

New Approach Methodologies (NAM) in Chemical Safety Assessment:
Applying US EPA Tools/Approaches in Practice



High Throughput Toxicokinetic Modeling

**Physicians
Committee**
for Responsible Medicine



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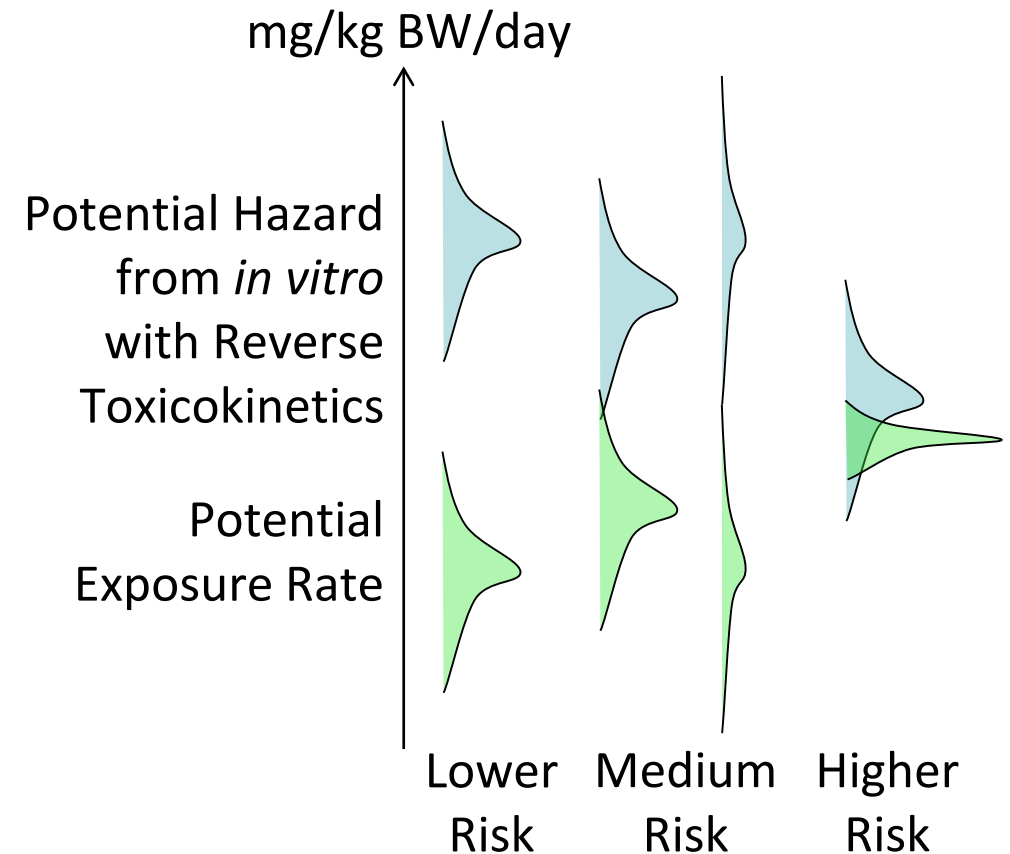
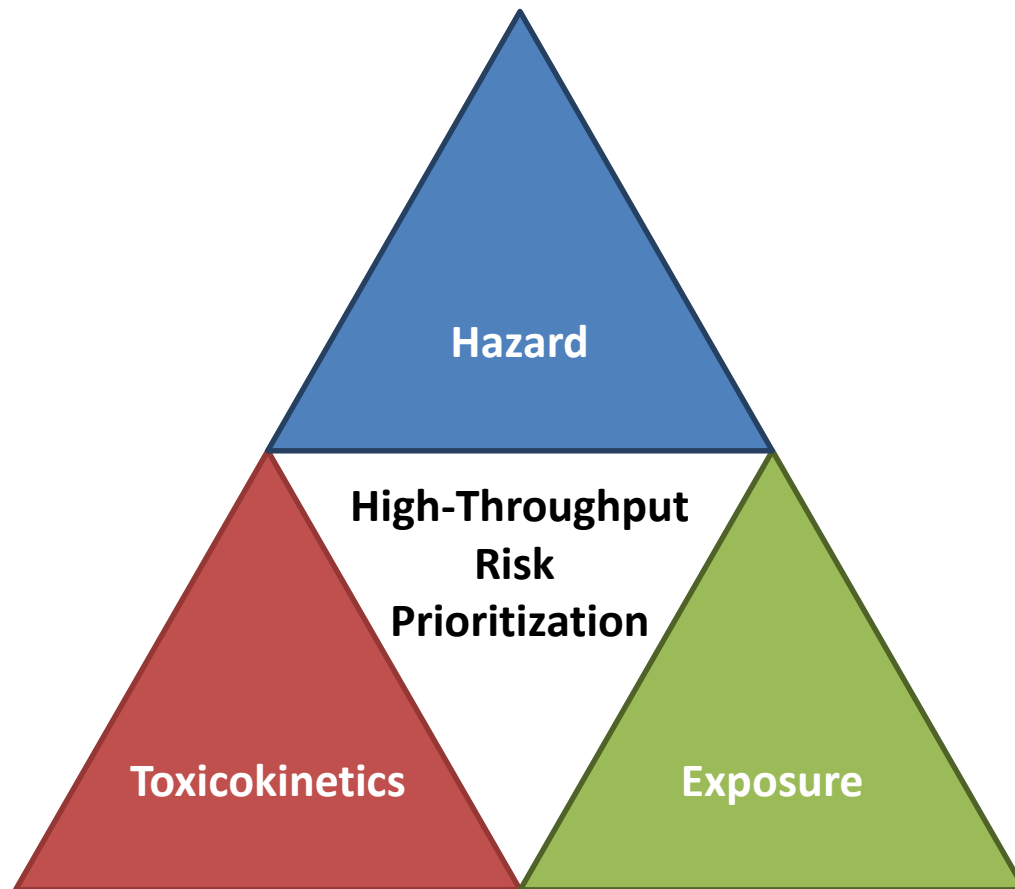
Center for Computational Toxicology and Exposure, US-EPA, RTP, NC

