

# 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 ToCS README file 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 parameter calculations, 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 initial interface of the ToCS app. At the top, there is a navigation bar with tabs: 'General Parameters' (which is active), 'Model Specifications', 'Compound Selection', 'Advanced (Optional) Parameters', and 'Run Simulation'. Below the navigation bar, the interface is divided into three main sections:

- INSTRUCTIONS:** A text area containing 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." It also describes the four outputs: Concentration-time profiles, Steady state (SS) concentration, In vivo extrapolation (IVIVE), and Parameter calculations.
- OUTPUT:** A dropdown menu labeled "Select the desired output." with the option "Select". Below the dropdown, a note says "Must not be equal to Select."
- SPECIES:** A dropdown menu labeled "Select the species to analyze." with the option "Select". Below the dropdown, a note says "Must not be equal to Select."

The opening interface to the ToCS app.

## Example 1

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

- Advantame (CAS: 714229-20-6)
- Caffeine (CAS: 58-08-2)
- Carboxin (CAS: 5234-68-4)
- Phenol (CAS: 108-95-2)
- Pirinixic acid (CAS: 50892-23-4)
- Triadimenol (CAS: 55219-65-3)
- Chemical1 (CAS: 111-11-1)
- Chemical2 (CAS: 222-22-2)

without using httk's preloaded in silico parameters for hepatic clearance, fraction unbound in plasma, or caco-2 permeability, where Chemical1 and Chemical2 are fictional compounds.

## 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. 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 ToCS application. The top navigation bar includes links for 'General Parameters' (which is active), 'Model Specifications', 'Compound Selection', 'Advanced (Optional) Parameters', and 'Run Simulation'. The main area is divided into three sections: 'INSTRUCTIONS', 'OUTPUT', and 'SPECIES'.

- INSTRUCTIONS:** A text box containing instructions for using the simulator, mentioning four output types: concentration-time profiles, steady state concentrations, 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 set to 'Parameter calculations'.
- SPECIES:** A dropdown menu set to 'Human'.

Below the main sections, there are several hyperlinks for additional resources: 'Vignettes (ToCS tutorials)', 'Report ToCS issues/suggestions', 'httk publication', and 'httk CRAN webpage'.

The completed general parameters tab for example 1.

## Model Specifications Tab

As shown in the image below under the *Model* card, we select 'Schmitt' for the first drop down menu, which is the only option. Then, we select *No* under the second drop down menu since we do not want the program to simulate chemicals with in silico generated parameters for hepatic clearance, fraction unbound in plasma, and caco-2 permeability. There are no user selections under the *Dosing* card. The completed tab should look like the image below, and the user can proceed to the next tab.

**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

**DOSING**

No options for this category.

The completed model specifications tab for example 1.

## Compound Selection Tab

We keep the first drop menu in the *Preloaded Compounds* card on *Choose from all available chemicals* and then under the second drop down, we search by either compound name or CAS for all eight compounds. All but two compounds (Chemical1 and Chemical2) are available, so we select the six available compounds under the *Preloaded Compounds* tab. Thus, we have to upload the chemical data for Chemical1 and Chemical2. 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 fictional chemical data and upload the following csv file (CSV\_vignettes.csv) by clicking *Browse* under the *Uploaded Data* card.

A csv file with two fictional chemicals.

Compound	CAS	CAS.Checksum	DTXSID	Formula	All.Compound.Names	logHenry	logHenry.Reference	logMA
Chemical1	111-11-1	NA	DTXSID1111111	NA	NA	NA	NA	NA
Chemical2	222-22-2	NA	DTXSID2222222	NA	NA	NA	NA	NA

Now that all simulation chemicals are uploaded, the final *Compound Selection* tab should look like the image below.

**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.

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

**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\_vignettes.csv
Upload complete

The completed compound selection tab for example 1.

## Advanced (Optional) Parameters Tab

In the *Advanced Parameters* tab, we are not going to customize any additional parameters for this example and so we leave all inputs as is. The *Advanced Parameters* tab should look like the image below.

