U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

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

Kristen Windoloski, Contractor

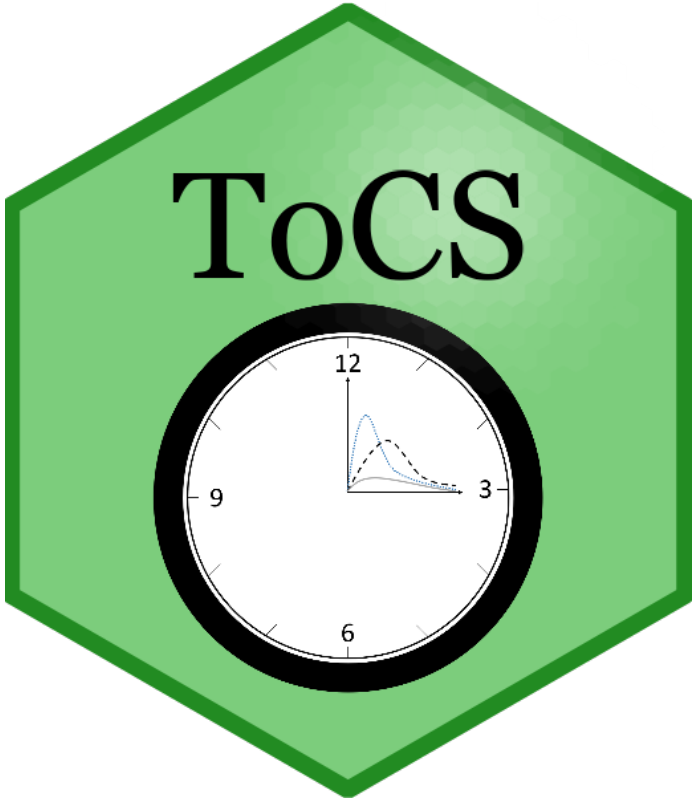
Office of Scientific Coordination and Computational Sciences (OSCCS)

Office of Laboratory Operations and Applied Science (OLOAS)

Session I: Introduction to ToCS

Overview of ToCS

- ToCS stands for ‘Toxicokinetic Chemical Simulator’ and is an easy-to-use graphical user interface (GUI) tool
- Utilizes computational modeling software to make high-throughput toxicokinetic (TK) chemical predictions
- Predict ADME profiles and characteristics, prioritize chemicals using in vitro to in vivo extrapolation, and generate TK parameters
- No programming skills are required

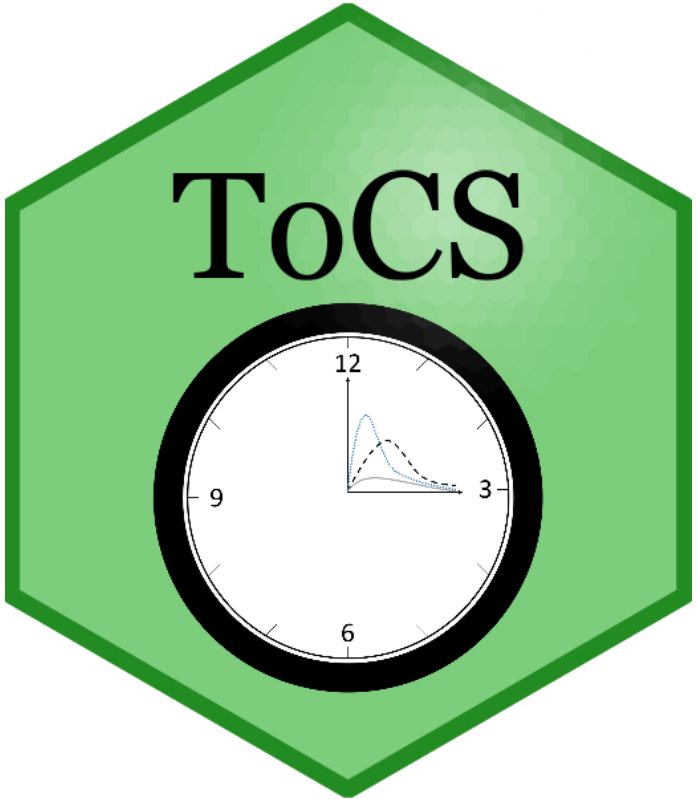


Overview of ToCS

- Uses models and functions from the EPA's httk R package

- Use ToCS to:

  - Conduct a high throughput preliminary screening, prioritization, and characterization of chemicals
  - Perform a post market assessment of food relevant compounds
  - Obtain parameters to use in other predictive models or compare with in vivo data
  - Simulate ingredients used in products marketed as dietary supplements



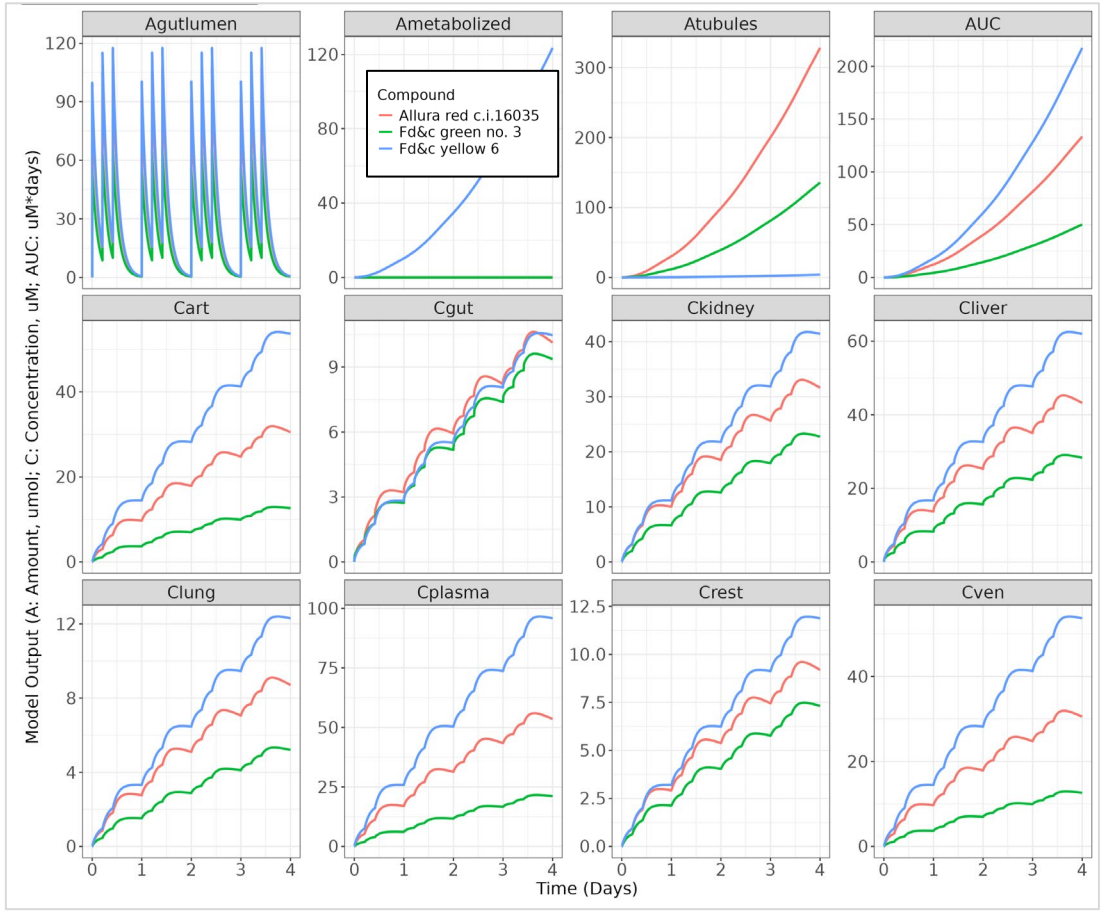
Outputs of ToCS

Concentration-Time Profiles Module	Steady State Concentrations Module
• ADME time course data (Amounts and concentrations over time) • Summary statistics (Tmax, Cmax, and AUC)	• Analytical steady state in desired concentration/tissue • Estimate of the time (days) it takes to reach steady state behavior following constant oral dosing
In Vitro to In Vivo Extrapolation (IVIVE) Module	**Parameter Calculations Module**
• OEDs (the external dose needed to produce the internal bioactive conc.) compared with exposure data (if provided by the user) • BERs if exposure data is provided by the user	• Toxicokinetic parameters (half-life, total plasma clearance, elimination rate, volume of distribution) • Partition coefficients in different tissues

Abbreviations: ADME – absorption, distribution, metabolism, excretion; Cmax – maximal concentration; Tmax – time to Cmax; AUC – area under the curve; OED – oral equivalent dose; BER – bioactivity exposure ratio

Food Relevant Features

- Models with oral exposure route
- Ability to make a non-uniform exposure protocol (mimics food consumption at mealtimes)
- Customization of bioavailability settings
  - Use of in silico $Caco2.Pab$ values
  - Ability to run simulations with 100% bioavailability - more conservative



- Contains explicit list of food chemicals available for simulation
  - 109-118 chemicals for human simulations (954-956 chemicals using in silico CL_{int} and F_{up})
  - 25-30 chemicals for rat simulations (no human data)

