SBML Model Report

Model name: “Reddyhoff2015 - Acetaminophen metabolism and toxicity”

April 19, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Dennis Reddyhoff[1] and Vijayalakshmi Chelliah[2] at April 19th 2016 at 5:49 p. m. and last time modified at April 19th 2016 at 9:01 p. m. Table 1 shows 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	0	compartments	1
species types	0	species	5
events	0	constraints	0
reactions	10	function definitions	1
global parameters	11	unit definitions	2
rules	0	initial assignments	3

Model Notes

Reddyhoff2015 - Acetaminophen metabolism and toxicityThis model examines acetaminophen metabolism and related hepatotoxicity. Multiple pathways associated with APAP metabolism

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has been included in the model. Using numerical, sensitivity and timescale analysis, key parameters involved in the toxicity has been identified. The model analysis highlights a critical acetaminophen dose in terms of the model parameters.

This model is described in the article:Timescale analysis of a mathematical model of acetaminophen metabolism and toxicity.Reddyhoff D, Ward J, Williams D, Regan S, Webb SJ Theor Biol. 2015 Dec 7;386:132-46.

Abstract:

Acetaminophen is a widespread and commonly used painkiller all over the world. However, it can cause liver damage when taken in large doses or at repeated chronic doses. Current models of acetaminophen metabolism are complex, and limited to numerical investigation though provide results that represent clinical investigation well. We derive a mathematical model based on mass action laws aimed at capturing the main dynamics of acetaminophen metabolism, in particular the contrast between normal and overdose cases, whilst remaining simple enough for detailed mathematical analysis that can identify key parameters and quantify their role in liver toxicity. We use singular perturbation analysis to separate the different timescales describing the sequence of events in acetaminophen metabolism, systematically identifying which parameters dominate during each of the successive stages. Using this approach we determined, in terms of the model parameters, the critical dose between safe and overdose cases, timescales for exhaustion and regeneration of important cofactors for acetaminophen metabolism and total toxin accumulation as a fraction of initial dose.

This model is hosted on BioModels Database and identified by: MODEL1603080000.

To cite BioModels Database, please use: BioModels: Content, Features, Functionality and Use.

2 Unit Definitions

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

2.1 Unit `volume`

Name volume

Definition ml

2.2 Unit `substance`

Name substance

Definition mmol

2.3 Unit area

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

Definition m^2

2.4 Unit length

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

Definition m

2.5 Unit time

Notes Second is the predefined SBML unit for time.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
compartment	compartment		3	1	litre	☑	

3.1 Compartment compartment

This is a three dimensional compartment with a constant size of one ml.

Name compartment

4 Species

This model contains five species. Section 9 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
Sulphate__PAPS	Sulphate_PAPS	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
GSH	GSH	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
NAPQI	NAPQI	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
Paracetamol_APAP	Paracetamol_APAP	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
Protein_adducts	Protein_adducts	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟

5 Parameters

This model contains eleven global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
P0	P0		$1.32 \cdot 10^{-13}$		☑
dG	dG		2.000		☑
bG	bG		$1.374 \cdot 10^{-14}$		☑
kGSH	kGSH		$1.6 \cdot 10^{18}$		☑
kG	kG		2.990		☑
kS	kS		$2.26 \cdot 10^{14}$		☑
bS	bS		$2.65 \cdot 10^{-14}$		☑
dS	dS		2.000		☑
k450	k450		0.315		☑
kN	kN		0.032		☑
kPSH	kPSH		110.000		☑

6 Initialassignments

This is an overview of three initialassignments.

6.1 Initialassignment Sulphate__PAPS

Derived unit contains undeclared units

Math $\frac{\mathrm{bS}}{\mathrm{dS}}$

6.2 Initialassignment GSH

Derived unit contains undeclared units

Math $\frac{\mathrm{bG}}{\mathrm{dG}}$

6.3 Initialassignment Paracetamol_APAP

Derived unit contains undeclared units

Math P0

7 Function definition

This is an overview of one function definition.

7.1 Function definition Constant_flux__irreversible

Name Constant flux (irreversible)