**MODEL CONDITIONS**

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 below this will be set to this value.

0.0001

**MODEL SOLVER**

No options for this category.

**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)

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**

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.

The screenshot shows the 'Run Simulation' tab of the Toxicokinetic Chemical Simulator (ToCS). At the top, there are tabs for General Parameters, Model Specifications, Compound Selection, Advanced (Optional) Parameters, and Run Simulation, with 'Run Simulation' being the active tab. The interface is divided into three main sections: ACTIONS, SELECTED COMPOUNDS, and RESULTS.

**ACTIONS:** Contains instructions to click the 'Run Simulation' button when all information has been entered, and a 'Run Simulation' button itself. It also contains a 'Reset Session' button and a note about resetting the session.

**SELECTED COMPOUNDS:** A list titled 'Selected Compounds' containing: Acephate, Caffeine, Carboxin, Chemical1, Chemical2, Phenol, Pirinixic acid, and Triadimenol.

**RESULTS:** A list of results grouped under 'Parameter Plots': Parameter Table, Partition Coefficient Plots, Partition Coefficient Table, and Simulation Parameters. Each item has a collapse/expand arrow icon to its right.

The run simulation tab prior to simulation completion for example 1.

Once the simulation is complete, users will see a group of four plots appear under the *Parameter Plots* tab in the *Results* card. The plots show each compound's elimination rate ( $1/h$ , top left), half life ( $h$ , top right), total plasma clearance ( $L/h/kg BW$ , bottom left), and volume of distribution ( $L/kg BW$ , bottom right). The users have the option to download this figure as is using the *Download Figure 1* button. The user's interface should look like the image below.

**ACTIONS**

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

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.

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

**SELECTED COMPOUNDS**

Selected\_Compounds

- Acephate
- Caffeine
- Carboxin
- Chemical1
- Chemical2
- Phenol
- Pirinixic acid
- Triadimenol

**RESULTS**

Parameter Plots

Compound	Elimination Rate (1/h)
Chemical1	~0.01
Triadimenol	~0.02
Pirinixic acid	~0.03
Caffeine	~0.15
Acephate	~0.20
Phenol	~0.30
Chemical2	~0.32
Carboxin	~0.35

Compound	Half Life (h)
Carboxin	~10
Chemical2	~10
Phenol	~10
Acephate	~10
Caffeine	~10
Pirinixic acid	~10
Triadimenol	~10
Chemical1	~50000

Figure 1: Plots of the estimated elimination rate (1/h), volume of distribution (L/kg BW), half life (h), and total plasma clearance (L/h/kg BW) for all selected compounds. Compounds are listed in ascending order in each plot based on their parameter values.

Parameter Table

Partition Coefficient Plots

Partition Coefficient Table

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

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.

**ACTIONS**

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

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.

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

**SELECTED COMPOUNDS**

Selected\_Compounds

- Acephate
- Caffeine
- Carboxin
- Chemical1
- Chemical2
- Phenol
- Pirinixic acid
- Triadimenol

**RESULTS**

Parameter Plots

Compound	Elimination Rate (1/h)
Chemical1	~10^-5
Triadimenol	~10^-4
Pirinixic acid	~10^-3
Caffeine	~10^-2
Acephate	~10^-2
Phenol	~10^-1
Chemical2	~10^-1
Carboxin	~10^0

Compound	Half Life (h)
Carboxin	~10
Chemical2	~10
Phenol	~10
Acephate	~10
Caffeine	~10
Pirinixic acid	~10
Triadimenol	~10
Chemical1	~50000

Figure 1: Plots of the estimated elimination rate (1/h), volume of distribution (L/kg BW), half life (h), and total plasma clearance (L/h/kg BW) for all selected compounds. Compounds are listed in ascending order in each plot based on their parameter values.

Parameter Table

Partition Coefficient Plots

Partition Coefficient Table

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.

