



U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program





Toxicokinetic Chemical Simulator (ToCS): A Graphical User Interface for High- Throughput Chemical Analysis

Kristen Windoloski, Contractor

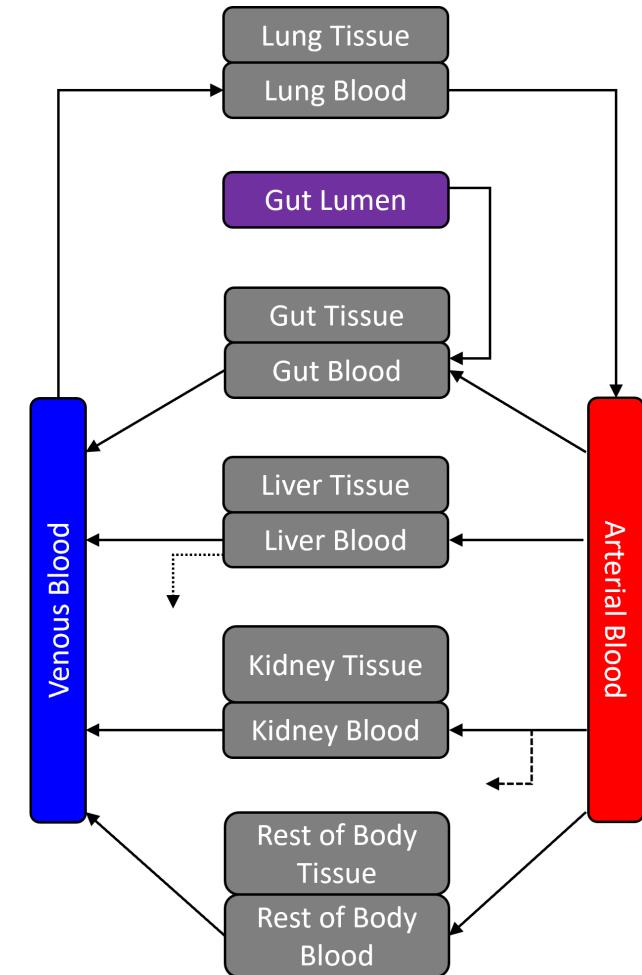
Office of Scientific Coordination and Computational Sciences (OSCCS)

Office of Laboratory Operations and Applied Science (OLOAS)

Session II: Concentration-Time Profile Module

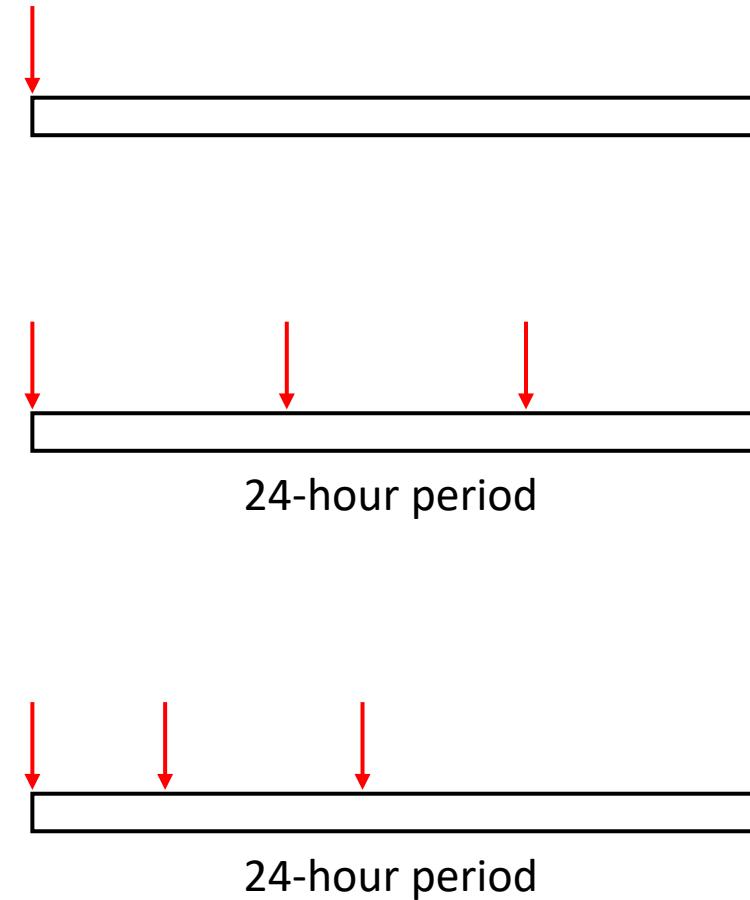
PBTK Modeling Overview

- Physiologically-based toxicokinetic (PBTK) or pharmacokinetic (PBPK) models predict how a chemical moves through the body
- Illustrates absorption, distribution, metabolism, and excretion (ADME) processes ('what the body does to the chemical')
- Models consist of a system of ordinary differential equations (ODEs), where each equation describes the rate of change of the chemical amount/concentration in a model compartment over time
 - Compartments typically represent specific organs or tissues (may include other anatomical elements)
 - May consist of lumped compartments

