

# Concentration-Time Profile Simulation Examples

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March 13, 2025

If you have not already read the *Introduction to the ToCS App* vignette, it is highly recommended to do so to get a general idea of the app's layout and obtain a detailed description of common user inputs across all output modules. Users should also review the README file on the ToCS GitHub page ([github.com/KristenWindoloski/ToCS](https://github.com/KristenWindoloski/ToCS)) to setup ToCS if they have not accessed the app yet. This vignette assumes that you have access the ToCS app GUI already.

## Introduction

This vignette provides three examples that use the ToCS app to generate concentration-time profiles, each example with different parameters selected. To begin, open the app by using any of the methods described in the README file. You have correctly accessed the app if your screen looks like the image below.

The screenshot shows the opening interface of the Toxicokinetic Chemical Simulator (ToCS) app. The interface has a top navigation bar with five tabs: "General Parameters", "Model Specifications", "Compound Selection", "Advanced (Optional) Parameters", and "Run Simulation". The "General Parameters" tab is currently selected. Below the navigation bar, there are three main panels. The left panel, titled "INSTRUCTIONS", contains text explaining the app's purpose and providing links for more information. The middle panel, titled "OUTPUT", has a dropdown menu labeled "Select the desired output." with a "Select" button and a red error message "Must not be equal to Select." below it. The right panel, titled "SPECIES", has a dropdown menu labeled "Select the species to analyze." with a "Select" button and a red error message "Must not be equal to Select." below it.

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 toxicokinetic (TK) outputs: 1) Concentration-time profiles, which returns chemical concentrations in bodily compartments over time, 2) Steady state (SS) concentrations, which returns SS concentrations in bodily compartments from an oral infusion, 3) In vitro in vivo extrapolation (IVIVE), which returns oral equivalent doses to in vitro bioactive concentrations, 4) Parameter calculations, which 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 'httk', refer to <https://doi.org/10.18637/jss.v079.i04> and/or <https://cran.r-project.org/web/packages/httk>

For additional guidance on ToCS, please refer to the vignettes (<https://github.com/KristenWindoloski/ToCS/tree/main/vignettes>). To report issues or suggestions for improvement, visit <https://github.com/KristenWindoloski/ToCS/issues>.

**OUTPUT**

Select the desired output.

Select

Must not be equal to Select.

**SPECIES**

Select the species to analyze.

Select

Must not be equal to Select.

The opening interface to the ToCS app.

# Model States

Before jumping into several examples, we define the output states that users will see in plots and tables generated by ToCS for this module. Below, we list the model chosen and all of its output states.

- 1compartment
  - Agutlumen = Amount of chemical in the gut lumen
  - Ccompartment = Plasma concentration of chemical in main absorption compartment
  - Ametabolized = Amount of chemical metabolized by the main compartment
  - AUC = Area under the curve of the plasma concentration
- 3compartment
  - Aintestine = Amount of chemical in the intestine
  - Cliver = Concentration of chemical in the liver
  - Csyscomp = Concentration of chemical in the systemic compartment
  - Cplasma = Concentration of chemical in the plasma
  - Atubules = Amount of chemical excreted by the systemic compartment through the tubules
  - Ametabolized = Amount of chemical metabolized by the liver
  - AUC = Area under the curve of plasma concentration
- pbtk
  - Agutlumen = Amount of chemical in the gut lumen
  - Cgut = Concentration of chemical in the gut
  - Cliver = Concentration of chemical in the liver
  - Cven = Concentration of chemical in veins
  - Clung = Concentration of chemical in the lung
  - Cart = Concentration of chemical in arteries
  - Crest = Concentration of chemical in rest of body
  - Ckidney = Concentration of chemical in kidney
  - Cplasma = Concentration of chemical in plasma
  - Atubules = Amount of chemical excreted by the kidney through the tubules
  - Ametabolized = Amount of chemical metabolized by the liver
  - AUC = Area under the curve of plasma concentration
- fetal\_pbtk
  - All outputs in the pbtk model for maternal concentrations and amounts plus:
  - Cadipose = Concentration of chemical in adipose tissue
  - Rblood2plasma = Dynamic maternal ratio of blood to plasma (unitless)
  - fAUC = Fetal area under the curve of the fetal plasma concentration
  - Cplacenta = Concentration of chemical in placenta
  - Cfliver = Concentration of chemical in fetal liver
  - Cfven = Concentration of chemical in fetal veins
  - Cfart = Concentration of chemical in fetal arteries
  - Cfgut = Concentration of chemical in fetal gut
  - Cflung = Concentration of chemical in fetal lung
  - Cfrest = Concentration of chemical in fetal rest of body
  - Cfthyroid = Concentration of chemical in fetal thyroid
  - Cfkidney = Concentration of chemical in fetal kidney
  - Cfbrain = Concentration of chemical in fetal brain
  - Cfplasma = Concentration of chemical in fetal plasma
  - Rfblood2plasma = Dynamic fetal ratio of blood to plasma (unitless)
  - Qcardiac = Amount of blood flowing from cardiac tissue (L/day)
  - Qthyroid = Amount of blood flowing from thyroid tissue (L/day)

Amount outputs have units of  $\mu\text{mol}$ , while concentration outputs are in  $\mu\text{M}$ . The area under the curve outputs have units  $\mu\text{M}\cdot\text{days}$ . Any other units are specified above when defined. The user can also check the figure captions for units. If the user wants further details on the models and their formulations, they are encouraged to check out the `httk` documentation (<https://cran.r-project.org/web/packages/httk/index.html>).

# Example 1

Let's say we want to run a simulation that outputs human concentration-time profiles over the course of one day for four compounds: Abamectin (CAS: 71751-41-2), Bisphenol-A (CAS: 80-05-7), Cyanazine (CAS: 21725-46-2), and Dimethoate (CAS: 60-51-5). The simulation will be for a single 5 mg/kg oral exposure of each compound and use the PBTK model without including in silico generated parameters in place of in vitro data.

## General Parameters Tab

Since the main output we want is concentration-time profiles, we select *Concentration-time profiles* from the drop down menu under the *Output* card. Under the *Species* card, we select *Human* species. Thus, the completed first tab should look like the page below.

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 toxicokinetic (TK) outputs: 1) Concentration-time profiles, which returns chemical concentrations in bodily compartments over time, 2) Steady state (SS) concentrations, which returns SS concentrations in bodily compartments from an oral infusion, 3) In vitro in vivo extrapolation (IVIVE), which returns oral equivalent doses to in vitro bioactive concentrations, 4) Parameter calculations, which 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 'httk', refer to <https://doi.org/10.18637/jss.v079.i04> and/or <https://cran.r-project.org/web/packages/httk>

For additional guidance on ToCS, please refer to the vignettes (<https://github.com/KristenWindolowski/ToCS/tree/main/vignettes>). To report issues or suggestions for improvement, visit <https://github.com/KristenWindolowski/ToCS/issues>.

OUTPUT

Select the desired output.

Concentration-time profiles

SPECIES

Select the species to analyze.

Human

A completed opening interface to the ToCS app.

Now, we move on to the *Model Specifications* tab.

## Model Specifications Tab

On the *Dosing* card, we leave the first two drop down menus as their default values. For the dosing frequency, we select *Single Dose* from the drop down menu. This prompts the appearance of a textbox where we can input the number of mg/kg to be administered. We change its value to 5 since we want a single 5 mg/kg exposure. On the *Model* card, we select *pbtk* for the pbtk model on the first drop down menu. Since we do not want to use in silico generated parameters for this simulation, we select *No* for the second drop down menu under the *Model* card. Finally, since we only want to run our simulation for one day, we edit the bottom box in the *Model* card to be 1 instead of the default value of 10. Now the *Model Specifications* tab is completed and should look like the image below, so we can proceed to the *Compound Selection* tab.