**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
Acephate
Caffeine
Carboxin
Chemical1
Chemical2
Phenol
Pirinixic acid
Triadimenol

**RESULTS**

Parameter Plots

Parameter Table

**Download Table 1**

Show 10 entries Search:

CompoundName	EliminationRate	VolumeOfDistribution	HalfLife	TotalClearance
1 Acephate	0.1885	0.4934	3.677	0.09303
2 Caffeine	0.1613	0.9294	4.297	0.1499
3 Carboxin	0.3438	1.165	2.016	0.4005
4 Chemical1	0.00001431	3.133	48440	0.00004483
5 Chemical2	0.3103	2.105	2.234	0.6531
6 Phenol	0.2868	1.528	2.417	0.4382
7 Pirinixic acid	0.04467	0.1742	15.52	0.007782
8 Triadimenol	0.004059	1.918	170.8	0.007785

Showing 1 to 8 of 8 entries

Table 1: Table of estimated elimination rates (1/h), volumes of distribution (L/kg BW), half lives (h), and total plasma clearances (L/h/kg BW) for all selected compounds.

Partition Coefficient Plots

Partition Coefficient Table

Simulation Parameters

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.

**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
Acephate
Caffeine
Carboxin
Chemical1
Chemical2
Phenol
Pirinixic acid
Triadimenol

**RESULTS**

Partition Coefficient Plots

**Download Figure 2**

Figure 2: Plots of the estimated partition coefficients (unitless) using Schmitt's method for all tissues available (adipose, bone, brain, gut, heart, kidney, muscle, red blood cells, rest, skin, spleen).

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.

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.

**Selected Compounds**

Selected\_Compounds

- Acephate
- Caffeine
- Carboxin
- Chemical1
- Chemical2
- Phenol
- Pirinixic acid
- Triadimenol

**RESULTS**

Partition Coefficient Plots

[Download Figure 2](#)

CompoundName

- Acephate
- Caffeine
- Carboxin
- Chemical1
- Chemical2
- Phenol
- Pirinixic acid
- Triadimenol

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.

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

SELECTED COMPOUNDS  
Selected Compounds  
Acephate  
Caffeine  
Carboxin  
Chemical1  
Chemical2  
Phenol  
Pirinixic acid  
Triadimenol

RESULTS  
Parameter Plots  
Parameter Table  
Partition Coefficient Plots  
Partition Coefficient Table  
[Download Table 2](#)

Show 10 entries Search: \_\_\_\_\_

CompoundName	AdiposePC	BonePC	BrainPC	GutPC	HeartPC	KidneyPC	LiverPC	LungPC	MusclePC	SkinPC
1 Acephate	0.3215	0.3908	0.6517	0.9064	0.9987	2.518	2.753	0.5698	0.583	0.877
2 Caffeine	0.6593	0.6355	1.047	1.68	1.417	3.335	3.471	1.286	1.011	1.27
3 Carboxin	15.72	4.178	6.522	11.71	15.34	21.14	26.3	3.669	4.382	8.36
4 Chemical1	20630	5984	5360	16690	22540	24590	30850	2079	3880	672
5 Chemical2	7.639	2.504	3.341	7.08	8.235	11.74	13.66	2.515	2.451	4.21
6 Phenol	4.016	1.652	2.849	4.724	4.589	8.555	9.381	2.363	2.04	3.61
7 Pirinixic acid	19.25	16.5	18.28	24.91	49.98	89.58	128.9	25.23	28.38	67.9
8 Triadimenol	57.25	15.19	17.79	42.74	58.35	68.95	87.26	8.083	12.06	22.

Showing 1 to 8 of 8 entries

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).

Previous 1 Next

Simulation Parameters

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

The fifth and final tab offers the user the option to download all of the user parameter selection and chemical information used to generate the simulation. The user can download this information by clicking the *Download Simulation Parameters* button. The user's screen should look like the image below.