Comparison of ToCS to Other GUIs

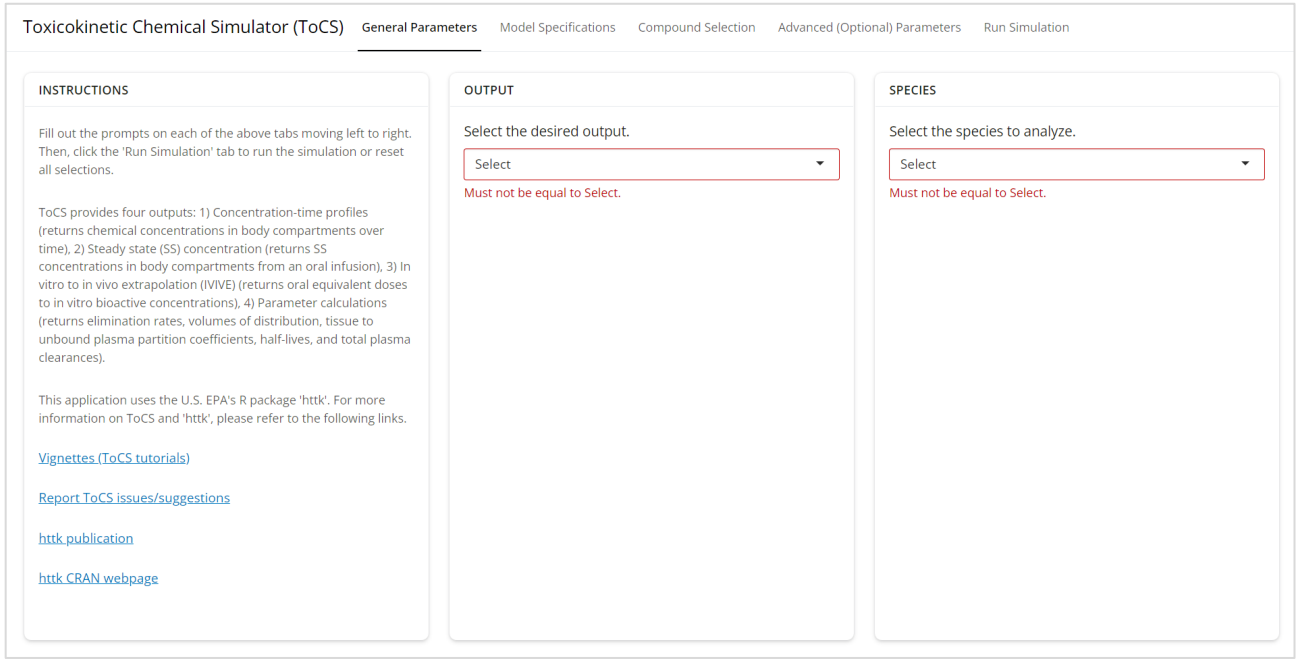
Feature	ToCS	ICE*
httk software version	2.7.0	2.2.2
Species	Human, rat, mouse, dog, rabbit	Human, rat
Food chemical subset	Yes	No
Loads in silico caco-2 permeability values	Yes	No
Customize parameter calculation methods	Yes	No
Dosing routes	Oral	Oral, iv, inhalation
ADME dosing	Single, evenly recurring, and non-uniform	Single, evenly recurring
Inclusion of full pregnancy model	Yes	No
AUC and Tmax calculated for plasma and all tissues	Yes	Plasma only

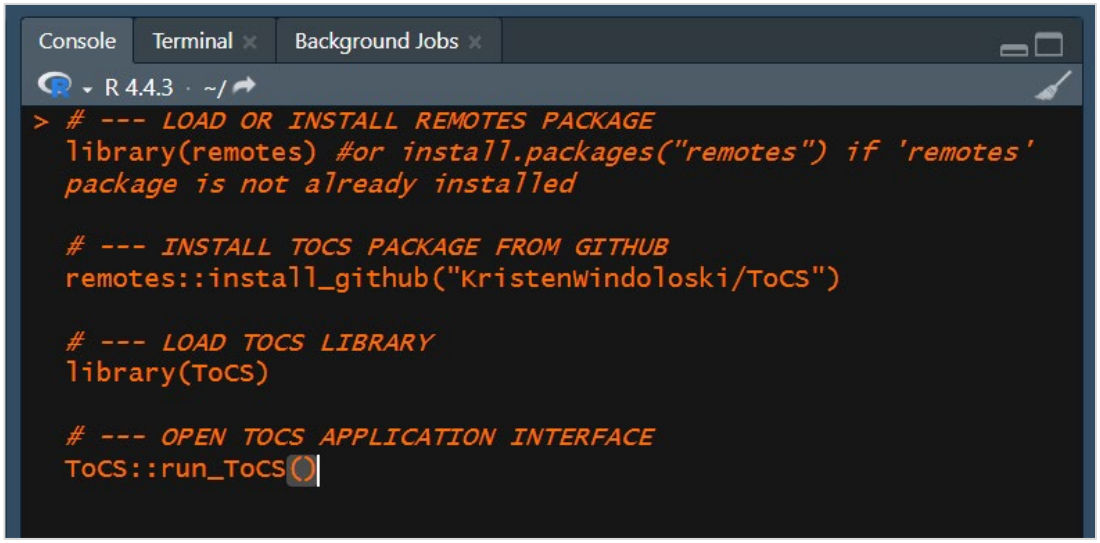
Feature	ToCS	ICE*
Analytical SS concentrations	Plasma and all tissues	Plasma only
Estimates days to plasma SS	Yes	No
OED calculation	Plasma and all tissues	Plasma only
Convert nominal in vitro bioactive conc to free conc	Yes	No
OED quantile returned	User's choice	5% and 50%
Option to view all OED samples	Yes	No
Built-in bioactivity data	No	Yes
Bioactivity exposure ratio (BER) calculation	Yes	No
Volume of distribution, elimination rate, total plasma clearance, and partition coefficient calculations	Yes	No

*Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/)

Accessing the ToCS Interface

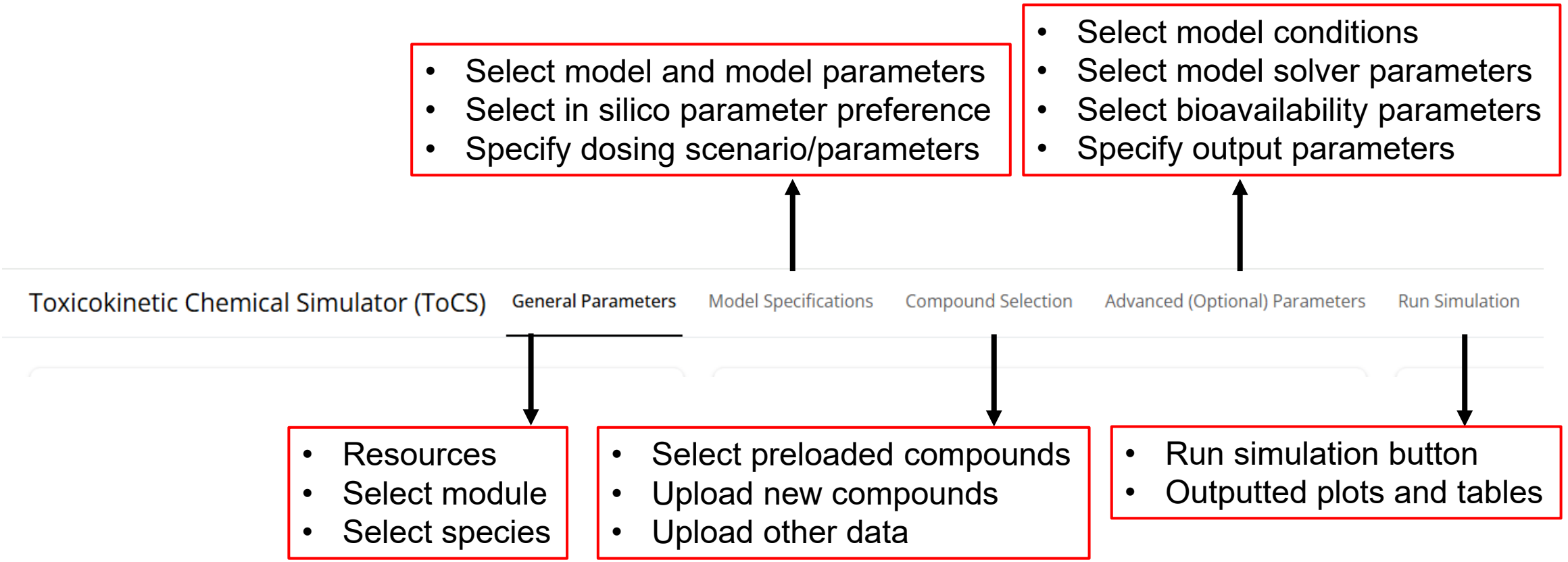
1. Web Application
   - pub-connect.foodsafetyrisk.org/tocs
   - No programming needed





