



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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Contractor

Office of Scientific Coordination and Computational Sciences (OSCCS)

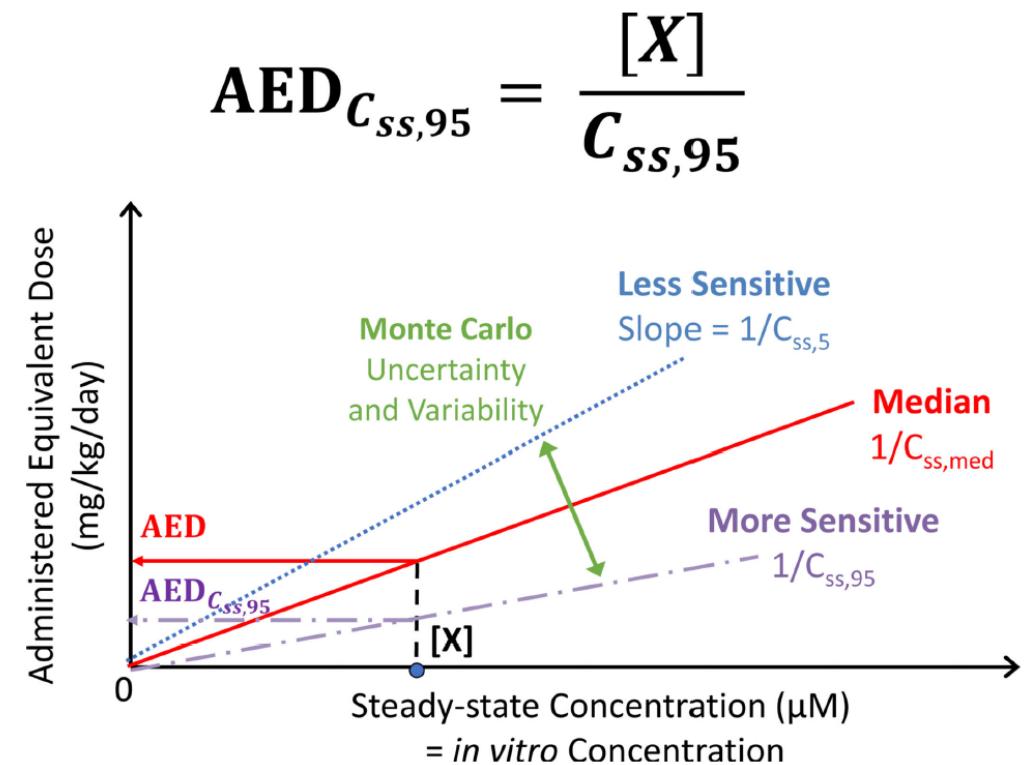
October XX, 2025

Session III: In Vitro to In Vivo Extrapolation (IVIVE) Module

IVIVE Background

FDA

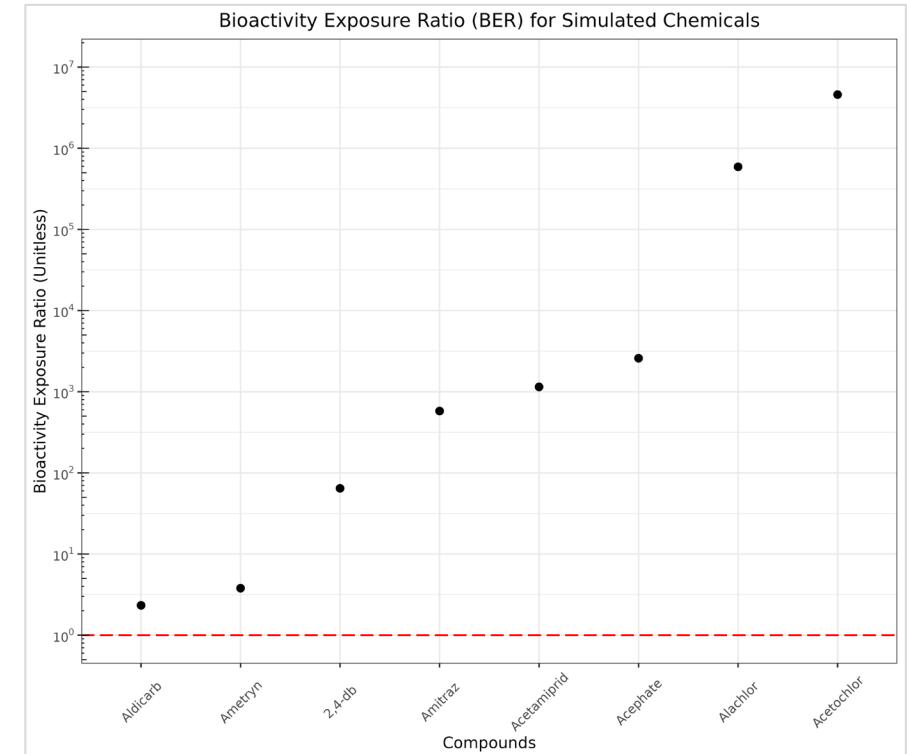
- A new approach method (NAM) that uses in vitro data to predict in vivo effects of a chemical
- Toxicokinetic IVIVE estimates the in vivo external dose (oral equivalent dose – OED) needed to produce an internal bioactive concentration comparable to that seen in vitro
- If chemical exposure data is available,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