Toxicokinetic Chemical Simulator (ToxC) 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 log<sub>10</sub> scale y-axis.

**SELECTED COMPOUNDS**

Selected\_Compounds

- Acephate
- Caffeine
- Carboxin
- Chemical1
- Chemical2
- Phenol
- Pirimic acid
- Triadimenol

**RESULTS**

Parameter Plots

Parameter Table

Partition Coefficient Plots

Partition Coefficient Table

Simulation Parameters

**Download Simulation Parameters**

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

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 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.

**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.

Parameter calculations

**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?

No

The completed general parameters tab for example 2.

## Model Specifications Tab

Here, we only see one drop down menu under the *Model* card, which is selected as 'Schmitt'. The *Model Specifications* tab should look like the image below.

**MODEL**

Select a model to simulate.

Schmitt

**DOSING**

No options for this category.

The completed model specifications tab for example 2.

## Compound Selection Tab

We keep the first drop menu in the *Preloaded Compounds* card on *Choose from all available chemicals* and then 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.

The screenshot shows the 'Compound Selection' tab of the ToCS interface. At the top, there are tabs for General Parameters, Model Specifications, Compound Selection (which is active), Advanced (Optional) Parameters, and Run Simulation. The Compound Selection tab contains three main sections: INSTRUCTIONS, PRELOADED COMPOUNDS, and UPLOADED DATA.

**INSTRUCTIONS:** A link to 'Uploaded Physical-Chemical Data File Folder'.

**PRELOADED COMPOUNDS:** A dropdown menu set to 'Choose from all available chemicals'. Below it, a list box contains the selected compounds: 80-05-7, Bisphenol-a; 94-26-8, Butylparaben; 68-22-4, Norethindrone; 94-13-3, Propylparaben; 156052-68-5, Zoxamide.

**UPLOADED DATA:** A section for uploading CSV files, currently showing '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. Under the first 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, 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* for the second drop down. Finally, suppose that we want to lower the p-value threshold for the in vitro intrinsic hepatic clearance rate. Thus, we set the fourth box to 0.01 instead of 0.05. The completed *Advanced Parameters* tab should look like the image below.

**MODEL CONDITIONS**

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

No, do not include protein binding

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

No, do not adjust the fraction of unbound plasma

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.

0.01

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

0.0001

**MODEL SOLVER**

No options for this category.

**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)

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)