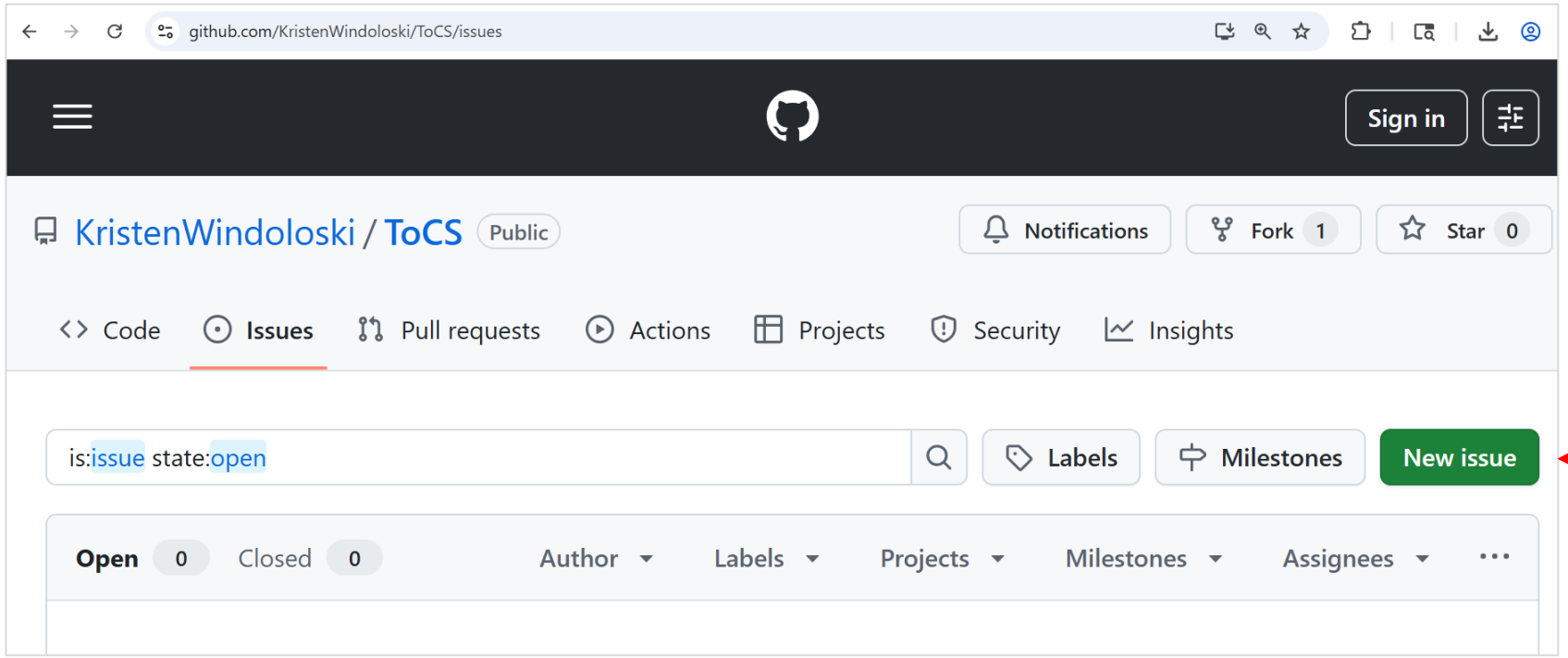
2. R Package
   - Install in R from the ToCS GitHub
   - Some programming needed

Interface Structure



Getting Help and Reporting Issues

- README file (https://github.com/KristenWindoloski/ToCS)
- Vignettes (https://github.com/KristenWindoloski/ToCS/tree/main/vignettes)



Click the “New Issue” button if any bugs or errors arise when using ToCS

Limitations and Challenges

- Generalized models - no chemical-specific physiological components, pathways, or compartments
  - More appropriate for reporting high-throughput preliminary toxicokinetics and risk estimation
  - Suggest ToCS be used as an earlier stage analytical software for screening and to guide further chemical studies

- Use caution when using the optional in silico parameters
  - A different output is achieved if the parameter data sets were loaded in another order

- Challenges users may face:
  - Uploading data
  - Entering non-uniform dosing schedule/long lists of numbers
  - Singular bioactivity data (one data point per compound)
  - Plotting customization

Future Work

- Include new httk models into ToCS (PFAS, time-dependent parameter version, and 1st trimester pregnancy models)
- Update non-uniform dosing input structure
- Estimation of additional parameters
- Incorporate user feedback (new analyses and methods, food relevant features, etc.)
- Fix programming bugs as needed

An Overview of the httk R Package

The httk R package

- Built by the U.S. EPA in 2015 and is continually maintained and updated
- Provides toxicokinetic analysis models and functions for chemical compounds
- Contains chemical data for over 17,000 compounds
- Newest version (2.7.0) contains time-varying parameter pbtk models, a three-trimester pregnancy model, and a PFAS model

httk: High-Throughput Toxicokinetics

Pre-made models that can be rapidly tailored to various chemicals and species using chemical-specific in vitro data and physiological information. These tools allow incorporation of chemical toxicokinetics ("TK") and in vitro-in vivo extrapolation ("IVIVE") into bioinformatics, as described by Pearce et al. (2017) (<doi:10.18637/jss.v079.i04>). Chemical-specific in vitro data characterizing toxicokinetics have been obtained from relatively high-throughput experiments. The chemical-independent ("generic") physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models included here can be parameterized with in vitro data or in silico predictions which are provided for thousands of chemicals, multiple exposure routes, and various species. High throughput toxicokinetics ("HTTK") is the combination of in vitro data and generic models. We establish the expected accuracy of HTTK for chemicals without in vivo data through statistical evaluation of HTTK predictions for chemicals where in vivo data do exist. The models are systems of ordinary differential equations that are developed in MCSim and solved using compiled (C-based) code for speed. A Monte Carlo sampler is included for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and propagating parameter uncertainty (Wambaugh et al., 2019 <doi:10.1093/toxsci/kfz205>). Empirically calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for using IVIVE to convert concentrations from high-throughput screening experiments (for example, Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Version:	2.7.3
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods, Rdpack (≥ 2.3), ggplot2, dplyr
Suggests:	knitr, rmarkdown, gplots, scales, EnvStats, MASS, RColorBrewer, stringr, reshape, viridis, gmodels, colorspace, cowplot, ggrepel, forcats, smatr, gridExtra, readxl, ks, testthat, ggpubr, tidyverse
Published:	2025-09-12
DOI:	10.32614/CRAN.package.httk
Author:	John Wambaugh [aut, cre], Sarah Davidson-Fritz [aut], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Mark Sfeir [aut], Matt Linakis [aut], Dustin Kapraun [aut], Kimberly Truong [aut], Colin Thomson [aut], Meredith Scherer [aut], Annabel Meade [aut], Celia Schacht [aut], Leonie Lautz [aut], Todor Antonijevic [ctb], Miyuki Breen [ctb], Shannon Bell [ctb], Xiaoqing Chang [ctb], Jimena Davis [ctb], Elaina Kenyon [ctb], Gilberto Padilla Mercado [ctb], Katie Paul Friedman [ctb], Nathan Pollesch [ctb], Noelle Sinski [ctb], Nisha Sipes [ctb], James Sluka [ctb], Caroline Stevens [ctb], Barbara Wetmore [ctb], Lily Whipple [ctb], Woodrow Setzer [ctb]
Maintainer:	John Wambaugh <wambaugh.research at gmail.com>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-httk/issues
License:	MIT + file LICENSE
Copyright:	This package is primarily developed by employees of the U.S. Federal government as part of their official duties and is therefore public domain.
URL:	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	README, NEWS
CRAN checks:	httk results

Documentation:

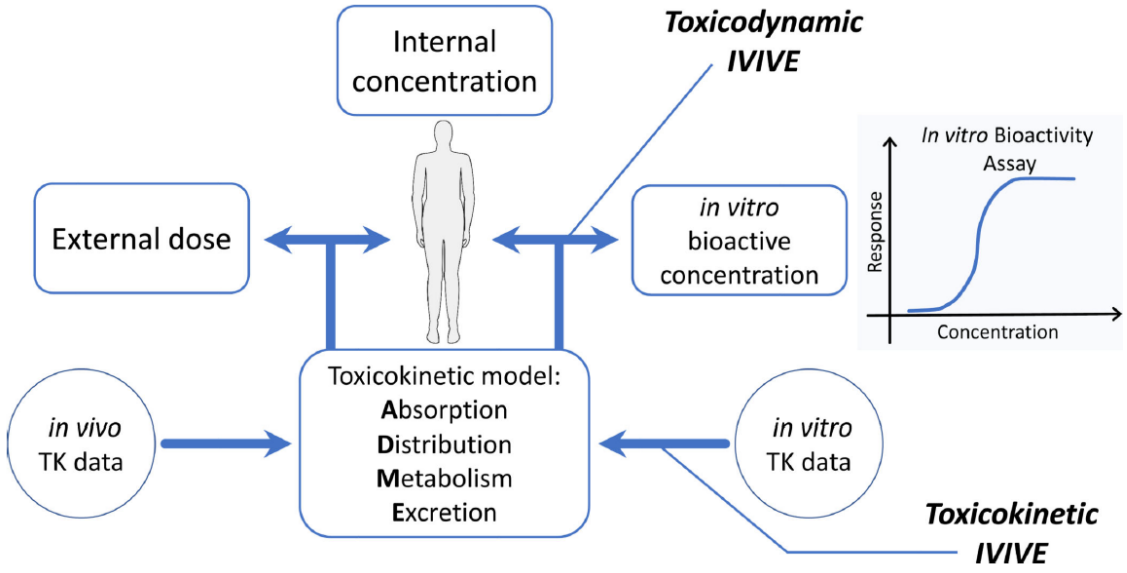
Reference manual:	httk.html , httk.pdf
Vignettes:	1) Introduction to HTTK (source, R code) 2) Introduction to IVIVE (source, R code) a) Pearce (2017): HTTK Basics (source, R code) b) Ring (2017) HTTK-Pop: Generating subpopulations (source, R code) c) Pearce (2017): Evaluation of Tissue Partitioning (source, R code) d) Frank (2018): Neuronal Network IVIVE (source, R code) e) Truong (2025) Full Human Gestational IVIVE (source, R code) f) Wambaugh (Submitted): HTTK for PFAS (source, R code) g) Meade (Submitted): High Throughput Dermal Exposure Model (source, R code) j) Scherer (Submitted): In Vitro Distribution (source, R code)

