

Parameter Calculations Examples

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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) 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 two examples that use the ToCS app to generate steady state concentrations, 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 and highlighted with a red underline. 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. There is also a question "Do you want to use human in vitro data if in vitro data for the selected species is missing?" with a "Select" button and a red error message "Must not be equal to Select." below it.

The opening interface to the ToCS app.

Example 1

Let's say that we want to calculate human TK parameters for nine sample chemicals:

- Acephate (CAS: 30560-19-1)
- Advantame (CAS: 714229-20-6)
- Caffeine (CAS: 58-08-2)
- Carboxin (CAS: 5234-68-4)
- Phenol (CAS: 108-95-2)
- Picloram (CAS: 1918-02-1)
- Pirinixic acid (CAS: 50892-23-4)
- Titanium dioxide (CAS: 13463-67-7)
- Triadimensol (CAS: 55219-65-3)

without using httk's preloaded in silico parameters for hepatic clearance, fraction unbound in plasma, or caco-2 permeability.

General Parameters Tab

Since we want to calculate human TK parameters, we select *Parameter calculations* for the first drop down menu under the *Output* card and *Human* for the first drop down under the *Species* card. Then, as with examples in other vignettes, we select *Yes* for the second drop down under the *Species* card. The completed *General Parameters* tab should look like the image below. The user should now move on to the *Model Specifications* tab.

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 contains text explaining the simulation process and the outputs provided by ToCS. It mentions that ToCS provides 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 also provides links for more information on the 'httk' R package and additional guidance on ToCS.

OUTPUT: This section has a dropdown menu labeled 'Select the desired output.' The selected option is 'Parameter calculations'.

SPECIES: This section has a dropdown menu labeled 'Select the species to analyze.' The selected option is 'Human'. Below this, there is another dropdown menu labeled 'Do you want to use human in vitro data if in vitro data for the selected species is missing?' with the selected option being 'Yes'.

The completed general parameters tab for example 1.

Model Specifications Tab

As shown in the image below, there are no user selections under the *Dosing* card. Under the *Model* card, we omit the first drop down menu and leave it on *None* as the models described in the *Introduction to ToCS* vignette are not used to calculate parameters. Finally, we select *No* under the second drop down menu under the *Model* card since we do not want the program to simulate chemicals with only in silico generated parameters. The completed tab should look like the image below, and the user can proceed to the next tab.

The completed model specifications tab for example 1.

Compound Selection Tab

Under the *Preloaded Compounds* tab, we search by either compound name or CAS for all nine compounds. All but two compounds (advantame and titanium dioxide) are available, so we select the seven available compounds under the *Preloaded Compounds* tab. Thus, we have to upload the chemical data for advantame and titanium dioxide. So, we copy the SampleCSV file in the *Uploaded Compound File Folder* under the *Instructions* card and enter the appropriate chemical information for each compound, as shown in the table below. See the *Introduction to ToCS* vignette for more information on upload instructions. For the purpose of this example, we use fake chemical data and upload the following csv file (CSV_PCvignette.csv) by clicking *Browse* under the *Uploaded Compounds* card.

| Compound | CAS | CAS.Checksum | DTXSID | Formula | All.Compound.Names | logHenry | lo |
|------------------|------------|--------------|---------------|---------|--------------------|----------|----|
| Titanium Dioxide | 13463-67-7 | NA | DTXSID3021352 | NA | NA | NA | N |

| Compound | CAS | CAS.Checksum | DTXSID | Formula | All.Compound.Names | logHenry | logP |
|-----------|-------------|--------------|----------------|---------|--------------------|----------|------|
| Advantame | 714229-20-6 | NA | DTXSID00991787 | NA | NA | NA | NA |

Now that all simulation chemicals are uploaded, 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

Below is a downloadable folder containing information on upload file formatting if compounds to be analyzed are not included in the preloaded compounds list. The uploaded file must be formatted exactly how the 'SampleCSV' file is structured (keeping columns even if there is no data). The header descriptions of the CSV and the minimal data inputs required for the CSV are in the 'DataDescriptions' and 'RequiredData' PDFs, respectively.

[Uploaded Compound File Folder](#)

PRELOADED COMPOUNDS

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.

- 30560-19-1, Acephate
- 5234-68-4, Carboxin
- 1918-02-1, Picloram
- 55219-65-3, Triadimenol
- 108-95-2, Phenol
- 50892-23-4, Pirinixic acid
- 58-08-2, Caffeine

UPLOADED COMPOUNDS

Upload a CSV file of data for compounds not in the preloaded list (if desired). See the 'Instructions' panel to the left for directions on file formatting requirements.

Browse... CSV_PCvignette.csv

Upload complete

The completed compound selection tab for example 1.

Advanced (Optional) Parameters Tab

The *Advanced Parameters* tab is much more bare than for other modules, but since we are not going to customize any additional parameters for this example, we leave all inputs as is. The *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

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.

Enter the Ratio of Distribution coefficient D of totally charged species and that of the neutral form.

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

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

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

MODEL SOLVER

No options for this category.

BIOAVAILABILITY

No options for this category.