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

FDA

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

Special IVIVE Options for Compound Selection in ToCs

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: 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

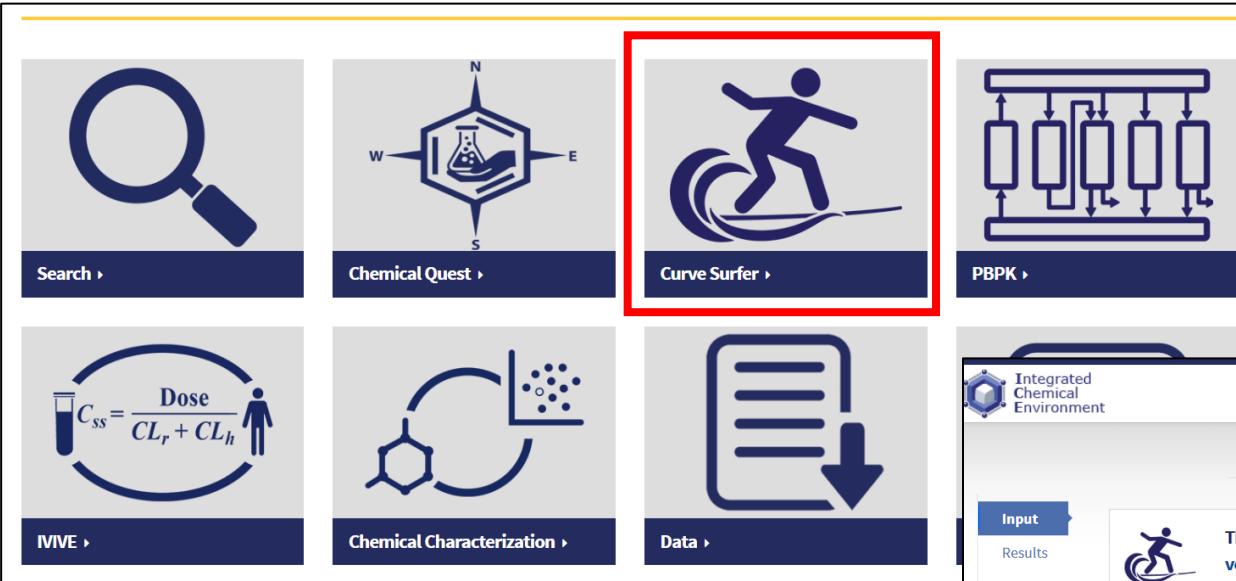
Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call	Top	AC50
CCTE_Simmons_AUR_TPO	Thyroid Bioactivity	NP_062226.2	Tpo	159 42	279	-	-	-	Active	1	-84.53	6.16
TOX21_p450_CYP3A4_Antagonist	-	NP_059488.2	CYP3A4	-	-	-	-	-	Active	0.9983	-41.53	43.65
TOX21_p450_CYP2C9_Antagonist	-	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 ICE Platform