The screenshot shows the 'Model Specifications' tab of the 'Toxicokinetic Chemical Simulator (ToCS)'. The interface has a top navigation bar with tabs: 'General Parameters', 'Model Specifications' (active), 'Compound Selection', 'Advanced (Optional) Parameters', and 'Run Simulation'. The 'Model Specifications' tab is divided into two main sections: 'DOSING' and 'MODEL'. In the 'DOSING' section, 'oral' is selected for administration method, 'mg/kg' for units, and 'Single Dose' for frequency. A text box for dose amount contains the value '5'. In the 'MODEL' section, 'pbtk' is selected for the model, 'No, do not load in silico parameters' is selected for the in silico parameters option, and a text box for simulation time contains the value '1'.

The completed model specifications tab for the pbtk model with a single oral dose of 5 mg/kg.

## Compound Selection Tab

Since we want to simulate four compounds (abamectin, bisphenol-a, cyanazine, and dimethoate), we keep the first drop menu in the *Preloaded Compounds* card on *Choose from all available chemicals* selection and try searching the second drop down menu to see if the program is able to simulate those chemicals with the current data in httk. To see the available compounds, click on the empty box in the center column. By either scrolling or typing in the textbox, we see that the names of all four compounds are also available, so we select those. Since all of the compounds we need are available, we do not need to upload a CSV file under the *Uploaded Data* card and leave it untouched. Then, we proceed to the next tab.

Toxicokinetic Chemical Simulator (ToCS)

General ParametersModel SpecificationsCompound SelectionAdvanced (Optional) ParametersRun 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.  

71751-41-2, Abamectin

80-05-7, Bisphenol-a

21725-46-2, Cyanazine

60-51-5, Dimethoate

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

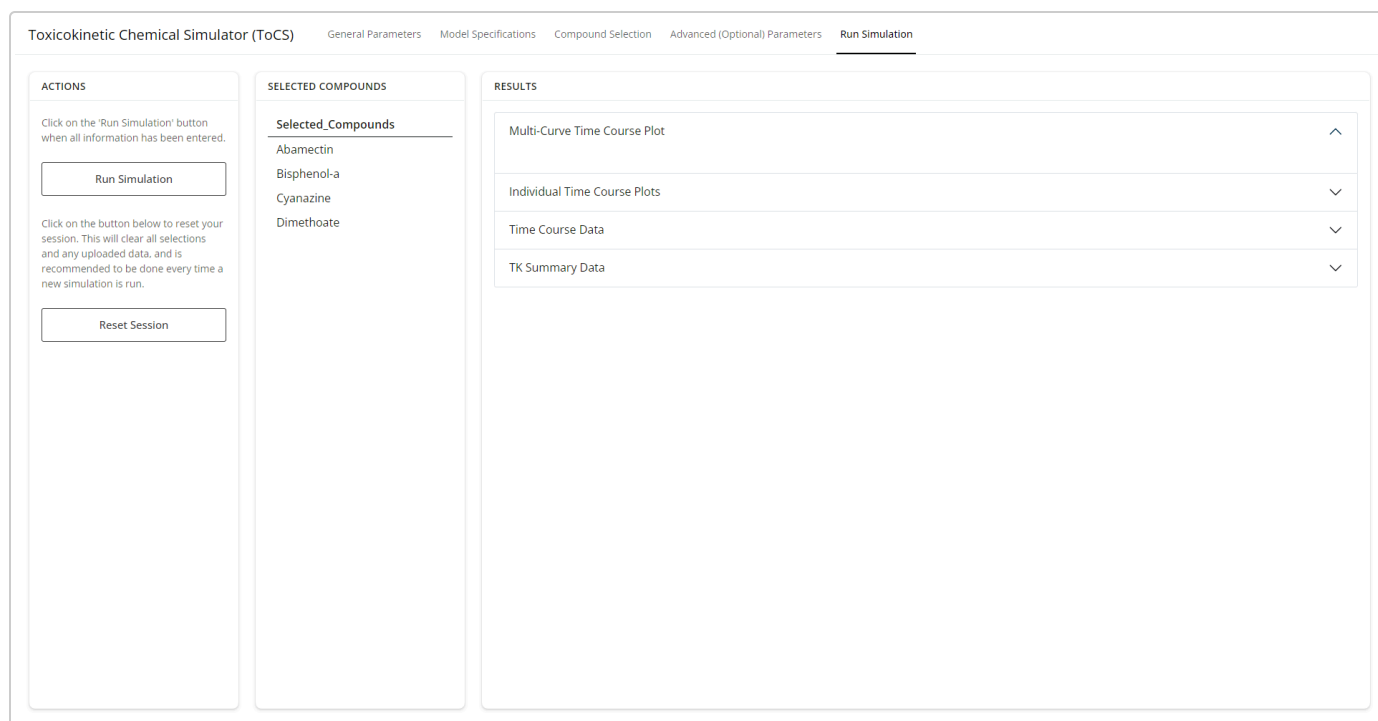
The completed compound selection card for example 1.

## Advanced (Optional) Parameters Tab

For simplicity of this example, we will leave all selections and inputs on this tab alone and proceed to the next and final tab.

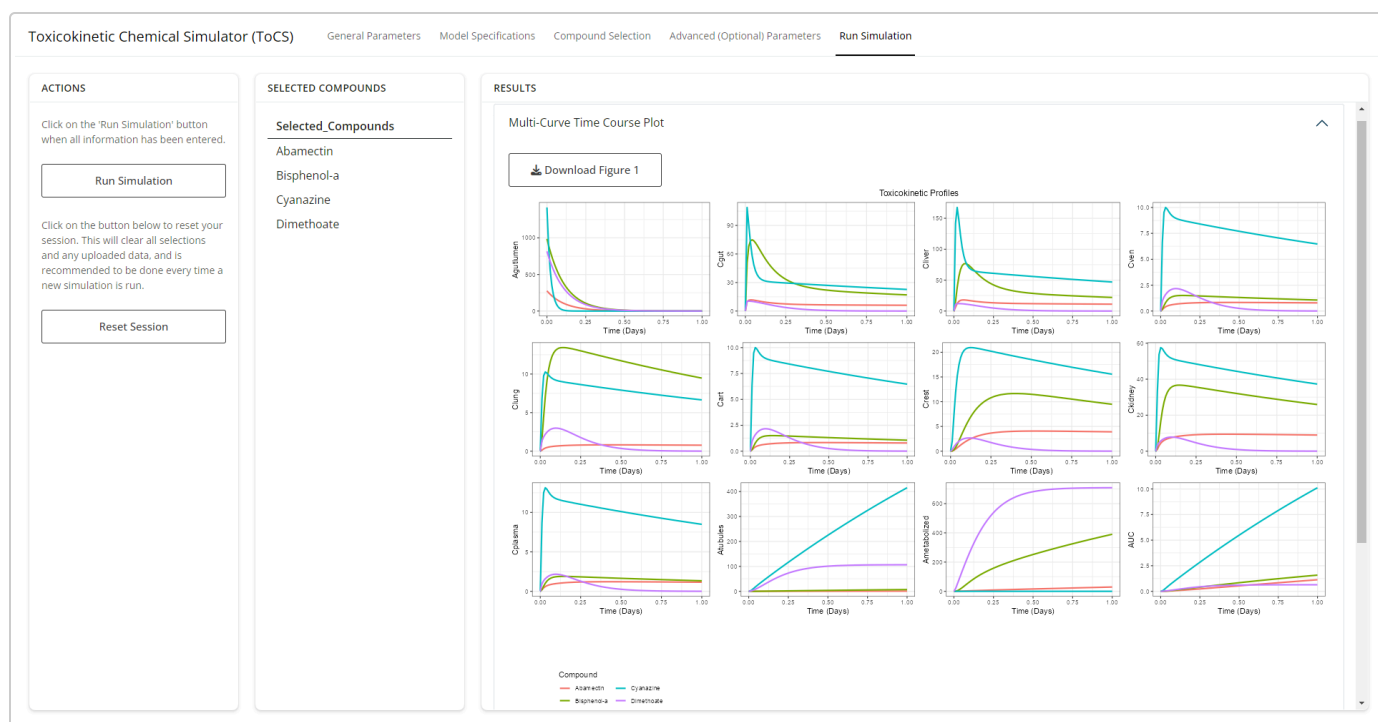
## Run Simulation Tab

All input selections are complete and the correct compounds appear under the *Selected Compounds* card, as shown in the image below. Therefore, we hit the *Run Simulation* button under the *Actions* card so ToCS can compute the solution. The output will appear in the *Results* window when complete. Depending on the number of compounds selected to simulate, the results may take several seconds to populate.