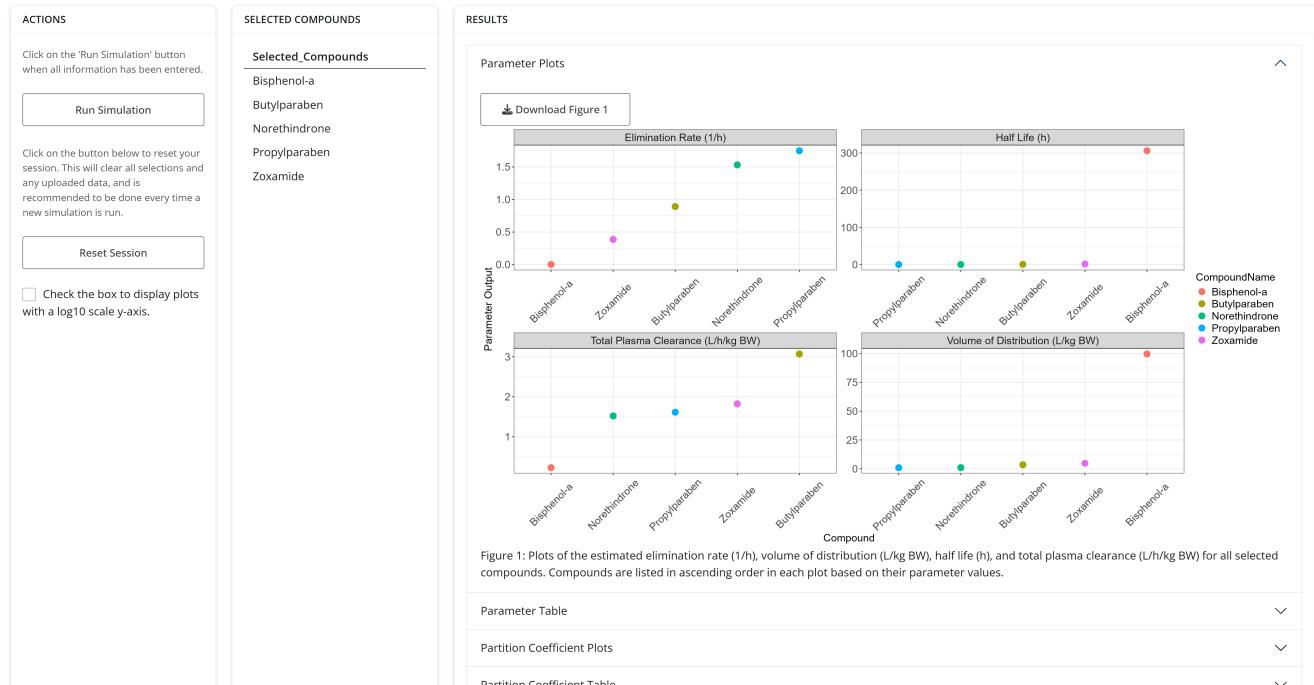
**OUTPUT SPECIFICATION**

No options for this category.

The completed advanced parameters tab for example 2.