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

*10/23/2020
Happy Mole Day!*

Calculating Chemical Risk

- High throughput risk prioritization based upon *in vitro* screening requires comparison to exposure (for example, NRC, 1983)
- Data obtained *in vitro* must be placed in an *in vivo* context: *in vitro-in vivo* extrapolation (IVIVE)



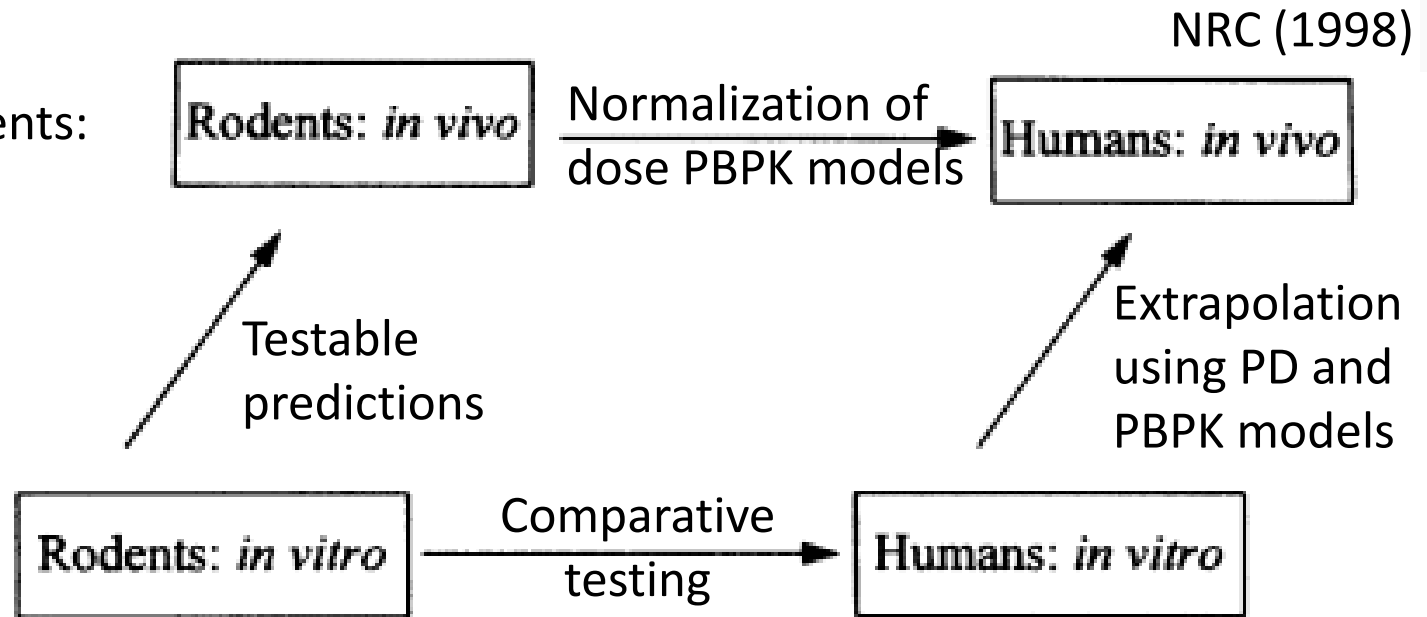
In Vitro - In Vivo Extrapolation (IVIVE)

- IVIVE is the use of *in vitro* data to predict phenomena *in vivo*
- IVIVE can be broken down into two components:

- IVIVE-PK/TK

(Pharmacokinetics/Toxicokinetics):

- Fate of molecules/chemicals in body
- Considers absorption, distribution, metabolism, excretion (ADME)
- Can use empirical PK or physiologically-based (PBPK)