OUTPUT SPECIFICATION

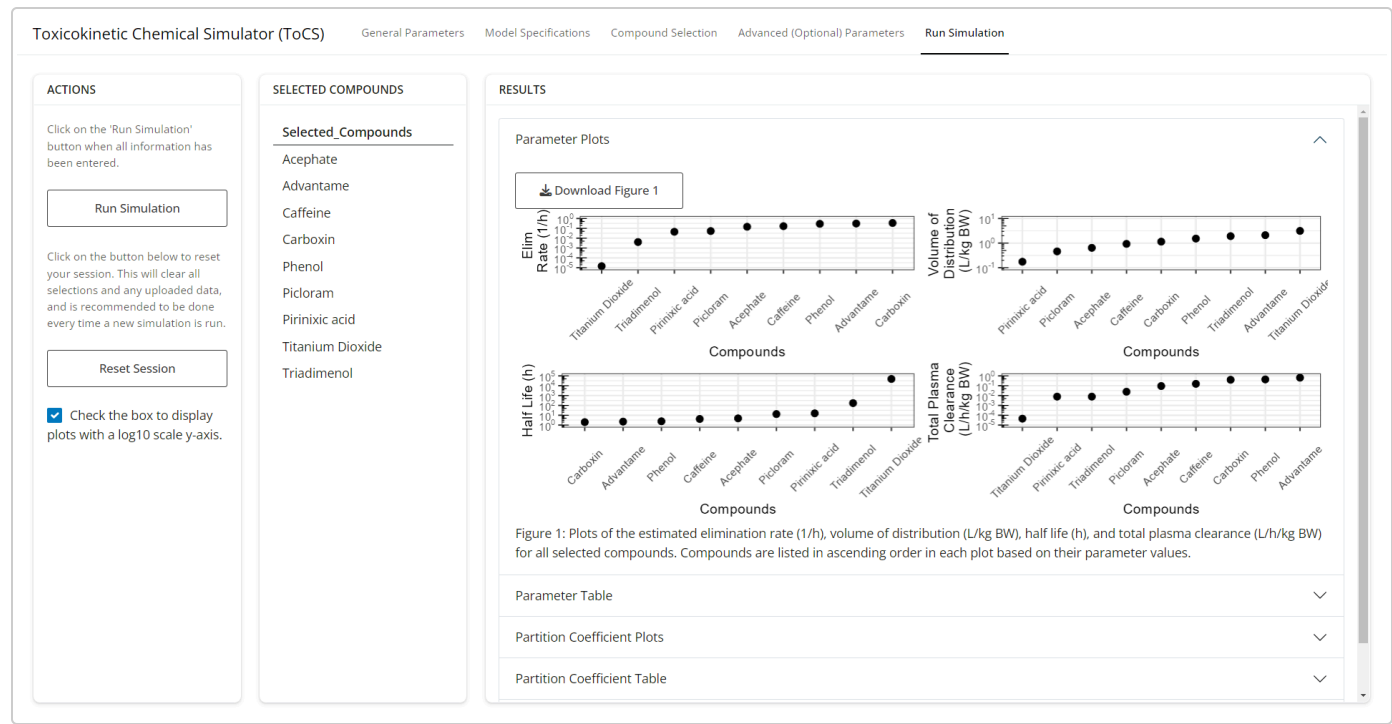
No options for this category.

The completed advanced parameters tab for example 1.

Run Simulation Tab

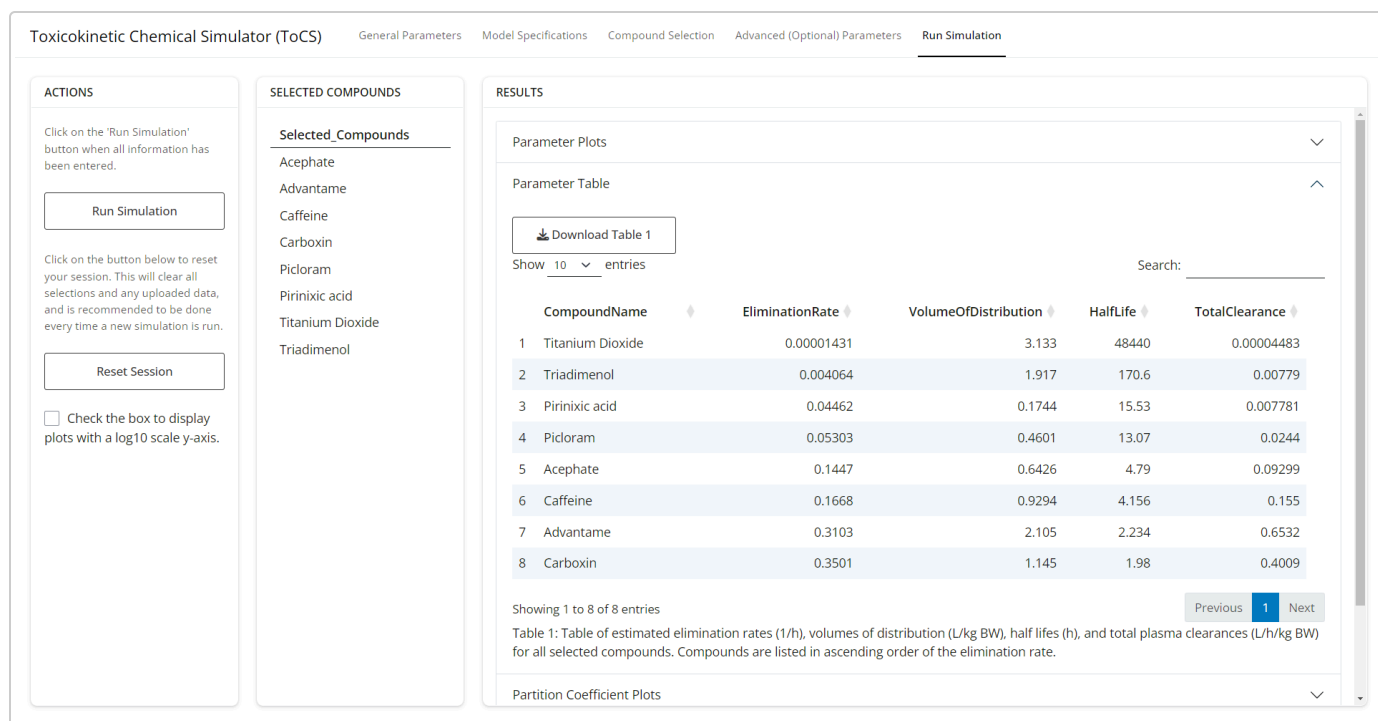
Now that all user selections have been made and all of the desired simulation compounds appear under the *Selected Compounds* card, we hit the *Run Simulation* button under the Actions card. The page prior to simulation completion should look like the image below, with five drop downs where results will appear under the *Results* card.