Argument v

Mathematical Expression

$$v \tag{1}$$

8 Reactions

This model contains ten 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 5: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	reaction_1	R1	$\mathrm{Paracetamol\_APAP} \xrightarrow{\mathrm{Paracetamol\_APAP}} \mathrm{NAPQI}$	
2	R2	R2	$\mathrm{NAPQI} \xrightarrow{\mathrm{NAPQI}} \mathrm{Paracetamol\_APAP}$	
3	R3	R3	$\mathrm{Paracetamol\_APAP} \xrightarrow{\mathrm{Paracetamol\_APAP}} \emptyset$	
4	R4	R4	$\mathrm{NAPQI} \xrightarrow{\mathrm{NAPQI}} \mathrm{Protein\_adducts}$	
5	R5	R5	$\mathrm{NAPQI} + \mathrm{GSH} \xrightarrow{\mathrm{NAPQI,\ GSH}} \emptyset$	
6	R6	R6	$\mathrm{GSH} \xrightarrow{\mathrm{GSH}} \emptyset$	
7	R7	R7	$\emptyset \longrightarrow \mathrm{GSH}$	
8	R8	R8	$\mathrm{Paracetamol\_APAP} + \mathrm{Sulphate\_\_PAPS} \xrightarrow{\mathrm{Paracetamol\_APAP,\ Sulphate\_\_PAPS}} \emptyset$	
9	R9	R9	$\mathrm{Sulphate\_\_PAPS} \xrightarrow{\mathrm{Sulphate\_\_PAPS}} \emptyset$	
10	R10	R10	$\emptyset \longrightarrow \mathrm{Sulphate\_\_PAPS}$	

8.1 Reaction `reaction_1`

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

Name R1

Reaction equation

$$\text{Paracetamol\_APAP} \xrightarrow{\text{Paracetamol\_APAP}} \text{NAPQI} \tag{2}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
`Paracetamol_APAP`	Paracetamol_APAP	

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
`Paracetamol_APAP`	Paracetamol_APAP	

Product

Table 8: Properties of each product.

Id	Name	SBO
`NAPQI`	NAPQI	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}\left(\text{compartment}\right) \cdot \text{k450} \cdot [\text{Paracetamol\_APAP}] \tag{3}$$

8.2 Reaction `R2`

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

Name R2

Reaction equation

$$\text{NAPQI} \xrightarrow{\text{NAPQI}} \text{Paracetamol\_APAP} \tag{4}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
NAPQI	NAPQI	

Modifier

Table 10: Properties of each modifier.

Id	Name	SBO
NAPQI	NAPQI	

Product

Table 11: Properties of each product.

Id	Name	SBO
Paracetamol_APAP	Paracetamol_APAP	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{vol}\,(\text{compartment}) \cdot \text{kN} \cdot [\text{NAPQI}] \tag{5}$$

8.3 Reaction R3

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name R3

Reaction equation

$$\text{Paracetamol\_APAP} \xrightarrow{\text{Paracetamol\_APAP}} \emptyset \tag{6}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Paracetamol_APAP	Paracetamol_APAP	

Modifier

Table 13: Properties of each modifier.

Id	Name	SBO
Paracetamol_APAP	Paracetamol_APAP	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{kG} \cdot [\mathrm{Paracetamol\_APAP}] \tag{7}$$

8.4 Reaction R4

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

Name R4

Reaction equation

$$\mathrm{NAPQI} \xrightarrow{\mathrm{NAPQI}} \mathrm{Protein\_adducts} \tag{8}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
NAPQI	NAPQI	

Modifier

Table 15: Properties of each modifier.

Id	Name	SBO
NAPQI	NAPQI	

Product

Table 16: Properties of each product.

Id	Name	SBO
Protein_adducts	Protein_adducts	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{vol}\,(\text{compartment}) \cdot \text{kPSH} \cdot [\text{NAPQI}] \tag{9}$$

8.5 Reaction R5

This is an irreversible reaction of two reactants forming no product influenced by two modifiers.

Name R5

Reaction equation

$$\text{NAPQI} + \text{GSH} \xrightarrow{\text{NAPQI, GSH}} \emptyset \tag{10}$$

Reactants

Table 17: Properties of each reactant.

Id	Name	SBO
NAPQI	NAPQI	
GSH	GSH	

Modifiers

Table 18: Properties of each modifier.

Id	Name	SBO
NAPQI	NAPQI	
GSH	GSH	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{kGSH} \cdot [\mathrm{NAPQI}] \cdot [\mathrm{GSH}] \tag{11}$$

8.6 Reaction R6

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name R6

Reaction equation

$$\mathrm{GSH} \xrightarrow{\mathrm{GSH}} \emptyset \tag{12}$$

Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
GSH	GSH	

Modifier

Table 20: Properties of each modifier.

Id	Name	SBO
GSH	GSH	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{dG} \cdot [\mathrm{GSH}] \tag{13}$$

8.7 Reaction R7

This is an irreversible reaction of no reactant forming one product.

Name R7

Reaction equation

$$\emptyset \longrightarrow \mathrm{GSH} \tag{14}$$

Product

Table 21: Properties of each product.

Id	Name	SBO
GSH	GSH	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \text{vol}\left(\text{compartment}\right) \cdot \text{Constant\_flux\_\_irreversible}\left(\text{bG}\right) \tag{15}$$

$$\text{Constant\_flux\_\_irreversible}\left(\text{v}\right) = \text{v} \tag{16}$$

$$\text{Constant\_flux\_\_irreversible}\left(\text{v}\right) = \text{v} \tag{17}$$

8.8 Reaction R8

This is an irreversible reaction of two reactants forming no product influenced by two modifiers.