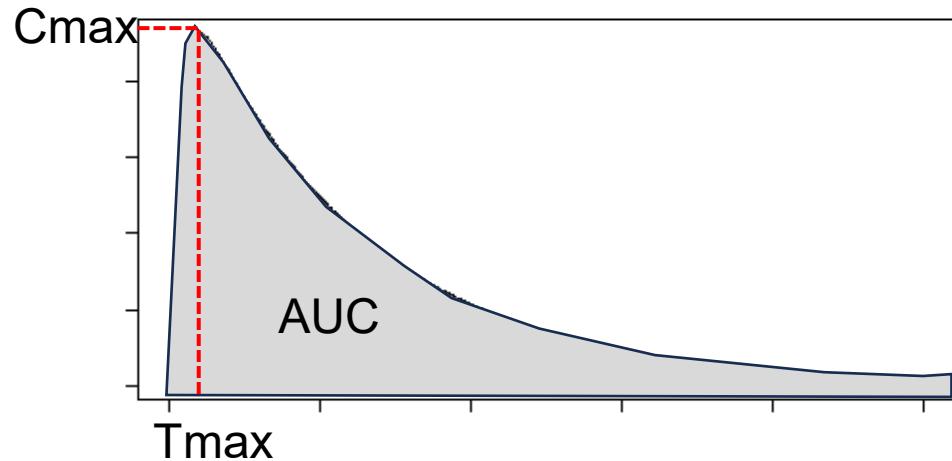


Available Dosing Scenarios

- Single Dose
 - One dose that does not repeat
 - Example: 1 dose at 8:00am
- Multiple Doses
 - Evenly distributed daily doses (ideal for pharmaceuticals)
 - Dose amounts and times must be the same daily during every administration
 - Example: 1 dose every 8 hrs
 - Unevenly distributed doses (ideal for food)
 - Dose amounts may be different during every dose
 - Dose times can be uneven across 24 hrs
 - Doses do not need to occur daily
 - Example: 1 dose at 8:00am, 12:00pm, and 6:00pm daily



Concentration-Time Profile Module Outputs



- Plots and tables of the concentrations or amounts of a chemical over time in each model compartment
- Summary statistics of the concentration-time profile curves within each model compartment
 - Cmax – maximal concentration or amount
 - Tmax – time to Cmax
 - AUC – area under the curve
 - Represents the total exposure of the chemical over time

Concentration-Time Profile Module Inputs

Required:

- Species and species preferences (if applicable)
- Model selection
- Number of simulation days
- In silico parameter preference
- Dosing method, units, frequency, and amount
- Chemicals to simulate

Optional:

- Initial compartment values
- Bioavailability settings
- Model solver settings
- Model calculation preferences involving the hepatic clearance, fraction unbound in plasma, ratio of chemical concentration in blood to plasma, and partition coefficients

Example 1 Scenario

- Obtain the concentration-time profiles of five indirect food additives during all three trimesters of human pregnancy

Chemical Name	CASRN
Cyclohexylamine	108-91-8
Triethanolamine	102-71-6
4,4'-sulfonyldiphenol (Bisphenol S)	80-09-1
Ethanolamine	141-43-5
Dodecylguanidine acetate (Diodine)	2439-10-3

- Use the available in silico parameters
- Orally consumes 0.5 mg/kg BW of each chemical twice a day (every 12 hours), every day for the entire pregnancy

Example 1: General Parameters Tab

Toxicokinetic Chemical Simulator (ToCS) [General Parameters](#) [Model Specifications](#) [Compound Selection](#) [Advanced \(Optional\) Parameters](#) [Run Simulation](#)

INSTRUCTIONS

Fill out the prompts on each of the above tabs moving left to right. Then, click the 'Run Simulation' tab to run the simulation or reset all selections.

ToCS provides four outputs: 1) Concentration-time profiles (returns chemical concentrations in body compartments over time), 2) Steady state (SS) concentration (returns SS concentrations in body compartments from an oral infusion), 3) In vitro to in vivo extrapolation (IVIVE) (returns oral equivalent doses to in vitro bioactive concentrations), 4) Parameter calculations (returns elimination rates, volumes of distribution, tissue to unbound plasma partition coefficients, half-lives, and total plasma clearances).

This application uses the U.S. EPA's R package 'httk'. For more information on ToCS and 'httk', please refer to the following links.

[Vignettes \(ToCS tutorials\)](#)

[Report ToCS issues/suggestions](#)

[httk publication](#)

[httk CRAN webpage](#)

OUTPUT

Select the desired output.

Concentration-time profiles ▾

SPECIES

Select the species to analyze.

Human ▾

Example 1: Model Specifications Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters **Model Specifications** Compound Selection Advanced (Optional) Parameters Run Simulation

MODEL

Select a model to simulate.

full_pregnancy

Select whether to use in silico generated parameters for compounds with missing in vitro data. These parameters will not overwrite existing in vitro data, and it will expand the number of compounds available.

Yes, load in silico parameters

DOSING

Select the administration method of the compound(s).

oral

Select the units of the administered dose(s).

mg/kg

Select the dosing frequency.

Multiple Doses

Are equal doses given evenly across a 24 hour period (i.e. 1 mg/kg BW every 8 hours)?

Yes

Enter the amount administered during every dose (in the specified units).

0.5

Select how often the above dose is administered (every ____ hours).

0 2.5 4 5 7.5 10 12.5 15 17.5 20 22.5 24

Example 1: Compound Selection Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications **Compound Selection** Advanced (Optional) Parameters Run Simulation

INSTRUCTIONS

Click on the appropriate link(s) below to download guidance on how to upload data under the 'Uploaded Data' card. Follow the 'Instructions' document in the downloaded folder to correctly format the file you want to upload.