The httk R package

- Contains generalized mathematical models (same structure for each chemical, but use of chemical-specific parameters)

- Chemical specific parameters include:

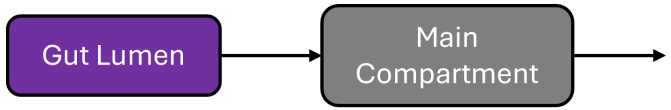
  - In vitro intrinsic hepatic clearance
  - In vitro fraction unbound in plasma
  - Molecular weight
  - Octanol water partition coefficient
  - Many others…

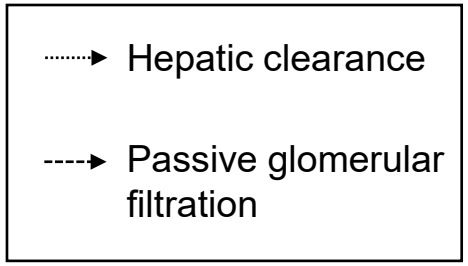


Breen, M., Ring, C.L., Kreutz, A., Goldsmith, M.R. and Wambaugh, J.F. (2021). High-throughput PBTK models for in vitro to in vivo extrapolation. *Expert opinion on drug metabolism & toxicology*

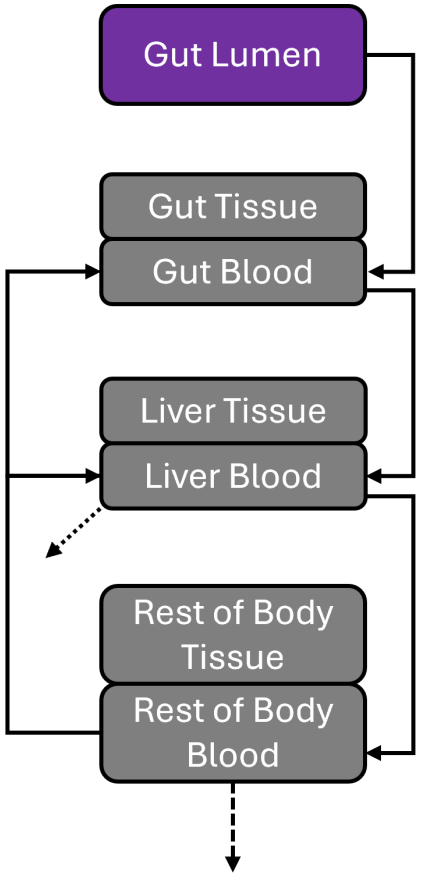
httk Models

1compartment

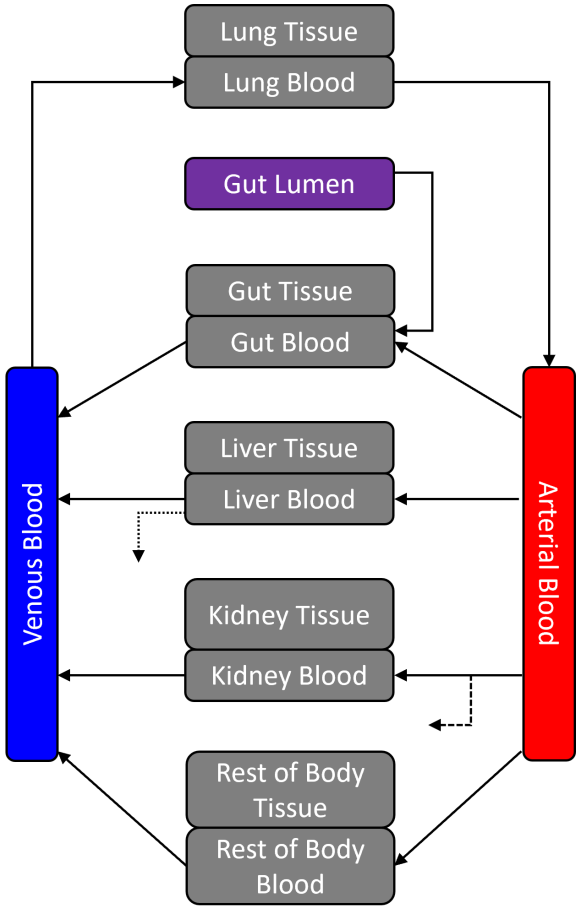




3compartment

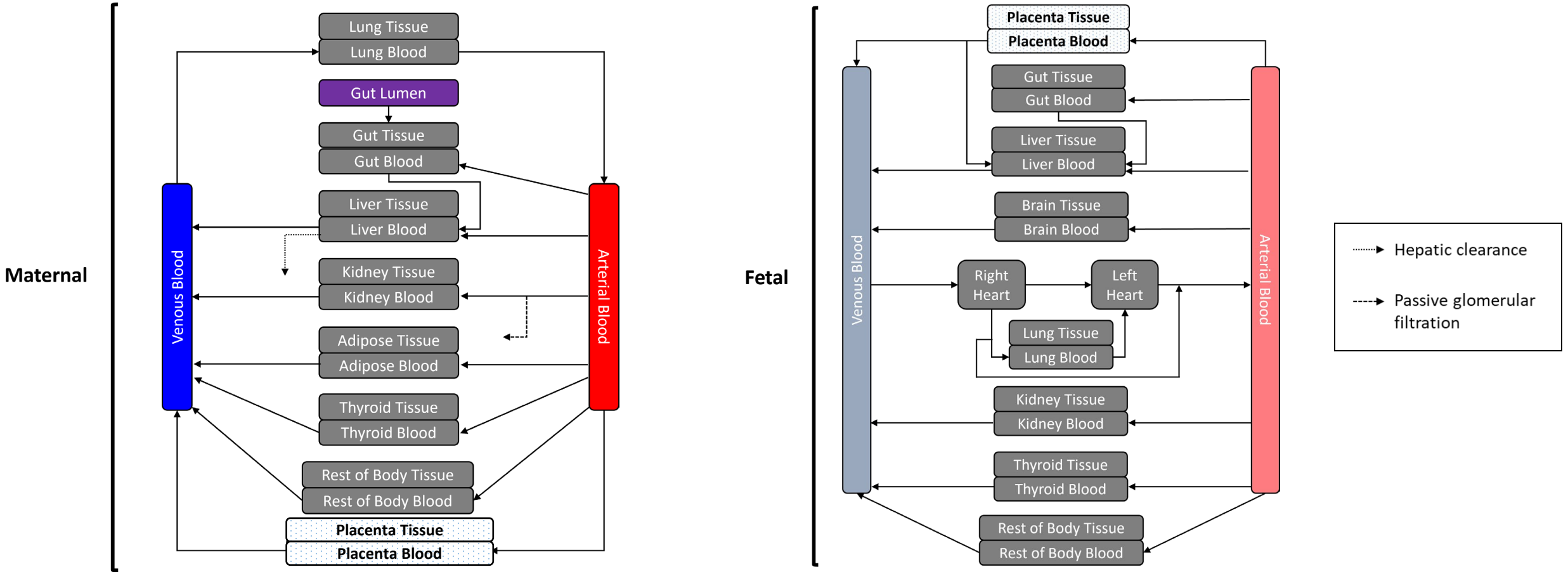


pbtk



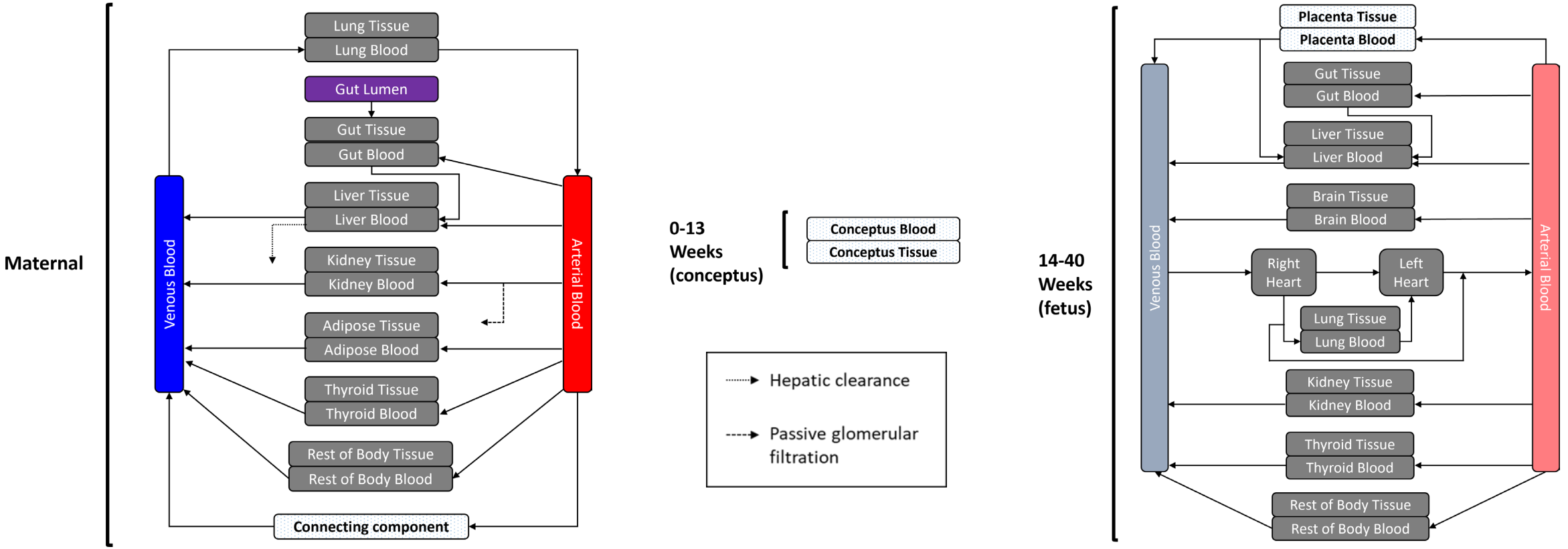
httk Models

fetal_pbtk model (2nd and 3rd trimesters)