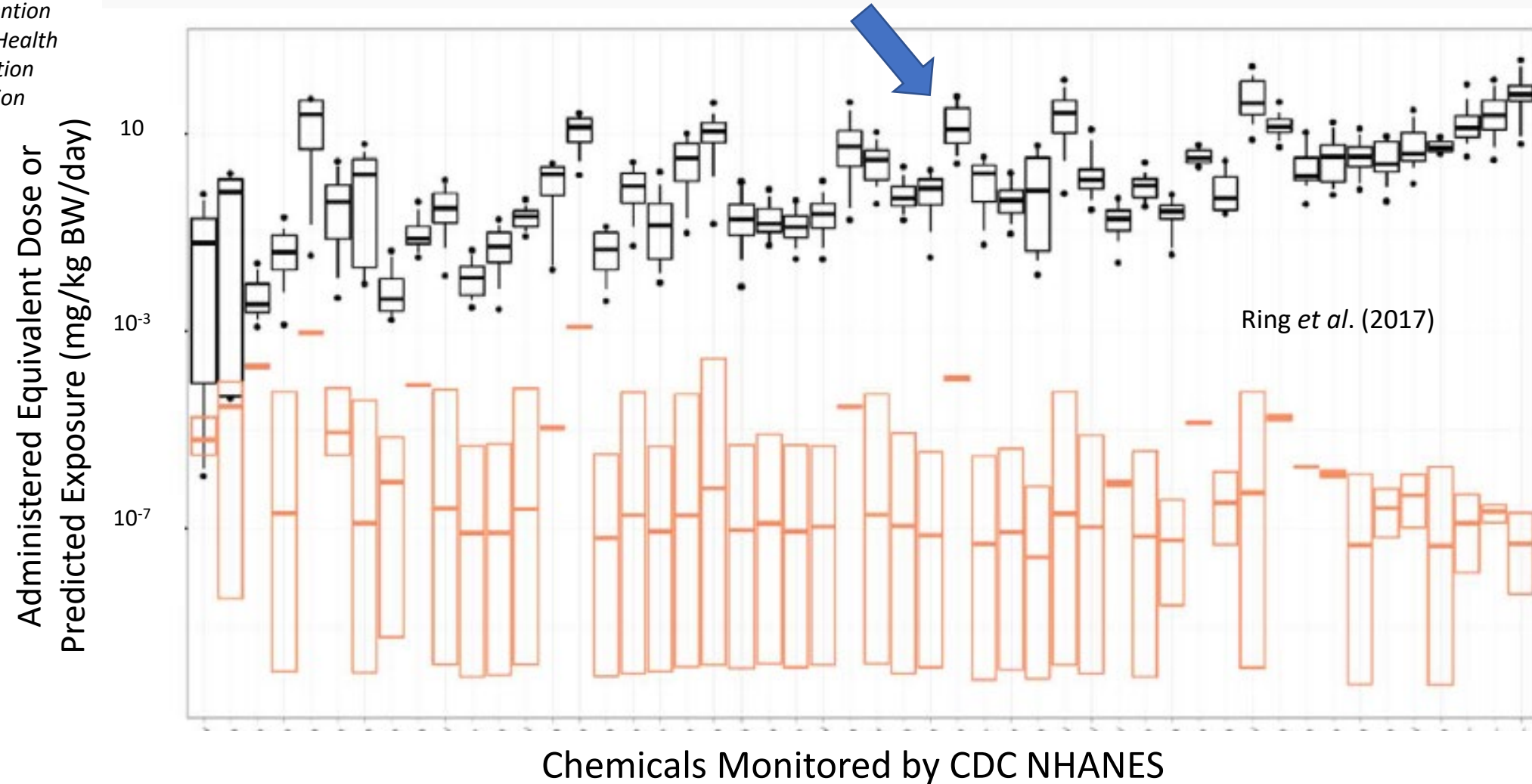


“The Parallelogram Approach” (Sobels, 1982)

- IVIVE-PD/TD **(Pharmacodynamics/Toxicodynamics):**
 - Effect of molecules/chemicals at biological target *in vivo*
 - Perturbation as adverse/therapeutic effect, reversible/ irreversible effects