FDA



Select the assays you want to consider for the bioactivity

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 Results

Run Reset

Help Video Report an Issue Cite ICE

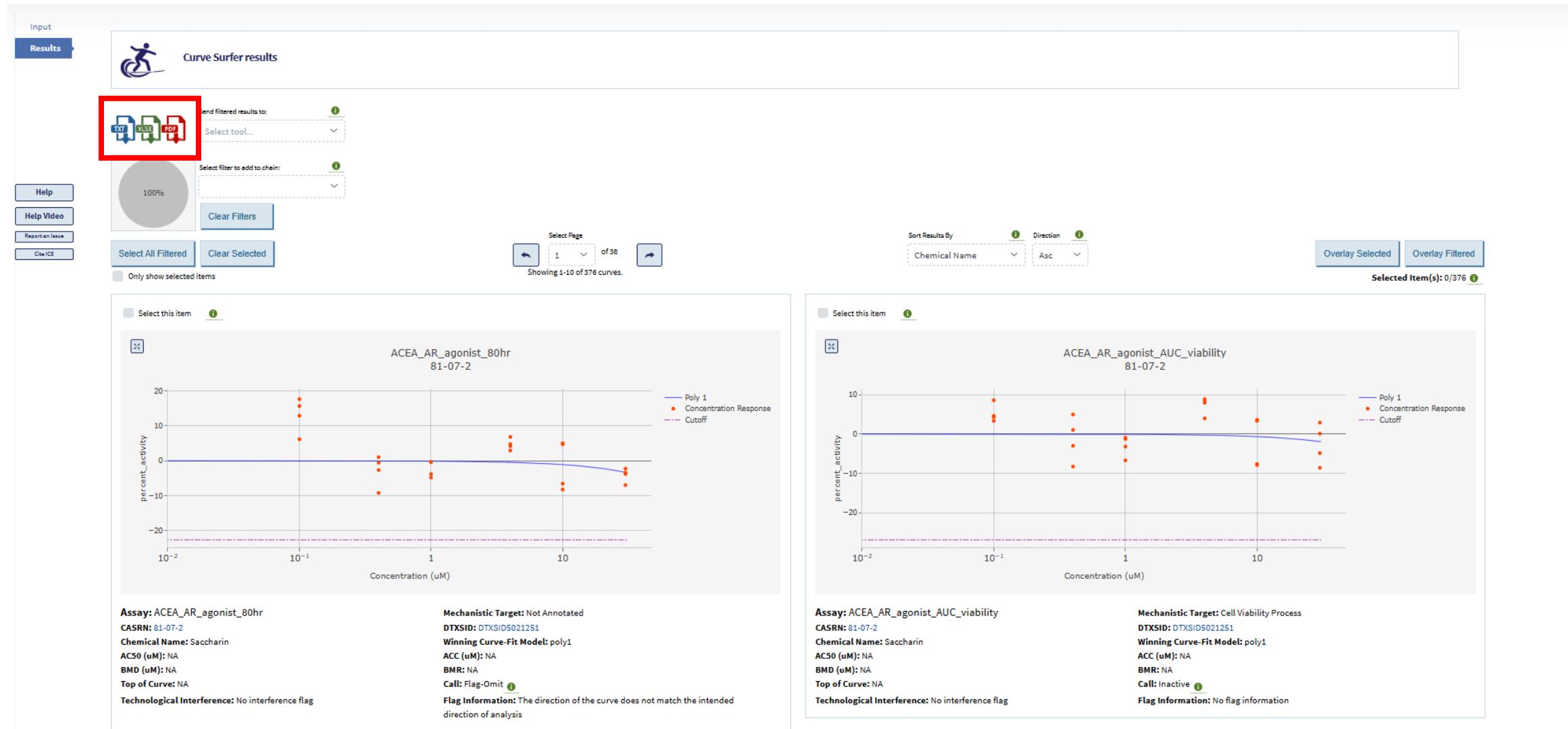
Chemical Input Select Chemicals Quick List CASRNs User Chemical Identifiers 81-07-2

Data Input Select Assays

Assays	Description	Data Type
<input checked="" type="checkbox"/> Tyrosine Iodinase Activity	cHTS	in vitro
<input checked="" type="checkbox"/> Thyroxine Deiodinase Activity	cHTS	in vitro
<input checked="" type="checkbox"/> Thyroid Hormone Transport	cHTS	in vitro
<input checked="" type="checkbox"/> Thyroid Hormone Generation	cHTS	in vitro
<input checked="" type="checkbox"/> Regulation of Hormone Levels	cHTS	in vitro
<input checked="" type="checkbox"/> Aromatase Activity	cHTS	in vitro
<input checked="" type="checkbox"/> Cholesterol Transport	cHTS	in vitro
<input checked="" type="checkbox"/> Not Annotated	cHTS	in vitro

