



# U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program





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

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**Office of Scientific Coordination and Computational Sciences (OSCCS)**

**Office of Laboratory Operations and Applied Science (OLOAS)**

# **Session III:**

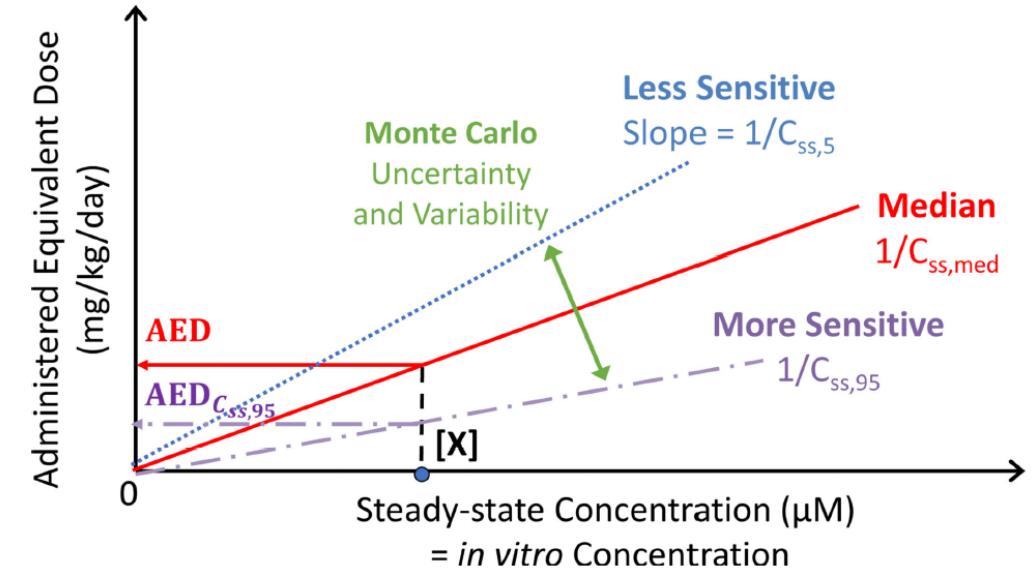
# **In Vitro to In Vivo Extrapolation (IVIVE)**

## **Module**

# IVIVE Background

- A new approach method (NAM) that uses in vitro data to predict in vivo effects of a chemical
- Toxicokinetic IVIVE estimates the in vivo external dose (oral equivalent dose – OED) needed to produce an internal bioactive concentration comparable to that seen in vitro
- If chemical exposure data is available, then a bioactivity exposure ratio (BER) can be calculated to estimate potential health risk of the chemical
  - $\text{BER} < 1$ : A chemical may pose a health risk and should be investigated further

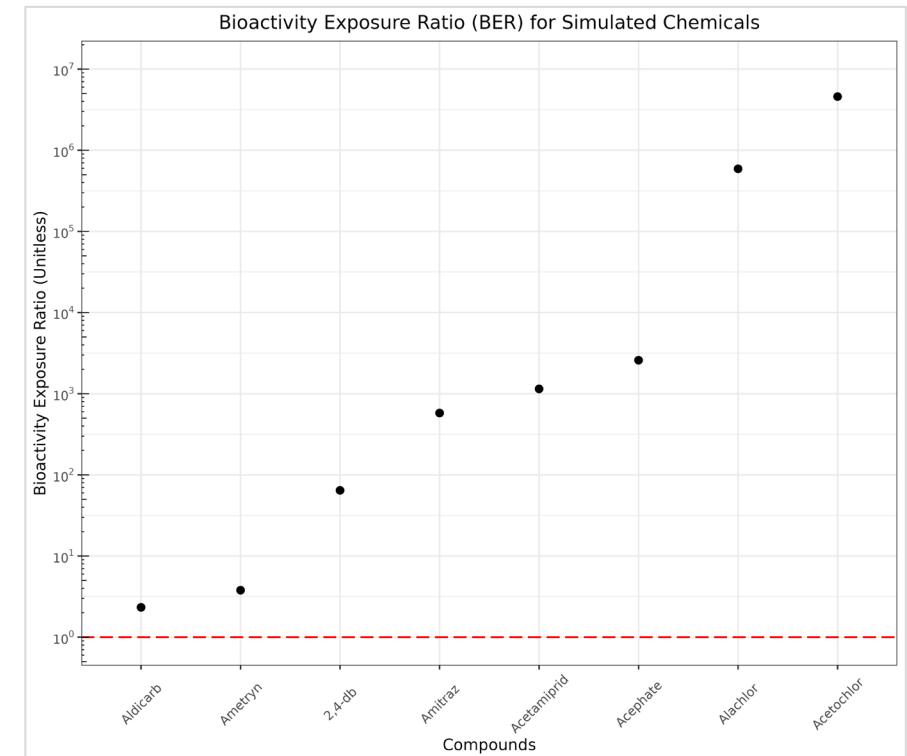
$$\text{AED}_{C_{ss,95}} = \frac{[X]}{C_{ss,95}}$$



Breen, M., Ring, C.L., Kreutz, A., Goldsmith, M.R. and Wambaugh, J.F. (2021). High-throughput PBTK models for in vitro to in vivo extrapolation. *Expert opinion on drug metabolism & toxicology*

# IVIVE Module Outputs

- Plot and table of oral equivalent doses (OEDs)
  - Represents the in vivo external chemical dose needed to achieve the internal chemical concentration that causes bioactivity in vitro
- Plot and table of the bioactivity exposure ratio (BER) for each compound
  - A measure of risk, comparing current exposure level with the OED
  - Prediction is only available if exposure data is provided by the user



# IVIVE Module Inputs

## Required:

- Species and species preferences (if applicable)
- Model selection
- In silico parameter preference
- IVIVE conditions and output preference
- Chemicals to simulate
- In vitro bioactivity data

## Optional:

- In vivo exposure data
- Bioavailability settings
- Output units, concentration type (plasma, blood), and tissue compartment
- Monte Carlo sampling parameters
- Model calculation preferences for hepatic clearance, fraction unbound, and partition coefficients

# IVIVE Conditions for Selection

Assumption Selection	Metabolic Clearance		Bioactive Concentration In Vivo			Bioactive Concentration In Vitro	
	Restrictive	Non-Restrictive*	Free Venous Plasma	Total Venous Plasma	Total Specified Tissue	Nominal	Free
NULL	X				X	X	
Honda1	X		X				X
Honda2	X		X			X	
Honda3	X			X		X	
Honda4		X			X	X	

\*Protein binding NOT taken into account in liver clearance

# In Vitro Bioactivity Data (Required for IVIVE)

- Needed to compute an oral equivalent dose (OED)
- Data could be retrieved from:
  - EPA's CompTox Dashboard (<https://comptox.epa.gov/dashboard>)
  - NTP's ICE platform (<https://ice.ntp.niehs.nih.gov/>)
  - Internal databases
  - Literature publications

# Bioactivity Data: EPA's CompTox Dashboard

**B**

Chemical Details

Executive Summary

Physchem Prop.