httk Models

Full_pregnancy model



Additional Information on httk

Websites

https://github.com/USEPA/CompTox-ExpoCast-httk

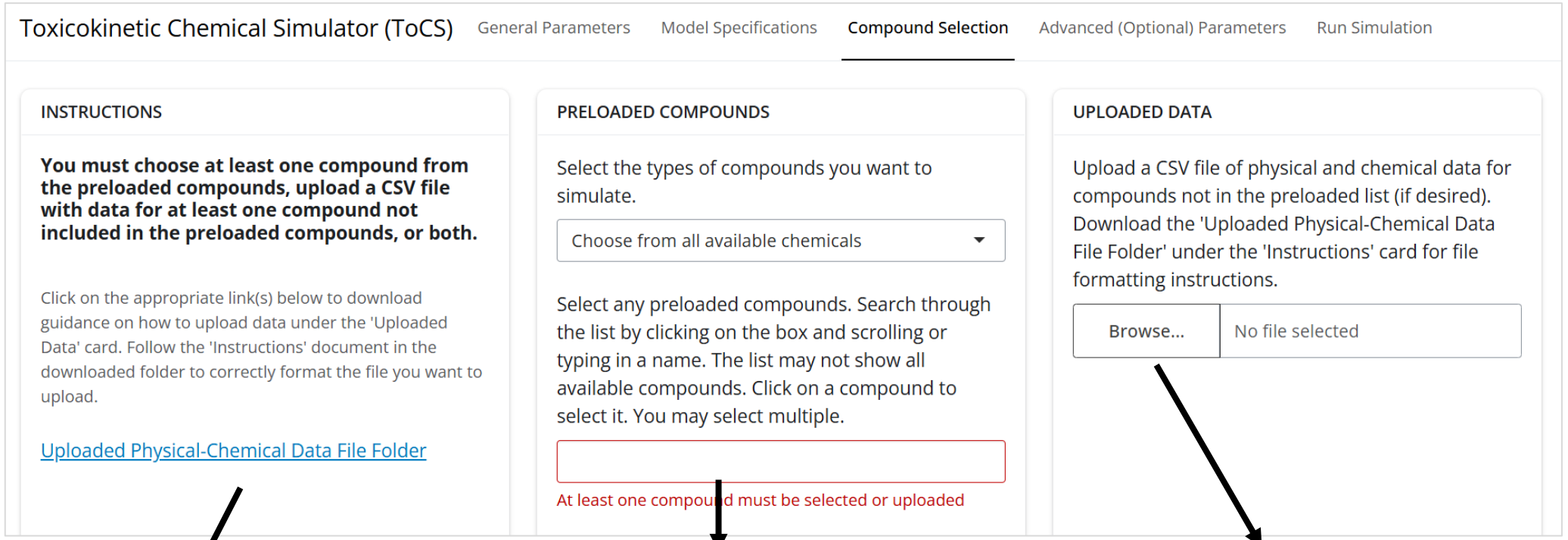
https://cran.r-project.org/web/packages/httk/index.html

Select Publications

1. Breen, M., Ring, C.L., Kreutz, A., Goldsmith, M., and Wambaugh, J.F. (2021). High-throughput PBTK models for in vitro to in vivo extrapolation. *Expert Opin. Drug Metab. Toxicol.* 17(8), 903–921. doi: 10.1080/17425255.2021.1935867.
2. Breen, M., Wambaugh, J.F., Bernstein, A., Sfeir, M., and Ring, C.L. (2022). Simulating toxicokinetic variability to identify susceptible and highly exposed populations. *J. Expo. Sci. Environ. Epidemiol.* 32(6), 855-863. doi: 10.1038/s41370-022-00491-0.
3. Kapraun, D.F., Sfeir, M., Pearce, R.G., Davidson-Fritz, S.E., Lumen, A., Dallmann, A., et al. (2022). Evaluation of a rapid, generic human gestational dose model. *Reprod. Toxicol.* 113, 172-188. doi: 10.1016/j.reprotox.2022.09.004.
4. Pearce, R.G., Setzer, R.W., Strope, C.L., Wambaugh, J.F., and Sipes, N.S. (2017). httk: R package for high-throughput toxicokinetics. *J. Stat. Softw.* 79(4), 1-26. doi: 10.18637/jss.v079.i04.
5. Truong, K.T., Wambaugh, J.F., Kapraun, D.F., Davidson-Fritz, S.E., Eytcheson, S., Judson, R.S., et al. (2025). Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity. *Toxicology* 515, 154157. doi: 10.1016/j.tox.2025.154157.
6. Wambaugh, J.F., Wetmore, B.A., Ring, C.L., Nicolas, C.I., Pearce, R.G., Honda, G.S., et al. (2019). Assessing toxicokinetic uncertainty and variability in risk prioritization. *Toxicol. Sci.* 172(2), 235-251. doi: 10.1093/toxsci/kfz205.

Chemical Selection

Compound Selection Interface



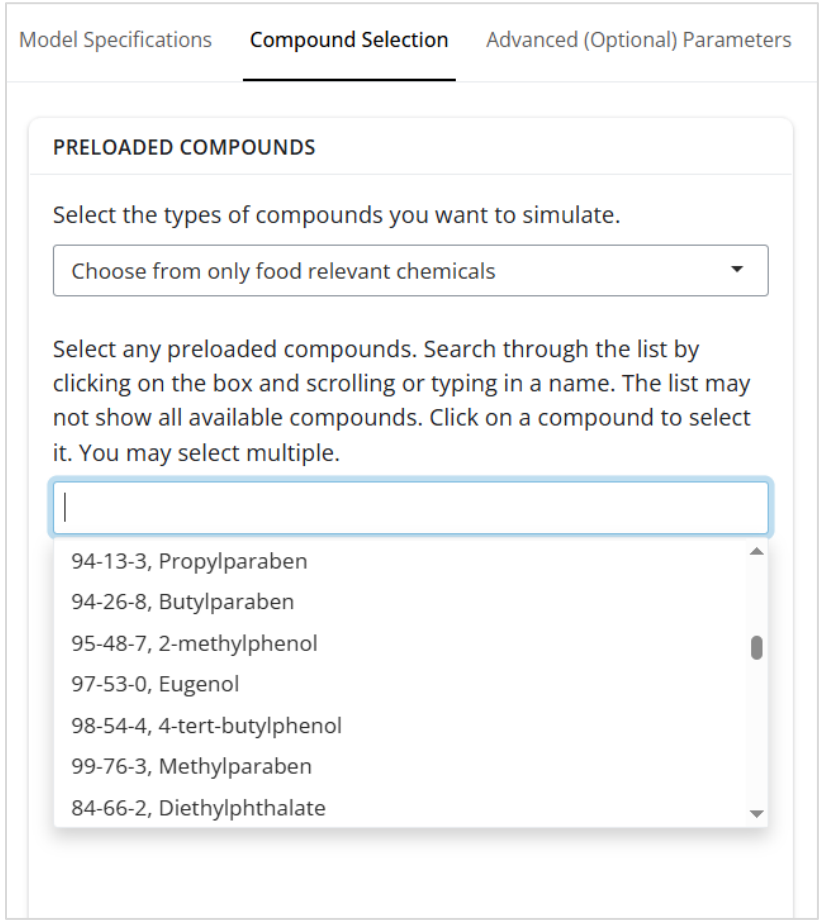
Downloadable folder detailing how to upload physicochemical data to simulate new compounds

Drop-down list of chemicals with data already preloaded into httk, contains only compounds with adequate data for simulation

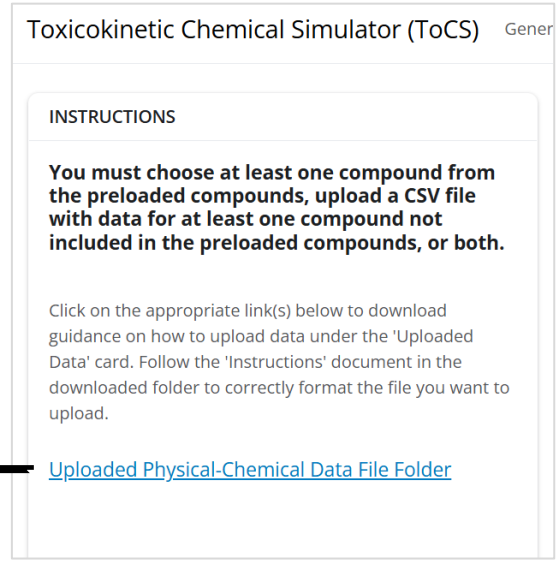
Click here to upload a CSV file of physicochemical data for chemicals not available in the preloaded drop-down list