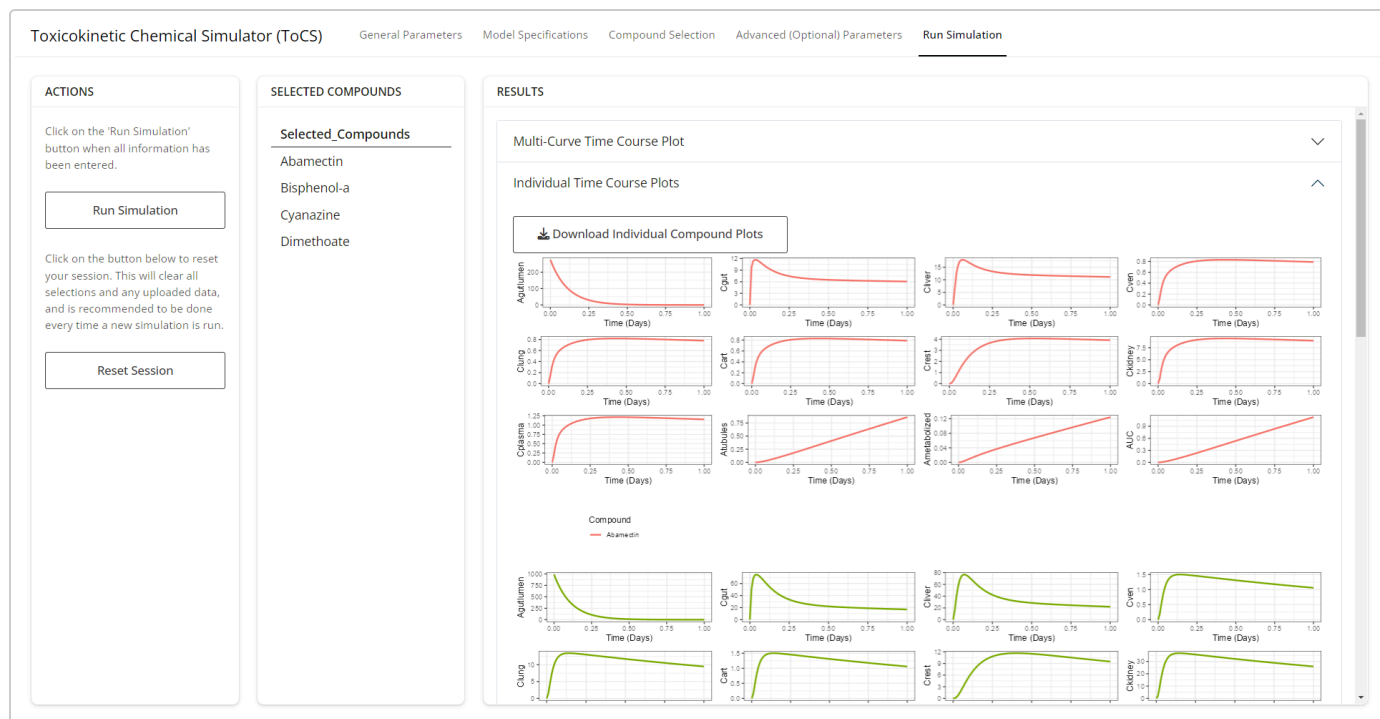
The run simulations tab appearance before the “Run Simulation” button under the *Actions* card is clicked.

The image below shows the first drop down in the *Results* card once the simulation is complete. The user sees the complete time course curves of all four chemicals in each model compartments overlaying each other. The legend for the figure is located in the bottom right corner, and a figure description describing the y-axis of each subplot is located below the figure. The user also has the option to download this figure by clicking *Download Figure 1*.



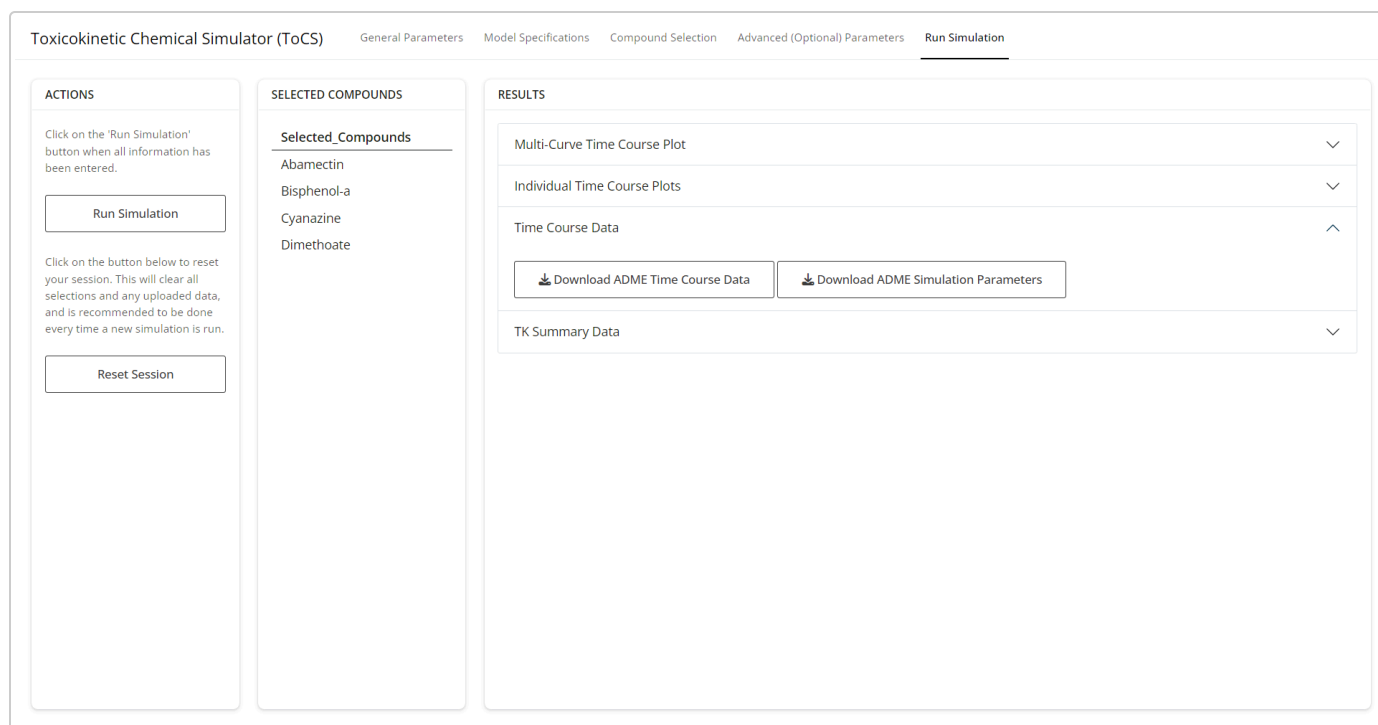
The multi-curve plot output and download option for example 1.