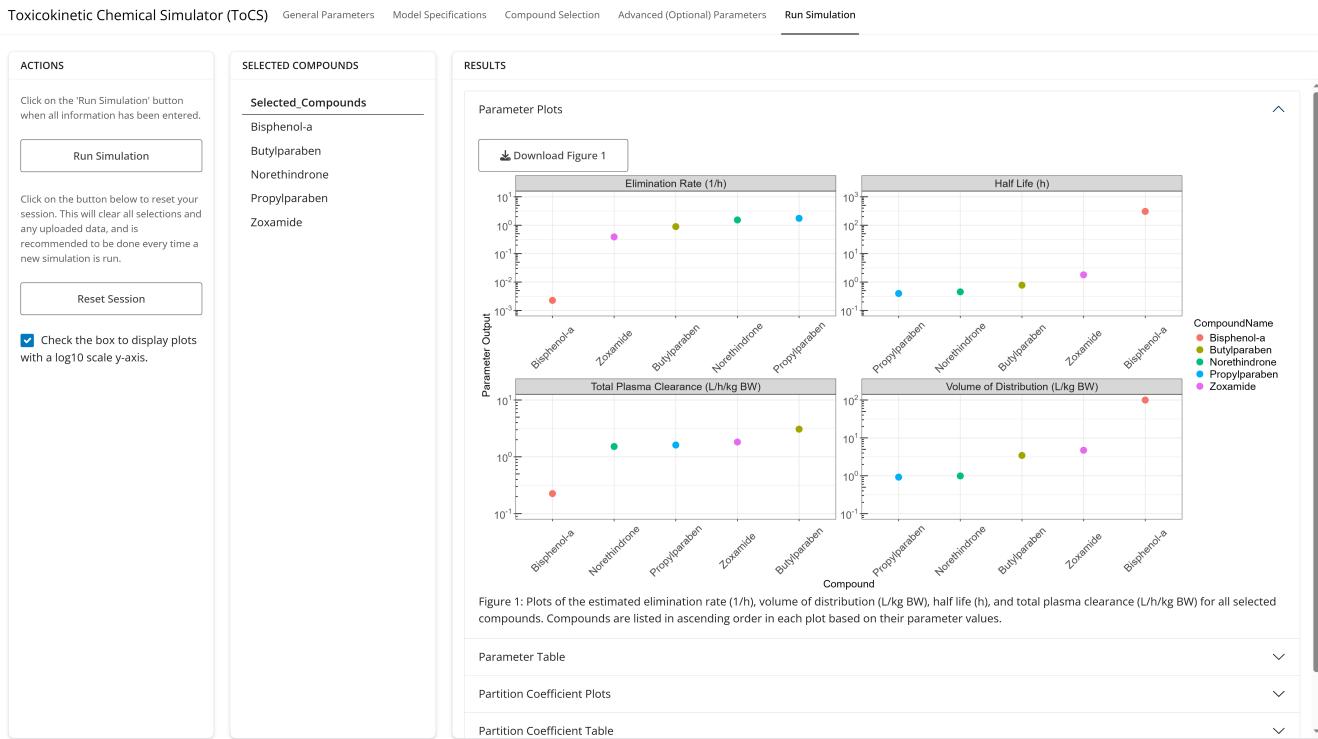
## Run Simulation Tab

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), half life (h, top right), total plasma clearance ( $L/h/kg BW$ , bottom left), and volume of distribution ( $L/kg BW$ , 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 log10 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.

**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

CompoundName	EliminationRate	VolumeOfDistribution	HalfLife	TotalClearance
1 Bisphenol-a	0.002266	99.63	305.9	0.2258
2 Butylparaben	0.8916	3.442	0.7774	3.069
3 Norethindrone	1.532	0.9919	0.4524	1.52
4 Propylparaben	1.748	0.9228	0.3965	1.613
5 Zoxamide	0.3865	4.717	1.793	1.823

Showing 1 to 5 of 5 entries

Table 1: Table of estimated elimination rates (1/h), volumes of distribution (L/kg BW), half lives (h), and total plasma clearances (L/h/kg BW) for all selected compounds.