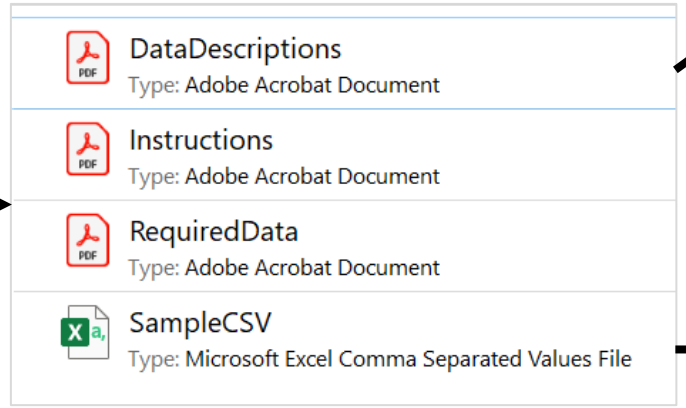
Compound Selection: Preloaded Drop-Down List

- Contains compounds with data already in httk
- Search the drop-down list by:
  - Typing in the CAS number (recommended)
  - Typing in the compound name
  - Scrolling the list (all compounds are not visible)

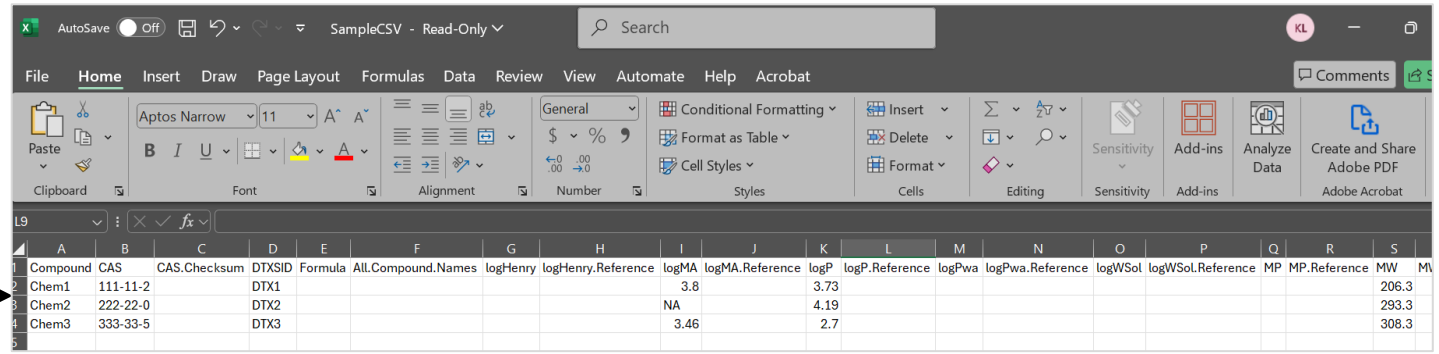


Compound Selection: Upload Your Own Compounds





Variable Name	Description	Units
Compound	Name of chemical compound	
CAS	Chemical Abstracts Service Registry Number	
CAS.Checksum	Is CAS valid?	
DTXSID	DSSTox Structure ID	
Formula	The proportions of atoms within the chemical compound	
All.Compound.Names	All names of chemical as they occur in the data	
logHenry	The log10 Henry's law constant	log10(atmosphers*m^3/mole)
logHenry.Reference	Reference for logHenry	
logMA	The log10 phospholipid water partition coefficient (PC) or "Membrane affinity"	log10 unitless ratio
logMA.Reference	Reference for logMA	
logP	The log10 octanol:water PC	log10 unitless ratio
logP.Reference	Reference for logP	
logPwa	The log10 water:air PC	log10 unitless ratio
logPwa.Reference	Reference for logPwa	
logWSol	The log10 water solubility	log10 (mole/L)
logWSol.Reference	Reference for logWSol	
MP	The chemical compound melting point	Degrees celcius
MP.Reference	Reference for MP	



Compound Selection: Uploaded Data

Required Data

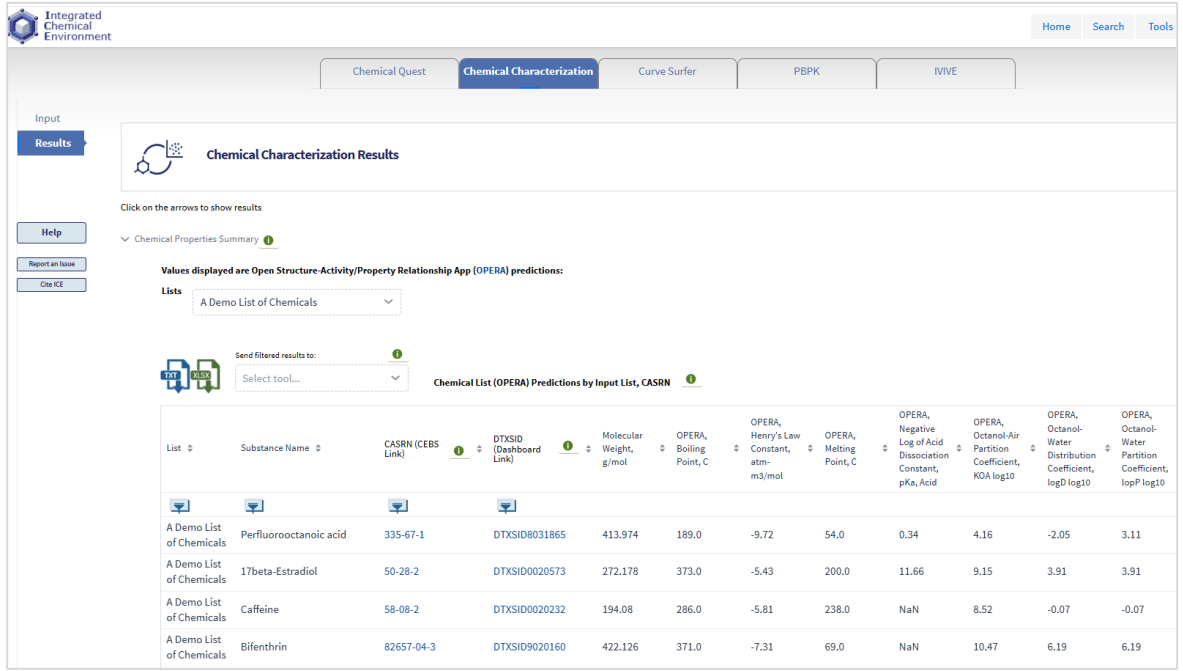
- Compound name
- CAS number
- DTXSID
- Molecular weight
- Log10 octanol:water partition coefficient
- In vitro intrinsic hepatic clearance
- In vitro fraction unbound in presence of plasma proteins

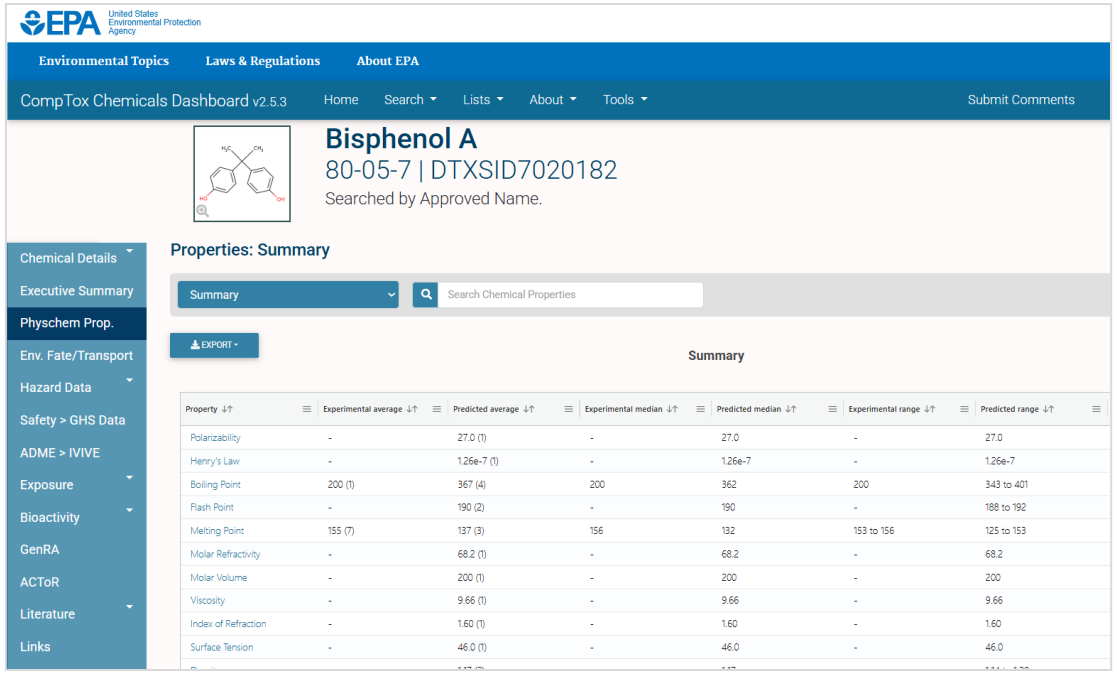
Optional Data

- Log10 Henry's law constant
- Log10 phospholipid water partition coefficient
- Log10 water air partition coefficient
- Log10 water solubility
- Melting point
- Hydrogen acceptor equilibria concentration
- Hydrogen donor equilibria concentration
- In vivo measured fractional systemic bioavailability of an oral dose
- Caco-2 apical-to-basal membrane permeability
- Probability that there is no clearance observed
- In vivo fraction of oral dose absorbed and entering gut lumen
- In vivo fraction of oral dose surviving first pass metabolism in the gut
- In vivo fraction of oral dose surviving first pass hepatic clearance
- Ratio of blood to plasma chemical concentration

Where Can I Find Physicochemical Data?