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

Bioactivity Data: NTP ICE Platform



Bioactivity Data: NTP ICE Platform

A1	m4id	Assay	Direction	CASRN	DTXSID	Chemical	Mechanist	ModeOfAct	Call	Flag	Inform	AC50	ACC	BMD	Concentra	BMR	TopOfCurv	AssayRes	WinningCu	InvitroAss	Technolog	Concentra	Reference	URL
1	8362706	ACEA_AR_ down	81-07-2	DTXSID502 Saccharin	Not Annotated	Flag-Omit	The direct	NA	NA	NA	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:6.1c	invitroDBv	https://clowd		
2	8357437	ACEA_AR_ down	81-07-2	DTXSID502 Saccharin	Cell Viability	AcuteToxicity	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:3.34	invitroDBv	https://clowd		
3	8364559	ACEA_AR_ up	81-07-2	DTXSID502 Saccharin	Not Annotated	Flag-Omit	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 4	Cell-based	(1:0:1:-0.0	invitroDBv	https://clowd		
4	8366417	ACEA_AR_ down	81-07-2	DTXSID502 Saccharin	Cell Viability	AcuteToxicity	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	percent_ac	Poly 1	Cell-based	(1:0:1:-2.3	invitroDBv	https://clowd		
5	8355438	ACEA_ER_ down	81-07-2	DTXSID502 Saccharin	Not Annotated	Flag-Omit	The direct	NA	NA	NA	NA	NA	NA	uM	NA	NA	percent_ac	Gain-Loss	Cell-based	(1:0:0.06:-4	invitroDBv	https://clowd		
6	8360707	ACEA_ER_ down	81-07-2	DTXSID502 Saccharin	Cell Viability	AcuteToxicity	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	percent_ac	Gain-Loss	Cell-based	(1:0:0.06:-3	invitroDBv	https://clowd		
7	12492251	ATG_AP_2 up	81-07-2	DTXSID502 Saccharin	Cell Differentiation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
8	12528643	ATG_E2F_C up	81-07-2	DTXSID502 Saccharin	Regulation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.1	invitroDBv	https://clowd		
9	12733354	ATG_ERRa up	81-07-2	DTXSID502 Saccharin	Steroid Hormone	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd		
10	12737904	ATG_ERRg up	81-07-2	DTXSID502 Saccharin	Steroid Hormone	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
11	12551388	ATG_FoxO up	81-07-2	DTXSID502 Saccharin	Cell Differentiation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
12	12555937	ATG_GATA up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.1	invitroDBv	https://clowd		
13	12565035	ATG_GRE up	81-07-2	DTXSID502 Saccharin	Glucocorticoids	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
14	12569584	ATG_HIF1α up	81-07-2	DTXSID502 Saccharin	Cellular Response	AcuteToxicity	Flag-Omit	The poly	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd		
15	12756067	ATG_HNF4 up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
16	12574133	ATG_HNF6 up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
17	12760944	ATG_LXRα up	81-07-2	DTXSID502 Saccharin	Liver X Receptor	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 5	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
18	12765494	ATG_LXRβ up	81-07-2	DTXSID502 Saccharin	Liver X Receptor	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
19	12615074	ATG_Myb_ up	81-07-2	DTXSID502 Saccharin	Regulation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd		
20	12619622	ATG_Myc_ up	81-07-2	DTXSID502 Saccharin	Cell Population	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
21	12633269	ATG_NRF1 up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
22	12637818	ATG_NRF2 up	81-07-2	DTXSID502 Saccharin	Cellular Response	AcuteToxicity	Flag-Omit	Inactive	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
23	12789432	ATG_NURF up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0.0	invitroDBv	https://clowd		
24	12793982	ATG_PPAR up	81-07-2	DTXSID502 Saccharin	Peroxisome	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
25	12798531	ATG_PPAR up	81-07-2	DTXSID502 Saccharin	Peroxisome	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
26	12803081	ATG_PPAR up	81-07-2	DTXSID502 Saccharin	Peroxisome	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Exp 4	Cell-based	(1:0:09:0.2	invitroDBv	https://clowd		
27	12651465	ATG_Pax6 up	81-07-2	DTXSID502 Saccharin	Cell Development	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
28	12830381	ATG_RORγ up	81-07-2	DTXSID502 Saccharin	Regulation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
29	12683308	ATG_SREB up	81-07-2	DTXSID502 Saccharin	Cellular Response	AcuteToxicity	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 1	Cell-based	(1:0:09:0,	invitroDBv	https://clowd		
30	12687857	ATG_STAT1 up	81-07-2	DTXSID502 Saccharin	Regulation	Cancer	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:-0.	invitroDBv	https://clowd		
31	12674120	ATG_Soy Gm up	81-07-2	DTXSID502 Saccharin	Regulation	NA	Inactive	NA	NA	NA	NA	NA	NA	uM	NA	NA	log2_fold_i	Poly 2	Cell-based	(1:0:09:0.	invitroDBv	https://clowd		