If we wanted to view the plots under this tab using a log10 y-axis, we would check the bottom box under the *Actions* card, and then the user would see the plots in the image shown below which makes it clearer to distinguish the parameter values of smaller magnitudes.



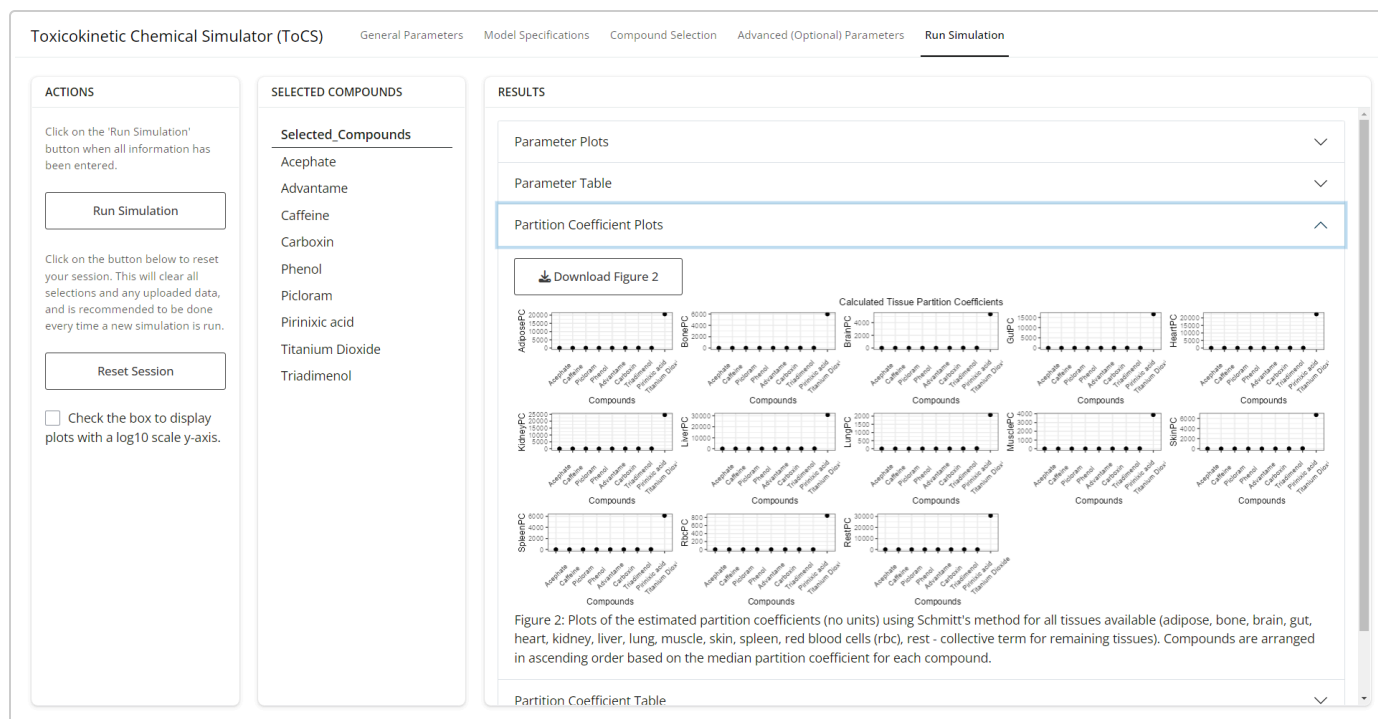
The parameter plots with log10 y-axis drop down under the run simulation tab for example 1.

Under the next drop down tab, there is a table of the parameter values from the previous tab. The user has the option to download the table by clicking the *Download Table 1* button. The drop down tab should look like the image below.