[Uploaded Physical-Chemical Data File Folder](#)

PRELOADED COMPOUNDS

Select the types of compounds you want to simulate.

Choose from all available chemicals ▾

Select any preloaded compounds. Search through the list by clicking on the box and scrolling or typing in a name. The list may not show all available compounds. Click on a compound to select it. You may select multiple.

108-91-8, Cyclohexylamine 102-71-6, Triethanolamine
141-43-5, Ethanolamine 80-09-1, 4,4'-sulfonyldiphenol
2439-10-3, Dtxsid3020548

UPLOADED DATA

Upload a CSV file of physical and chemical data for compounds not in the preloaded list (if desired). Download the 'Uploaded Physical-Chemical Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... No file selected

Example 1: Advanced Parameters Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection **Advanced (Optional) Parameters** Run Simulation

MODEL CONDITIONS	MODEL SOLVER	BIOAVAILABILITY	OUTPUT SPECIFICATION
No options for this category.			

Example 1: Run Simulation Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection Advanced (Optional) Parameters **Run Simulation**

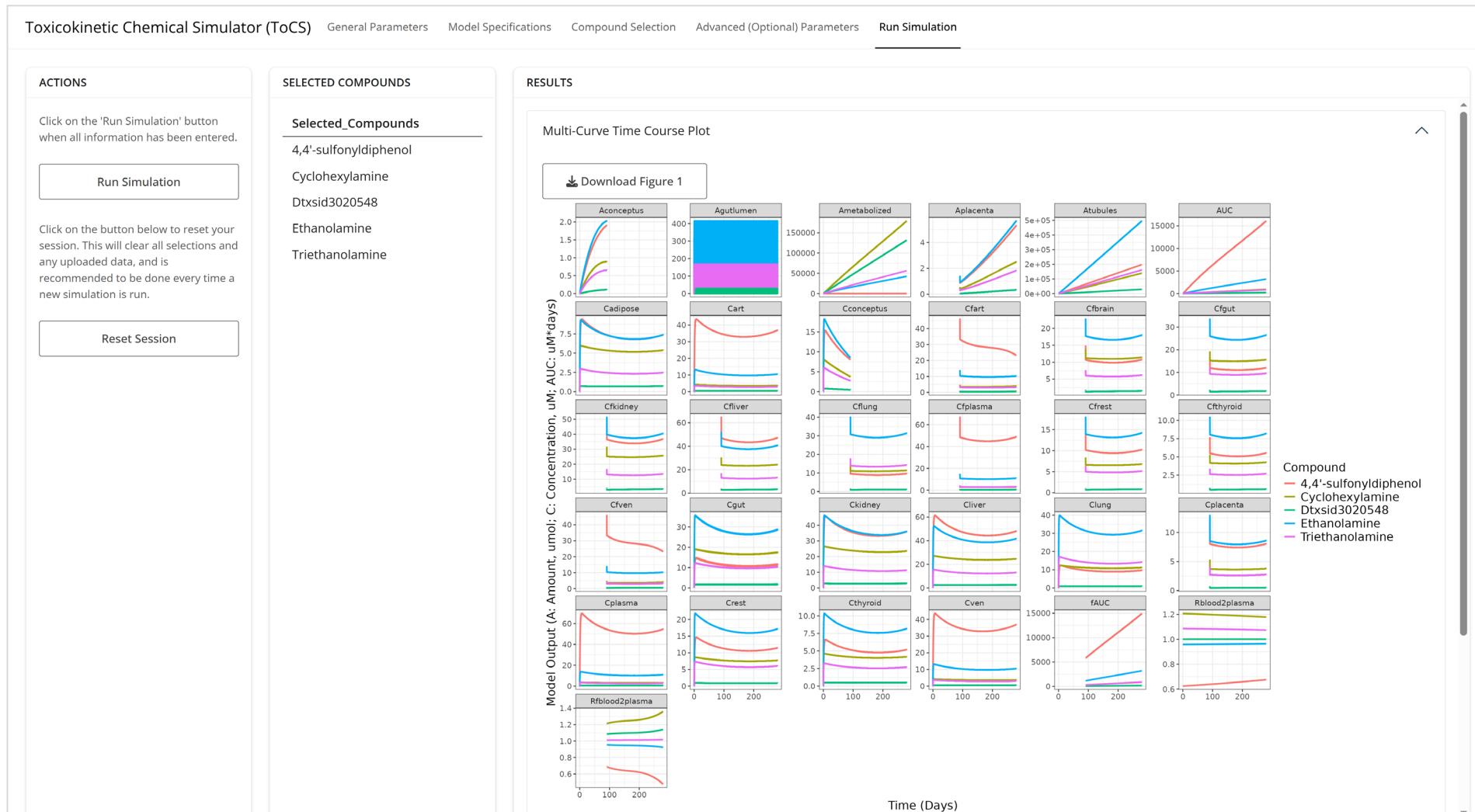
ACTIONS
Click on the 'Run Simulation' button when all information has been entered.
Run Simulation

Click on the button below to reset your session. This will clear all selections and any uploaded data, and is recommended to be done every time a new simulation is run.
Reset Session

SELECTED COMPOUNDS
Selected_Compounds
4,4'-sulfonyldiphenol
Cyclohexylamine
Dtxsid3020548
Ethanolamine
Triethanolamine

RESULTS
Multi-Curve Time Course Plot
[Click here to see definitions of each subplot heading.\(model compartment\)](#)
Individual Time Course Plots
Time Course Data
TK Summary Data

Example 1: Run Simulation Tab



Example 1: Run Simulation Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection Advanced (Optional) Parameters **Run Simulation**

ACTIONS

Click on the 'Run Simulation' button when all information has been entered.