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

FDA

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

SampleBioactivityData
Type: Microsoft Excel Comma Separated Values File

Instructions for Uploading Bioactivity Data

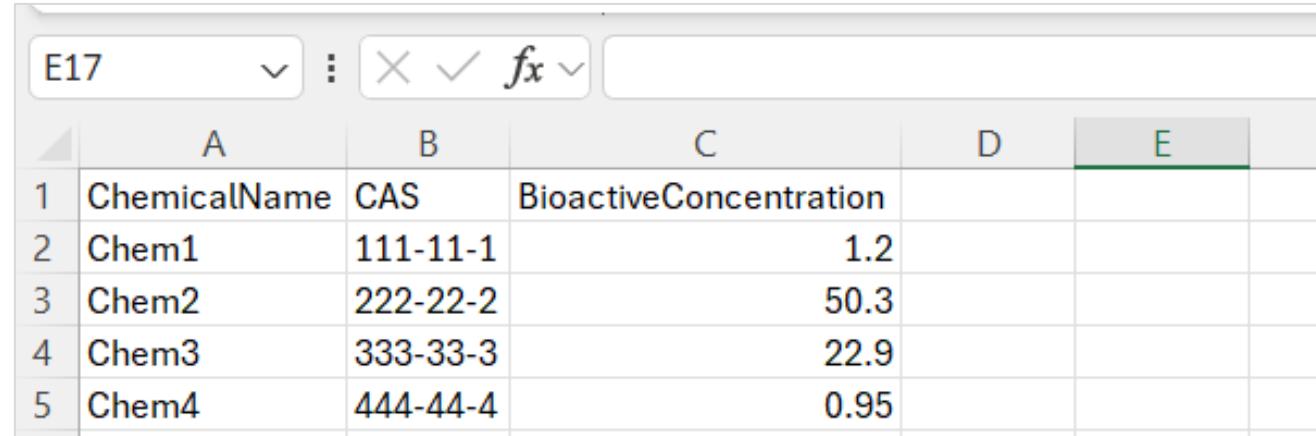
1. Take note of the chemical names and CAS numbers of the chemicals you selected to simulate. These same identifiers must be used in the bioactivity data file uploaded.
2. Prepare your CSV file to upload with bioactivity data. The file must be in the exact same format as the 'SampleBioactivityData.csv' 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.|

	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

FDA

- 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 data. The columns are labeled A, B, C, D, and E. The first row contains the column headers: "ChemicalName", "CAS", and "BioactiveConcentration". The subsequent four rows contain data for four different chemicals: Chem1, Chem2, Chem3, and Chem4. The "BioactiveConcentration" column for Chem1 is 1.2, for Chem2 is 50.3, for Chem3 is 22.9, and for Chem4 is 0.95. The "E17" cell is highlighted in blue, indicating it is the active cell.

	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 CompTox Dashboard

FDA

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

Search Monitoring Data

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	3.38e-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
Repro. Age Females	3.06e-5	3.31e-5	2.83e-5
Total	2.97e-5	3.08e-5	2.86e-5

Chemical Details Executive Summary Physchem Prop. Env. Fate/Transport Hazard Data Safety > GHS Data ADME > IVIVE Exposure Product & Use Categories Chemical Weight Fraction Chemical Functional Use Toxics Release Inventory Biomonitoring Data Exposure Predictions Production Volume