The second drop down in the *Results* card, as seen below, shows the user the same plots as seen in the first drop down tab but with each compound on a separate plot. The user has the option to download all individual plots as a zip file. A figure caption is also located under the very last plot in this tab.



The individual plots output and download option for example 1.

The third drop down in the *Results* card allows the user to download the time course simulation data that was used to generate the plots in the two drop downs above. The user can also download all of the inputted simulation parameters as well as the chemical data used in the simulations. The interface with these two download buttons is shown below.



The simulation data download feature for example 1.

Opening the bottom drop down in the *Results* card shows a toxicokinetic summary including the Tmax (time to maximal concentration), Cmax (maximal concentration), and AUC (area under the curve) of all simulated compounds within each model compartment. The table is available for download if the user clicks *Download Table 1*.

Toxicokinetic Chemical Simulator (ToCS)																																																																															
General Parameters   Model Specifications   Compound Selection   Advanced (Optional) Parameters <u>Run Simulation</u>																																																																															
<b>ACTIONS</b>  Click on the 'Run Simulation' button when all information has been entered.  <div>Run Simulation</div>  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.  <div>Reset Session</div>	<b>SELECTED COMPOUNDS</b>  <u>Selected_Compounds</u> Abamectin Bisphenol-a Cyanazine Dimethoate			<b>RESULTS</b>  <div>Multi-Curve Time Course Plot</div> <div>Individual Time Course Plots</div> <div>Time Course Data</div> <div> <div>Download ADME Time Course Data</div> <div>Download ADME Simulation Parameters</div> </div> <div>TK Summary Data</div>																																																																											
				<div>Download Table 1</div> <div>Show 10 entries</div> <div>Search:</div> <table> <thead> <tr> <th></th><th>Tmax.Abamectin</th><th>MaxValue.Abamectin</th><th>AUC.Abamectin</th><th>Tmax.Bisphenol-a</th><th>MaxValue.Bisphenol-a</th><th>AUC</th></tr> </thead> <tbody> <tr> <td>Agutlumen</td><td>0</td><td>275.6</td><td>30.96</td><td>0</td><td>987.4</td><td></td></tr> <tr> <td>Cgut</td><td>0.0312</td><td>11.68</td><td>7.139</td><td>0.0416</td><td>74.88</td><td></td></tr> <tr> <td>Cliver</td><td>0.0624</td><td>17.94</td><td>12.52</td><td>0.0728</td><td>76.8</td><td></td></tr> <tr> <td>Cven</td><td>0.4264</td><td>0.8299</td><td>0.7707</td><td>0.1352</td><td>1.502</td><td></td></tr> <tr> <td>Clung</td><td>0.4264</td><td>0.8184</td><td>0.76</td><td>0.1352</td><td>13.43</td><td></td></tr> <tr> <td>Cart</td><td>0.4264</td><td>0.8299</td><td>0.7704</td><td>0.1352</td><td>1.502</td><td></td></tr> <tr> <td>Crest</td><td>0.5096</td><td>4.065</td><td>3.538</td><td>0.3848</td><td>11.65</td><td></td></tr> <tr> <td>Ckidney</td><td>0.4264</td><td>9.432</td><td>8.739</td><td>0.1456</td><td>36.69</td><td></td></tr> <tr> <td>Cplasma</td><td>0.416</td><td>1.215</td><td>1.128</td><td>0.1352</td><td>1.89</td><td></td></tr> <tr> <td>Atubules</td><td>1</td><td>0.8622</td><td>0.4109</td><td>1</td><td>6.922</td><td></td></tr> </tbody> </table> <div>Showing 1 to 10 of 12 entries</div> <div>Previous 1 2 Next</div> <p>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.</p>				Tmax.Abamectin	MaxValue.Abamectin	AUC.Abamectin	Tmax.Bisphenol-a	MaxValue.Bisphenol-a	AUC	Agutlumen	0	275.6	30.96	0	987.4		Cgut	0.0312	11.68	7.139	0.0416	74.88		Cliver	0.0624	17.94	12.52	0.0728	76.8		Cven	0.4264	0.8299	0.7707	0.1352	1.502		Clung	0.4264	0.8184	0.76	0.1352	13.43		Cart	0.4264	0.8299	0.7704	0.1352	1.502		Crest	0.5096	4.065	3.538	0.3848	11.65		Ckidney	0.4264	9.432	8.739	0.1456	36.69		Cplasma	0.416	1.215	1.128	0.1352	1.89		Atubules	1	0.8622
	Tmax.Abamectin	MaxValue.Abamectin	AUC.Abamectin	Tmax.Bisphenol-a	MaxValue.Bisphenol-a	AUC																																																																									
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The toxicokinetic (TK) summary drop down table for example 1.



If we wanted to run another simulation, we would click the *Reset Session* button under the *Actions* card, which would clear all parameter inputs and simulations and return the interface to the *General Parameters* tab.

## Example 2

Let's say we want to run a simulation that outputs rat concentration-time profiles over the course of three days for five compounds: Valproic Acid (CAS: 99-66-1), Benzoic Acid (CAS: 65-85-0), Ethanol (CAS: 64-17-5), Titanium Dioxide (CAS: 13463-67-7), and Advantame (CAS: 714229-20-6). The simulation will be for three oral exposures a day every eight hours of 2 mg/kg each for each compound. We will use the 3-compartment model without including in silico generated parameters for missing in vitro data.

### General Parameters Tab

As with example 1, we select *Concentration-time profiles* as the desired output under the *Output* card. This time, however, we select *Rat* species for the first drop down under the *Species* card. Let's say that, in this example, we only want to use rat in vitro data instead of using human in vitro data for compounds missing rat data. Thus, we select *No* for the second drop down menu under the *Species* card. The first tab should now look like the image below.

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

**INSTRUCTIONS:** This section provides guidance on using the simulator. It states that users should fill out prompts on each tab moving left to right and click the 'Run Simulation' tab to run the simulation or reset all selections. It also lists the four toxicokinetic (TK) outputs: 1) Concentration-time profiles, 2) Steady state (SS) concentrations, 3) In vitro in vivo extrapolation (IVIVE), and 4) Parameter calculations. It mentions that the application uses the U.S. EPA's R package 'httk' and provides links for more information and additional guidance.

**OUTPUT:** This section allows users to select the desired output. A dropdown menu is set to 'Concentration-time profiles'.

**SPECIES:** This section allows users to select the species to analyze. A dropdown menu is set to 'Rat'. Below this, there is a question: 'Do you want to use human in vitro data if in vitro data for the selected species is missing?'. A dropdown menu for this question is set to 'No'.

The opening interface to the ToCS app for example 2.

### Model Specifications Tab

On the *Dosing* card, we again leave the first two drop down menus at their default selections. For the dosing frequency (third) drop down menu, we select *Multiple Doses*. A fourth drop down menu will then appear asking whether we want the multiple doses to be evenly distributed throughout the day. Since we want to administer a 2 mg/kg dose every 8 hours, we select *Yes* from the drop down menu. Finally, two additional user options appear. The first one asks the user to specify the amount of chemical exposure per administration, and so we enter 2 into the box. The second one is a slider that has the user specify the frequency of the dose, and so we move the slider to 8 hours.

On the *Model* card, we select *3compartment* model under the first drop down menu. For the second drop down menu, we select *No* since we do not want to use in silico generated parameters. Finally, we enter 3 in the final box under the *Model* card since we want to run the simulation for three days. Therefore, the final interface of the *Model Specifications* tab should look like the image below.

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

**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? For example, 1 mg/kg BW every 8 hours.  
Yes

Enter the amount administered during every dose (in the specified units).  
2

Select how often the above dose is administered (every \_\_\_\_ hours).  
0 8 24

**MODEL**

Select a model to simulate.  
3compartment

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.  
No, do not load in silico parameters

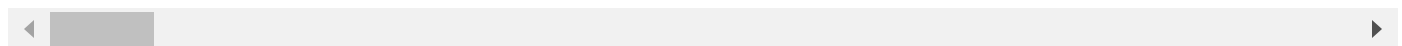
Enter the total simulation time (in days).  
3

The completed model specifications tab for example 2.