Env. Fate/Transport

Hazard Data

Safety > GHS Data

ADME > IVIVE

Exposure

**Bioactivity**

ToxCast: Summary

HTTr: Summary

HTPP: Summary

PubChem

ToxCast: Models

**Bioactivity Summary Grid**

EXPORT  Filter out non-representative sample (Repr.) results. i  Filter out 'background' from Intended Target Family

Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call	Top	AC50
CCTE_Simmons_AUR_TPO	Thyroid Bioactivity	NP_062226.2	Tpo	159   42	279	-	-	-	Active	1	-84.53	6.16
TOX21_p450_CYP3A4_Antagonist	-	NP_059488.2	CYP3A4	-	-	-	-	-	Active	0.9983	-41.53	43.65
TOX21_p450_CYP2C9_Antagonist	-	NP_000762.2	CYP2C9	-	-	-	-	-	Active	0.9551	-37.58	14.55
TOX21_p450_CYP1A2_Antagonist	-	NP_000752.2	CYP1A2	-	-	-	-	-	Active	1	-58.93	20.23
NVS_ENZ_oCOX2	-	NP_001009432.1	PTGS2	-	-	-	-	-	Active	0.9996	-33.52	15.74
NVS_NR_cAR	ToxCast AR Pathway Model	NP_001009012.1	AR	23	25	-	-	-	Active	0.9999	-37.07	20.98
NVS_NR_hPPARg	-	NP_056953.2	PPARG	-	-	-	-	-	Active	0.943	-44.76	25.00
ATG_PXR_TRANS	-	NP_071285.1	NR1 2	-	-	-	-	-	Active	0.9841	1.81	38.50
ATG_ERa_TRANS	ToxCast ER Pathway Model	NP_000116.2	ESR1	-	-	-	-	-	Active	1	3.32	41.44
BSK_SAq_Eselectin	-	NP_000441.2	SELE	-	-	-	-	-	Active	0.9504	0.14	4.26
CCTE_GLTED_hTTR_0.125uM	Thyroid Bioactivity	-	TTR	-	-	-	-	-	Active	1	102.92	26.13
ATG_RXRb_TRANS	-	NP_068811.1	RXRB	-	-	-	-	-	Active	0.9957	1.41	63.23
CCTE_Shaffer_MEAcute_syn	-	-	-	-	-	-	-	-	Active	0.9686	20.62	20.00

Rows: 21 of 1,133 Total Rows: 1,133 Filtered: 21

Denominator is the total number of sample assay endpoint pairs (including non-representative samples).

# Bioactivity Data: NTP's ICE Platform

Select the assays you want to consider for the bioactivity

Enter chemical identifiers for the chemical(s) you want to find bioactivity for

The Curve Surfer tool allows you to view and interact with concentration response curves from cHTS from ICE cHTS dataset, curated from EPA's invitrodb version 4.2.

**Input**

Run Reset

**Chemical Input**

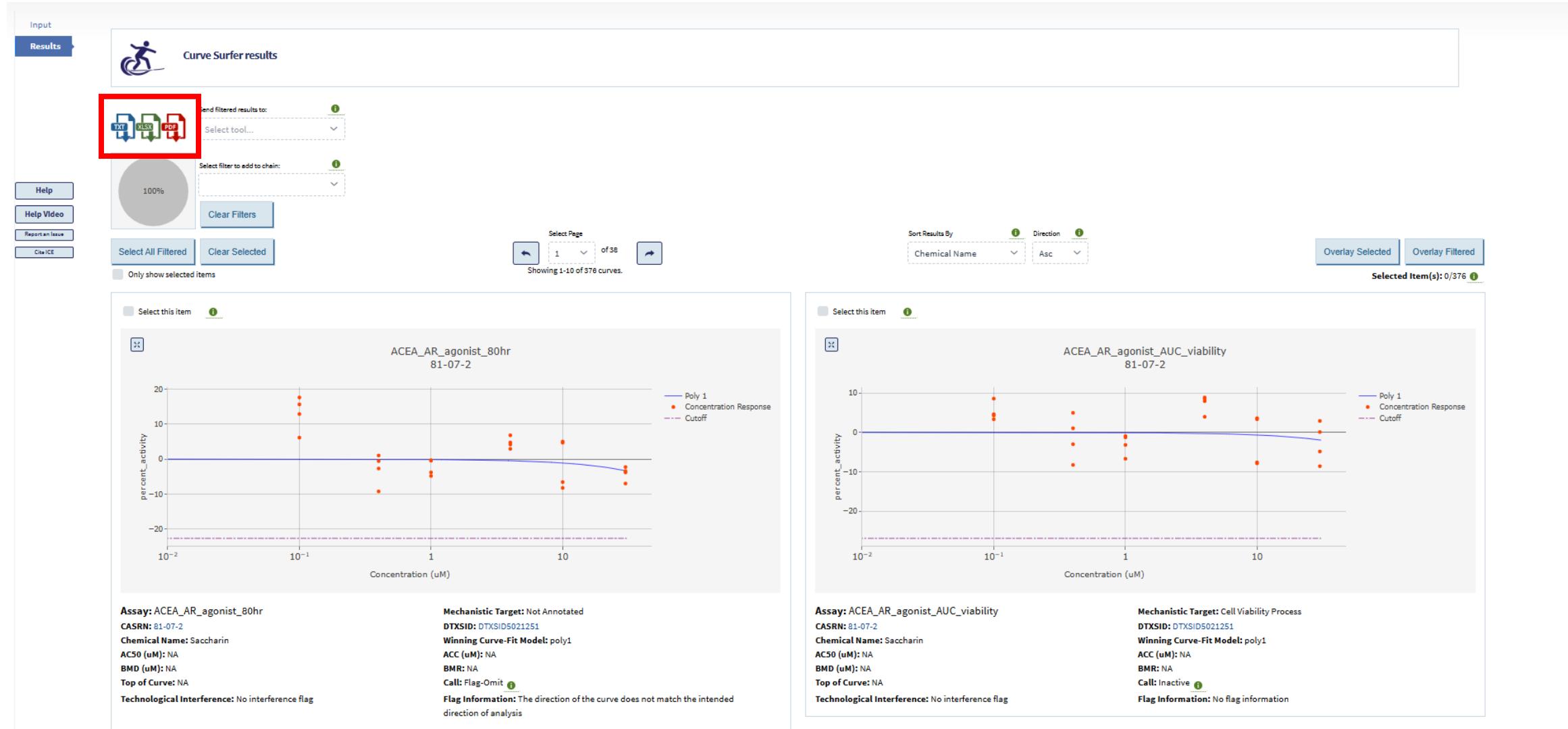
Select Chemicals Quick List CASRNs User Chemical Identifiers 81-07-2

**Data Input**

Select Assays

Assays	Description	Data Type
Tyrosine Iodinase Activity	cHTS	in vitro
Thyroxine Deiodinase Activity	cHTS	in vitro
Thyroid Hormone Transport	cHTS	in vitro
Thyroid Hormone Generation	cHTS	in vitro
Regulation of Hormone Levels	cHTS	in vitro
Aromatase Activity	cHTS	in vitro
Cholesterol Transport	cHTS	in vitro
Not Annotated	cHTS	in vitro

# Bioactivity Data: NTP's ICE Platform



# Bioactivity Data: NTP's ICE Platform

AutoSave Off Curve\_Data20250923165249-SNZSVK01U - Protected... • Saved to this PC

Search

Comments Share

File Home Insert Draw Page Layout Formulas Data Review View Automate Help Acrobat