National Health and Nutrition Examination Survey (NHANES) Data

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

Search Demographics Predictions Data

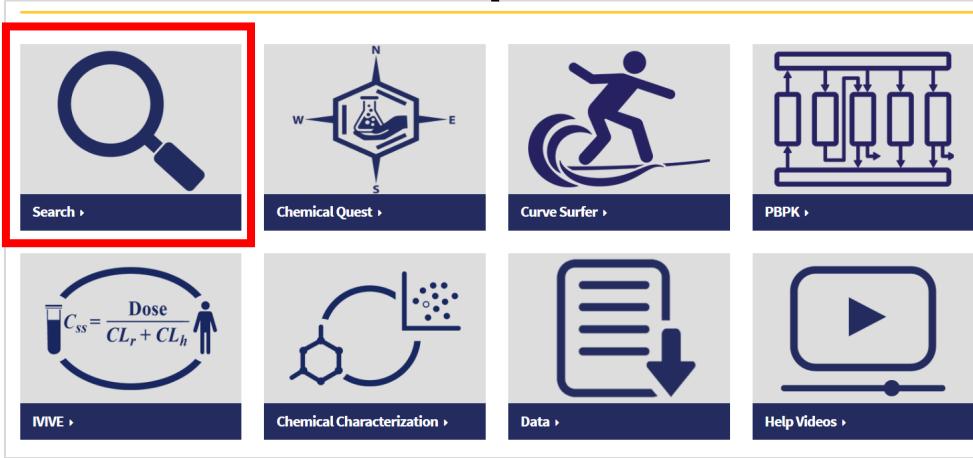
Demographics Predictions Data

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

Chemical Details Executive Summary Physchem Prop. Env. Fate/Transport Hazard Data Safety > GHS Data ADME > IVIVE Exposure Product & Use Categories Chemical Weight Fraction Chemical Functional Use Toxics Release Inventory Biomonitoring Data Exposure Predictions Production Volume

In Silico Predicted Data (EPA Models)

Exposure Data: NTP ICE Platform



Integrated Chemical Environment

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).

Scope of Search: Union

Help, Help Video, Report an Issue, Cite ICE

Chemical Input

Select Chemicals: 1 chemical quick list selected.

Quick List CASRNs: 82657-04-3, 103-90-2, 50-28-2, 56-23-5, 80-05-7

User Chemical Identifiers

Select Data Sets

Select Data Sets: 1

Data Set: SEEM3, Exposure Predictions (checked)



Integrated Chemical Environment

Results

Search Results

Selected Chemical Quick Lists (1)
Selected Assays (1)
Chemical Identifiers Not Returned By Query (5)
404-86-4, 15663-27-1, 50-28-2, 7782-49-2, 59-05-2
Chemical Identifiers Not Returned By Query

Help, Help Video, Report an Issue, Cite ICE

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 banner. As you navigate through the map, position in the map.

Details

Endpoint Record Count: 55

Clear Filter, CSV, XLSX

Record ID	Chemical Name	Substance Type	CASRN	DTXSID	QSAR Ready ID	Assay	Endpoint	Response	Unit
exposure_...	Acetaminophen	Chemical	103-90-2	DTXSID2020006	RZVAJINK... N	SEEM3, UHFFFAO... Exposure Predictions	95th percentile	1.889E-4	mg/kg/day
exposure_...	Acetaminophen	Chemical	103-90-2	DTXSID2020006	RZVAJINK... N	SEEM3, UHFFFAO... Exposure Predictions	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](#)

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 exposure data CSV

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

FDA

- 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 5th OED quantile (95th steady state concentration quantile)
- Use the Honda1 IVIVE assumption

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

Example 1: General Parameters Tab

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

INSTRUCTIONS

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

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

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

[Vignettes \(ToCS tutorials\)](#)
[Report ToCS issues/suggestions](#)
[httk publication](#)
[httk CRAN webpage](#)

OUTPUT

Select the desired output.

In vitro in vivo extrapolation (IVIVE)

SPECIES

Select the species to analyze.

Human

Example 1: Model Specifications Tab

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

MODEL

Select the model to simulate. If a species other than 'Human' is selected, '3compartments' 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

The screenshot shows the Microsoft Excel ribbon with the "Home" tab selected. The "Clipboard" group is expanded, showing options for Paste, Cut, Copy, and Format Painter. The "Font" group shows "Aptos Narrow" font, size 11, bold, italic, underline, and various alignment options. The "Align" group is partially visible. The active cell is D9. The data 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	
8					

The screenshot shows the Microsoft Excel ribbon with the "Home" tab selected. The "Clipboard" group is expanded, showing options for Paste, Cut, Copy, and Format Painter. The "Font" group shows "Aptos Narrow" font, size 11, bold, italic, underline, and various alignment options. The active cell is D23. The data 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