NTP's Integrated Chemical Environment (ICE)
(https://ice.ntp.niehs.nih.gov/)





EPA's CompTox Chemicals Dashboard
(https://comptox.epa.gov/dashboard)

Demo: Uploading Chemical Data

Calcium Benzoate

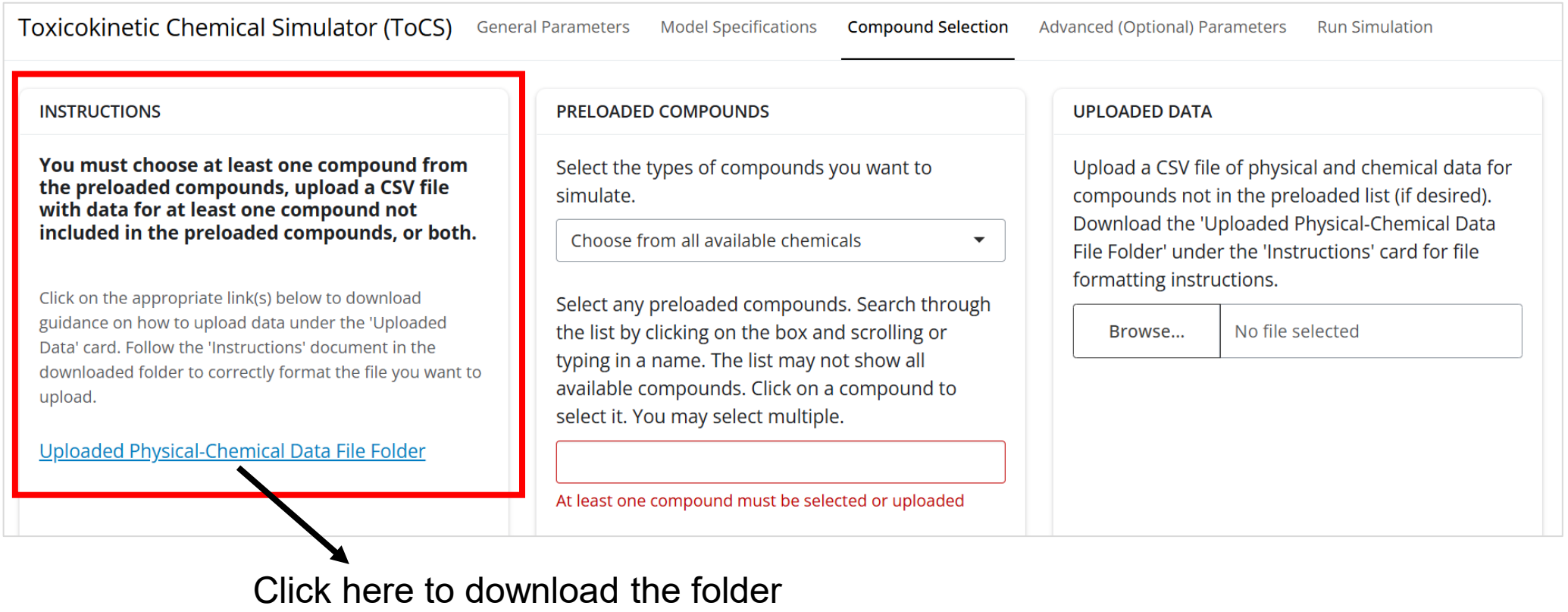
A direct food additive used as an antimicrobial agent

Demo: Uploading Physicochemical Data

1. Download physicochemical data folder
2. Copy SampleCSV file to a new file to edit
3. Search for chemical data within EPA's CompTox Dashboard
4. Update appropriate fields in new CSV file
5. Save CSV file and upload within ToCS interface

Demo: Uploading Physicochemical Data

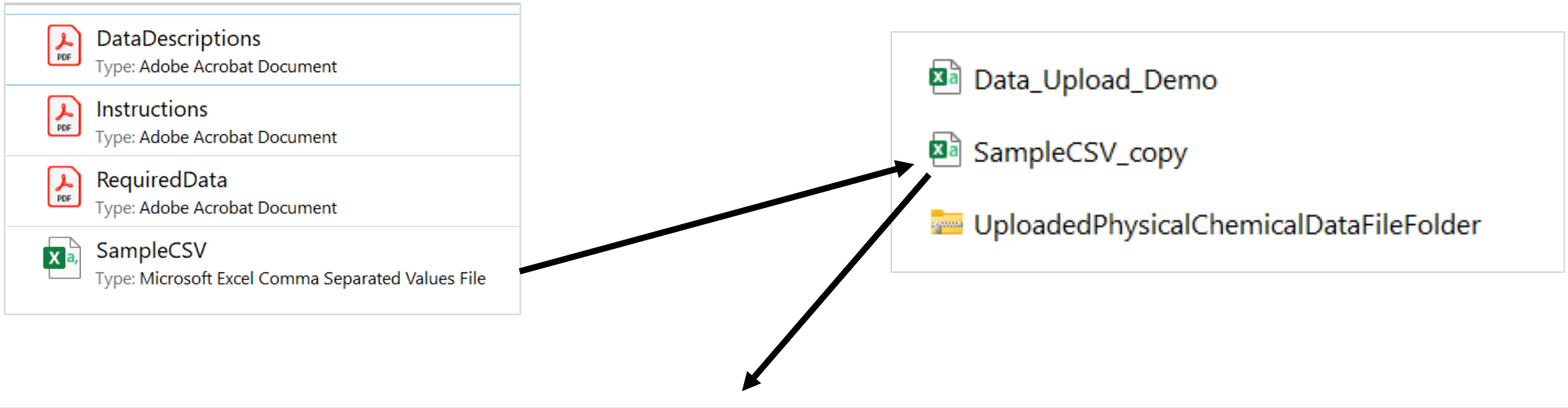
1. Download physicochemical data folder



Click here to download the folder

Demo: Uploading Physicochemical Data

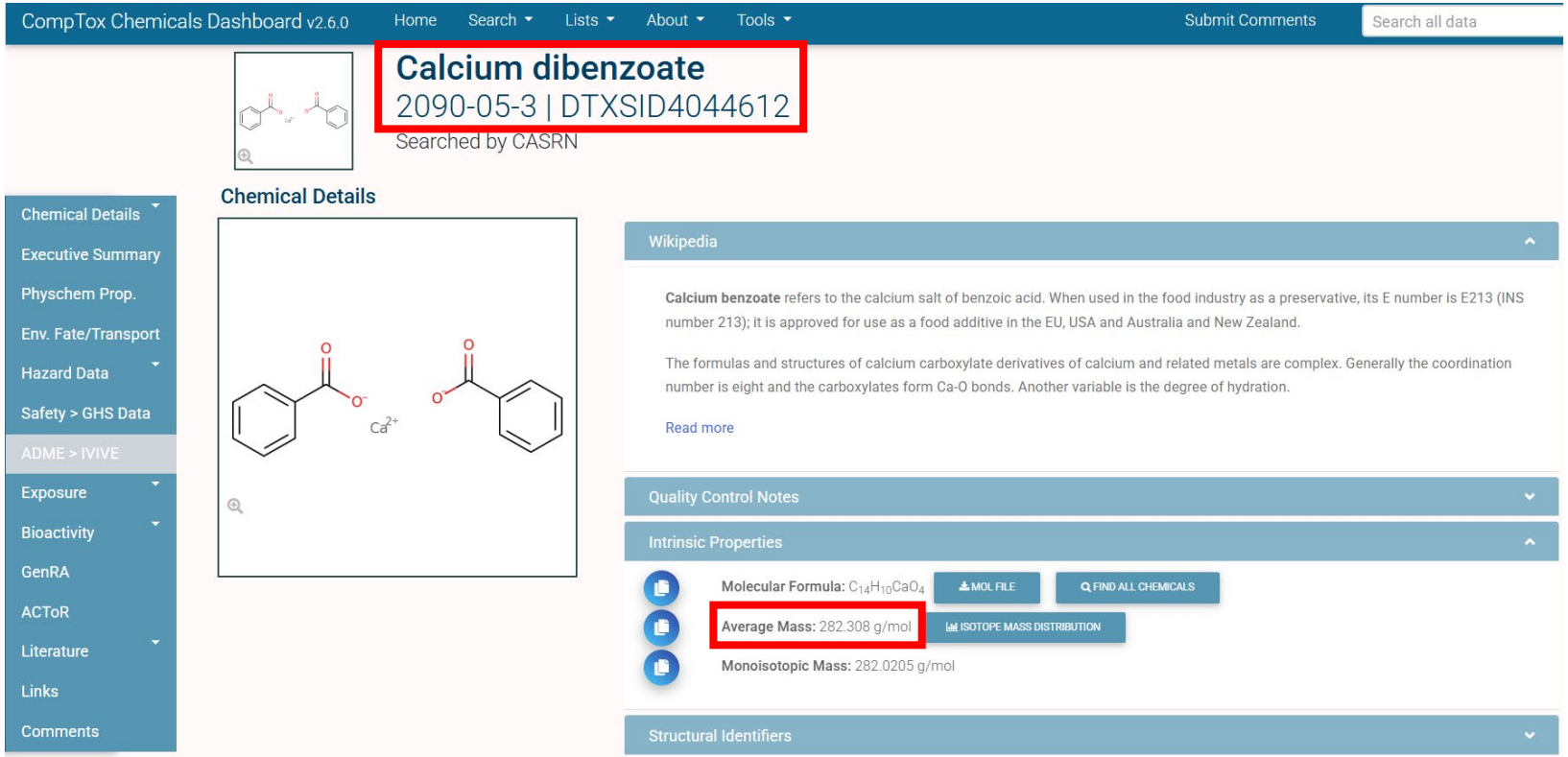
2. Copy SampleCSV file to a new file to edit