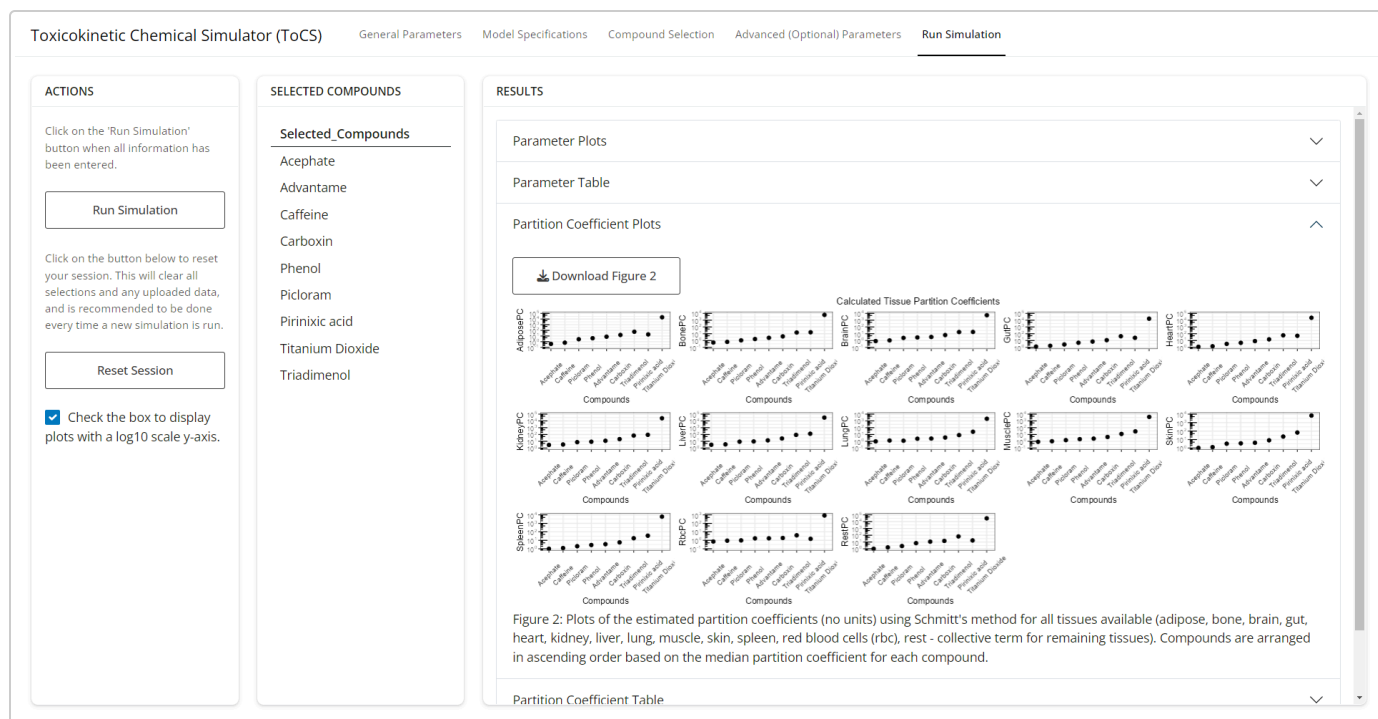
The parameter table drop down under the run simulation tab for example 1.

Under the third drop down tab, the user should see 13 plots, one per partition coefficient. This compilation of plots is available for download by clicking the *Download Figure 2* button at the top of the tab. The user's plots should look like the image below.



The partition coefficients plots with linear y-axis under the run simulation tab for example 1.

Now as with the first drop down tab, the user can change the scale on the y-axis of the partition coefficient plots to be a log10 y-axis scale in order to easier distinguish the smaller magnitudes. The user can download the partition coefficient plot by clicking the *Download Figure 2* button. The log10 y-axis scale plots should look like the image below.



The partition coefficients plots with log10 y-axis drop down under the run simulation tab for example 1.

Under the fourth drop down tab is a table of partition coefficients from the plots under the previous tab. Users can download the table of partition coefficients by clicking the *Download Table 2* button. The user's table should look like the image below.

As with other vignettes, we suggest that the user clicks the *Reset Session* button if they want to run another simulation.

Example 2

For this example, let's say that we want to calculate rat TK parameters for five unknown sample chemicals, where we will not allow chemicals to be included in our selection that only have enough data with the inclusion of in silico parameters. We will also customize several advanced parameters within this example.

General Parameters Tab

As with the previous example, we select *Parameter calculations* for the first drop down menu under the *Output* card. However, for this example, we select *Rat* for the first drop down under the *Species* card. Then, suppose we want to only use rat in vitro data instead of allowing human data to substitute for missing in vitro rat data, and so we select *No* for the second drop down under the *Species* card. The completed *General Parameters* tab should 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 contains text explaining 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 also provides information about the application's use of the U.S. EPA's R package 'httk' and links for additional guidance and reporting issues.

OUTPUT: This section has a label 'Select the desired output.' and a dropdown menu with 'Parameter calculations' selected.

SPECIES: This section has a label 'Select the species to analyze.' and a dropdown menu with 'Rat' selected. 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?' with a dropdown menu showing 'No'.

The completed general parameters tab for example 2.

Model Specifications Tab

Our selections on this page are the same as example 1. The first drop down menu under the *Model* card remains as is and, in the second drop down menu, we select *No* to not include chemical options with in silico generated parameters in place of in vitro data. 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

No options for this category.

MODEL

Select a model to simulate.

Schmitt

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

The completed model specifications tab for example 2.