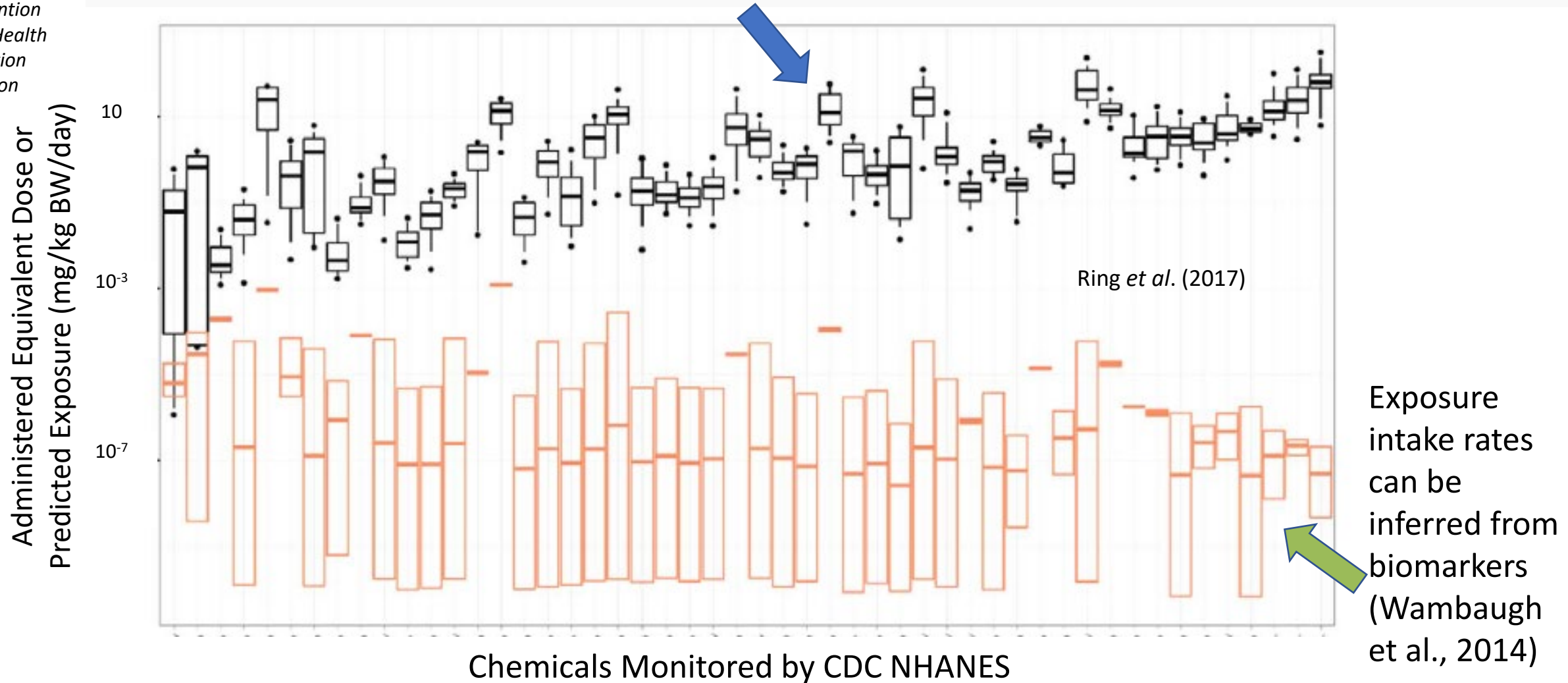
IVIVE Allows Chemical Prioritization

ToxCast + IVIVE can estimate doses needed to cause bioactivity (Wetmore et al., 2015)



IVIVE Allows Chemical Prioritization

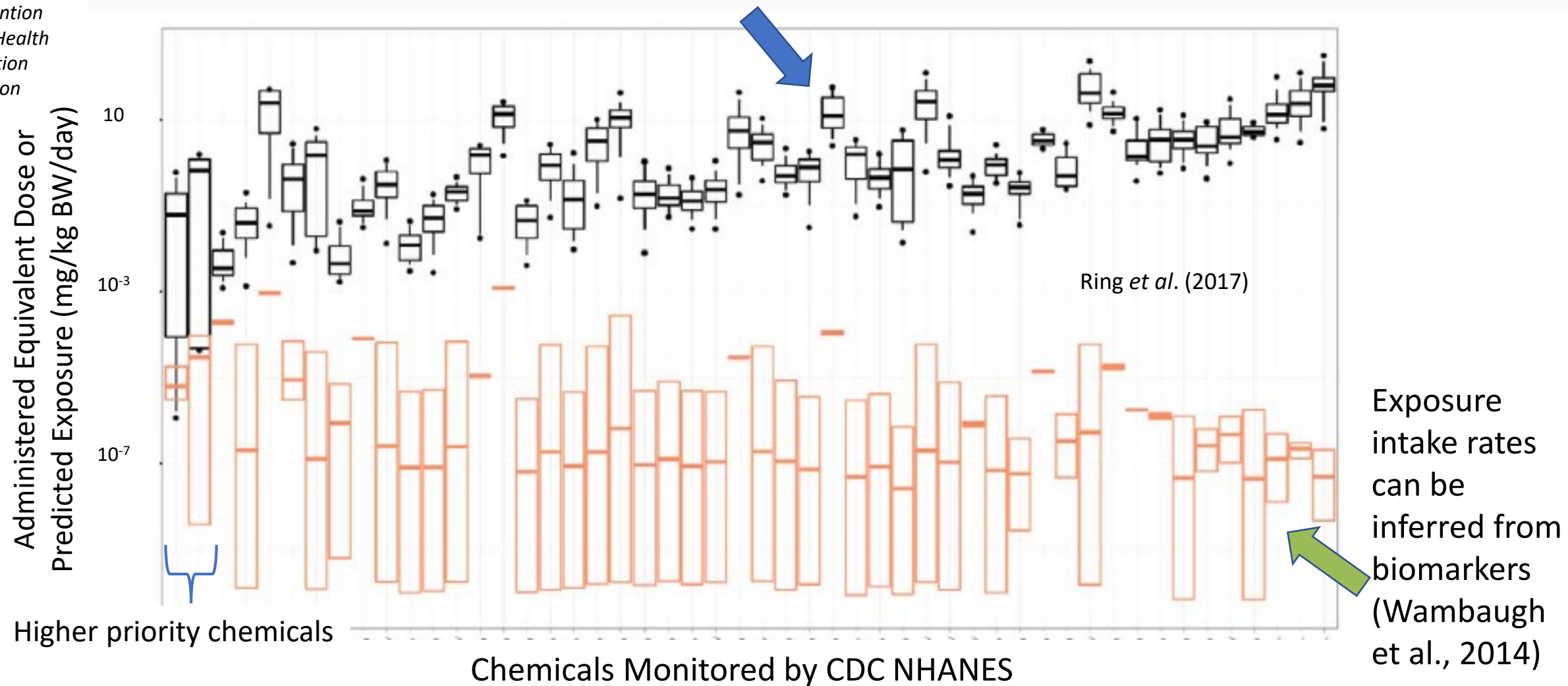
ToxCast + IVIVE can estimate doses needed to cause bioactivity (Wetmore et al., 2015)



