

DILIsym® User Training - DILIsym® Parameters From Data: Bile Acid Transporter Inhibition

DILI-sim Team

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Goal for This Training Session

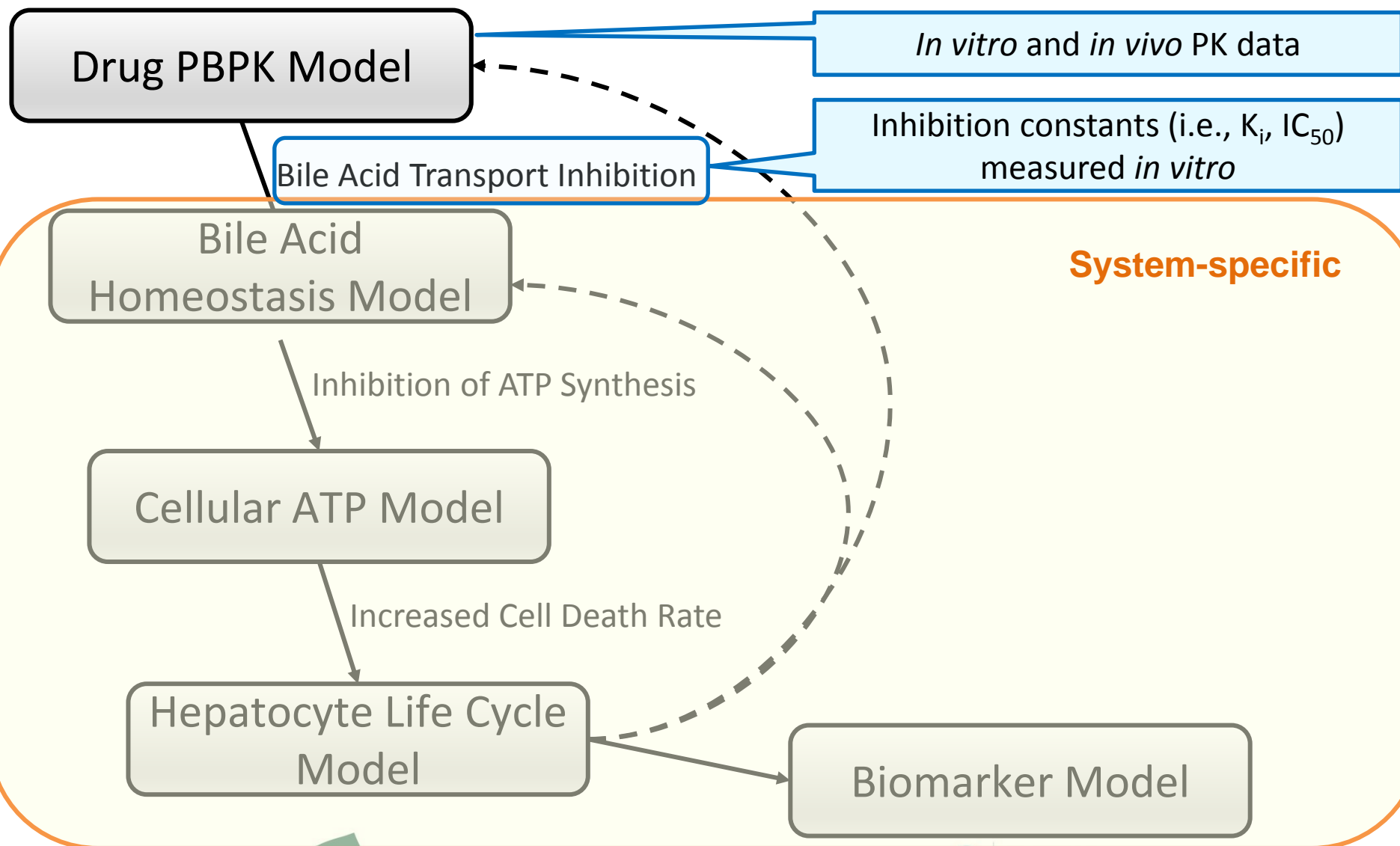
Participants should understand the following general concepts:

- Methods used to parameterize and to simulate bile acid transport disruption in DILIsym®

Modeling Compounds that Inhibit Bile Acid Transport: A Case Study with Troglitazone

- Introduction
 - Troglitazone hepatotoxicity was not detected in preclinical studies
 - 2% of patients developed ALT elevations >3X ULN in clinical trials
 - Withdrawn from the market due to idiosyncratic hepatotoxicity
- Modeling troglitazone-mediated hepatotoxicity that involves bile acid transport inhibition
 - Translate data to DILIsym[®] parameters
- Simulate troglitazone-mediated hepatotoxicity using DILIsym[®]
 - Simulate troglitazone-mediated hepatotoxicity in baseline human
 - Simulate troglitazone-mediated hepatotoxicity using human SimPops[™]


Data Inputs for Bile Acid Transport Inhibition



Translate Bile Acid Transport Inhibition Data to DILIsym[®] Parameters for Troglitazone

- Troglitazone competitively inhibits rat Bsep with a K_i of $1.3 \mu\text{M}^\dagger$
 - Will use this value for humans too; literature has shown that troglitazone has similar potency for rat and human BSEP
- Troglitazone inhibits human NTCP and rat Ntcp[‡]
 - IC_{50} values reported: $0.33 \mu\text{M}$ (human), $2.3 \mu\text{M}$ (rat)
 - Type of inhibition not known; assumed to be a competitive inhibitor
- Troglitazone is an inhibitor of human MRP4[§]
 - IC_{50} measured: $21 \mu\text{M}$
 - Type of inhibition not known; assumed to be a non-competitive inhibitor

Troglitazone m.w.
441.5 g/mol



DILIsym [®] Parameter	DILIsym [®] Parameter Input
Compound X BSEP inhibition constant	5.74E-04 mg/mL
Compound X BSEP alpha constant for inhibition	1e10 (competitive)
Compound X BSEP switch	1 (competitive)
Compound X NTCP inhibition constant	1.46E-04 mg/mL (human) 1.02E-03 mg/mL (rat)
Compound X NTCP alpha constant for inhibition	1e10 (competitive)
Compound X NTCP switch	1 (competitive)
Compound X basolateral inhibition constant	9.27E-03 mg/mL
Compound X basolateral alpha constant for inhibition	1 (non-competitive)
Compound X basolateral switch	0 (non-competitive)

[†]Funk 2001, Dawson 2011, [‡]Marion 2007, [§]Yang 2014

Translate Bile Acid Transport Inhibition Data to DILIsym[®] Parameters for Troglitazone Sulfate

- Troglitazone sulfate is a more potent inhibitor of BSEP compared to troglitazone[†]
 - Troglitazone sulfate competitively inhibits rat Bsep with a K_i of 0.23 μM
 - Will use this value for humans too
- Troglitazone sulfate effects on NTCP not known
 - Assumed to be the same as troglitazone[‡]
- Troglitazone sulfate is a non-competitive inhibitor of human MRP4 with a K_i of 8 μM [§]
 - Rat Mrp4 K_i is assumed to be the same as humans

Troglitazone sulfate
m.w. : 521.6 g/mol



DILIsym [®] Parameter	DILIsym [®] Parameter Input
Compound X metabolite B BSEP inhibition constant	1.20E-04 mg/mL
Compound X metabolite B BSEP alpha constant for inhibition	1e10 (competitive)
Compound X metabolite B BSEP switch	1 (competitive)
Compound X metabolite B NTCP inhibition constant	1.46E-04 mg/mL (human) 1.02E-03 mg/mL (rat)
Compound X metabolite B NTCP alpha constant for inhibition	1e10 (competitive)
Compound X metabolite B NTCP switch	1 (competitive)
Compound X metabolite B basolateral inhibition constant	4.17E-03 mg/mL
Compound X metabolite B basolateral alpha constant for inhibition	1 (non-competitive)
Compound X metabolite B basolateral switch	0 (non-competitive)