Compound Selection Tab

We select five compounds from the drop down menu under the *Preloaded Compounds* card to simulate:

- Bisphenol-a (CAS: 80-05-7)
- Butylparaben (CAS: 94-26-8)
- Norethindrone (CAS: 68-22-4)
- Propylparaben (CAS: 94-13-3)
- Zoxamide (CAS: 156052-68-5)

Then, since there are no additional compounds we want to simulate, we advance to the next tab. The completed *Compound Selection* page should look like the image below.

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

INSTRUCTIONS

Below is a downloadable folder containing information on upload file formatting if compounds to be analyzed are not included in the preloaded compounds list. The uploaded file must be formatted exactly how the 'SampleCSV' file is structured (keeping columns even if there is no data). The header descriptions of the CSV and the minimal data inputs required for the CSV are in the 'DataDescriptions' and 'RequiredData' PDFs, respectively.

[Uploaded Compound File Folder](#)

PRELOADED COMPOUNDS

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.

80-05-7, Bisphenol-a
94-26-8, Butylparaben
68-22-4, Norethindrone
94-13-3, Propylparaben
156052-68-5, Zoxamide

UPLOADED COMPOUNDS

Upload a CSV file of data for compounds not in the preloaded list (if desired). See the 'Instructions' panel to the left for directions on file formatting requirements.

Browse...
No file selected

The completed compound selection tab for example 2.

Advanced Parameters Tab

In this example, we decide to change some of the default values of the advanced parameters under the *Model Conditions* card. First, suppose that we want to lower the p-value threshold for the in vitro intrinsic hepatic clearance rate. Thus, we set the first box to *0.01* instead of *0.05*. Then, under the fourth drop down box, suppose that we want to not include protein binding when accounting for liver clearance. Therefore, we select *No, do not include protein binding*. Then finally, suppose we do not want to adjust the fraction unbound in the presence of plasma proteins for lipid binding. Therefore, we select *No, do not adjust the fraction of unbound plasma*. The completed *Advanced Parameters* tab should look like the two images below.

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

MODEL CONDITIONS

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.

Enter the Ratio of Distribution coefficient D of totally charged species and that of the neutral form.

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

MODEL SOLVER

No options for this category.

BIOAVAILABILITY

No options for this category.

OUTPUT SPECIFICATION

No options for this category.

The completed upper part of the advanced parameters tab for example 2.

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

MODEL CONDITIONS

values below this will be set to this value.

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

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

Select whether to use regressions when calculating partition coefficients.

MODEL SOLVER

No options for this category.

BIOAVAILABILITY

No options for this category.

OUTPUT SPECIFICATION

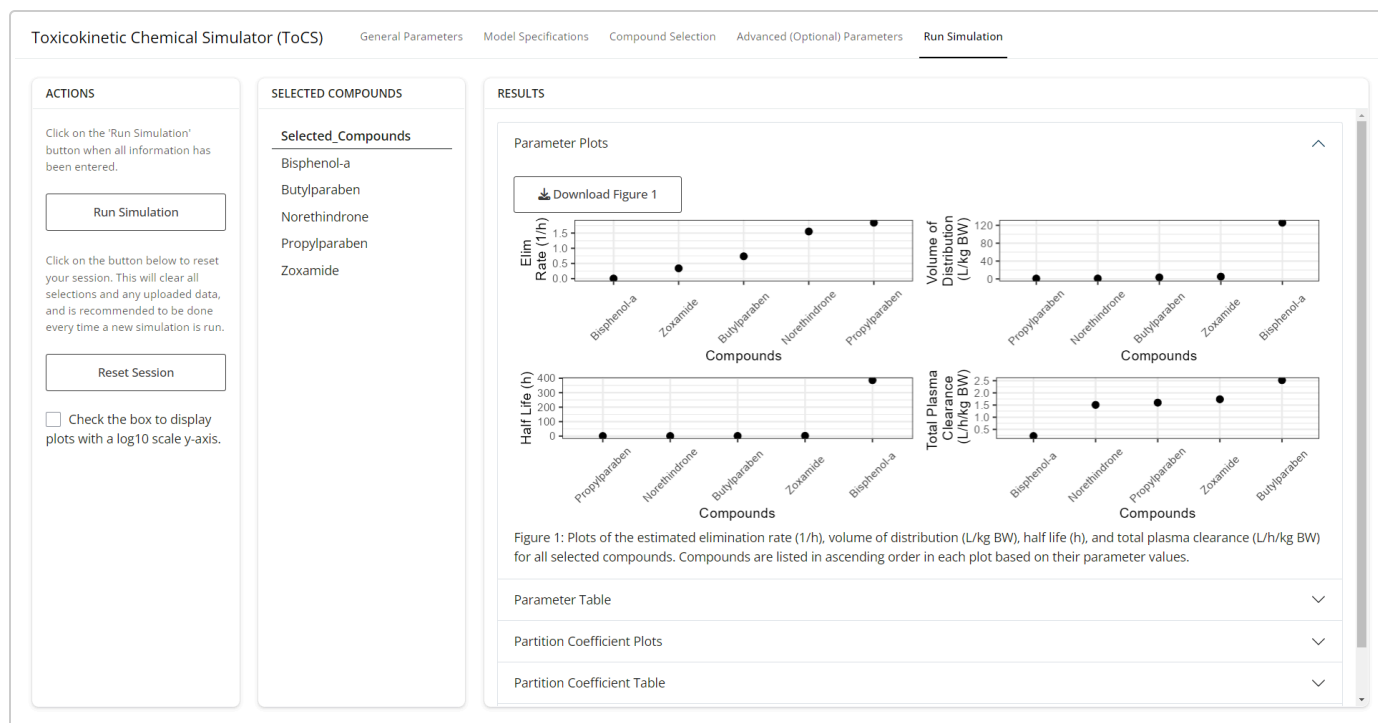
No options for this category.