IVIVE Allows Chemical Prioritization

CDC NHANES:
U.S. Centers for
Disease Control
and Prevention
National Health
and Nutrition
Examination
Survey

ToxCast + IVIVE can estimate doses needed to cause bioactivity (Wetmore et al., 2015)



- We make various assumptions that allow simple conversion of an *in vitro* concentration $[X]$ (μM) into an **administered equivalent dose** (AED) with units of mg/kg body weight/day:

$$\text{AED} = F_{IVIVE} \times [X]$$

- **AED** is the **external dose rate** that would be needed to **cause a given steady-state plasma concentration**
- F_{IVIVE} is a scaling factor that varies by chemical

- For a given chemical, $F_{IVIVE} = 1 / C_{ss,95}$
- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure

$$AED_{95} = \frac{[X]}{C_{ss,95}}$$

- The dashboard provides $C_{ss,95}$ values for >1000 chemicals
- The “95” refers to the upper 95th percentile – due to human variability and measurement uncertainty there are a range of possible C_{ss} values
- All of this assumes that the individuals have enough time to come to “steady-state” with respect to their daily exposures
 - Here that means that their daily average plasma concentration is unchanged 24 hours later

ADME on the CompTox Chemicals Dashboard



- Toxicokinetics describes absorption, distribution, metabolism, excretion (ADME)
- The dashboard provides ADME information for >1000 chemicals

The screenshot shows the CompTox Chemicals Dashboard in a web browser. The browser's address bar displays 'comptox.epa.gov/dashboard'. A navigation bar at the top includes links for 'Apps', 'Confluence', 'CompTox Dashboard', 'Article Request', 'Absence Request', 'Travel Forms', 'Bitbucket', 'EHP', 'Change Password', and 'FAITAS'. The main header features the EPA logo and the text 'United States Environmental Protection Agency'. The dashboard title is 'CompTox Chemicals Dashboard', followed by '882 Thousand Chemicals'. Below this are three tabs: 'Chemicals' (selected), 'Product/Use Categories', and 'Assay/Gene'. A search bar is present with the placeholder text 'Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey'. Below the search bar is a checkbox for 'Identifier substring search'. Further down, there is a prompt to 'See what people are saying, read the dashboard comments!' with a link, and a link to 'Cite the Dashboard Publication'. At the bottom, the section 'Latest News' is visible with a link to 'Read more news'.