## Compound Selection Tab

We first try to search for the compounds we desire to simulate by keeping the first drop menu in the *Preloaded Compounds* card on *Choose from all available chemicals* and then searching through the second drop down menu. Typing in the chemical names or CAS numbers shows that three of the five desired chemicals (valproic acid, benzoic acid, ethanol) are present on the preloaded compounds list and two chemicals are not (titanium dioxide and advantame). Therefore, we select valproic acid, benzoic acid, and ethanol on the *Preloaded Compounds* card and will have to upload the remaining two compounds under the *Uploaded Data* card. To get the chemical information for titanium dioxide and advantame into the program, we copy the *SampleCSV.csv* file in the *Uploaded Physical-Chemical File Folder* under the *Instructions* card and enter the appropriate chemical information for each compound. See the *Introduction to ToCS* vignette for more information on upload instructions. For the purpose of this example, we use fictional chemical data and upload the following csv file by clicking *Browse* under the *Uploaded Data* card.

Compound	CAS	CAS.Checksum	DTXSID	Formula	All.Compound.Names	logHenry	lo
Titanium Dioxide	13463-67-7	NA	DTXSID3021352	NA	NA	NA	N
Advantame	714229-20-6	NA	DTXSID00991787	NA	NA	NA	N



Once we have the three compounds selected under the *Preloaded Compounds* card and the two compounds uploaded under the *Uploaded Data* card (with the csv file name CSV\_CTPvignette.csv), we then proceed to the next tab. The final *Compound Selection* tab should look like the image below.

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.  

99-66-1, Valproic acid  
65-85-0, Benzoic acid  
64-17-5, Ethanol

**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...
CSV\_CTPvignette.csv

Upload complete

The completed compound selection tab for example 2.

## Advanced (Optional) Parameters Tab

Suppose that we want to customize parameters other than just the basic simulation information needed. For this example, let's say we want to change the starting amount of each compound in the gut lumen and gut to be 10 umol instead of 0 umol. So, we select *Yes, enter my own initial amounts* under the first drop down menu in the *Model Conditions* card. Consequently, an additional seven text boxes appear under this drop down. Since we only want to change the amounts in the gut lumen and gut, we change the first two text boxes to be 10 instead of 0. There are no other changes we want to make, so we leave the remaining selections as is and proceed to the final tab, *Run Simulation*. The completed advanced parameters page should look like the image below.

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)?

Yes, enter my own initial amounts

Enter the initial amount (in umol) of compound(s) in the gut lumen at  $t = 0$ .

10

Enter the initial amount (in umol) of compound(s) in the gut at  $t = 0$ .

10

Enter the initial amount (in umol) of compound(s) in the liver at  $t = 0$ .

0

Enter the initial amount (in umol) of compound(s) in the rest of body at  $t = 0$ .

0

Enter the initial amount (in umol) of

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.

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 -1

-3

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

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 -1

-12

BIOAVAILABILITY

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

1.6

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)

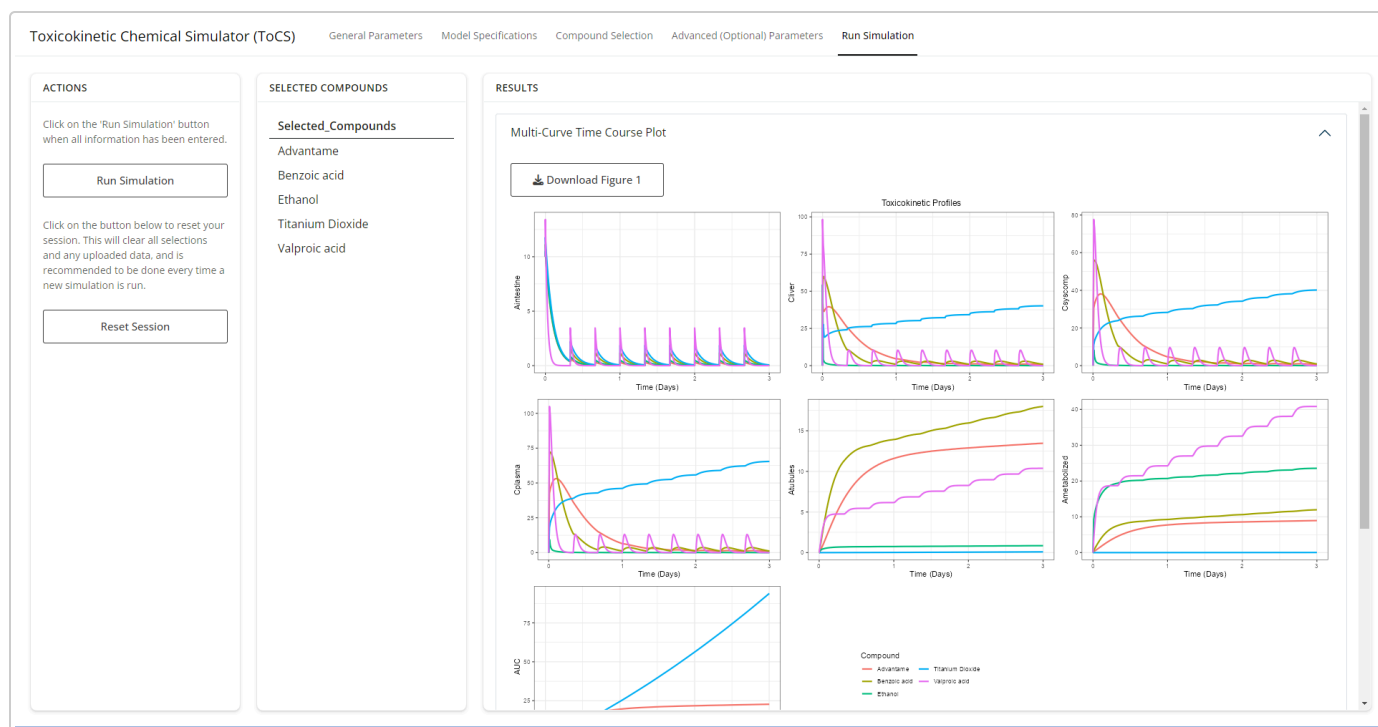
OUTPUT SPECIFICATION

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.

The completed advanced parameters tab for example 2.