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Reset Session

SELECTED COMPOUNDS

Selected Compounds

4,4'-sulfonyldiphenol
Cyclohexylamine
Dtxsid3020548
Ethanolamine
Triethanolamine

RESULTS

Multi-Curve Time Course Plot

Individual Time Course Plots

Download Individual Compound Plots

Model Output (A: Amount, umol; C: Concentration, μM ; AUC: uM^2days)

Compound
— 4,4'-sulfonyldiphenol

Example 1: Run Simulation Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection Advanced (Optional) Parameters **Run Simulation**

ACTIONS		SELECTED COMPOUNDS		RESULTS																																																																																
Click on the 'Run Simulation' button when all information has been entered. Run Simulation		Selected_Compounds 4,4'-sulfonyldiphenol Cyclohexylamine Dtxsid3020548 Ethanolamine Triethanolamine		Multi-Curve Time Course Plot Individual Time Course Plots Time Course Data Download ADME Time Course Data Download ADME Simulation Parameters TK Summary Data Download Table 1 Show 10 entries Search: _____																																																																																
				<table border="1"> <thead> <tr> <th></th> <th>Tmax.4,4'-sulfonyldiphenol</th> <th>MaxValue.4,4'-sulfonyldiphenol</th> <th>AUC.4,4'-sulfonyldiphenol</th> <th>Tmax.Cyclohexylamine</th> <th>MaxValue.Cyclohexylamine</th> <th>AUC.Cycl</th> </tr> </thead> <tbody> <tr><td>Agutlumen</td><td>0.1668</td><td>118</td><td>16530</td><td>0.8334</td><td>245.1</td><td></td></tr> <tr><td>Cgut</td><td>6.667</td><td>14.86</td><td>3225</td><td>3.333</td><td>19.1</td><td></td></tr> <tr><td>Cliver</td><td>6.833</td><td>61.46</td><td>13460</td><td>3.167</td><td>27.19</td><td></td></tr> <tr><td>Ckidney</td><td>7</td><td>45.94</td><td>10060</td><td>3.333</td><td>26.51</td><td></td></tr> <tr><td>Clung</td><td>6.5</td><td>12.37</td><td>2710</td><td>3.333</td><td>12.44</td><td></td></tr> <tr><td>Cven</td><td>7</td><td>43.57</td><td>9876</td><td>3.333</td><td>4.171</td><td></td></tr> <tr><td>Cart</td><td>6.833</td><td>43.57</td><td>9877</td><td>3.333</td><td>4.174</td><td></td></tr> <tr><td>Cadipose</td><td>7</td><td>9.424</td><td>2065</td><td>3.333</td><td>5.968</td><td></td></tr> <tr><td>Cthyroid</td><td>6.833</td><td>6.62</td><td>1450</td><td>3.333</td><td>4.624</td><td></td></tr> <tr><td>Crest</td><td>7</td><td>14.66</td><td>3209</td><td>3.5</td><td>8.654</td><td></td></tr> </tbody> </table> Showing 1 to 10 of 21 entries Previous 1 2 3 4 Next					Tmax.4,4'-sulfonyldiphenol	MaxValue.4,4'-sulfonyldiphenol	AUC.4,4'-sulfonyldiphenol	Tmax.Cyclohexylamine	MaxValue.Cyclohexylamine	AUC.Cycl	Agutlumen	0.1668	118	16530	0.8334	245.1		Cgut	6.667	14.86	3225	3.333	19.1		Cliver	6.833	61.46	13460	3.167	27.19		Ckidney	7	45.94	10060	3.333	26.51		Clung	6.5	12.37	2710	3.333	12.44		Cven	7	43.57	9876	3.333	4.171		Cart	6.833	43.57	9877	3.333	4.174		Cadipose	7	9.424	2065	3.333	5.968		Cthyroid	6.833	6.62	1450	3.333	4.624		Crest	7	14.66	3209	3.5	8.654	
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Example 2 Scenario

- Obtain the human concentration-time profiles of three food color additives using the pbtk model over 30 days

Chemical Name	CASRN
FD&C Yellow 6	2783-94-0
FD&C Green 1	2353-45-9
Ponceau 4R	2611-82-7

- Do not use the available in silico parameters
- Orally consume 1 mg/kg BW of each chemical at the start of every other day
- Use the default caco-2 apical-to-basal membrane permeability value

Example 2: General Parameters Tab

The screenshot shows the 'General Parameters' tab of the ToCS application. The interface is divided into three main sections: INSTRUCTIONS, OUTPUT, and SPECIES.

INSTRUCTIONS: Provides instructions for using the application, mentioning four output types: Concentration-time profiles, Steady state (SS) concentration, In vitro to in vivo extrapolation (IVIVE), and Parameter calculations. It also notes the use of the U.S. EPA's R package 'httk'.