ADME on the CompTox Chemicals Dashboard



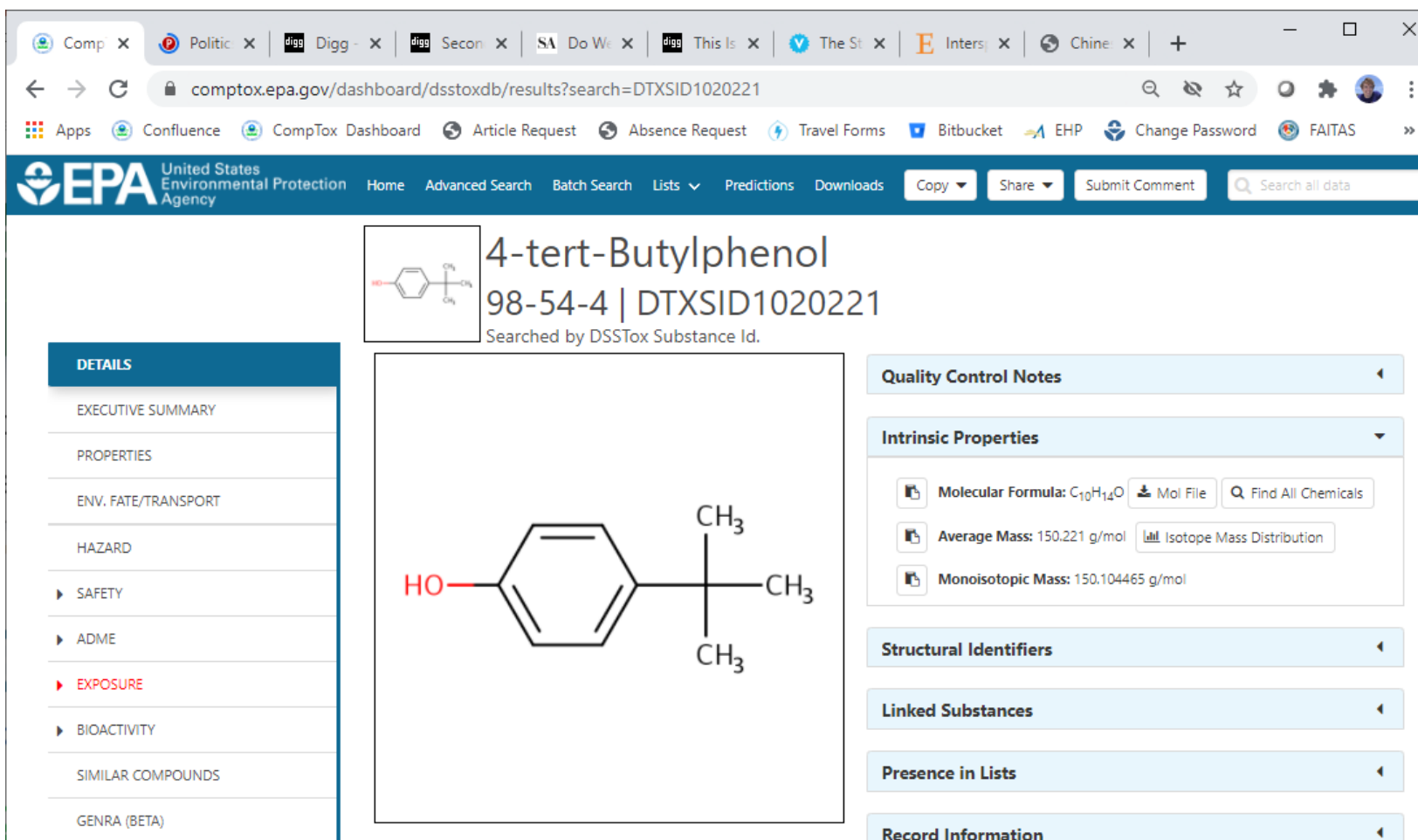
- Toxicokinetics describes absorption, distribution, metabolism, excretion (ADME)
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The screenshot displays the CompTox Chemicals Dashboard interface. At the top, the EPA logo and navigation links (Apps, Confluence, CompTox Dashboard, Article Request, Absence Request, Travel Forms, Bitbucket, EHP, Change Password, FAITAS) are visible. The main header reads "CompTox Chemicals Dashboard" and "882 Thousand Chemicals". Below this, there are three tabs: "Chemicals" (selected), "Product/Use Categories", and "Assay/Gene". A search bar contains the text "4-tert-butylphenol". The search results list three items:

Chemical Structure	Chemical Name	DTXSID
<chem>CC(C)(C)c1ccc(O)cc1</chem>	4-tert-Butylphenol	DTXSID1020221
<chem>CC(C)(C)c1ccc(O)cc1</chem>	4-tert-Butylphenol formaldehyde resin	DTXSID7047805
<chem>[Na+].[O-]c1ccc(C(C)(C)C)cc1</chem>	4-tert-Butylphenol sodium salt	DTXSID2042351

ADME on the CompTox Chemicals Dashboard

- Toxicokinetics describes absorption, distribution, metabolism, excretion (ADME)
- The dashboard provides ADME information for >1000 chemicals



The screenshot shows the EPA CompTox Chemicals Dashboard for 4-tert-Butylphenol (DTXSID1020221). The dashboard includes a sidebar with navigation links: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE (highlighted in red), BIOACTIVITY, SIMILAR COMPOUNDS, and GENRA (BETA). The main content area displays the chemical name, CAS number (98-54-4), and DTXSID (DTXSID1020221). A chemical structure diagram of 4-tert-Butylphenol is shown. The right sidebar contains sections for Quality Control Notes, Intrinsic Properties (Molecular Formula: C₁₀H₁₄O, Average Mass: 150.221 g/mol, Monoisotopic Mass: 150.104465 g/mol), Structural Identifiers, Linked Substances, Presence in Lists, and Record Information.