[†]Funk 2001, Dawson 2011, [‡]Marion 2007, [§]Yang 2014

Defining Drug Toxicity Parameters in DILIsym®: Human Troglitazone BA Inhibition

DILIsym® Parameter	DILIsym® Parameter Input
Compound X BSEP inhibition constant	5.74E-04 mg/mL
Compound X BSEP alpha constant for inhibition	1e10 (competitive)
Compound X BSEP switch	1 (competitive)
Compound X NTCP inhibition constant	1.46E-04 mg/mL (human)
Compound X NTCP alpha constant for inhibition	1e10 (competitive)
Compound X NTCP switch	1 (competitive)
Compound X basolateral inhibition constant	9.27E-03 mg/mL
Compound X basolateral alpha constant for inhibition	1 (non-competitive)
Compound X basolateral switch	0 (non-competitive)

DILIsym Parameter Customization

Molecule: All Molecules Mechanisms: All Mechanisms

Molecule	Mechanism	Variable	Value	Units
CompX	inhBATransport	Compound X NTCP inhibition constant	1.4600e-04 mg/mL	
		Compound X NTCP alpha constant for inhibition	1.0000e+10 dimensionless	
		Compound X NTCP switch	1 dimensionless	
		Compound X BSEP inhibition constant	5.7400e-04 mg/mL	
		Compound X BSEP alpha constant for inhibition	1.0000e+10 dimensionless	
		Compound X BSEP switch	1 dimensionless	
		Compound X basolateral inhibition constant	0.0093 mg/mL	
		Compound X basolateral alpha constant for inhibition	1 dimensionless	
		Compound X basolateral switch	0 dimensionless	
		Compound X ASBT inhibition constant	1.0000e+10 mg/mL	

Panel View Save w/ Custom Cancel Changes Save As New Save As New w/ Custom

Simulating Troglitazone-Mediated Hepatotoxicity in Human SimPops™

HUMANS

Troglitazone 400mg/day for 6 months

DILIsym v4B

File Results View Help

SimSingle Setup

New SimSingle Load SimSingle

Human_TGZ_400mg_6mo

Input Parameters

Species Parameters_Species_Human_v4B Customize

Drug Parameters_Drug_Human_Troglitazone_v4B Customize

Caloric Intake Parameters_Calories_Human_v4B Customize

Comp W Dosing Parameters_CompWDosing_Blank_v4B Customize

Comp X Dosing 400mgperday_6months_oral Customized

Comp Y Dosing Parameters_CompYDosing_Human_v4B Customize

Time 6_months Customized

Solver Parameters_Solver_Default_v4B Customize

Input Panel Panel_Blank Viewer

Simulate Run in Parallel **SimPops** Param Sweep Data Comparison

Specify Data

Plot Table Export Save Results SimSingle

SimPops™

Human_troglitazone_bile_acid_v3B_6

DILIsym SimPops

SimSingle Base File Human_TGZ_400mg_6mo

SimPops File Human_troglitazone_bile_acid_v3B_6

Sample size of SimPops (n) 331

Variables included in SimPops

- Body_mass
- CDCA_amidation_Vmax
- CDCAamide_baso_Vmax
- CDCAamide_canal_Vmax
- CDCAamide_uptake_Vmax
- CompX_Met_B_bil_cl
- CompX_Vmax_L_B
- Km_CDCAamide_tox_direct
- Km_LCAsulfate_tox_direct
- LCA_synthesis_Vmax
- LCAamide_sulfation_Vmax
- LCAsulfate_canal_Vmax

