

9.10 Reaction J10

This is an irreversible reaction of one reactant forming one product.

Name J10

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Liver compartment (CLiver) to the Venous compartment (CVen) in moles/hour.

Reaction equation

$$\mathrm{CLiver} \longrightarrow \mathrm{CVen} \tag{19}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
CLiver	CLiver	

Product

Table 30: Properties of each product.

Id	Name	SBO
CVen	CVen	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_{10} = \frac{\frac{\mathrm{QLiver+QGut}}{\mathrm{vol(VLiver)}} \cdot \mathrm{CLiver} \cdot \mathrm{Ratioblood2plasma}}{\mathrm{Kliver2plasma} \cdot \mathrm{Fraction\_unbound\_plasma}} \tag{20}$$

9.11 Reaction J11

This is an irreversible reaction of one reactant forming one product.

Name J11

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Arterial compartment (CArt) to the Kidney compartment (CKidney) in moles/hour.

Reaction equation

$$\mathrm{CArt} \longrightarrow \mathrm{CKidney} \tag{21}$$

Reactant

Table 31: Properties of each reactant.

Id	Name	SBO
CArt	CArt	

Product

Table 32: Properties of each product.

Id	Name	SBO
CKidney	CKidney	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_{11} = \frac{\mathrm{QKidney}}{\mathrm{vol}\,(\mathrm{VArt})} \cdot \mathrm{CArt} \tag{22}$$

9.12 Reaction J12

This is an irreversible reaction of one reactant forming one product.

Name J12

SBO:0000185 transport reaction

Notes Transfer of compound from the Kidney compartment (CKidney) to the Kidney tubules (species CTubules in the compartment „KidenyTubules„) in moles/hour.

Reaction equation

$$\mathrm{CKidney} \longrightarrow \mathrm{CTubules} \tag{23}$$

Reactant

Table 33: Properties of each reactant.

Id	Name	SBO
CKidney	CKidney	

Product

Table 34: Properties of each product.

Id	Name	SBO
CTubules	CTubules	

Kinetic Law

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_{12} = \frac{\frac{\mathrm{Qgfr}}{\mathrm{vol(VKidney)}} \cdot \mathrm{CKidney}}{\mathrm{Kkidney2plasma}} \tag{24}$$

9.13 Reaction J13

This is an irreversible reaction of one reactant forming one product.

Name J13

SBO:0000185 transport reaction

Notes Blood born transfer of compound from the Kidney compartment (CKidney) to the Venous compartment (CVen) in moles/hour.

Reaction equation

$$\text{CKidney} \longrightarrow \text{CVen} \tag{25}$$

Reactant

Table 35: Properties of each reactant.

Id	Name	SBO
CKidney	CKidney	

Product

Table 36: Properties of each product.

Id	Name	SBO
CVen	CVen	

Kinetic Law

Derived unit $(3600\ \text{s})^{-1} \cdot \text{mol}$

$$v_{13} = \frac{\frac{\text{QKidney}}{\text{vol(VKidney)}} \cdot \text{CKidney} \cdot \text{Ratioblood2plasma}}{\text{Kkidney2plasma} \cdot \text{Fraction\_unbound\_plasma}} \tag{26}$$

10 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

10.1 Species CArt

Name CArt

SBO:0000247 simple chemical

Notes Amount of APAP in the arteries of the gut in moles.

Initial amount 0

Species type `APAP`

This species takes part in five reactions (as a reactant in `J1`, `J5`, `J7`, `J11` and as a product in `J3`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CArt} = v_3 - v_1 - v_5 - v_7 - v_{11} \tag{27}$$

10.2 Species `CGut`

Name CGut

SBO:0000247 simple chemical

Notes Amount of APAP in the gut (small intestine) blood in moles.

Initial amount 0

Species type `APAP`

This species takes part in three reactions (as a reactant in `J9` and as a product in `J1`, `J2`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CGut} = v_1 + v_2 - v_9 \tag{28}$$

10.3 Species `AGutlumen`

Name AGutlumen

SBO:0000247 simple chemical

Notes Amount of APAP in the lumen of the gut in moles.