A1 : fx m4id

1	m4id	Assay	Direction	CASRN	DTXSID	Chemical	Mechanist	ModeOf	Call	Flag	Inform	AC50	ACC	BMD	Concentra	BMR	TopOfCurv	Assay	Resp	WinningCu	InvitroAssa	Technolog	Concentra	Reference	URL
2	8362706	ACEA_AR_	down	81-07-2	DTXSID502	Saccharin	Not Annot	-	Flag-Omit	The direct	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:6.1c	invitroDBv	https://clowd			
3	8357437	ACEA_AR_	down	81-07-2	DTXSID502	Saccharin	Cell Viabili	AcuteTo	-	Inactive	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:3.34	invitroDBv	https://clowd			
4	8364559	ACEA_AR_	up	81-07-2	DTXSID502	Saccharin	Not Annot	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 4	Cell-based	(1:0:-1:0.0	invitroDBv	https://clowd				
5	8366417	ACEA_AR_	down	81-07-2	DTXSID502	Saccharin	Cell Viabili	AcuteTo	-	Inactive	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:-2.3	invitroDBv	https://clowd			
6	8355438	ACEA_ER_	down	81-07-2	DTXSID502	Saccharin	Not Annot	-	Flag-Omit	The direct	NA	NA	NA	uM	NA	NA	percent_ac	Gain-Loss	Cell-based	(1:0:006:-4	invitroDBv	https://clowd			
7	8360707	ACEA_ER_	down	81-07-2	DTXSID502	Saccharin	Cell Viabili	AcuteTo	-	Inactive	NA	NA	NA	uM	NA	NA	percent_ac	Gain-Loss	Cell-based	(1:0:006:3	invitroDBv	https://clowd			
8	12492251	ATG_AP_	2_up	81-07-2	DTXSID502	Saccharin	Cell Differ	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
9	12528643	ATG_E2F_	C_up	81-07-2	DTXSID502	Saccharin	Regulation	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.1	invitroDBv	https://clowd			
10	12733354	ATG_ERRa	up	81-07-2	DTXSID502	Saccharin	Steroid Ho	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd			
11	12737904	ATG_ERRg	up	81-07-2	DTXSID502	Saccharin	Steroid Ho	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
12	12551388	ATG_FoxO	up	81-07-2	DTXSID502	Saccharin	Cell Differ	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
13	12555937	ATG_GATA	up	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.1	invitroDBv	https://clowd			
14	12565035	ATG_GRE	up	81-07-2	DTXSID502	Saccharin	Glucocorti	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
15	12569584	ATG_HIF1	c_up	81-07-2	DTXSID502	Saccharin	Cellular Re	AcuteTo	-	Flag-Omit	The polyne	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd		
16	12756067	ATG_HNF4	up	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
17	12574133	ATG_HNF6	up	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
18	12760944	ATG_LXRa	up	81-07-2	DTXSID502	Saccharin	Liver X Rec		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 5	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
19	12765494	ATG_LXRb	up	81-07-2	DTXSID502	Saccharin	Liver X Rec		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
20	12615074	ATG_Myb	_up	81-07-2	DTXSID502	Saccharin	Regulation	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd			
21	12619622	ATG_Myc	_up	81-07-2	DTXSID502	Saccharin	Cell Popul	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
22	12633269	ATG_NRF1	up	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
23	12637818	ATG_NRF2	up	81-07-2	DTXSID502	Saccharin	Cellular Re	AcuteTo	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
24	12789432	ATG_NURF	up	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd			
25	12793982	ATG_PPAR	up	81-07-2	DTXSID502	Saccharin	Peroxisom	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
26	12798531	ATG_PPAR	up	81-07-2	DTXSID502	Saccharin	Peroxisom	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
27	12803081	ATG_PPAR	up	81-07-2	DTXSID502	Saccharin	Peroxisom	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 4	Cell-based	(1:0:09:0.2	invitroDBv	https://clowd			
28	12651465	ATG_Pax6	_up	81-07-2	DTXSID502	Saccharin	Cell Devel	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
29	12830381	ATG_RORg	up	81-07-2	DTXSID502	Saccharin	Regulation	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
30	12683308	ATG_SREB	up	81-07-2	DTXSID502	Saccharin	Cellular Re	AcuteTo	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0,	invitroDBv	https://clowd			
31	12687857	ATG_STAT	_up	81-07-2	DTXSID502	Saccharin	Regulation	Cancer	-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd			
32	12674210	ATG_Soy	down	81-07-2	DTXSID502	Saccharin	Regulation		-	Inactive	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:0.	invitroDBv	https://clowd			

Export MetaData Query +

Display Settings

Ready

Determine the bioactive concentration for each compound by exploring only “active” calls and using your desired measure and calculation method (generally use the AC50 or ACC)

# Uploading a CSV File of Bioactivity Data

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

**INSTRUCTIONS**

You must choose at least one compound from the preloaded compounds, upload a CSV file with data for at least one compound not included in the preloaded compounds, or both.

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](#)

[Bioactivity Data File Folder](#)

[Exposure Data File Folder](#)

**PRELOADED COMPOUNDS**

Select an IVIVE assumption to implement. For any input nominal bioactive concentration in vitro, the Honda1 assumption is recommended. Leave on 'NULL' if no assumptions are to be applied. See the 'IVIVE Simulation Examples' vignette for the description of the below assumption categories.

NULL

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.

At least one compound must be selected or uploaded

**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

Upload a CSV file with in vitro bioactive concentrations (uM units) for all selected compounds. Download the 'Bioactivity Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... No file selected !

**Required**

Upload a CSV file of exposure data for all selected compounds (optional). Download the 'Exposure Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... No file selected

Downloadable folder with instructions for uploading bioactivity data CSV

Click 'Browse' to find and upload the CSV file of bioactivity data

# Uploading a CSV File of Bioactivity Data

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Spe

**INSTRUCTIONS**

You must choose at least one compound from the preloaded compounds, upload a CSV file with data for at least one compound not included in the preloaded compounds, or both.

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](#)

[Bioactivity Data File Folder](#) **Red Box**

[Exposure Data File Folder](#)

**Instructions** Type: Microsoft Word Document

**SampleBioactivityData** Type: Microsoft Excel Comma Separated Values File

**Instructions for Uploading Bioactivity Data**

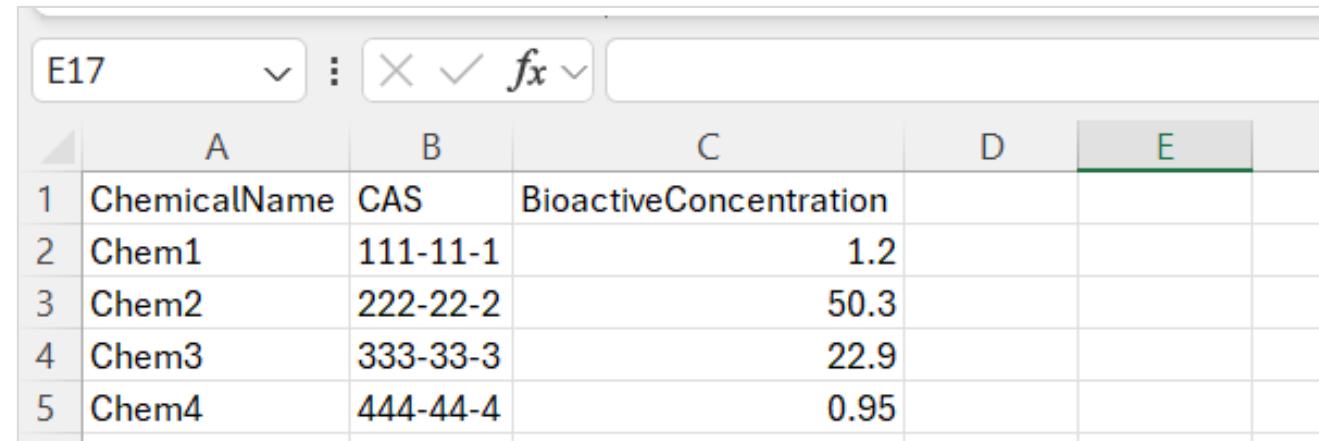
1. Take note of the chemical names and CAS numbers of the chemicals you selected to simulate. These same identifiers must be used in the bioactivity data file uploaded.
2. Prepare your CSV file to upload with bioactivity data. The file must be in the exact same format as the 'SampleBioactivityData.csv' file available in the downloaded folder. It is recommended that you copy the 'SampleBioactivityData.csv' file into a new file and edit the information to suit your simulation. The file must have the same column names and be in the same order as the sample file. There should be no empty cells in the file that you upload – every chemical simulated must have their chemical name, CAS number, and bioactive concentration (uM units, typically AC50 or ACC values) identified.
3. Once you have created your CSV file, click the 'Browse' button on the interface and select your CSV file.|

E17

	A	B	C	D	E
1	ChemicalName	CAS	BioactiveConcentration		
2	Chem1	111-11-1		1.2	
3	Chem2	222-22-2		50.3	
4	Chem3	333-33-3		22.9	
5	Chem4	444-44-4		0.95	

# Uploading a CSV File of Bioactivity Data

- Copy and paste the SampleBioactivityData.csv file into the location of choice and rename as desired.
- Leave the column headers as is. Delete the entries in all other rows.
- Fill in each chemical name that you will be simulating and their corresponding CAS numbers. These identifiers MUST match the names and CAS numbers from the preloaded list or uploaded chemical data.
- Fill in the in vitro bioactive concentration (in uM units) for each compound. Only one bioactive concentration per compound is permitted.
- Save the CSV file.
- Upload CSV file to ToCS interface.