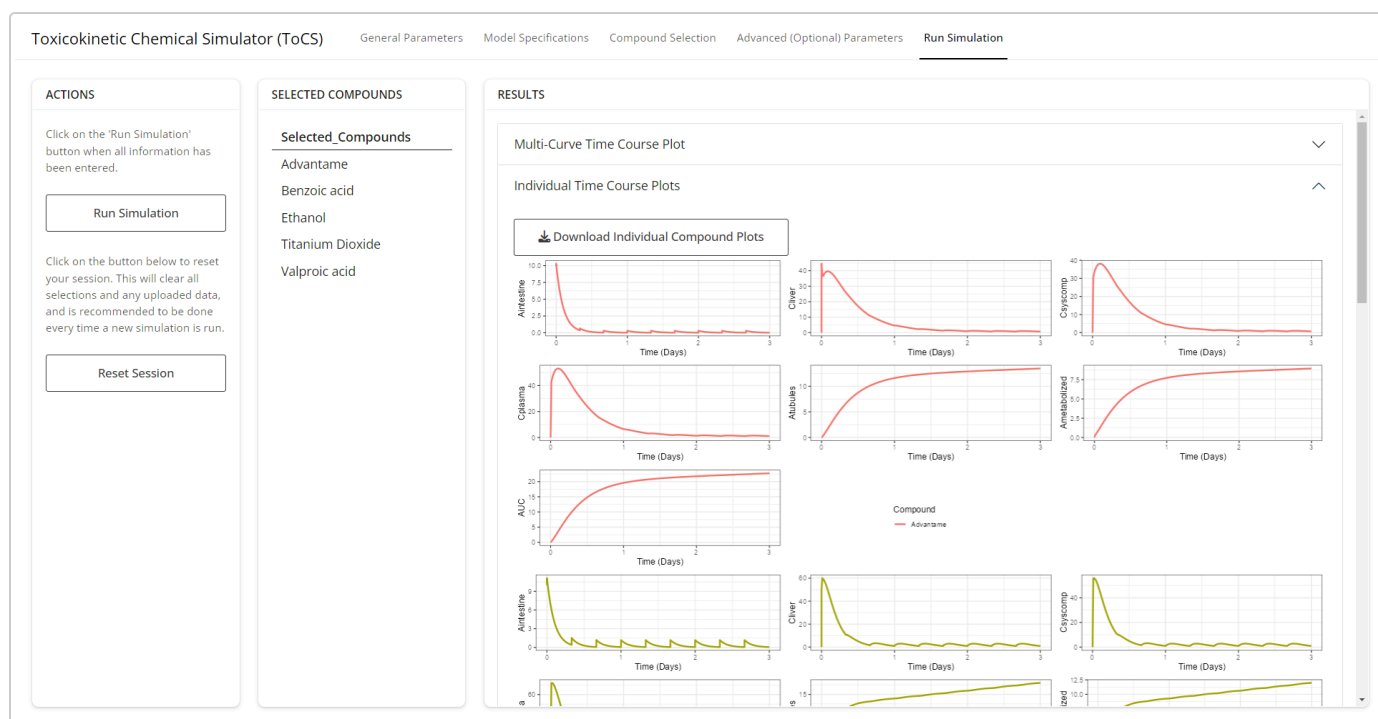
## Run Simulation Tab

Now that we've filled out all simulation information and the correct compounds appear under the *Selected Compounds* card. Thus, we click the *Run Simulation* button under the *Actions* card. The image of the completed simulation is shown below. The first tab illustrates the time course plots of all five compounds for each model compartment. The user has the option to download the plot by clicking *Download Figure 1*.



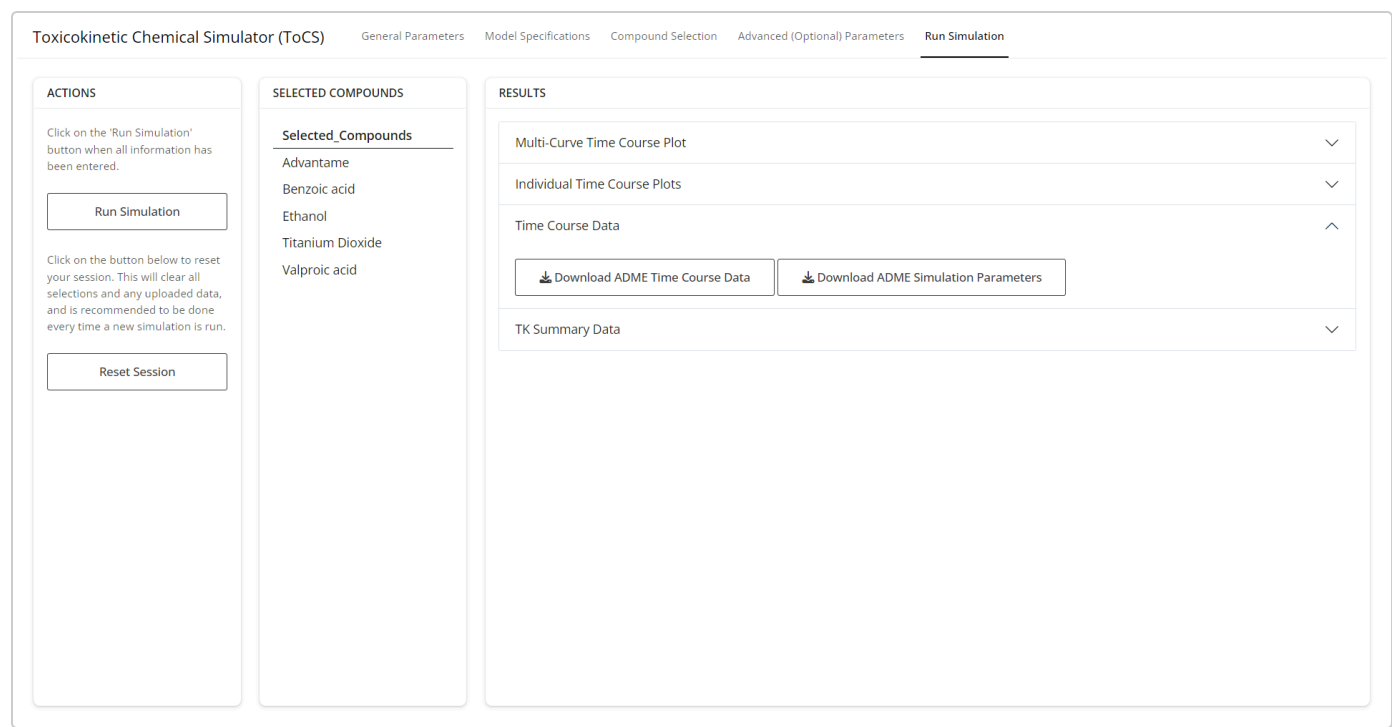
The multi-curve time course plot for example 2.

By closing the *Multi-Curve Time Course Plot* drop down, we view the *Individual Time-Course Plots* drop down and see the same plots as shown in the drop down above but all on a separate plots (one figure per compound). The user can download the individual plots by clicking the *Download Individual Compound Plots* button, where all the plots will download as a zip file.