The completed lower part of the advanced parameters tab for example 2.

Run Simulation Tab

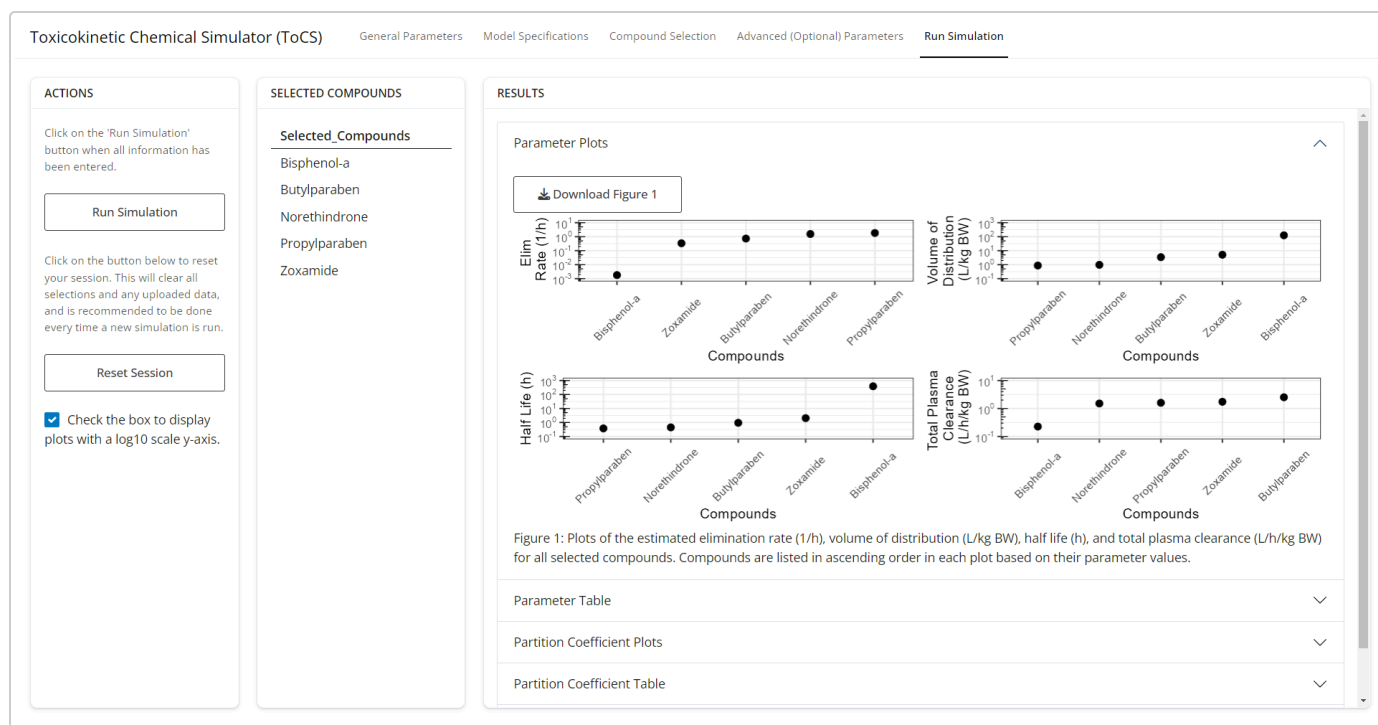
Now that all user selections have been made and all compounds appear under the *Selected Compounds* card, we can hit the *Run Simulation* button under the *Actions* card to initiate the simulation. Below is an image of what the *Run Simulation* tab should look like once the simulation is complete. The plots show each

compound's elimination rate ($1/h$, top left), volume of distribution (L/kg BW, top right), half life (h , bottom left), and total plasma clearance ($L/h/kg$ BW, bottom right). Users have the option to download the figure by clicking the *Download Figure 1* button.



The linear y-axis parameter plots under the parameter plots tab for example 2.

Since it is impossible to tell the volume of distribution and half life values for four of the five compounds in the plot above, we change the y-axis scale to be a \log_{10} y-axis by clicking the checkbox under the *Actions* tab. Then, the plots should look like the image below, which allows the user to clearly see the magnitude of all parameter predictions.



The log10 y-axis parameter plots under the parameter plots tab for example 2.

Under the second drop down menu and shown in the image below, the parameter values from the plots shown in the previous tab are stated in a table. Users can download this table by clicking the *Download Table 1* button at the top of the 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

☐ Check the box to display plots with a log10 scale y-axis.