The screenshot shows a Microsoft Excel spreadsheet with a single sheet containing bioactivity data. The data is organized into columns labeled A, B, and C. Column A contains row numbers (1, 2, 3, 4, 5). Column B contains the chemical names (Chem1, Chem2, Chem3, Chem4). Column C contains the CAS numbers (111-11-1, 222-22-2, 333-33-3, 444-44-4). Column D contains the bioactive concentrations (1.2, 50.3, 22.9, 0.95). The first row is a header row with column labels: ChemicalName, CAS, and BioactiveConcentration.

	A	B	C	D	E
1	ChemicalName	CAS	BioactiveConcentration		
2	Chem1	111-11-1		1.2	
3	Chem2	222-22-2		50.3	
4	Chem3	333-33-3		22.9	
5	Chem4	444-44-4		0.95	

## In Vivo Exposure Data (Optional)

- Needed to compute the bioactivity exposure ratio (BER)
- Data could be retrieved from:
  - EPA's CompTox Dashboard (<https://comptox.epa.gov/dashboard>)
  - NTP's ICE platform (<https://ice.ntp.niehs.nih.gov/>)
  - FDA's Cumulative Estimated Daily Intake (CEDI) public database (<https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=CEDI>)

# Exposure Data: EPA's CompTox Dashboard

National Health and Nutrition Examination Survey (NHANES) Inferences (mg/kg-bw/day)

Search Monitoring Data

Demographic ↓↑	Median ↓↑	Upper Bound (Median) ↓↑	Lower Bound (Median) ↓↑
Age 6-11	4.33e-5	4.92e-5	3.80e-5
Age 12-19	2.93e-5	3.30e-5	2.55e-5
Age 20-65	3.02e-5	3.27e-5	2.79e-5
Age 65+	2.10e-5	2.31e-5	1.91e-5
BMI < 30	3.16e-5	3.30e-5	3.02e-5
BMI > 30	2.55e-5	2.74e-5	2.38e-5
Females	2.80e-5	3.03e-5	2.58e-5
Males	3.15e-5	3.37e-5	2.94e-5
Reproto. Age Females	3.06e-5	3.31e-5	2.83e-5
Total	2.97e-5	3.08e-5	2.86e-5

Monitoring Data

National Health and  
Nutrition Examination Survey  
(NHANES) Data

Exposure - Exposure Predictions (mg/kg-bw/day)

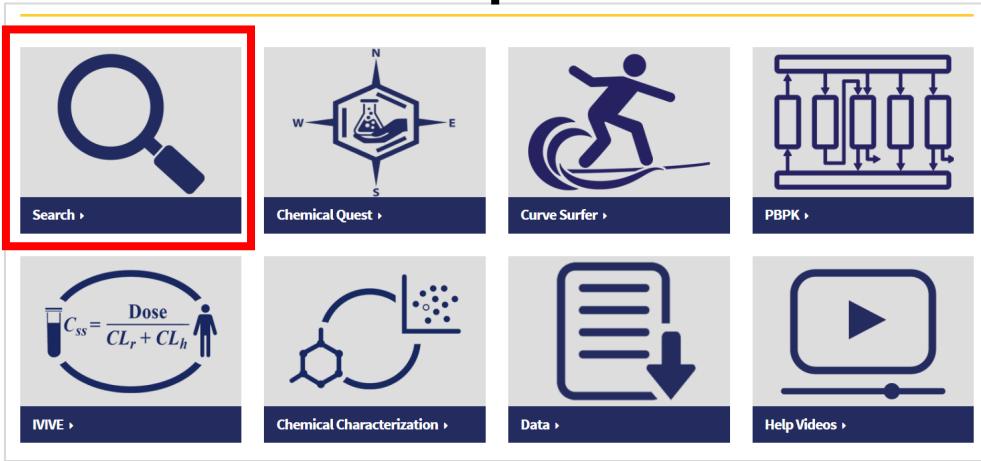
Search Demographics Predictions Data

Demographic ↓↑	Predictor ↓↑	Median ↓↑	Upper 95%ile ↓↑	Units ↓↑
	(2) SEEM2 Heuristic,SEEM3 Con:			
Age 6-11	SEEM2 Heuristic	6.30e-5	1.05e-2	mg/kg/day
Age 12-19	SEEM2 Heuristic	5.87e-5	1.72e-2	mg/kg/day
Age 20-65	SEEM2 Heuristic	5.68e-5	1.15e-2	mg/kg/day
Age 66+	SEEM2 Heuristic	6.61e-5	1.95e-2	mg/kg/day
BMI <= 30	SEEM2 Heuristic	6.25e-5	1.36e-2	mg/kg/day
BMI > 30	SEEM2 Heuristic	7.07e-5	1.86e-2	mg/kg/day
Females	SEEM2 Heuristic	1.24e-5	2.90e-3	mg/kg/day
Males	SEEM2 Heuristic	3.87e-5	6.31e-3	mg/kg/day

Demographics Predictions Data

In Silico Predicted Data  
(EPA Models)

# Exposure Data: NTP's ICE Platform



**Input**

The Search tool allows you to query ICE data using chemical quick list selections (chemical selection of data sets organized by toxicity endpoints of regulatory interest).

Run    Reset    Scope of Search: Union

Help    Help Video    Report an Issue    Cite ICE

**Chemical Input**

Select Chemicals    1 chemical quick list selected.

Quick List CASRNs    User Chemical Identifiers

82657-04-3  
103-90-2  
50-28-2  
56-23-5  
80-05-7

**Select Data Sets**

Select Data Sets    1

Data Set

SEEM3, Exposure Predictions

**Input**

**Results**

Search Results

> Selected Chemical Quick Lists (1)  
> Selected Assays (1)  
Selected Chemical Quick Lists (1)  
Selected Assays (1)

> Chemical Identifiers Not Returned By Query (5)  
Chemical Identifiers Not Returned By Query

404-86-4, 15663-27-1, 50-28-2, 7782-49-2, 59-05-2

**View Data Tables**

Data Table    Data Summary    Download

**Interact with Results**

To zoom in to a specific data type, click on the box within the table, click on the banner. As you navigate through the map, position in the map.

**Details**

Endpoint Record Count: 55

Record ID	Chemical Name	Substance Type	CASRN	DTXSID	QSAR Ready ID	Assay	Endpoint	Response	Unit
exposure_...	Acetaminophen	Chemical	103-90-2	DTXSID2020006	RZVAJINK...	SEEM3, UHFFFAO...	95th percentile	1.889E-4	mg/kg/day
exposure_...	Acetaminophen	Chemical	103-90-2	DTXSID2020006	RZVAJINK...	SEEM3, UHFFFAO...	5th percentile	3.677E-9	mg/kg/day

# Exposure Data: FDA CEDI Database

Be careful of units! ToCS needs mg/kg-BW/day.

**FDA U.S. FOOD & DRUG ADMINISTRATION**

**Cumulative Estimated Daily Intake (CEDI)**

FDA Home | Food Ingredient and Packaging Inventories | CEDI Database | Cumulative Estimated Daily Intake (CEDI)

**Database updated May 2024**

As part of the premarket notification process for food contact substances (FCSS), the Office of Food Additive Safety (OFAS) maintains a database of cumulative estimated daily intakes (CEDIs) for a large number of FCSSs. This database is referred to as the CEDI database and is publicly available. FDA updates the CEDI database as additional information becomes available.

The CEDIs in the database were calculated using information currently available at the time and may be subject to revision on the basis of new information as it is made available and evaluated or existing information is re-evaluated by OFAS.