Name R8

Reaction equation

$$\text{Paracetamol\_APAP} + \text{Sulphate\_\_PAPS} \xrightarrow{\text{Paracetamol\_APAP, Sulphate\_\_PAPS}} \emptyset \tag{18}$$

Reactants

Table 22: Properties of each reactant.

Id	Name	SBO
Paracetamol_APAP	Paracetamol_APAP	
Sulphate__PAPS	Sulphate_PAPS	

Modifiers

Table 23: Properties of each modifier.

Id	Name	SBO
Paracetamol_APAP	Paracetamol_APAP	
Sulphate__PAPS	Sulphate_PAPS	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{kS} \cdot [\mathrm{Paracetamol\_APAP}] \cdot [\mathrm{Sulphate\_\_PAPS}] \tag{19}$$

8.9 Reaction R9

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name R9

Reaction equation

$$\mathrm{Sulphate\_\_PAPS} \xrightarrow{\mathrm{Sulphate\_\_PAPS}} \emptyset \tag{20}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
Sulphate__PAPS	Sulphate_PAPS	

Modifier

Table 25: Properties of each modifier.

Id	Name	SBO
Sulphate__PAPS	Sulphate_PAPS	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{dS} \cdot [\mathrm{Sulphate\_\_PAPS}] \tag{21}$$

8.10 Reaction R10

This is an irreversible reaction of no reactant forming one product.

Name R10

Reaction equation

$$\emptyset \longrightarrow \text{Sulphate\_\_PAPS} \tag{22}$$

Product

Table 26: Properties of each product.

Id	Name	SBO
Sulphate__PAPS	Sulphate_PAPS	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{vol}\,(\text{compartment}) \cdot \text{Constant\_flux\_\_irreversible}\,(\text{bS}) \tag{23}$$

$$\text{Constant\_flux\_\_irreversible}\,(\text{v}) = \text{v} \tag{24}$$

$$\text{Constant\_flux\_\_irreversible}\,(\text{v}) = \text{v} \tag{25}$$

9 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.

Identifiers for kinetic laws highlighted in gray cannot be verified to evaluate to units of SBML `substance` per `time`. As a result, some SBML interpreters may not be able to verify the consistency of the units on quantities in the model. Please check if

- parameters without an unit definition are involved or
- volume correction is necessary because the `hasOnlySubstanceUnits` flag may be set to `false` and `spacialDimensions`> 0 for certain species.

9.1 Species Sulphate__PAPS

Name Sulphate_PAPS

Initial concentration $1.325 \cdot 10^{-14}\ \text{mmol} \cdot \text{ml}^{-1}$

Initial assignment Sulphate__PAPS

This species takes part in five reactions (as a reactant in R8, R9 and as a product in R10 and as a modifier in R8, R9).

$$\frac{\text{d}}{\text{d}t}\text{Sulphate\_\_PAPS} = v_{10} - v_8 - v_9 \tag{26}$$

9.2 Species GSH

Name GSH

Initial concentration $6.87 \cdot 10^{-15}$ mmol $\cdot$ ml^{-1}

Initial assignment GSH

This species takes part in five reactions (as a reactant in R5, R6 and as a product in R7 and as a modifier in R5, R6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GSH} = v_7 - v_5 - v_6 \tag{27}$$

9.3 Species NAPQI

Name NAPQI

Initial concentration 0 mmol $\cdot$ ml^{-1}

This species takes part in seven reactions (as a reactant in R2, R4, R5 and as a product in reaction_1 and as a modifier in R2, R4, R5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NAPQI} = v_1 - v_2 - v_4 - v_5 \tag{28}$$

9.4 Species Paracetamol_APAP

Name Paracetamol_APAP

Initial concentration $1.32 \cdot 10^{-13}$ mmol $\cdot$ ml^{-1}

Initial assignment Paracetamol_APAP

This species takes part in seven reactions (as a reactant in reaction_1, R3, R8 and as a product in R2 and as a modifier in reaction_1, R3, R8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Paracetamol\_APAP} = v_2 - v_1 - v_3 - v_8 \tag{29}$$

9.5 Species Protein_adducts

Name Protein_adducts

Initial concentration 0 mmol $\cdot$ ml^{-1}

This species takes part in one reaction (as a product in R4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Protein\_adducts} = v_4 \tag{30}$$

SBML2LaTeX was developed by Andreas Dräger[a], Hannes Planatscher[a], Dieudonné M Wouamba[a], Adrian Schröder[a], Michael Hucka[b], Lukas Endler[c], Martin Golebiewski[d] and Andreas Zell[a]. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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