SELECTED COMPOUNDS

Selected_Compounds

Bisphenol-a
Butylparaben
Norethindrone
Propylparaben
Zoxamide

RESULTS

Parameter Plots

Parameter Table

Download Table 1

Show **10** entries Search: _____

| | CompoundName | EliminationRate | VolumeOfDistribution | HalfLife | TotalClearance |
|---|---------------|-----------------|----------------------|----------|----------------|
| 1 | Bisphenol-a | 0.001795 | 125.8 | 386.2 | 0.2258 |
| 2 | Zoxamide | 0.3392 | 5.124 | 2.043 | 1.738 |
| 3 | Butylparaben | 0.7339 | 3.435 | 0.9445 | 2.521 |
| 4 | Norethindrone | 1.552 | 0.9713 | 0.4466 | 1.507 |
| 5 | Propylparaben | 1.841 | 0.8684 | 0.3765 | 1.599 |

Showing 1 to 5 of 5 entries Previous **1** Next

Table 1: Table of estimated elimination rates (1/h), volumes of distribution (L/kg BW), half lifes (h), and total plasma clearances (L/h/kg BW) for all selected compounds. Compounds are listed in ascending order of the elimination rate.

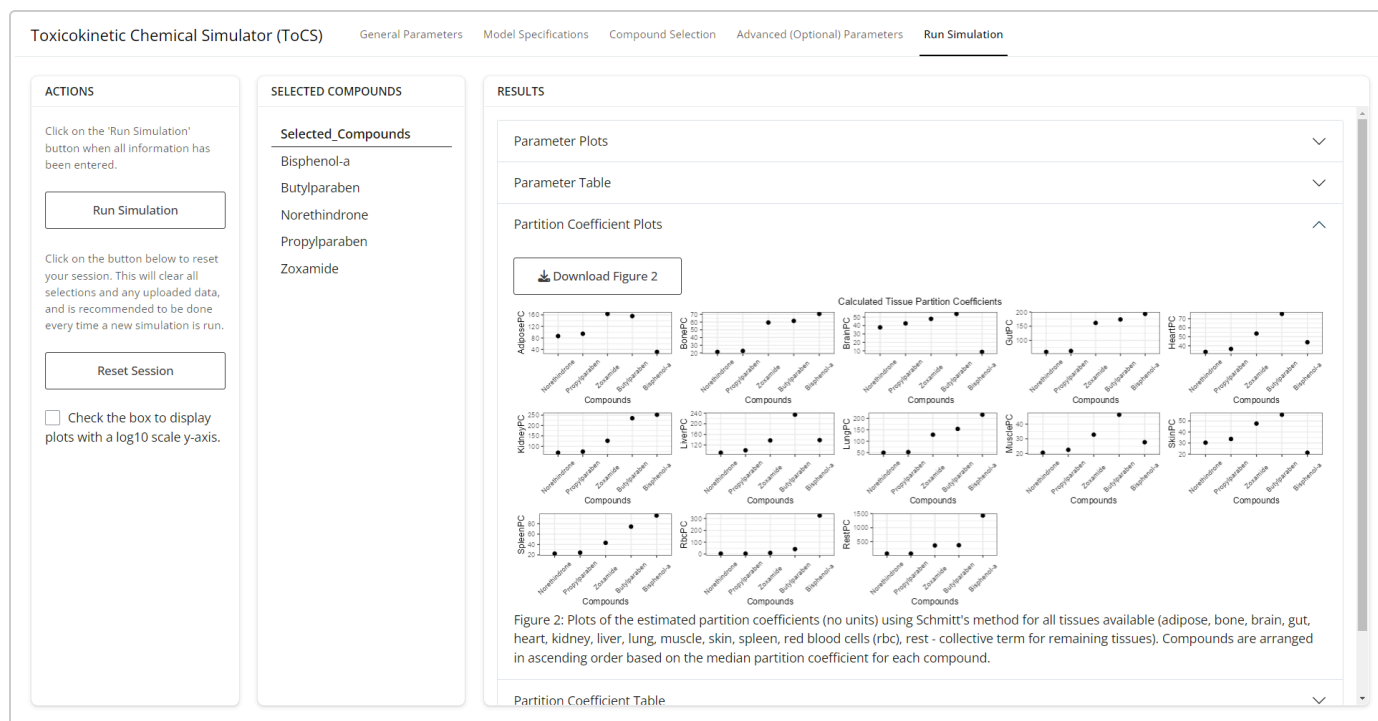
Partition Coefficient Plots

Partition Coefficient Table

Simulation Parameters

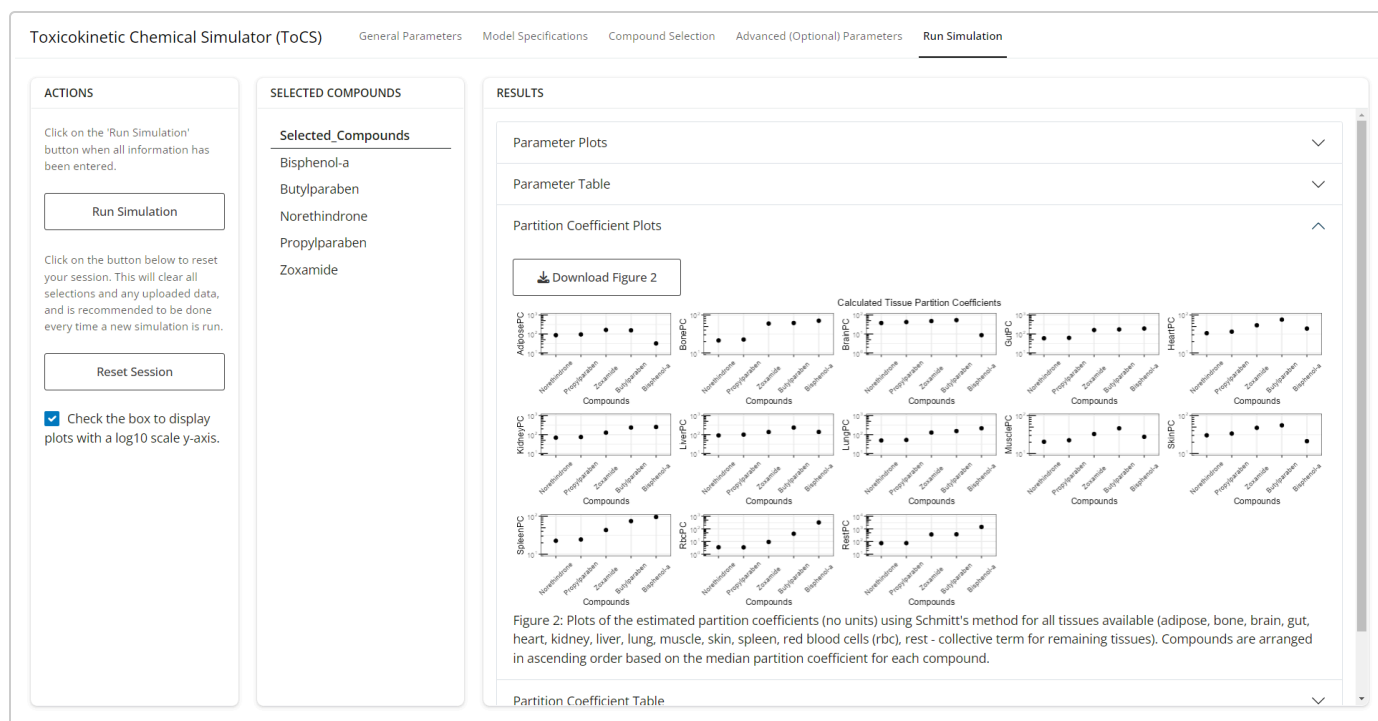
The table of parameter plot values for example 2.

Under the third drop down menu in the *Results* card are 13 partition coefficient plots with one value per compound, as shown in the image below. Users can download these plots by clicking the *Download Figure 2* button at the top of the tab.



The linear y-axis partition coefficient plots for example 2.

As with the plots under the first results tab, users can transform the scale of the y-axis to be a log10 scale by checking the box under the *Actions* card. This will produce the image shown below and give the user a better visual understanding of how the partition coefficients compare to one another.



The log10 y-axis partition coefficient plots for example 2.

Under the fourth drop down menu (shown in the image below), the parameter values from the plots shown in the previous tab are stated in a table. Users can download this table by clicking the *Download Table 1* button at the top of the 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

☐ Check the box to display plots with a log10 scale y-axis.

SELECTED COMPOUNDS

Selected_Compounds

Bisphenol-a