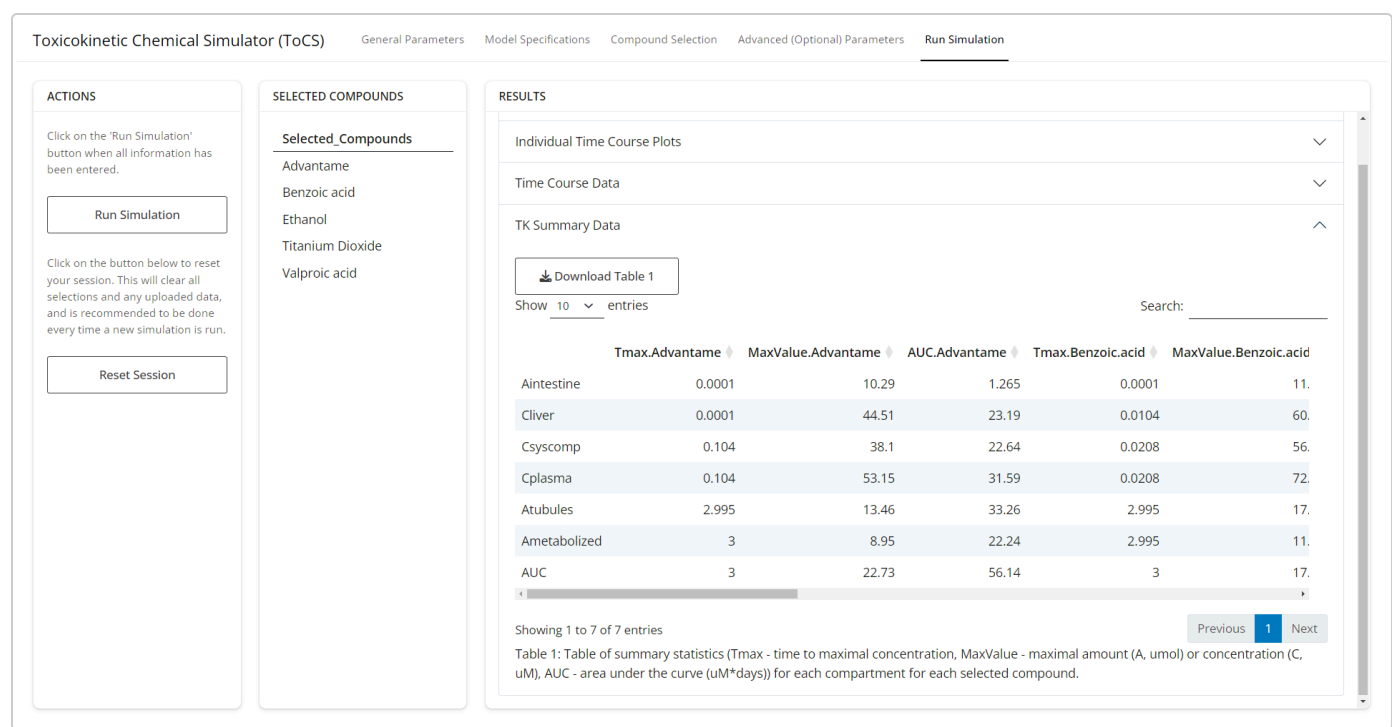


The individual time course plots for example 2.

The final image below shows the user’s option to download the simulation results as well as the simulation parameters used to generate the solution. The fourth drop down tab shows a table of simulation summary statistics for each compound in each model compartment. The user has the option to download the table by clicking the *Download Table 1*.



The time course data download and simulation parameter data tab for example 2.



The TK summary data tab for example 2.

As with Example 1, we suggest that the user clicks the *Reset Session* button under the *Actions* card if the user wishes to run a new simulation.

## Example 3

Let's say we want to run a simulation that outputs rat concentration-time profiles for two days for three compounds: Docusate sodium (CAS: 577-11-7), Phenol (CAS: 108-95-2), and Potassium Benzoate (CAS: 582-25-2). The simulation will be for three oral exposures a day, but the exposures will happen at hours 0, 6, and 12 every day and will be 1 mg/kg each at hours 0 and 6 and 0.2 mg/kg at hour 12. We will use the 1-compartment model and include compounds with only in silico generated parameters in place of missing in vitro data. We would like the output at every hour during the simulation.

### General Parameters Tab

As with the previous examples, we select *Concentration-time profiles* as the desired output under the *Output* card. As with example 2, we select *Rat* species for the first drop down under the *Species* card. Now, suppose that we are okay with substituting human in vitro data for compounds missing rat in vitro data, so we select *Yes* for the second drop down menu under the *Species* card. The first tab should now look like the page below.

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 toxicokinetic (TK) outputs: 1) Concentration-time profiles, which returns chemical concentrations in bodily compartments over time, 2) Steady state (SS) concentrations, which returns SS concentrations in bodily compartments from an oral infusion, 3) In vitro in vivo extrapolation (IVIVE), which returns oral equivalent doses to in vitro bioactive concentrations, 4) Parameter calculations, which 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 'httk', refer to <https://doi.org/10.18637/jss.v079.i04> and/or <https://cran.r-project.org/web/packages/httk>

For additional guidance on ToCS, please refer to the vignettes (<https://github.com/KristenWindoloski/ToCS/tree/main/vignettes>). To report issues or suggestions for improvement, visit <https://github.com/KristenWindoloski/ToCS/issues>.

OUTPUT

Select the desired output.

Concentration-time profiles

SPECIES

Select the species to analyze.

Rat

Do you want to use human in vitro data if in vitro data for the selected species is missing?

Yes

The completed general parameters tab for example 3.

### Model Specifications Tab

Under the *Dosing* card, we keep the first two drop downs on their default values. Under the third drop down, we select *Multiple Doses* since we want to give three doses per day. Then, since the doses we want to give are not evenly distributed throughout the day, we select *No* for the resulting fourth drop down menu. Finally, a fifth box appears where we will enter our dosing regime. We enter all of the times (in days) we want to administer the compounds first, then list the amount of compound at each dosing time directly after. Since we want to administer the compounds at hours 0, 6, and 12 each day for two days, the first part of the list we enter is *0, 0.25, 0.5, 1, 1.25, 1.5*. Then, the second part of the list is comprised of the dosing amounts, which are 1 mg/kg for the first two doses of the day and then 0.2 mg/kg for the last dose of each day, so we enter *1, 1, 0.2, 1, 1, 0.2* as the second part of the list.

Under the *Model* card, we select *1compartment* for the first drop down menu. For the second drop down menu, we select *Yes* since we want to include compounds with only in silico generated parameters (hepatic clearance, fraction unbound) into the compound list. Finally, we enter 2 into the last box under the *Model* card since we want to run the simulation for two days. The completed *Model Specification* card should appear the same as the image below.

The screenshot displays the 'Model Specifications' tab of the Toxikokinetic Chemical Simulator (ToCS). The interface is divided into two main sections: 'DOSING' and 'MODEL'.

**DOSING Section:**

- Select the administration method of the compound(s):** A dropdown menu with 'oral' selected.
- Select the units of the administered dose(s):** A dropdown menu with 'mg/kg' selected.
- Select the dosing frequency:** A dropdown menu with 'Multiple Doses' selected.
- Are equal doses given evenly across a 24 hour period? For example, 1 mg/kg BW every 8 hours.** A dropdown menu with 'No' selected.
- 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.** A text input field containing '0,0.25,0.5,1,1.25,1.5,1,1,0.2,1,1,0.2'.

**MODEL Section:**

- Select a model to simulate.** A dropdown menu with '1compartment' selected.
- 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.** A dropdown menu with 'Yes, load in silico parameters' selected.
- Enter the total simulation time (in days).** A text input field containing '2'.

The completed model specifications tab for example 3.

## Compound Selection Tab

Because we are loading all in silico generated parameters into ToCS, the *Preloaded Compounds* card will take a few moments to load. When it does, we keep the first drop menu in the *Preloaded Compounds* card on *Choose from all available chemicals* selection and then type in the compound names or CAS numbers for each compound into the second search bar, where we can select all three compounds. The completed *Compound Selection* tab should look like the image below.



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.

577-11-7, Docusate sodium
108-95-2, Phenol
582-25-2, Potassium benzoate

**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

The completed compound selection tab for example 3.

Note that if under the *General Parameters* tab we selected *No* for using human in vitro data in place of missing rat in vitro data, then docusate sodium and potassium benzoate would not be available for simulation since they do not have rat in vitro data.

## Advanced (Optional) Parameters Tab

Since we want to output the solution at every hour, we add a list of output times (in days) to the textbox under the *Output Specification* card on the right of the page. Each time should be separated by a comma, and we can enter times as either whole numbers, decimals, or fractions. Since there are no other customizations we want to make, the completed *Advanced Parameters* tab should look like the image below.

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)

Enter the minimum acceptable chemical fraction unbound in presence of plasma proteins. All values below this will be set to this value.

0.0001

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.

MODEL SOLVER

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

Isoda

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.