Initial amount 0.0093

Species type `APAP`

Initial assignment `AGutlumen`

This species takes part in one reaction (as a reactant in `J2`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AGutlumen} = -v_2 \tag{29}$$

10.4 Species CLung

Name CLung

SBO:0000247 simple chemical

Notes Amount of APAP in the lung blood in moles.

Initial amount 0

Species type APAP

This species takes part in two reactions (as a reactant in J3 and as a product in J4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CLung} = v_4 - v_3 \tag{30}$$

10.5 Species CVen

Name CVen

SBO:0000247 simple chemical

Notes Amount of APAP in the venous blood in moles.

Initial amount 0

Species type APAP

This species takes part in four reactions (as a reactant in J4 and as a product in J6, J10, J13).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CVen} = v_6 + v_{10} + v_{13} - v_4 \tag{31}$$

10.6 Species CRest

Name CRest

SBO:0000247 simple chemical

Notes Amount of APAP in the „rest of the body„ in moles.

Initial amount 0

Species type APAP

This species takes part in two reactions (as a reactant in J6 and as a product in J5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CRest} = v_5 - v_6 \tag{32}$$

10.7 Species CLiver

Name CLiver

SBO:0000247 simple chemical

Notes Amount of APAP in the liver blood in moles.

Initial amount 0

Species type APAP

This species takes part in four reactions (as a reactant in J8, J10 and as a product in J7, J9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CLiver} = v_7 + v_9 - v_8 - v_{10} \tag{33}$$

10.8 Species CMetabolized

Name CMetabolized

SBO:0000247 simple chemical

Initial amount 0

Species type METAB

This species takes part in one reaction (as a product in J8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CMetabolized} = v_8 \tag{34}$$

10.9 Species CKidney

Name CKidney

SBO:0000247 simple chemical

Notes Amount of APAP in the kidney blood in moles.

Initial amount 0

Species type APAP

This species takes part in three reactions (as a reactant in J12, J13 and as a product in J11).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CKidney} = v_{11} - v_{12} - v_{13} \tag{35}$$

10.10 Species CTubules

Name CTubules

SBO:0000247 simple chemical

Notes Amount of APAP in the Kidney Tubules in moles.

Initial amount 0

Species type APAP

This species takes part in one reaction (as a product in J12).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CTubules} = v_{12} \tag{36}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000002 quantitative systems description parameter: A numerical value that defines certain characteristics of systems or system functions. It may be part of a calculation, but its value is not determined by the form of the equation itself, and may be arbitrarily assigned

SBO:0000016 unimolecular rate constant: Numerical parameter that quantifies the velocity of a chemical reaction involving only one reactant.

SBO:0000064 mathematical expression: Formal representation of a calculus linking parameters and variables of a model

SBO:0000167 biochemical or transport reaction: An event involving one or more physical entities that modifies the structure, location or free energy of at least one of the participants

SBO:0000182 conversion: Biochemical reaction that results in the modification of some covalent bonds

SBO:0000185 transport reaction: Movement of a physical entity without modification of the structure of the entity

SBO:0000247 simple chemical: Simple, non-repetitive chemical entity

SBO:0000281 equilibrium constant: Quantity characterizing a chemical equilibrium in a chemical reaction, which is a useful tool to determine the concentration of various reactants or products in a system where chemical equilibrium occurs

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

SBO:0000380 biochemical coefficient: number used as a multiplicative or exponential factor for quantities, expressions or function

SBO:0000381 biochemical proportionality coefficient: A multiplicative factor for quantities, expressions or functions

SBO:0000468 volume: A quantity representing the three-dimensional space occupied by all or part of an object

SBO:0000470 mass fraction: For a given substance, A, its mass fraction (x A) is defined as the ratio of its mass (m A) to the total mass (m total) in which it is present, where the sum of all mass fractions is equal to 1. This provides a means to express concentration in a dimensionless size.

SBO:0000504 mass of an entity pool: The mass that comprises an entity pool

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