Butylparaben
Norethindrone
Propylparaben
Zoxamide

RESULTS

Parameter Table

Partition Coefficient Plots

Partition Coefficient Table

Download Table 2

Show **10** entries Search: _____

| CompoundName | AdiposePC | BonePC | BrainPC | GutPC | HeartPC | KidneyPC | LiverPC | LungPC | Mus |
|-----------------|-----------|--------|---------|-------|---------|----------|---------|--------|-----|
| 1 Norethindrone | 86.54 | 21.32 | 37.78 | 59.07 | 33.1 | 68.8 | 90.74 | 49.22 | |
| 2 Propylparaben | 94.47 | 22.57 | 42.54 | 62.31 | 36.39 | 74.42 | 99.95 | 52.17 | |
| 3 Zoxamide | 163.3 | 59.46 | 47.89 | 161.5 | 53.56 | 126.6 | 137.1 | 128.2 | |
| 4 Butylparaben | 155.7 | 61.52 | 53.81 | 173.8 | 75.48 | 235.3 | 234 | 153.7 | |
| 5 Bisphenol-a | 31.7 | 70.63 | 8.674 | 193.5 | 43.86 | 252.2 | 138.4 | 215.8 | |

Showing 1 to 5 of 5 entries Previous **1** Next

Table 2: Table of partition coefficients for all selected compounds in each of the available tissues (adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, skin, spleen, red blood cells (rbc), rest - collective term for remaining tissues). The compounds are listed in ascending order based on the median partition coefficient of each compound across all tissues. The median partition coefficient for each compound is shown in the last column of the table.

Simulation Parameters

The partition coefficients table for example 2.

The final drop down tab under the *Results* card gives the user the option to download all model parameters and chemical information for all 5 chemicals.

Toxicokinetic Chemical Simulator (ToCS)

General ParametersModel SpecificationsCompound SelectionAdvanced (Optional) ParametersRun 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

☐ Check the box to display plots with a log10 scale y-axis.

SELECTED COMPOUNDS

Selected_Compounds

Bisphenol-a

Butylparaben

Norethindrone

Propylparaben

Zoxamide

RESULTS

Parameter Plots

Parameter Table

Partition Coefficient Plots

Partition Coefficient Table

Simulation Parameters

Download Simulation Parameters

The simulation parameters tab for example 2.

As with the previous example, we suggest that the user clicks the *Reset Session* button if they want to run another simulation.