Load initial conditions for SimPops ☒

Select DILIsym Outouts New output panel All

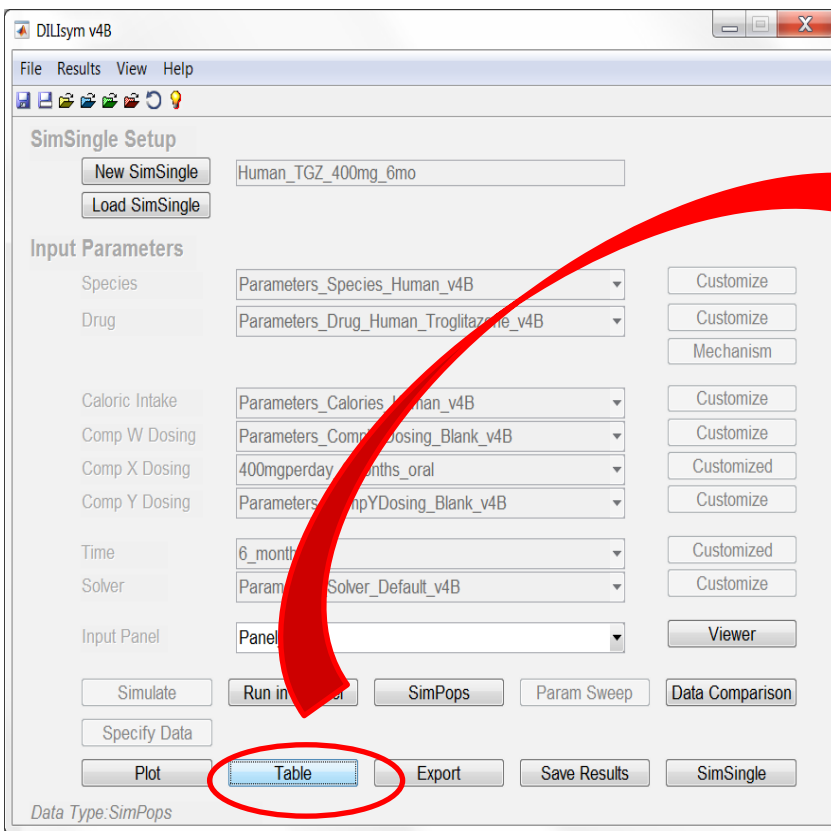
Save SimPops results to data file ☒


Run Cancel

Exploring Troglitazone-Mediated Hepatotoxicity in Human SimPops™




Load SimPops™ Results

HUMANS



 DILIsm v4B Output Table

Group	Subgroup	Output Variable	Metric	Value	Units
All Groups	All Subgroups	None Selected	None Selected		
Outcomes	Outcomes	Number of deaths	Count	1	dimensionless
Outcomes	Outcomes	ALT at or over 3x ULN	Count	10	dimensionless
Outcomes	Outcomes	Bilirubin over 2x ULN	Count	6	dimensionless
	Outcomes	Hy's Law cases	Count	6	dimensionless

 Calculate  Reset 

Troglitazone 400mg/day for 6 months

Output	Incidence
Number of deaths	1 / 331 (0.3%)
ALT elevations > 3X	10 / 331 (3.0%)
Bilirubin elevations > 2X	6 / 331 (1.8 %)
Hy's Law cases	6 / 331 (1.8 %)

Simulation Results



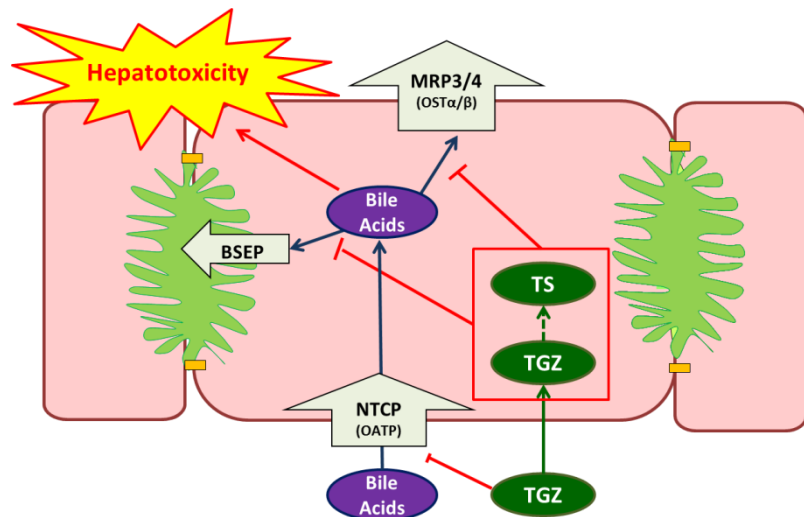
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What is the Contribution of Troglitazone Sulfate to the Hepatotoxicity?