OUTPUT: A dropdown menu titled 'Select the desired output.' currently set to 'Concentration-time profiles'.

SPECIES: A dropdown menu titled 'Select the species to analyze.' currently set to 'Human'.

Example 2: Model Specifications Tab



Toxicokinetic Chemical Simulator (ToCS) General Parameters **Model Specifications** Compound Selection Advanced (Optional) Parameters Run Simulation

MODEL

Select a model to simulate.

Select whether to use in silico generated parameters for compounds with missing in vitro data. These parameters will not overwrite existing in vitro data, and it will expand the number of compounds available.

Enter the total simulation time (in days).

DOSING

Select the administration method of the compound(s).

Select the units of the administered dose(s).

Select the dosing frequency.

Are equal doses given evenly across a 24 hour period (i.e. 1 mg/kg BW every 8 hours)?

Enter a list of dose amounts (in the specified units) and times (in days) administered. The list must be entered as time1, time2, dose1, dose2, etc. For example, if at 0, 0.5, and 2 days the doses of 1, 3, and 4 mg/kg/BW were given, respectively, enter 0, 0.5, 2, 1, 3, 4 in the box.

Example 2: Compound Selection Tab

The screenshot shows the 'Compound Selection' tab of the ToCS application. The interface is divided into three main sections: 'INSTRUCTIONS', 'PRELOADED COMPOUNDS', and 'UPLOADED DATA'.

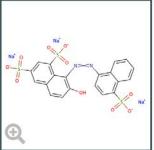
- INSTRUCTIONS:** A section containing instructions and a link to download guidance on how to upload data.
- PRELOADED COMPOUNDS:** A section where users can select compound types from a dropdown menu and search through a list of preloaded compounds by name.
- UPLOADED DATA:** A section where users can upload a CSV file of physical and chemical data for compounds not in the preloaded list. A file named 'Example2ChemUpload.csv' is currently uploaded.

Key UI elements include:

- A dropdown menu labeled 'Choose from all available chemicals'.
- A text input field containing the text '2783-94-0, Fd&c yellow 6 2353-45-9, Fd&c green no. 3'.
- A 'Browse...' button for file selection.
- A file name indicator 'Example2ChemUpload.csv'.
- A blue button labeled 'Upload complete'.

Example 2: Uploading Data for Ponceau 4R

CompTox Chemicals Dashboard v2.6.0 Home Search ▾ Lists ▾ About ▾ Tools ▾ Submit Comments Search all data

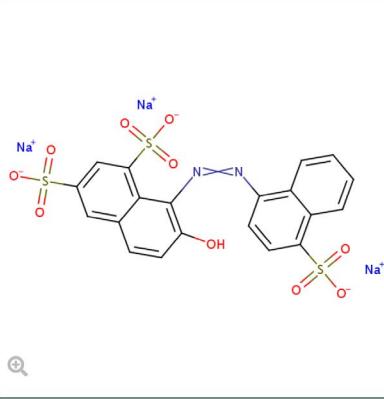


C.I. Acid Red 18, trisodium salt
2611-82-7 | DTXSID9021213
 Searched by CASRN

Chemical Details

- [Chemical Details](#)
- [Executive Summary](#)
- [Physchem Prop.](#)
- [Env. Fate/Transport](#)
- [Hazard Data](#)
- [Safety > GHS Data](#)
- ADME > IVIVE**
- [Exposure](#)
- [Bioactivity](#)
- [GenRA](#)
- [ACToR](#)
- [Literature](#)
- [Links](#)
- [Comments](#)

Chemical Details



Wikipedia

Ponceau 4R (known by more than 100 synonyms, including as C.I. 16255, cochineal red A, C.I. acid red 18, brilliant scarlet 3R, brilliant scarlet 4R, new coccine,) is a synthetic colourant that may be used as a food colouring. It is denoted by E Number E124. Its chemical name is 1-(4-sulfo-1-naphthylazo)-2-naphthol-6,8-disulfonic acid, trisodium salt. Ponceau (17th century French for "poppy-coloured") is the generic name for a family

[Read more](#)

Quality Control Notes

Intrinsic Properties

Molecular Formula: $C_{20}H_{11}N_2Na_3O_{10}S_3$

Average Mass: 604.46 g/mol

Monoisotopic Mass: 603.926891 g/mol

[MOL FILE](#)

[FIND ALL CHEMICALS](#)

[ISOTOPE MASS DISTRIBUTION](#)