MODEL CONDITIONS	MODEL SOLVER	BIOAVAILABILITY	OUTPUT SPECIFICATION
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 (mgpkpd) (default) or umol/kg BW/day (umolpkpd). <input type="button" value="mgpkpd"/>
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 Previous 1 Next

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

Oral Equivalent Dose Plot

[Download Figure 1](#)

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

or exposure (mgpkgpday)

Type

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)
Butylparaben	~1
Acetophenone	~1
Resorcinol	~5
2-methylphenol	~25
4-methylphenol	~35
Methyl salicylate	~160

Type

- Exposure (pink dot)
- OED (blue dot)

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
- OED

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

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	~10 ^{0.5}
4-methylphenol	~10 ^{1.5}
Resorcinol	~10 ^{2.5}
2-methylphenol	~10 ^{3.5}
Methyl salicylate	~10 ^{9.5}
Butylparaben	~10 ^{5.5}

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

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

INSTRUCTIONS

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

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

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

[Vignettes \(ToCS tutorials\)](#)
[Report ToCS issues/suggestions](#)
[httk publication](#)
[httk CRAN webpage](#)

OUTPUT

Select the desired output.

In vitro in vivo extrapolation (IVIVE)

SPECIES

Select the species to analyze.

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, '3compartments' 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: Advanced Parameters

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

MODEL CONDITIONS	MODEL SOLVER	BIOAVAILABILITY	OUTPUT SPECIFICATION
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 (mgpkgsday) (default) or umol/kg BW/day (umolpkgsday). <input type="button" value="mgpkgsday"/>
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 regressions when calculating partition coefficients. <input type="button" value="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. <input type="text" value="0.05"/>		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)"/>	
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"/>		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)"/>	
		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)"/>	

Example 2: Run Simulation

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

ACTIONS		SELECTED COMPOUNDS		RESULTS			
Click on the 'Run Simulation' button when all information has been entered. Run Simulation		Selected_Compounds Benzophenone Eugenol Saccharin Theobromine		Oral Equivalent Dose Table Download Table 1 Download OED Simulation Parameters Show 10 entries			
				Search: _____			
				Benzophenone ◆ OED_5 0.1186 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	Eugenol ◆ 26.1	Saccharin ◆ 0.0005806	Theobromine ◆ 155.2
				Showing 1 to 10 of 502 entries Previous 1 2 3 4 5 ... 51 Next			
				Oral Equivalent Dose Plot Download Figure 1 pday			
				In vitro-in vivo extrapolation (IVIVE) from the pbtk model			

Example 2: Run Simulation

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

- Benzophenone
- Eugenol
- Saccharin
- Theobromine

RESULTS

Oral Equivalent Dose Plot

[Download Figure 1](#)

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

Type

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

Compounds

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 quantile 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

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

- Benzophenone
- Eugenol
- Saccharin
- Theobromine

RESULTS

Oral Equivalent Dose Plot

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

Download Figure 1

OED in whole body plasma or exposure (mgpk/day)

Compounds: Saccharin, Benzophenone, Eugenol, Theobromine

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 quantile 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

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

Benzophenone
Eugenol
Saccharin
Theobromine

RESULTS

Oral Equivalent Dose Table

Oral Equivalent Dose Plot

Bioactivity Exposure Ratio Table

Download Table 2

Show 10 entries

Search: _____

	CompoundName	BER
1	Benzophenone	0.5025
2	Eugenol	73.94
3	Saccharin	0.0004682
4	Theobromine	8971

Showing 1 to 4 of 4 entries

Table 2: Table of the bioactivity exposure ratio (BER) for each selected compound.

Bioactivity Exposure Ratio Plot

Example 2: Run Simulation

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

- Benzophenone
- Eugenol
- Saccharin
- Theobromine

RESULTS

Oral Equivalent Dose Table

Oral Equivalent Dose Plot

Bioactivity Exposure Ratio Table

Bioactivity Exposure Ratio Plot

[Download Figure 2](#)

Compound	Bioactivity Exposure Ratio (BER)
Saccharin	~2e-4
Benzophenone	~8e-3
Eugenol	~8e+1
Theobromine	~1e+4

Bioactivity Exposure Ratio (BER) for Simulated Chemicals

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.

Try It On Your Own!

FDA

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 90th quantile steady state concentration (10th OED quantile)
- Allow the use of in silico parameters

Questions?