CompTox Chemicals Dashboard

4-tert-Butylphenol
98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

DETAILS

- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- SAFETY
- ADME
- EXPOSURE**
- BIOACTIVITY
- SIMILAR COMPOUNDS
- GENRA (BETA)

Intrinsic Properties

- Molecular Formula: C₁₀H₁₄O
- Average Mass: 150.221 g/mol
- Monoisotopic Mass: 150.104465 g/mol

Structural Identifiers

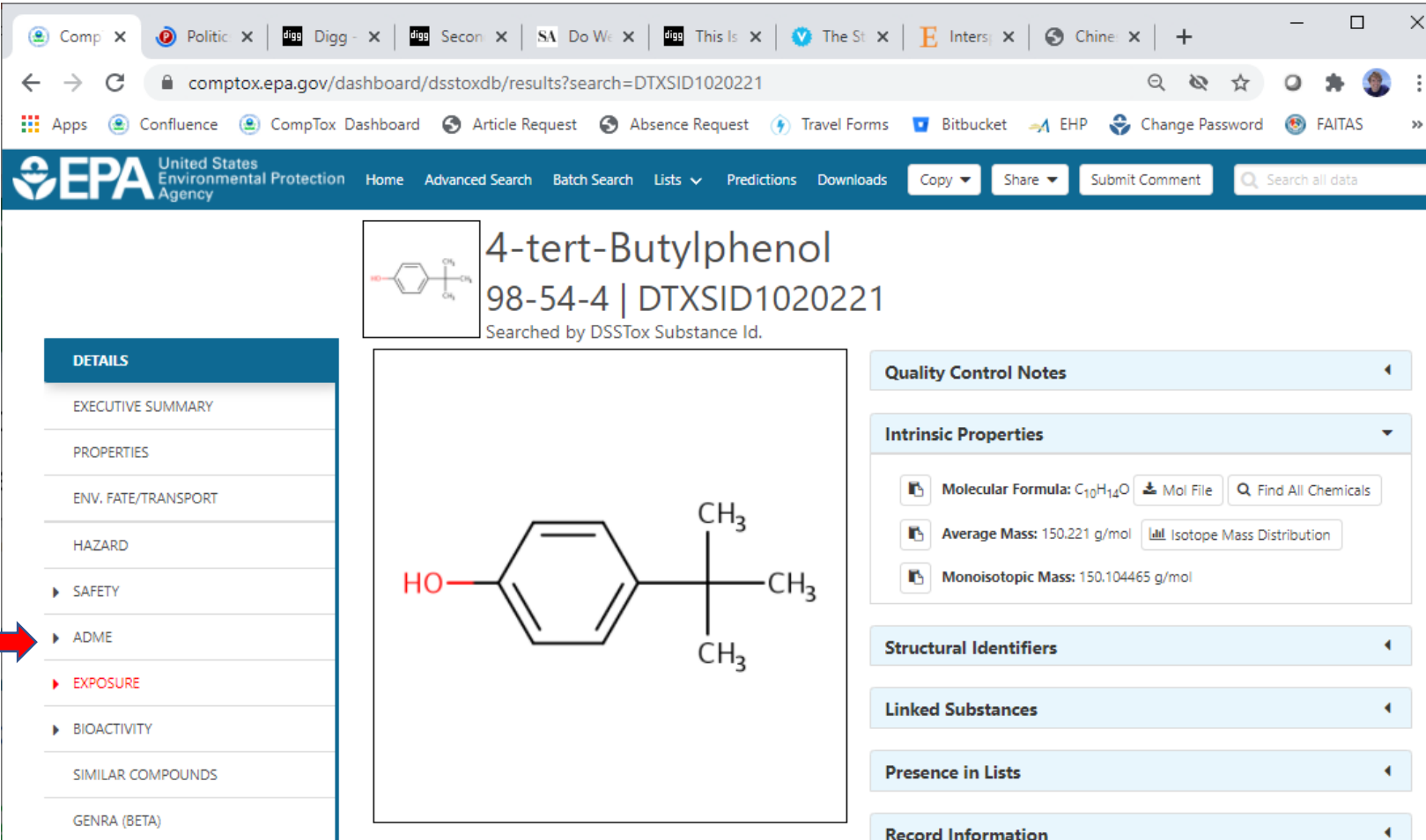
Linked Substances

Presence in Lists

Record Information

ADME on the CompTox Chemicals Dashboard

- Toxicokinetics describes absorption, distribution, metabolism, excretion (ADME)
- The dashboard provides ADME information for >1000 chemicals



The screenshot shows the EPA CompTox Chemicals Dashboard for 4-tert-Butylphenol (DTXSID1020221). The interface includes a top navigation bar with the EPA logo and various links. The main content area displays the chemical name, CAS number (98-54-4), and a search result. A sidebar on the left lists various categories, with 'ADME' highlighted. The right sidebar contains sections for Quality Control Notes, Intrinsic Properties (Molecular Formula, Average Mass, Monoisotopic Mass), Structural Identifiers, Linked Substances, Presence in Lists, and Record Information.