Structural Identifiers

Linked Substances

Example 2: Uploading Data for Ponceau 4R

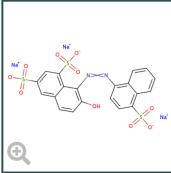
CompTox Chemicals Dashboard v2.6.0

Home Search ▾ Lists ▾ About ▾ Tools ▾

C.I. Acid Red 18, trisodium salt

2611-82-7 | DTXSID9021213

Searched by CASRN



Properties: Summary

EXPORT

Summary

Property ↓↑	≡ Experimental average	↓↑ ≡ Predicted average	↓↑ ≡ Experimental median	↓↑ ≡ Predicted median	↓↑ ≡ Experimental range	↓↑ ≡ Predicted range ↓↑ ≡	Unit ↓↑
Henry's Law	-	2.09e-11 (1)	-	2.09e-11	-	2.09e-11	atm-m ³ /mole
Boiling Point	-	326 (1)	-	326	-	326	°C
Melting Point	-	227 (1)	-	227	-	227	°C
LogD5.5	-	1.98 (1)	-	1.98	-	1.98	Log10 unitless
LogD7.4	-	0.780 (1)	-	0.780	-	0.780	Log10 unitless
Vapor Pressure	-	2.95e-10 (1)	-	2.95e-10	-	2.95e-10	mmHg
Water Solubility	0.132 (1)	0.132 (1)	0.132	0.132	0.132	0.132	mol/L
LogK _{oa} : Octanol-Air	-	9.48 (1)	-	9.48	-	9.48	Log10 unitless
LogK _{ow} : Octanol-Water	-	2.07 (1)	-	2.07	-	2.07	Log10 unitless
pKa Acidic Apparent	-	6.13 (1)	-	6.13	-	6.13	Log10 unitless

Example 2: Advanced Parameters Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection Advanced (Optional) Parameters Run Simulation

MODEL CONDITIONS

Would you like to change the initial compound amount in each compartment from its default value of 0 (no compound in the compartment when the simulation begins)?

No, keep the default amounts (default)

Select whether to recalculate the chemical concentration blood to plasma ratio from its in vitro or estimated value using the hematocrit, fraction unbound in presence of plasma proteins, and red blood cell partition coefficient.

Do not recalculate (default)

Select whether protein binding is taken into account in liver clearance.

Yes, include protein binding (default)

Select whether to adjust the chemical fraction unbound in presence of plasma proteins for lipid binding.

Yes, adjust the fraction of unbound plasma (default)

Select whether to use regressions when calculating partition coefficients.

Use regressions (default)

Enter the p-value threshold for the in vitro intrinsic hepatic clearance rate where clearance assay results with p-values above this threshold are set to zero.

0.05

Enter the minimum acceptable chemical fraction unbound in presence of plasma proteins. All values

MODEL SOLVER

Select the ODE solver method. See R documentation on the 'deSolve' function for method details.

lsoda

Enter the number of time steps per hour for the solver to take.

4

Select the exponent (power of 10) of the relative tolerance for the ODE solver.

Select the exponent (power of 10) of the desired absolute tolerance for the ODE solver.

BIOAVAILABILITY

Enter a default value for the Caco-2 apical-to-basal membrane permeability (denoted Caco2.Pab, 10^{-6} cm/s).

1.5

Select whether to use the Caco2.Pab value set above to estimate F_abs (the in vivo measured fraction of an oral dose absorbed from the gut lumen into the gut) if bioavailability data is unavailable.

Use the Caco2.Pab value selected above (default)

Select whether to use the Caco2.Pab value set above to calculate F_gut (the in vivo measured fraction of an oral dose that passes gut metabolism and clearance) if bioavailability data is unavailable.

Use the Caco2.Pab value selected above (default)

Select whether to overwrite in vivo F_abs and F_gut data (if available).

Do not overwrite in vivo values (default)

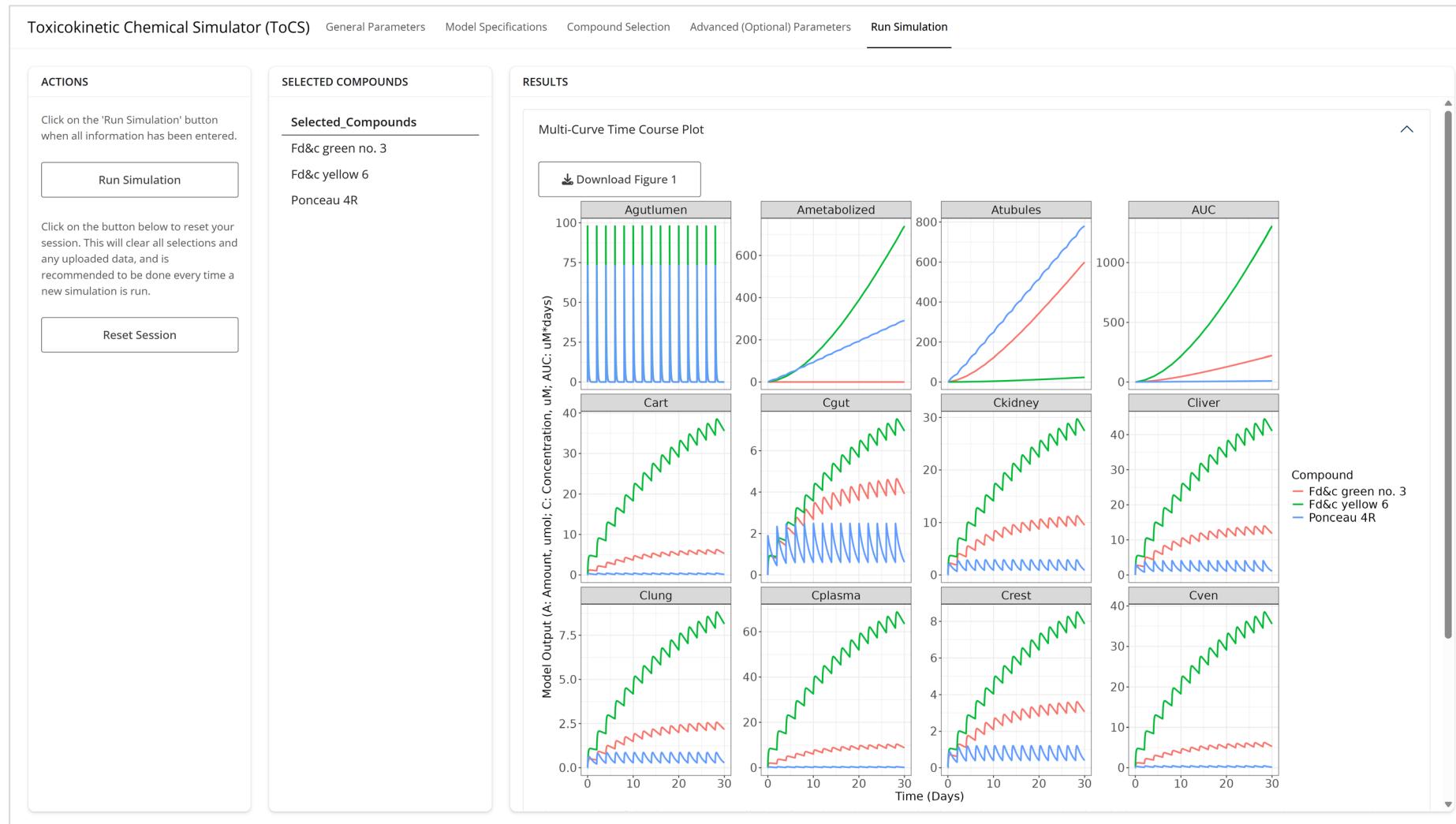
Select whether to keep F_abs and F_gut at 100% availability (which overwrites all other bioavailability parameter settings above).