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 -1

-12

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

-20 -18 -16 -14 -12 -10 -8 -6 -4 -2 -1

-12

BIOAVAILABILITY

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

1.6

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)

OUTPUT SPECIFICATION

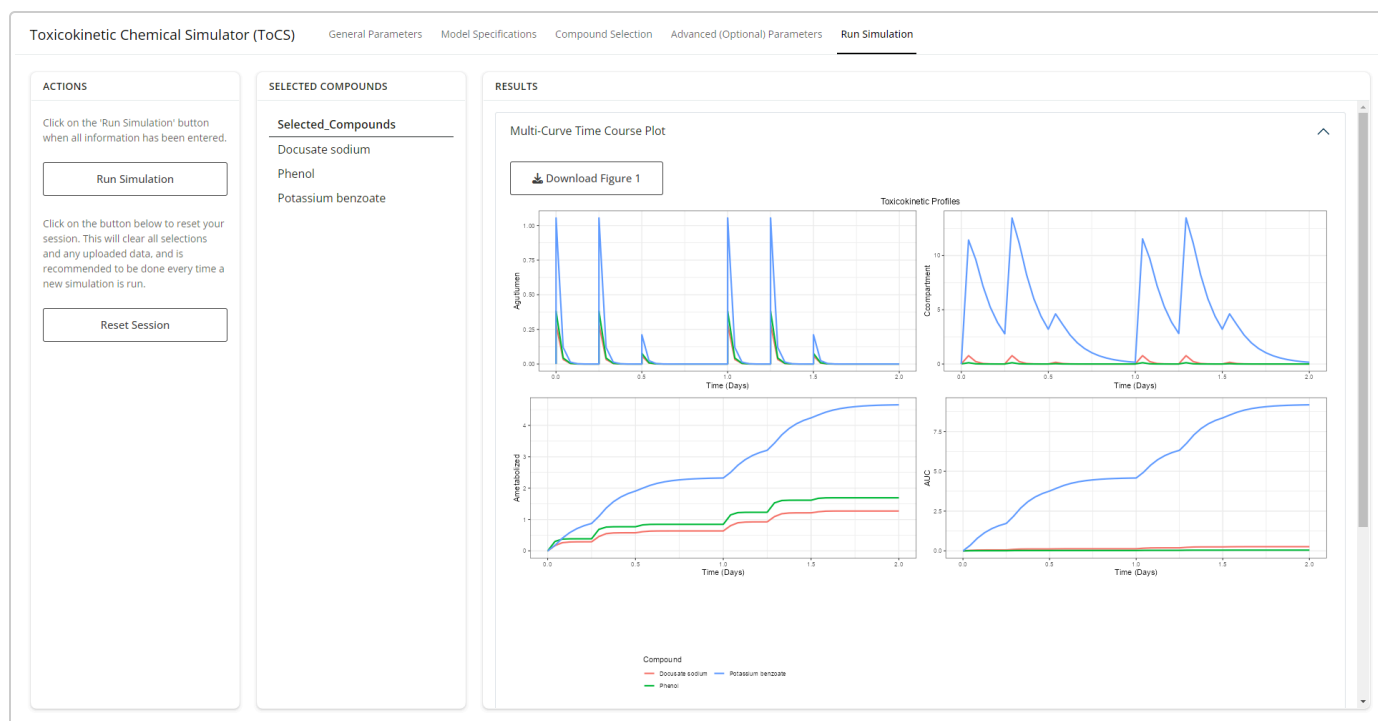
Enter the times (in days) to output concentrations. Leave blank if no specific times are needed. Enter a comma-separated list, such as 0, 1, 2, ... signifying output 0, 1, and 2 days after dosing begins.

0,1/24,2/24,3/24,4/24,5/24,0.25,7/24,8/

The completed advanced parameters tab for example 3.

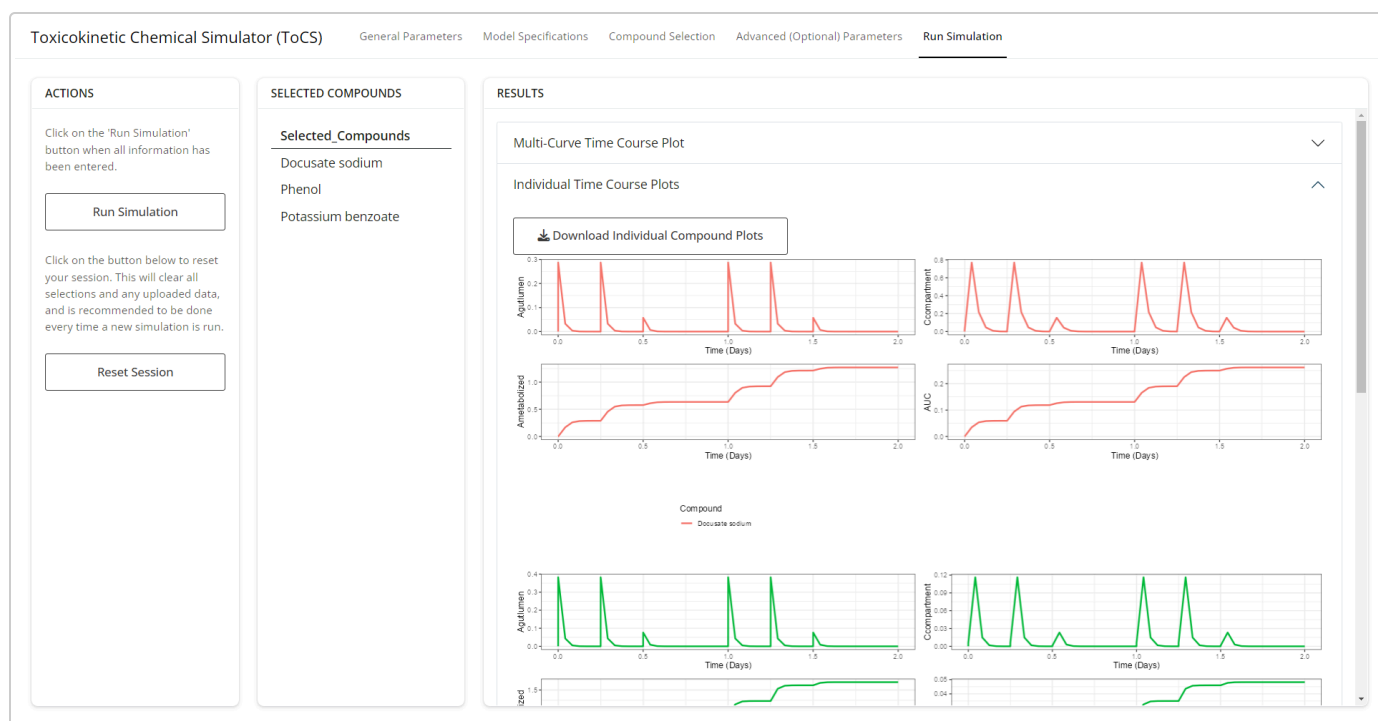
## Run Simulation Tab

Now that all previous tabs are completed and the three compounds we want to simulate are shown under the *Selected Compounds* card, we hit *Run Simulation* under the *Actions* card. When the simulation is complete, it should show the image below. This shows all three simulated compounds overlaying each other for each model compartment with the solution plotted for the times we specified on the previous tab (every hour). The user has the option to download the figure by clicking the *Download Figure 1* button at the top of the drop down menu.



The multi-curve time course plot tab results for example 3.

Below, we see the results for the individual time course plots drop down menu. The user has the option to download all individual plots as a zip file by clicking the *Download Individual Time Course Plots* button.



The individual time course plots tab results for example 3.

The two final tabs shown in the image below give the user the options to download the outputted simulation data, the simulation parameters, and a toxicokinetic summary including Tmax, Cmax, and AUC data for each compound within each model compartment.

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**

Docusate sodium

Phenol

Potassium benzoate

**RESULTS**

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: \_\_\_\_\_

	Tmax.Docusate.sodium	MaxValue.Docusate.sodium	AUC.Docusate.sodium	Tmax.Phenol	MaxValue
Agutlumen	0.0001	0.2872	0.03307	0.0001	
Ccompartment	0.04167	0.7697	0.1924	0.04167	
Ametabolized	1.667	1.27	1.648	1.625	
AUC	1.667	0.2616	0.3395	1.667	

Showing 1 to 4 of 4 entries    [Previous](#) **1** [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.

The time course data and TK summary data tab results for example 3.

As with previous examples, we suggest that the user clicks the *Reset Session* button under the *Actions* card if the user wishes to run a new simulation.