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	Compounc	CAS	CAS.Checl	DTXSID	Formula	All.Compo	logHenry	logHenry.F	logMA	logMA.Refe	logP	logP.Refer	logPwa	logPwa.Re	logWSol	logWSol.R	MP	MP.Refere	MW	MW.Refere	pKa_Accep	pKa_Accep	pKa_Donor	pK
2																								
3																								

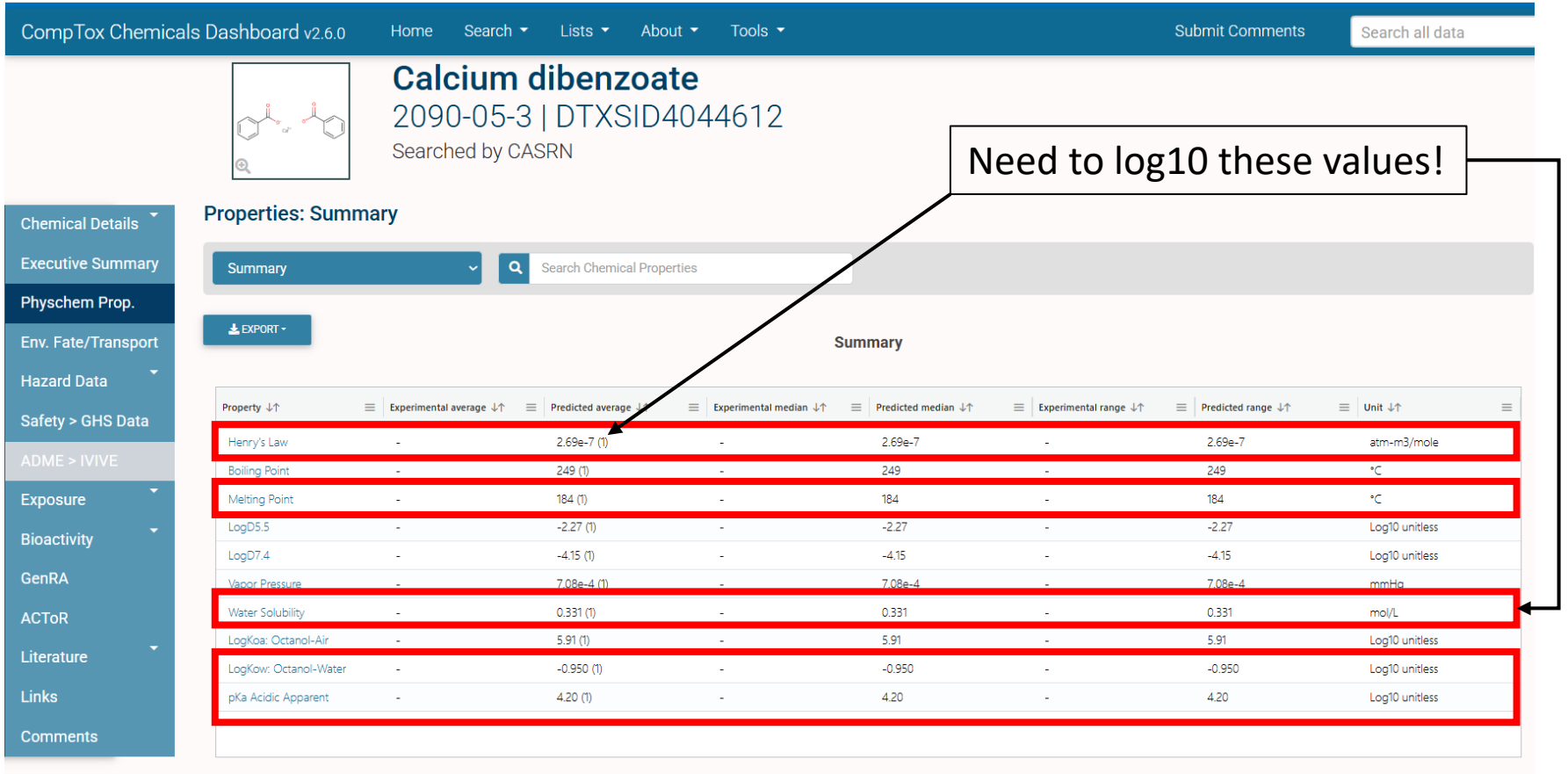
Demo: Uploading Physicochemical Data

3. Search for chemical data within EPA's CompTox Dashboard



Demo: Uploading Physicochemical Data

3. Search for chemical data within EPA's CompTox Dashboard



Demo: Uploading Physicochemical Data

4. Update appropriate fields in new CSV file

No real data available, so we set the clint and Funbound.plasma as 0.2 and 0.95 in this example

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	Compound	CAS	CAS.Checksum	DTXSID	Formula	All.Compound.Names	logHenry	logHenry.Reference	logMA	logMA.Reference	logP	logP.Reference	logPwa	logPwa.Reference	logWSol	logWSol.Reference
2	Calcium Benzoate	2090-05-3		DTXSID4044612			-6.57	EPA CompTox v2.6.0			-0.95	EPA CompTox v2.6.0			-0.480172006	EPA CompTox v2.6.0

	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	
1	MP	MP.Reference	MW	MW.Reference	pKa_Accept	pKa_Accept.Reference	pKa_Donor	pKa_Donor.Reference	All.Species	Dog.Foral	Dog.Foral.Reference	DTXSID.Reference	Formula.Reference	Human.Caco2.Pab	Human.
2	184	EPA CompTox v2.6.0	282.308	EPA CompTox v2.6.0	4.2	EPA CompTox v2.6.0						EPA CompTox v2.6.0			

	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	Human.Caco2.Pab.Reference	Human.Clint	Human.Clint.pValue	Human.Clint.pValue.Reference	Human.Clint.Reference	Human.Fabs	Human.Fabs.Reference	Human.Fgut	Human.Fgut.Reference	Human.Fhep	Human.Fhep.Reference
2		0.2			NA						

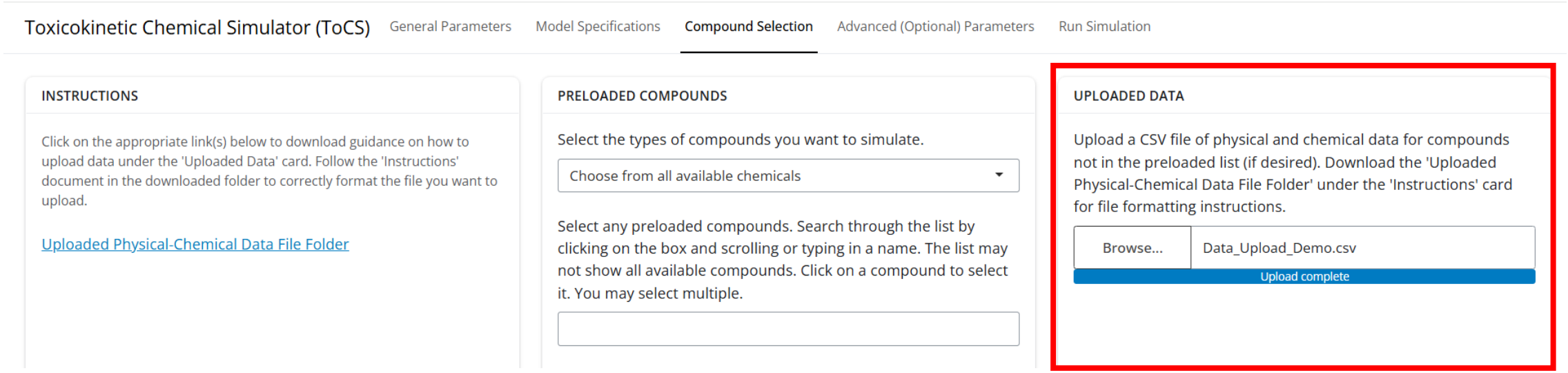
	AP	AQ	AR	AS	AT	AU	AV	AW	AX	AY
1	Human.Foral	Human.Foral.Reference	Human.Funbound.plasma	Human.Funbound.plasma.Reference	Human.Rblood2plasma	Human.Rblood2plasma.Reference	Monkey.Foral	Monkey.Foral.Reference	Mouse.Foral	Mouse.Foral.Refe
2			0.95	NA						

	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG
1	Mouse.Foral	Mouse.Foral.Reference	Mouse.Funbound.plasma	Mouse.Funbound.plasma.Reference	Rabbit.Funbound.plasma	Rabbit.Funbound.plasma.Reference	Rat.Clint	Rat.Clint.pValue	Rat.Clint.pValue.Reference	Rat.Clint.Refere
2										

	3D	BE	BF	BG	BH	BI	BJ	BK	BL	BM	BN
1	Clint	Rat.Clint.pValue	Rat.Clint.pValue.Reference	Rat.Clint.Reference	Rat.Foral	Rat.Foral.Reference	Rat.Funbound.plasma	Rat.Funbound.plasma.Reference	Rat.Rblood2plasma	Rat.Rblood2plasma.Reference	Chemical.Class
2											
3											

Demo: Uploading Physicochemical Data

5. Save CSV file and upload within ToCS interface



Questions?

10-Minute Break