- Troglitazone sulfate is a more potent BSEP inhibitor compared to troglitazone
- Systemic/hepatic exposure to troglitazone sulfate is greater than troglitazone

DILIsym® Parameter	DILIsym® Parameter Input	Adjusted DILIsym® Parameter Input
Compound X metabolite B BSEP inhibition constant	1.20E-04 mg/mL	1.00E+10 mg/mL
Compound X metabolite B NTCP inhibition constant	1.46E-04 mg/mL (human); 1.02E-03 mg/mL (rat)	1.00E+10 mg/mL
Compound X metabolite B basolateral inhibition constant	4.17E-03 mg/mL	1.00E+10 mg/mL

Turning Off Troglitazone Sulfate BA Inhibition

DILIsym Parameter Customization

Molecule: All Molecules Mechanisms: All Mechanisms

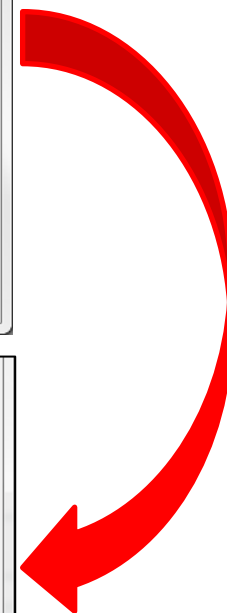
Molecule	Mechanism	Variable	Value	Units	
CompXMetB	inhBAtransport	Compound X ASBT inhibition constant	1.0000e+10	mg/mL	This par...
		Compound X metabolite B NTCP inhibition constant	1.4600e-04	mg/mL	This par...
		Compound X metabolite B NTCP alpha constant for inhibition	1.0000e+10	dimensionless	This par...
		Compound X metabolite B NTCP switch	1	dimensionless	0 = nonco...
		Compound X metabolite B BSEP inhibition constant	1.2000e-04	mg/mL	This par...
		Compound X metabolite B BSEP alpha constant for inhibition	1.0000e+10	dimensionless	This par...
		Compound X metabolite B BSEP switch	1	dimensionless	0 = nonco...
		Compound X metabolite B basolateral inhibition constant	0.0042	mg/mL	This par...
		Compound X metabolite B basolateral alpha constant for inhibition	1	dimensionless	This par...
Compound X metabolite B basolateral switch	0	dimensionless	0 = nonco...		

Panel View Save w/ Custom Cancel Changes Save As New Save As New w/ Custom

Molecule: All Molecules Mechanisms: All Mechanisms

Molecule	Mechanism	Variable	Value	Units	
CompXMetB	inhBAtransport	Compound X ASBT inhibition constant	1.0000e+10	mg/mL	This parameter represents the apical...
		Compound X metabolite B NTCP	1.0000e+10	mg/mL	This parameter represents the sod...
		Compound X metabolite B NTCP alpha co...	1.0000e+10	dimensionless	This parameter represents the sodium...
		Compound X metabolite B NTCP switch	1	dimensionless	0 = noncompetitive/mixed, 1 = compe...
		Compound X metabolite B BSEP	1.0000e+10	mg/mL	This parameter represents the bile...
		Compound X metabolite B BSEP alpha co...	1.0000e+10	dimensionless	This parameter represents the bile sal...
		Compound X metabolite B BSEP switch	1	dimensionless	0 = noncompetitive/mixed, 1 = compe...
		Compound X metabolite B basolateral	1.0000e+10	mg/mL	This parameter represents the bas...
		Compound X metabolite B basolateral alph...	1	dimensionless	This parameter represents the basolat...
Compound X metabolite B basolateral swit...	0	dimensionless	0 = noncompetitive/mixed, 1 = compe...		