**Information for FCS Notifiers**

As the safety evaluation is the responsibility of the notifier, potential notifiers are encouraged to approach OFAS through a prenotification consultation to determine if their proposed use is supported by the available data. This is especially critical if the current CEDI may change substantially as a result of the intended use. Notifiers are also encouraged to contact OFAS with new information that may be used to calculate CEDIs and include such information in notifications. See [Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations](#). Concerning the database, OFAS notes the following:

- The CEDI values listed in the database are primarily for FCSSs that are regulated under 21 CFR 175-178 and/or authorized by a Food Contact Substance Notification. Information on constituents, such as monomers, and other impurities may not currently be available.
- The listed CEDI values for polymeric FCSSs in the database are predominately for exposure to the associated low molecular weight oligomers.
- The CEDI values are expressed as both cumulative dietary concentration (CDC, parts-per-billion, ppb) and as cumulative estimated daily intake (CEDI, microgram/kilogram body weight/person/day, µg/kg bw/d).

**Search and display hints:**

- Select the specific substance below to view additional information (other names) for that substance.
- Select the specific regulation (21 CFR), to view the text of that regulation.
- To sort by a specific field, click on the column header for that field.
- To browse the records, use the Show All, First/Previous/Next/Last, and Jump To options at the bottom of the data table.
- To search for a specific substance/term, enter the term in the Search box and select Show Items to display only those records that contain the selected term. (The search results also includes terms not shown on this page, but included in the full record on the detail page.)
- The search results will return hits of records containing words that include the search term. For example, a search for the color red will return results that include terms such as reduce, ingredient, and cultured. To limit results to only the searched term, place a space before and after the word in the basic search or in the advanced search "this exact phrase" field.

Download data from this searchable database in Excel format. If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

Basic Search | Advanced Search | Field Search

Search:  Show Items | Clear

Records Found: 1252 | Show All | Page 1 of 26

CAS Reg. No.* (or other ID*)	Substance* (sorted A-Z)	CEDI* (µg/kg bw/d)	CDC* (ppb)	Calculation/update* Date	21 CFR*
78-63-7	(1,1,4,4-TETRAMETHYLtetramethylene)BIS(tert-BUTYL PEROXIDE)	0.01	0.2	Jun 17, 2010	177.1520 177.2600
68259-36-9	(2,4,4-TRIMETHYLPENT-2-YL)-N-PHENYL-1-NAPHTHYLAMINE	2.5	50	Jul 24, 2007	
6891-44-7	(2-(METHACRYLOYLOXY)ETHYL)TRIMETHYLAMMONIUM METHYL SULFATE	0.02	0.4	Sep 6, 2000	173.10 178.3520
68784-12-3	(2-ALKENYL(C15-21))SUCCINIC ANHYDRIDE	2.6	52	Oct 23, 2015	176.170
26401-86-5	(N-OCTYL)TIN S,S',S"-TRIS(ISOCTYL MERCAPTOACETATE)	0.385	7.7	Jul 22, 1985	178.2650
4118-16-5	1,1'-(6-PHENYL-1,3,5-TRIAZINE-2,4-DIYL)DIIMINO)BIS[9,10-ANTHRACENEDIONE]	0.025	0.5	Mar 21, 1985	178.3297
94-03-1	1,1'-OXYBIS(2-PROPANOL) DIBENZOATE	0.85	17	Jun 20, 2000	
1163733-25-2	1,1,2,2-TETRAFLUORO-2-[1,2,2-TRIFLUOROETHENYL]OXY]ETHANE SULFONYL FLUORIDE, POLYMER WITH 1,1,2,2-TETRAFLUOROETHENE, HYDROLYZED	0.0000265	0.00053	Nov 13, 2017	
1843-03-4	1,1,3-TRIS(5-TERT-BUTYL-4-HYDROXY-2-METHYLPHENYL)BUTANE	47	940	Nov 7, 1983	175.105 178.2010
75-37-6	1,1-DIFLUOROETHANE	0.55	11	Oct 15, 1992	178.3010 701.30
75-38-7	1,1-DIFLUOROETHENE	0.000035	0.0007	Feb 29, 2000	177.1350 177.1380 177.2510 177.2600
64253-30-1	1,11-(3,6,9-TRIOXAUNDECYL) BIS[3-(DODECYLTHIO)PROPIONATE]	0.6	12	Sep 26, 1996	178.2010
887192-39-4	1,12,23,34-TETRAAZACYCLOTETRATETRACONTANE-2,11,24,33-TETRONE	0.11	2.2	Aug 19, 2014	

# Uploading a CSV File of Exposure Data

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

**INSTRUCTIONS**

You must choose at least one compound from the preloaded compounds, upload a CSV file with data for at least one compound not included in the preloaded compounds, or both.

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](#)

[Bioactivity Data File Folder](#)

[Exposure Data File Folder](#)



A black arrow points downwards from this highlighted link to a callout box containing the text: 'Downloadable folder with instructions for uploading exposure data CSV'.

**PRELOADED COMPOUNDS**

Select an IVIVE assumption to implement. For any input nominal bioactive concentration in vitro, the Honda1 assumption is recommended. Leave on 'NULL' if no assumptions are to be applied. See the 'IVIVE Simulation Examples' vignette for the description of the below assumption categories.

NULL

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.

At least one compound must be selected or uploaded

**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

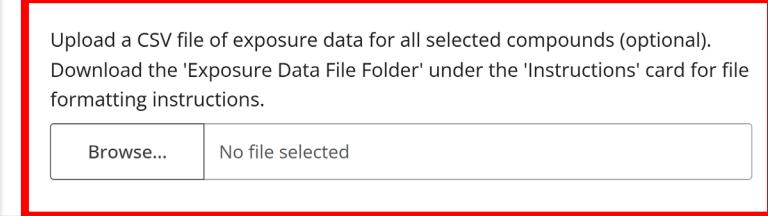
Upload a CSV file with in vitro bioactive concentrations (uM units) for all selected compounds. Download the 'Bioactivity Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... No file selected ⓘ

**Required**

Upload a CSV file of exposure data for all selected compounds (optional). Download the 'Exposure Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... No file selected



A black arrow points downwards from this highlighted area to a callout box containing the text: 'Click 'Browse' to find and upload the CSV file of exposure data'.

# Uploading a CSV File of Exposure Data

Toxicokinetic Chemical Simulator (ToCS) General Parameters Model Spe

**INSTRUCTIONS**

You must choose at least one compound from the preloaded compounds, upload a CSV file with data for at least one compound not included in the preloaded compounds, or both.

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](#)

[Bioactivity Data File Folder](#)

[Exposure Data File Folder](#)

Instructions  
Type: Microsoft Word Document

SampleExposureData  
Type: Microsoft Excel Comma Separated Values File

**Instructions for Uploading Exposure Data**

1. Take note of the chemical names and CAS numbers of the chemicals you selected to simulate. These same identifiers must be used in the exposure data file uploaded.
2. Prepare your CSV file to upload with exposure data. The file must be in the exact same format as the 'SampleExposureData.csv' file available in the downloaded folder. It is recommended that you copy the 'SampleExposureData.csv' file into a new file and edit the information to suit your simulation. The file must have the same column names and be in the same order as the sample file. There should be no empty cells in the ChemicalName or CAS columns, and at least one exposure estimate (mg/kg BW/day) per chemical must be uploaded (either an upper, median, or lower exposure estimate).
3. Once you have created your CSV file, click the 'Browse' button on the interface and select your CSV file.

	A	B	C	D	E	F	G
1	ChemicalName	CAS	Upper	Median	Lower		
2	Chem1	111-11-1	2.39E-04	5.99E-07			
3	Chem2	222-22-2	1.29E-04	1.31E-06			
4	Chem3	333-33-3	1.44E-06	3.37E-07	4.79E-08		
5	Chem4	444-44-4	2.11E-07	4.93E-08	4.74E-09		
6							

# Uploading a CSV File of Exposure Data

- Copy and paste the SampleExposureData.csv file into the location of choice and rename as desired.
- Leave the column headers as is. Delete the entries in all other rows.
- Fill in each chemical name that you will be simulating and their corresponding CAS numbers. These identifiers MUST match the names and CAS numbers from the preloaded list or uploaded chemical data.
- Fill in the upper, median, and lower exposure estimates (mg/kg-BW/day) as desired. There must be AT LEAST one exposure point per compound.
- Save the CSV file.
- Upload CSV file to ToCS interface.