Do not keep Fabs and Fgut at 100% availability (default)

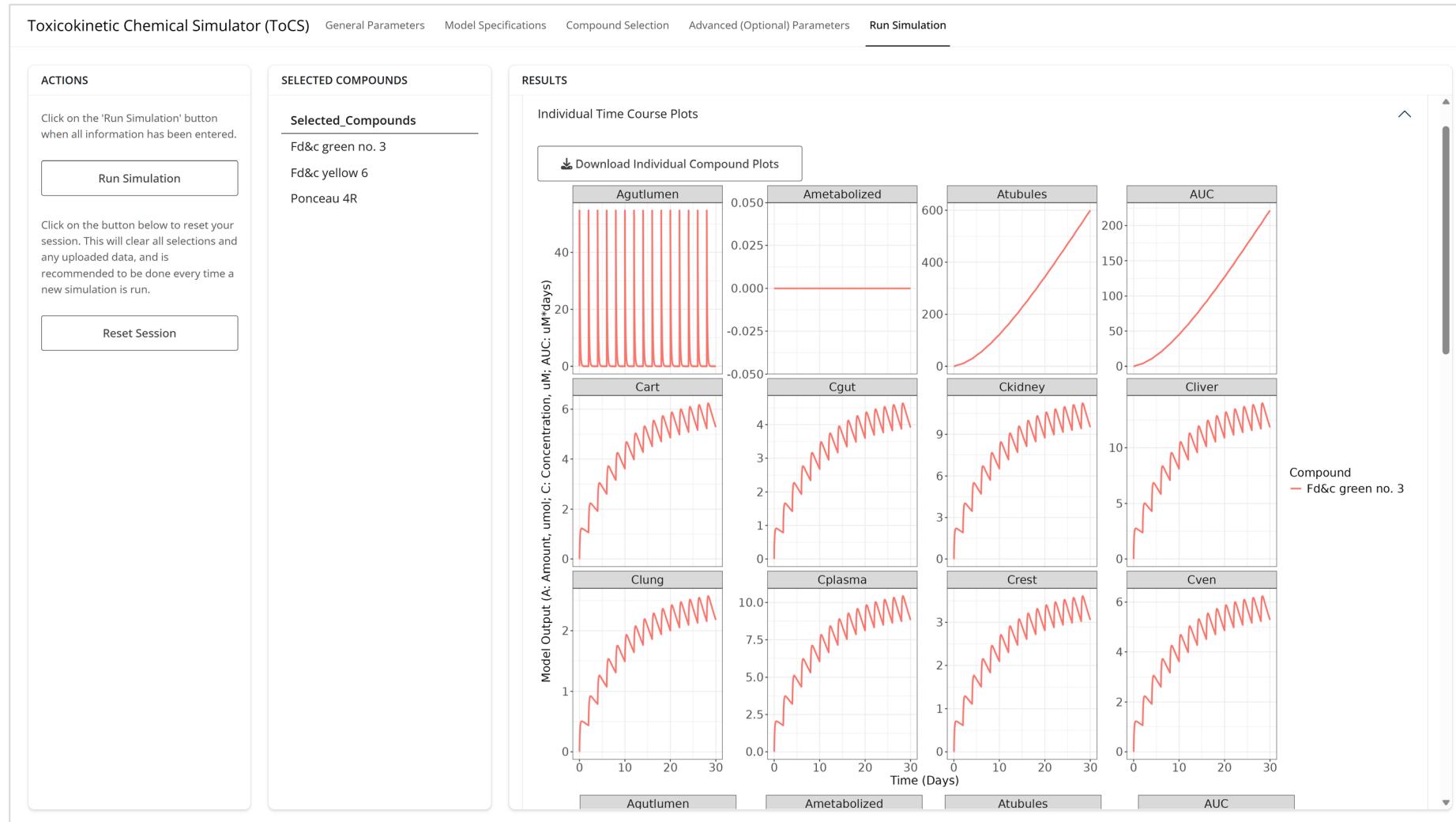
OUTPUT SPECIFICATION

Enter the times (in days) to output concentrations. Leave blank if no specific times are needed. Enter a comma-separated list, such as 0, 1, 2, ... signifying output 0, 1, and 2 days after dosing begins.