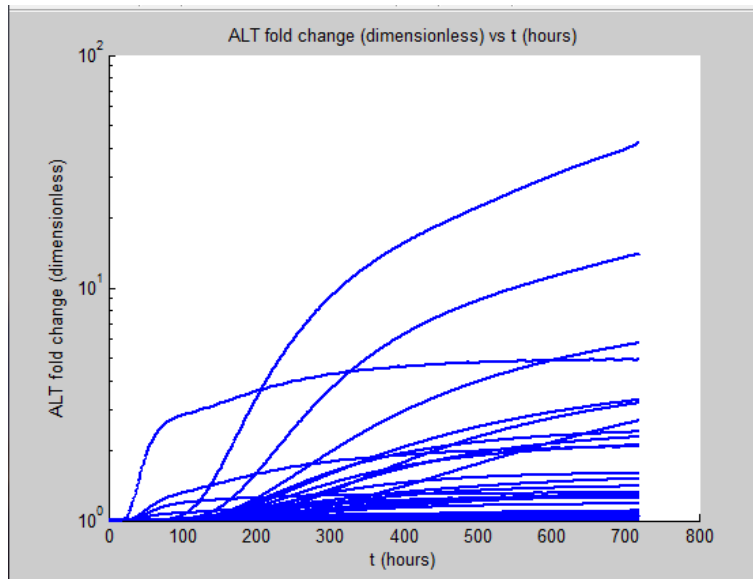
Panel View Save w/ Custom Cancel Changes Save As New Save As New w/ Custom



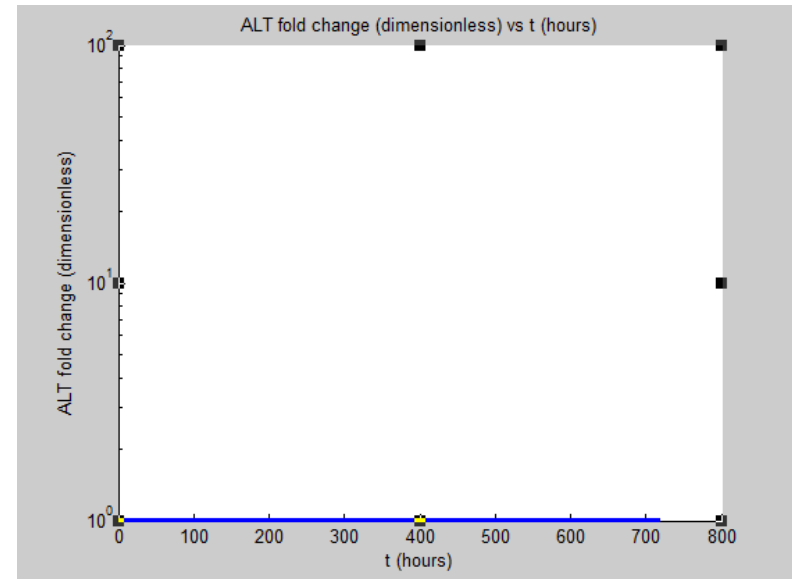
Troglitazone Sulfate is an Important Contributor for Hepatotoxicity

HUMANS

Troglitazone 400mg/day for 1 months



Troglitazone 400mg/day for 1 months – No troglitazone sulfate effects



Output	Incidence
Number of deaths	0 / 331 (0%)
ALT elevations > 3X	6 / 331 (1.8%)
Bilirubin elevations > 2X	1 / 331 (0.3%)
Hy's Law cases	1 / 331 (0.3%)

Output	Incidence
Number of deaths	0 / 331 (0%)
ALT elevations > 3X	0 / 331 (0%)
Bilirubin elevations > 2X	0 / 331 (0%)
Hy's Law cases	0 / 331 (0%)