	A	B	C	D	E	F	G
1	ChemicalName	CAS	Upper	Median	Lower		
2	Chem1	111-11-1	2.39E-04	5.99E-07			
3	Chem2	222-22-2	1.29E-04	1.31E-06			
4	Chem3	333-33-3	1.44E-06	3.37E-07	4.79E-08		
5	Chem4	444-44-4	2.11E-07	4.93E-08	4.74E-09		
6							

# Example 1 Scenario

- Obtain the bioactivity exposure ratios of six flavoring agents using the pbtk model

Chemical Name	CAS	Bioactive Concentration*	Exposure Upper^	Exposure Median^	Exposure Lower^
Butylparaben	94-26-8	14.06	1.51E-6	1.28E-6	1.09E-6
Acetophenone	98-86-2	15.90	0.263	6.07E-5	
Methyl salicylate	119-36-8	31.40	0.184	2.17E-4	
Resorcinol	108-46-3	6.626	5.85E-2	1.91E-5	
o-Cresol	95-48-7	47.30	0.105	3.22E-4	
p-Cresol	106-44-5	38.88	1.52	1.53E-3	

- Do not use the available in silico parameters
- Return the 5<sup>th</sup> OED quantile (95<sup>th</sup> steady state concentration quantile)
- Use the Honda1 IVIVE assumption

\* = uM  
^ = mg/kw-BW/day

# Example 1: General Parameters Tab

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

**INSTRUCTIONS:**  
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.  
  
▼

**SPECIES:**  
Select the species to analyze.  
  
▼

# Example 1: Model Specifications Tab

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

**MODEL**

Select the model to simulate. If a species other than 'Human' is selected, '3compartmentss' must be chosen.

pbtk

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

Select whether to return all oral equivalent dose (OED) samples for each compound or a selected quantile.

Only return a specified dose quantile (default)

Enter the steady state concentration quantile (as a decimal) to be used in the OED calculation. Selecting the 95th concentration quantile will output the 5th OED quantile.

0.95

**DOSING**

No options for this category.

# Example 1: Compound Selection Tab

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

**INSTRUCTIONS**

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

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

[Bioactivity Data File Folder](#)

[Exposure Data File Folder](#)

**PRELOADED COMPOUNDS**

Select an IVIVE assumption to implement. For any input nominal bioactive concentration in vitro, the Honda1 assumption is recommended. Leave on 'NULL' if no assumptions are to be applied. See the 'IVIVE Simulation Examples' vignette for the description of the below assumption categories.

Honda1

Select the types of compounds you want to simulate.

Choose from all available chemicals

Enter the volume fraction of fetal bovine serum used in the in vitro assay.

0.1

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.

94-26-8, Butylparaben | 98-86-2, Acetophenone | 119-36-8, Methyl salicylate  
108-46-3, Resorcinol | 95-48-7, 2-methylphenol | 106-44-5, 4-methylphenol

**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

Upload a CSV file with in vitro bioactive concentrations (uM units) for all selected compounds. Download the 'Bioactivity Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... BioactivityDataEx1.csv  
Upload complete

Upload a CSV file of exposure data for all selected compounds (optional). Download the 'Exposure Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... ExposureDataEx1.csv  
Upload complete

# Example 1: Bioactivity and Exposure Data Files

Microsoft Excel window titled "BioactivityDataEx1". The "Home" tab is selected. The ribbon shows AutoSave Off, and the status bar shows "BioactivityDataEx1".

The table has columns A, B, C, D, and E. Column D is currently selected.

	A	B	C	D	E
1	ChemicalName	CAS	BioactiveConcentration		
2	Butylparaben	94-26-8		14.06	
3	Acetophenone	98-86-2		15.9	
4	Methyl salicylate	119-36-8		31.4	
5	Resorcinol	108-46-3		6.626	
6	2-methylphenol	95-48-7		47.3	
7	4-methylphenol	106-44-5		38.88	

Microsoft Excel window titled "ExposureDataEx1". The "Home" tab is selected. The ribbon shows AutoSave Off, and the status bar shows "ExposureDataEx1".

The table has columns A, B, C, D, E, and F. Column D is currently selected.

	A	B	C	D	E	F
1	ChemicalName	CAS	Upper	Median	Lower	
2	Butylparaben	94-26-8	1.51E-06	1.28E-06	1.09E-06	
3	Acetophenone	98-86-2	0.263	6.07E-05		
4	Methyl salicylate	119-36-8	0.184	2.17E-04		
5	Resorcinol	108-46-3	5.85E-02	1.91E-05		
6	2-methylphenol	95-48-7	0.105	3.22E-04		
7	4-methylphenol	106-44-5	1.52	1.53E-03		
8						

# Example 1: Advanced Parameters Tab

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

<b>MODEL CONDITIONS</b>	<b>MODEL SOLVER</b>	<b>BIOAVAILABILITY</b>	<b>OUTPUT SPECIFICATION</b>
Enter the number of Monte Carlo samples generated for each compound. <input type="text" value="1000"/>	No options for this category.	Enter a default value for the Caco-2 apical-to-basal membrane permeability (denoted Caco2.Pab, $10^{-6}$ cm/s). <input type="text" value="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. <input type="button" value="Use the Caco2.Pab value selected above (default)"/>	Select the dose output units from either mg/kg BW/day (mgpkgd) (default) or umol/kg BW/day (umolpkgd). <input type="button" value="mpkgd"/>
Select whether to adjust the chemical fraction unbound in presence of plasma proteins for lipid binding. <input type="button" value="Yes, adjust the fraction of unbound plasma (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. <input type="button" value="Use the Caco2.Pab value selected above (default)"/>	
Select whether to use regressions when calculating partition coefficients. <input type="button" value="Use regressions (default)"/>		Select whether to overwrite in vivo F_abs and F_gut data (if available). <input type="button" value="Do not overwrite in vivo values (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. <input type="text" value="0.05"/>		Select whether to keep F_abs and F_gut at 100% availability (which overwrites all other bioavailability parameter settings above). <input type="button" value="Do not keep Fabs and Fgut at 100% availability (default)"/>	
Enter the minimum acceptable chemical fraction unbound in presence of plasma proteins. All values below this will be set to this value. <input type="text" value="0.0001"/>			

# Example 1: Run Simulation Tab

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

**ACTIONS**

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

**Run Simulation**

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

**Reset Session**

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

**SELECTED COMPOUNDS**

**Selected\_Compounds**

- 2-methylphenol
- 4-methylphenol
- Acetophenone
- Butylparaben
- Methyl salicylate
- Resorcinol

**RESULTS**

Oral Equivalent Dose Table

[Download Table 1](#) [Download OED Simulation Parameters](#)

Show 10 entries

CompoundName	CAS	OED
1 2-methylphenol	95-48-7	24.68
2 4-methylphenol	106-44-5	29.16
3 Acetophenone	98-86-2	0.5482
4 Butylparaben	94-26-8	0.3386
5 Methyl salicylate	119-36-8	159.2
6 Resorcinol	108-46-3	2.966

Showing 1 to 6 of 6 entries

Table 1: Table of the IVIVE oral equivalent doses (OED) (mgpkgday) for each selected compound.