Example 2: Run Simulation Tab



Example 2: Run Simulation Tab



Example 2: Run Simulation Tab

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Specifications Compound Selection Advanced (Optional) Parameters **Run Simulation**

ACTIONS	SELECTED COMPOUNDS	RESULTS																																																																		
Click on the 'Run Simulation' button when all information has been entered. Run Simulation	<u>Selected_Compounds</u> Fd&c green no. 3 Fd&c yellow 6 Ponceau 4R	Time Course Data Download ADME Time Course Data Download ADME Simulation Parameters TK Summary Data Download Table 1 Show 10 entries Search: <table border="1"> <thead> <tr> <th></th> <th>Tmax.Fd&c.green.no..3</th> <th>MaxValue.Fd&c.green.no..3</th> <th>AUC.Fd&c.green.no..3</th> <th>Tmax.Fd&c.yellow.6</th> <th>MaxValue.Fd&c.yellow.6</th> </tr> </thead> <tbody> <tr><td>Agutlumen</td><td>0.0001</td><td>54.78</td><td>95.34</td><td>0.0001</td><td>97</td></tr> <tr><td>Cgut</td><td>28.28</td><td>4.639</td><td>98.58</td><td>28.32</td><td>7.1</td></tr> <tr><td>Cliver</td><td>28.27</td><td>14.01</td><td>297.8</td><td>28.32</td><td>4</td></tr> <tr><td>Cven</td><td>28.31</td><td>6.24</td><td>132.5</td><td>28.34</td><td>38</td></tr> <tr><td>Clung</td><td>28.3</td><td>2.573</td><td>54.65</td><td>28.35</td><td>8.8</td></tr> <tr><td>Cart</td><td>28.31</td><td>6.24</td><td>132.5</td><td>28.34</td><td>38</td></tr> <tr><td>Crest</td><td>28.32</td><td>3.61</td><td>76.65</td><td>28.34</td><td>8.1</td></tr> <tr><td>Ckidney</td><td>28.3</td><td>11.24</td><td>238.7</td><td>28.33</td><td>29</td></tr> <tr><td>Cplasma</td><td>28.29</td><td>10.43</td><td>221.6</td><td>28.34</td><td>68</td></tr> <tr><td>Atubules</td><td>30</td><td>599.5</td><td>7470</td><td>30</td><td>23</td></tr> </tbody> </table> Showing 1 to 10 of 12 entries Previous 1 2 Next Table 1: Table of summary statistics (Tmax - time to maximal concentration, MaxValue - maximal amount (A, umol) or concentration (C, uM), AUC - area under the curve (uM*days)) for each compartment for each selected compound. Click here to see definitions of each row (model compartment)		Tmax.Fd&c.green.no..3	MaxValue.Fd&c.green.no..3	AUC.Fd&c.green.no..3	Tmax.Fd&c.yellow.6	MaxValue.Fd&c.yellow.6	Agutlumen	0.0001	54.78	95.34	0.0001	97	Cgut	28.28	4.639	98.58	28.32	7.1	Cliver	28.27	14.01	297.8	28.32	4	Cven	28.31	6.24	132.5	28.34	38	Clung	28.3	2.573	54.65	28.35	8.8	Cart	28.31	6.24	132.5	28.34	38	Crest	28.32	3.61	76.65	28.34	8.1	Ckidney	28.3	11.24	238.7	28.33	29	Cplasma	28.29	10.43	221.6	28.34	68	Atubules	30	599.5	7470	30	23
	Tmax.Fd&c.green.no..3	MaxValue.Fd&c.green.no..3	AUC.Fd&c.green.no..3	Tmax.Fd&c.yellow.6	MaxValue.Fd&c.yellow.6																																																															
Agutlumen	0.0001	54.78	95.34	0.0001	97																																																															
Cgut	28.28	4.639	98.58	28.32	7.1																																																															
Cliver	28.27	14.01	297.8	28.32	4																																																															
Cven	28.31	6.24	132.5	28.34	38																																																															
Clung	28.3	2.573	54.65	28.35	8.8																																																															
Cart	28.31	6.24	132.5	28.34	38																																																															
Crest	28.32	3.61	76.65	28.34	8.1																																																															
Ckidney	28.3	11.24	238.7	28.33	29																																																															
Cplasma	28.29	10.43	221.6	28.34	68																																																															
Atubules	30	599.5	7470	30	23																																																															

Try It On Your Own

Try your own simulation in the Concentration-Time Profiles module

OR

Obtain the rat concentration-time profiles of three chemicals of your choosing across 8 days and use the following inputs:

- Use rat parameter data only
- Use the 3-compartment model
- Give a 2 mg/kg dose of each chemical at the start of day 0, 2, 4, and 6
- Do not allow the use of in silico parameters
- Use 100% bioavailability
- Begin with 1 umol of each chemical in the gut

Questions?

10-Minute Break