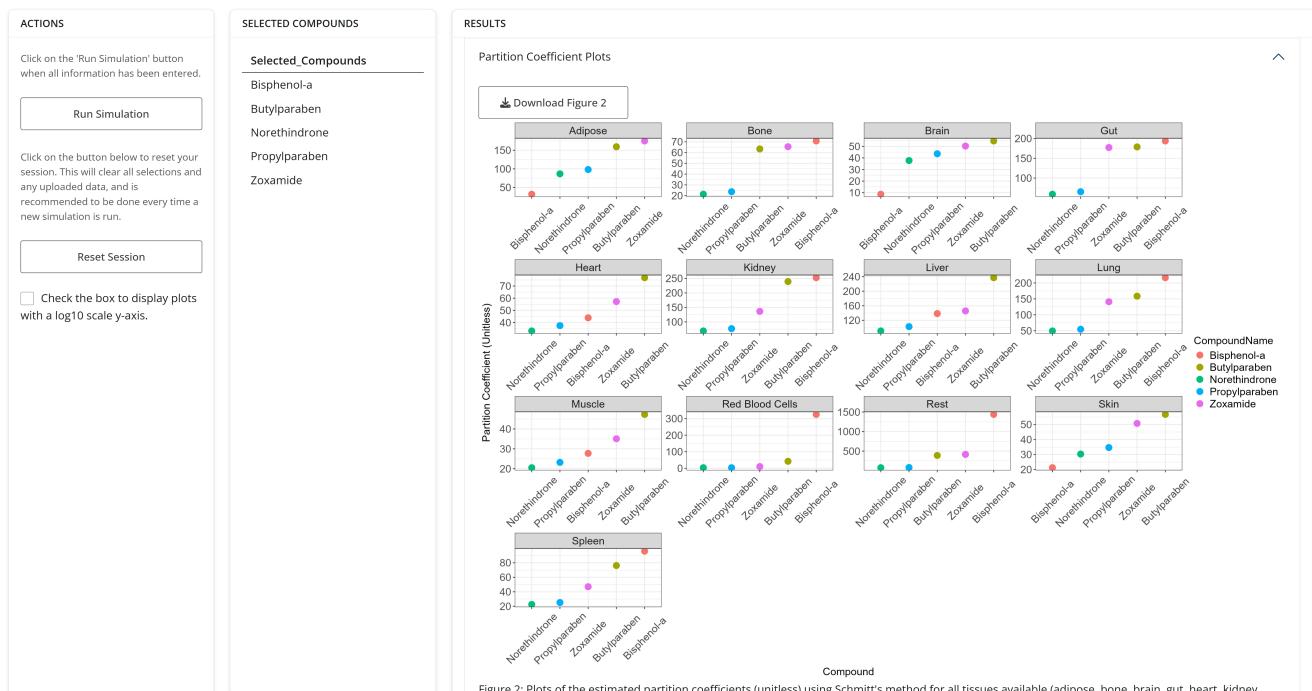
Partition Coefficient Plots

Partition Coefficient Table

Simulation Parameters

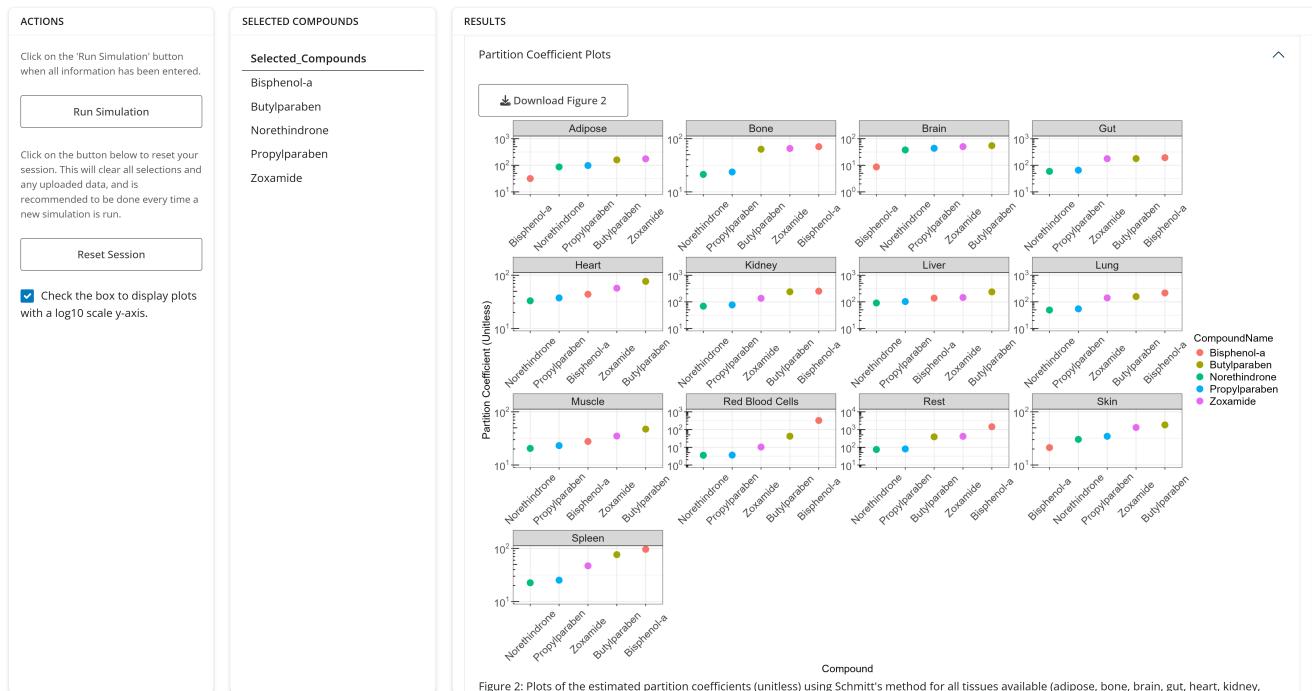
The table of parameter plot values for example 2.

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.