Oral Equivalent Dose Plot

[Download Figure 1](#)

In vitro-in vivo extrapolation (IVIVE) from the pbtk model

# Example 1: Run Simulation Tab

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

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

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

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

**SELECTED COMPOUNDS**  
**Selected\_Compounds**  
2-methylphenol  
4-methylphenol  
Acetophenone  
Butylparaben  
Methyl salicylate  
Resorcinol

**RESULTS**  
Oral Equivalent Dose Table  
Oral Equivalent Dose Plot  
**Download Figure 1**

In vitro-in vivo extrapolation (IVIVE) from the pbtk model

Compound	OED (mg/kg/day)	Type
Butylparaben	~1	Exposure
Acetophenone	~1	Exposure
Resorcinol	~5	OED
2-methylphenol	~25	OED
4-methylphenol	~35	OED
Methyl salicylate	~160	OED

Bioactivity Exposure Ratio Table

Figure 1: Plot of the oral equivalent dose (OED) for each selected compound (blue) and user-uploaded exposure estimates (pink). Compounds are arranged in ascending order of their OED values. Exposure estimates are shown as a distribution if more than one exposure estimate was provided for each compound. The pink dot represents the median exposure either uploaded by the user or calculated within ToCS. If the user only uploaded one exposure value for a compound, then the pink dot represents that value.

# Example 1: Run Simulation Tab

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

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

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

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

**SELECTED COMPOUNDS**  
**Selected\_Compounds**  
2-methylphenol  
4-methylphenol  
Acetophenone  
Butylparaben  
Methyl salicylate  
Resorcinol

**RESULTS**  
Oral Equivalent Dose Table  
Oral Equivalent Dose Plot  
[Download Figure 1](#)

**In vitro-in vivo extrapolation (IVIVE) from the pbtk model**

Type  
Exposure (pink dots)  
OED (blue dots)

Figure 1: Plot of the oral equivalent dose (OED) for each selected compound (blue) and user-uploaded exposure estimates (pink). Compounds are arranged in ascending order of their OED values. Exposure estimates are shown as a distribution if more than one exposure estimate was provided for each compound. The pink dot represents the median exposure either uploaded by the user or calculated within ToCS. If the user only uploaded one exposure value for a compound, then the pink dot represents that value.

Bioactivity Exposure Ratio Table

# Example 1: Run Simulation Tab

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

ACTIONS		SELECTED COMPOUNDS	RESULTS																					
<p>Click on the 'Run Simulation' button when all information has been entered.</p> <p><b>Run Simulation</b></p> <p>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.</p> <p><b>Reset Session</b></p> <p><input type="checkbox"/> Check the box to display plots with a log10 scale y-axis.</p>		<b>Selected_Compounds</b> 2-methylphenol 4-methylphenol Acetophenone Butylparaben Methyl salicylate Resorcinol	<b>Oral Equivalent Dose Table</b> <b>Oral Equivalent Dose Plot</b> <b>Bioactivity Exposure Ratio Table</b> <p><b>Download Table 2</b></p> <p>Show 10 entries</p> <p>Search: _____</p> <table border="1"> <thead> <tr> <th></th> <th>CompoundName</th> <th>BER</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>2-methylphenol</td> <td>235</td> </tr> <tr> <td>2</td> <td>4-methylphenol</td> <td>19.18</td> </tr> <tr> <td>3</td> <td>Acetophenone</td> <td>2.084</td> </tr> <tr> <td>4</td> <td>Butylparaben</td> <td>224200</td> </tr> <tr> <td>5</td> <td>Methyl salicylate</td> <td>865.2</td> </tr> <tr> <td>6</td> <td>Resorcinol</td> <td>50.7</td> </tr> </tbody> </table> <p>Showing 1 to 6 of 6 entries</p> <p>Table 2: Table of the bioactivity exposure ratio (BER) for each selected compound.</p> <p><b>Bioactivity Exposure Ratio Plot</b></p>		CompoundName	BER	1	2-methylphenol	235	2	4-methylphenol	19.18	3	Acetophenone	2.084	4	Butylparaben	224200	5	Methyl salicylate	865.2	6	Resorcinol	50.7
	CompoundName	BER																						
1	2-methylphenol	235																						
2	4-methylphenol	19.18																						
3	Acetophenone	2.084																						
4	Butylparaben	224200																						
5	Methyl salicylate	865.2																						
6	Resorcinol	50.7																						

# Example 1: Run Simulation Tab

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

**ACTIONS**  
Click on the 'Run Simulation' button when all information has been entered.  
**Run Simulation**  
Click on the button below to reset your session. This will clear all selections and any uploaded data, and is recommended to be done every time a new simulation is run.  
**Reset Session**  
 Check the box to display plots with a log10 scale y-axis.

**SELECTED COMPOUNDS**  
Selected\_Compounds  
2-methylphenol  
4-methylphenol  
Acetophenone  
Butylparaben  
Methyl salicylate  
Resorcinol

**RESULTS**  
Oral Equivalent Dose Table  
Oral Equivalent Dose Plot  
Bioactivity Exposure Ratio Table  
Bioactivity Exposure Ratio Plot  
**Download Figure 2**

**Bioactivity Exposure Ratio (BER) for Simulated Chemicals**

Compound	Bioactivity Exposure Ratio (BER)
Acetophenone	~0.5
4-methylphenol	~15
Resorcinol	~60
2-methylphenol	~200
Methyl salicylate	~800
Butylparaben	~300,000

Figure 2: Plot of the bioactivity exposure ratio (BER) values calculated from the oral equivalent dose and exposure estimate from each chemical. The red dotted line ( $BER = 1$ ) separates compounds with  $BER < 1$ , where these chemicals are suggested for prioritization.

## Example 2 Scenario

- Obtain the oral equivalent doses (OEDs) of four direct food additives using the pbtk model

Chemical Name	CAS	Bioactive Concentration*	Exposure Upper^	Exposure Median^	Exposure Lower^
Saccharin	81-07-2	4.324E-3	1.24	2.02E-7	
Theobromine	83-67-0	5.316	1.73E-2	4.19E-6	
Benzophenone	119-61-9	4.425	0.236	3.09E-4	
Eugenol	97-53-0	16.01	0.353	9.20E-5	

\* = uM  
^ = mg/kw-BW/day

- Do not use the available in silico parameters
- Run 500 Monte Carlo steady state samples
- Return the all OED samples
- Use the Honda1 IVIVE assumption

# Example 2: General Parameters Tab

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

- INSTRUCTIONS:** Provides instructions on how to use the simulator, mentioning four outputs: 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 titled "Select the desired output" currently set to "In vitro in vivo extrapolation (IVIVE)".
- SPECIES:** A dropdown menu titled "Select the species to analyze" currently set to "Human".

# Example 2: Model Specifications Tab

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

**MODEL**

Select the model to simulate. If a species other than 'Human' is selected, '3compartmentss' must be chosen.

pbtk

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

Select whether to return all oral equivalent dose (OED) samples for each compound or a selected quantile.

Return all OED samples (will also return the 5th dose quantile)

**DOSING**

No options for this category.

# Example 2: Compound Selection Tab

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

**INSTRUCTIONS**

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

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

[Bioactivity Data File Folder](#)

[Exposure Data File Folder](#)

**PRELOADED COMPOUNDS**

Select an IVIVE assumption to implement. For any input nominal bioactive concentration in vitro, the Honda1 assumption is recommended. Leave on 'NULL' if no assumptions are to be applied. See the 'IVIVE Simulation Examples' vignette for the description of the below assumption categories.

Honda1

Select the types of compounds you want to simulate.

Choose from all available chemicals

Enter the volume fraction of fetal bovine serum used in the in vitro assay.

0.1

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.

81-07-2, Saccharin 83-67-0, Theobromine 119-61-9, Benzophenone  
97-53-0, Eugenol

**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

Upload a CSV file with in vitro bioactive concentrations (uM units) for all selected compounds. Download the 'Bioactivity Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... BioactivityDataEx2.csv  
Upload complete

Upload a CSV file of exposure data for all selected compounds (optional). Download the 'Exposure Data File Folder' under the 'Instructions' card for file formatting instructions.

Browse... ExposureDataEx2.csv  
Upload complete

## Example 2: Bioactivity and Exposure Data

	A	B	C	D	E
1	ChemicalName	CAS	BioactiveConcentration		
2	Saccharin	81-07-2	4.32E-03		
3	Theobromine	83-67-0		5.316	
4	Benzophenone	119-61-9		4.425	
5	Eugenol	97-53-0		16.01	
6					

	A	B	C	D	E	F	G
1	ChemicalName	CAS	Upper	Median	Lower		
2	Saccharin	81-07-2	1.24	2.02E-07			
3	Theobromine	83-67-0	1.73E-02	4.19E-06			
4	Benzophenone	119-61-9	0.236	3.09E-04			
5	Eugenol	97-53-0	0.353	9.20E-05			
6							

# Example 2: Advanced Parameters Tab

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

<b>MODEL CONDITIONS</b>	<b>MODEL SOLVER</b>	<b>BIOAVAILABILITY</b>	<b>OUTPUT SPECIFICATION</b>
Enter the number of Monte Carlo samples generated for each compound. <input type="text" value="500"/>	No options for this category.	Enter a default value for the Caco-2 apical-to-basal membrane permeability (denoted Caco2.Pab, $10^{-6}$ cm/s). <input type="text" value="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. <input type="button" value="Use the Caco2.Pab value selected above (default)"/>	Select the dose output units from either mg/kg BW/day (mgpkgpday) (default) or umol/kg BW/day (umolpkgpday). <input type="button" value="mgpkgpday"/>
Select whether to adjust the chemical fraction unbound in presence of plasma proteins for lipid binding. <input type="button" value="Yes, adjust the fraction of unbound plasma (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. <input type="button" value="Use the Caco2.Pab value selected above (default)"/>	
Select whether to use regressions when calculating partition coefficients. <input type="button" value="Use regressions (default)"/>		Select whether to overwrite in vivo F_abs and F_gut data (if available). <input type="button" value="Do not overwrite in vivo values (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. <input type="text" value="0.05"/>		Select whether to keep F_abs and F_gut at 100% availability (which overwrites all other bioavailability parameter settings above). <input type="button" value="Do not keep Fabs and Fgut at 100% availability (default)"/>	
Enter the minimum acceptable chemical fraction unbound in presence of plasma proteins. All values below this will be set to this value. <input type="text" value="0.0001"/>			

# Example 2: Run Simulation Tab

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

ACTIONS		SELECTED COMPOUNDS		RESULTS																																																										
Click on the 'Run Simulation' button when all information has been entered. <b>Run Simulation</b>  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. <b>Reset Session</b>  <input type="checkbox"/> Check the box to display plots with a log10 scale y-axis.		<b>Selected_Compounds</b> Benzophenone Eugenol Saccharin Theobromine		<b>Oral Equivalent Dose Table</b> <a href="#">Download Table 1</a> <a href="#">Download OED Simulation Parameters</a> Show 10 entries Search: <table border="1"> <thead> <tr> <th></th> <th>Benzophenone</th> <th>Eugenol</th> <th>Saccharin</th> <th>Theobromine</th> </tr> </thead> <tbody> <tr> <td>OED_5</td> <td>0.1186</td> <td>26.1</td> <td>0.0005806</td> <td>155.2</td> </tr> <tr> <td>Samples</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>1</td> <td>1.108</td> <td>916</td> <td>0.006794</td> <td>95.68</td> </tr> <tr> <td>2</td> <td>1.048</td> <td>310.4</td> <td>0.002523</td> <td>10600</td> </tr> <tr> <td>3</td> <td>1.193</td> <td>342.7</td> <td>0.003931</td> <td>20150</td> </tr> <tr> <td>4</td> <td>0.2734</td> <td>240.7</td> <td>0.002491</td> <td>761.6</td> </tr> <tr> <td>5</td> <td>0.1364</td> <td>36.27</td> <td>0.0008988</td> <td>2926</td> </tr> <tr> <td>6</td> <td>0.4789</td> <td>122.1</td> <td>0.00146</td> <td>18820</td> </tr> <tr> <td>7</td> <td>0.6602</td> <td>146.5</td> <td>0.001596</td> <td>86.41</td> </tr> <tr> <td>8</td> <td>0.5193</td> <td>299.7</td> <td>0.003169</td> <td>2317</td> </tr> </tbody> </table> Showing 1 to 10 of 502 entries Previous <b>1</b> 2 3 4 5 ... 51 Next					Benzophenone	Eugenol	Saccharin	Theobromine	OED_5	0.1186	26.1	0.0005806	155.2	Samples					1	1.108	916	0.006794	95.68	2	1.048	310.4	0.002523	10600	3	1.193	342.7	0.003931	20150	4	0.2734	240.7	0.002491	761.6	5	0.1364	36.27	0.0008988	2926	6	0.4789	122.1	0.00146	18820	7	0.6602	146.5	0.001596	86.41	8	0.5193	299.7	0.003169	2317
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# Example 2: Run Simulation Tab

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

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**Reset Session**

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

**SELECTED COMPOUNDS**

**Selected\_Compounds**

- Benzophenone
- Eugenol
- Saccharin
- Theobromine

**RESULTS**

Oral Equivalent Dose Plot

[Download Figure 1](#)

In vitro-in vivo extrapolation (IVIVE) from the pbtk model

OED in whole body plasma or exposure (mg/kg/day)

Compounds

Type

- Exposure (purple dot)
- OED (red dot)

Figure 1: Boxplots of 500 oral equivalent dose (OED) samples for each selected compound (red shaded) and user-uploaded exposure estimates (purple). The black dots represent outliers and the red dots indicate the 5th quartile OED for each compound. Compounds are arranged in ascending order of their median OED value. Exposure estimates are shown as a distribution if more than one exposure estimate was provided for each compound. The purple dot represents the median exposure either uploaded by the user or calculated within ToCS. If the user only uploaded one exposure value for a compound, then the purple dot represents that value.

Bioactivity Exposure Ratio Table

Bioactivity Exposure Ratio Plot

# Example 2: Run Simulation Tab

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

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Bioactivity Exposure Ratio Table

Bioactivity Exposure Ratio Plot

# Example 2: Run Simulation Tab

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

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# Example 2: Run Simulation Tab

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

ACTIONS		SELECTED COMPOUNDS		RESULTS	
Click on the 'Run Simulation' button when all information has been entered. <b>Run Simulation</b>		<b>Selected_Compounds</b> Benzophenone Eugenol Saccharin Theobromine		Oral Equivalent Dose Table Oral Equivalent Dose Plot Bioactivity Exposure Ratio Table Bioactivity Exposure Ratio Plot <a href="#">Download Figure 2</a>	
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<input checked="" type="checkbox"/> Check the box to display plots with a log10 scale y-axis.					

**Bioactivity Exposure Ratio (BER) for Simulated Chemicals**

Compound	Bioactivity Exposure Ratio (BER)
Saccharin	~10 <sup>-3</sup>
Benzophenone	~10 <sup>0</sup>
Eugenol	~10 <sup>1</sup>
Theobromine	~10 <sup>4</sup>

Figure 2: Plot of the bioactivity exposure ratio (BER) values calculated from the oral equivalent dose and exposure estimate from each chemical. The red dotted line ( $BER = 1$ ) separates compounds with  $BER < 1$ , where these chemicals are suggested for prioritization.

# IVIVE Background

Try your own simulation in the IVIVE module

OR

Obtain the human bioactivity exposure ratios for the following chemicals

Chemical Name	CASRN	Bioactive Concentration (uM)	Exposure (mg/kg-BW/day)
FD&C Red 40	25956-17-6	11.58	6.77
Carminic acid	1260-17-9	4.365	7.39E-3
FD&C Green 3	2353-45-9	5.998	1.40E-4
FD&C Yellow 6	2783-94-0	12.59	12.1

and use the following inputs:

- Use the pbtk model and the Honda1 IVIVE condition
- Use the 90<sup>th</sup> quantile steady state concentration (10<sup>th</sup> OED quantile)
- Allow the use of in silico parameters

# Questions?