**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

**Download Table 2**

Show 10 entries Search:

CompoundName	AdiposePC	BonePC	BrainPC	GutPC	HeartPC	KidneyPC	LiverPC	LungPC	MusclePC	SkinPC
1 Bisphenol-a	31.77	70.8	8.686	194	43.92	252.5	138.5	216.5	27.73	21.2
2 Butylparaben	159.5	63.36	54.7	178.9	76.83	239.1	237.1	158.5	47.31	56.7
3 Norethindrone	86.6	21.33	37.79	59.12	33.11	68.84	90.79	49.26	20.51	30.3
4 Propylparaben	98.15	23.66	43.64	65.4	37.51	76.84	102.7	54.62	23.19	34.6
5 Zoxamide	175.1	65.46	50.27	177.4	57.23	136.4	145.8	141	35.06	50.7

Showing 1 to 5 of 5 entries

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).

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 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**

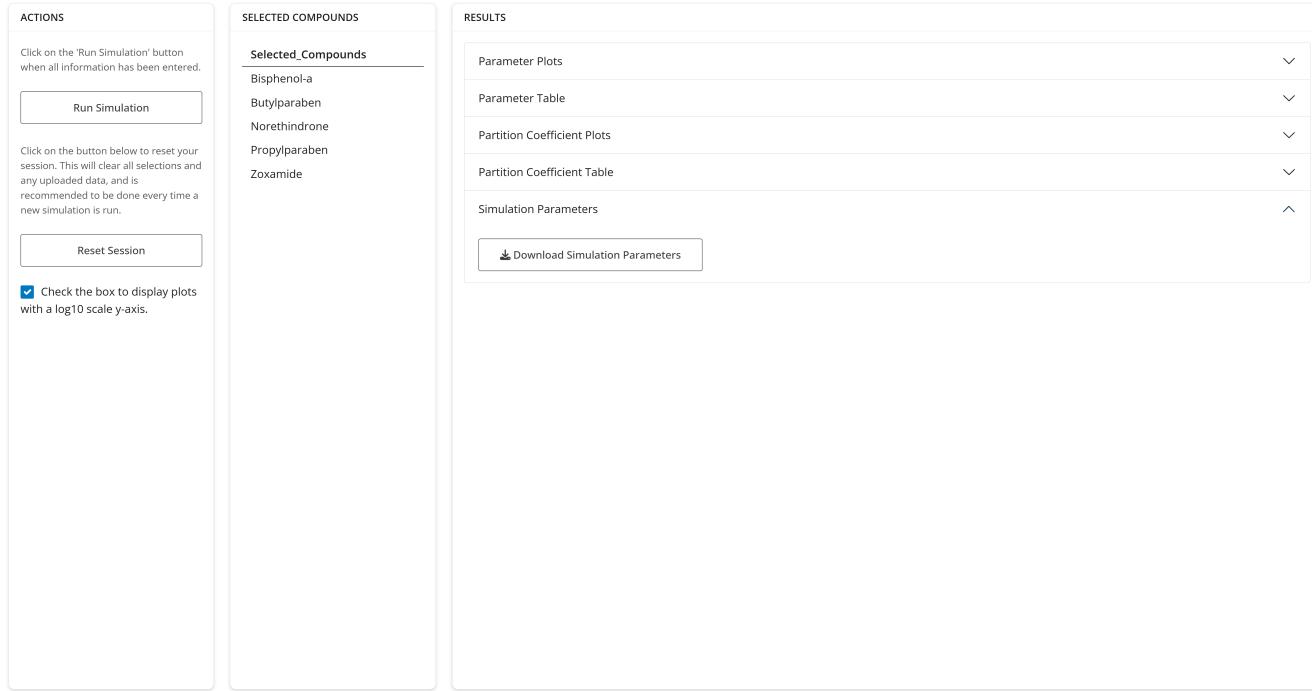
Selected\_Compounds

Bisphenol-a  
Butylparaben  
Norethindrone  
Propylparaben  
Zoxamide

**RESULTS**

Parameter Plots  
Parameter Table  
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.