4-tert-Butylphenol
98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

DETAILS

- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- SAFETY
- ADME**
- EXPOSURE
- BIOACTIVITY
- SIMILAR COMPOUNDS
- GENRA (BETA)

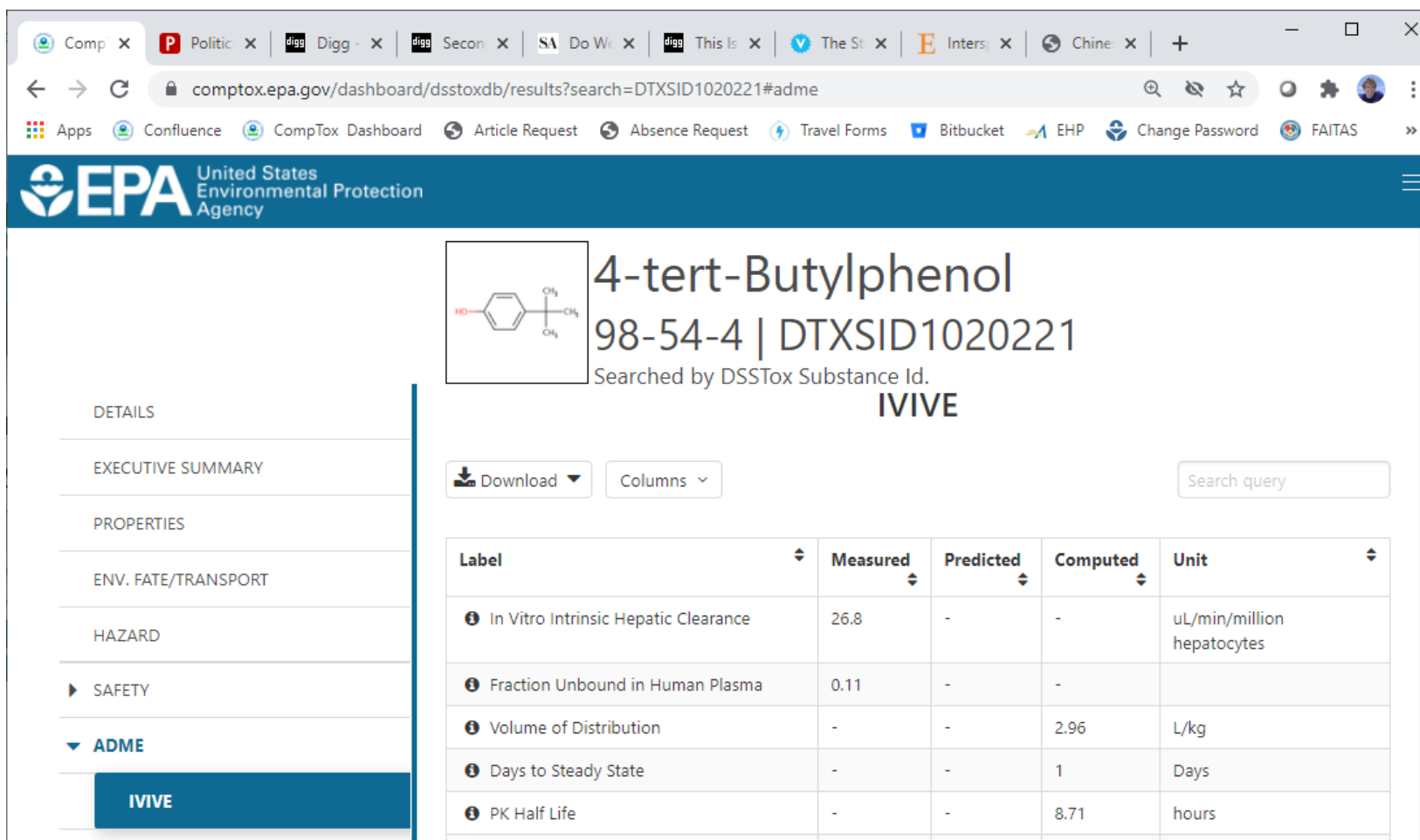
Intrinsic Properties

- Molecular Formula: C₁₀H₁₄O
- Average Mass: 150.221 g/mol
- Monoisotopic Mass: 150.104465 g/mol

Click here
for ADME
information

ADME on the CompTox Chemicals Dashboard

- Toxicokinetics describes absorption, distribution, metabolism, excretion (ADME)
- The dashboard provides ADME information for >1000 chemicals

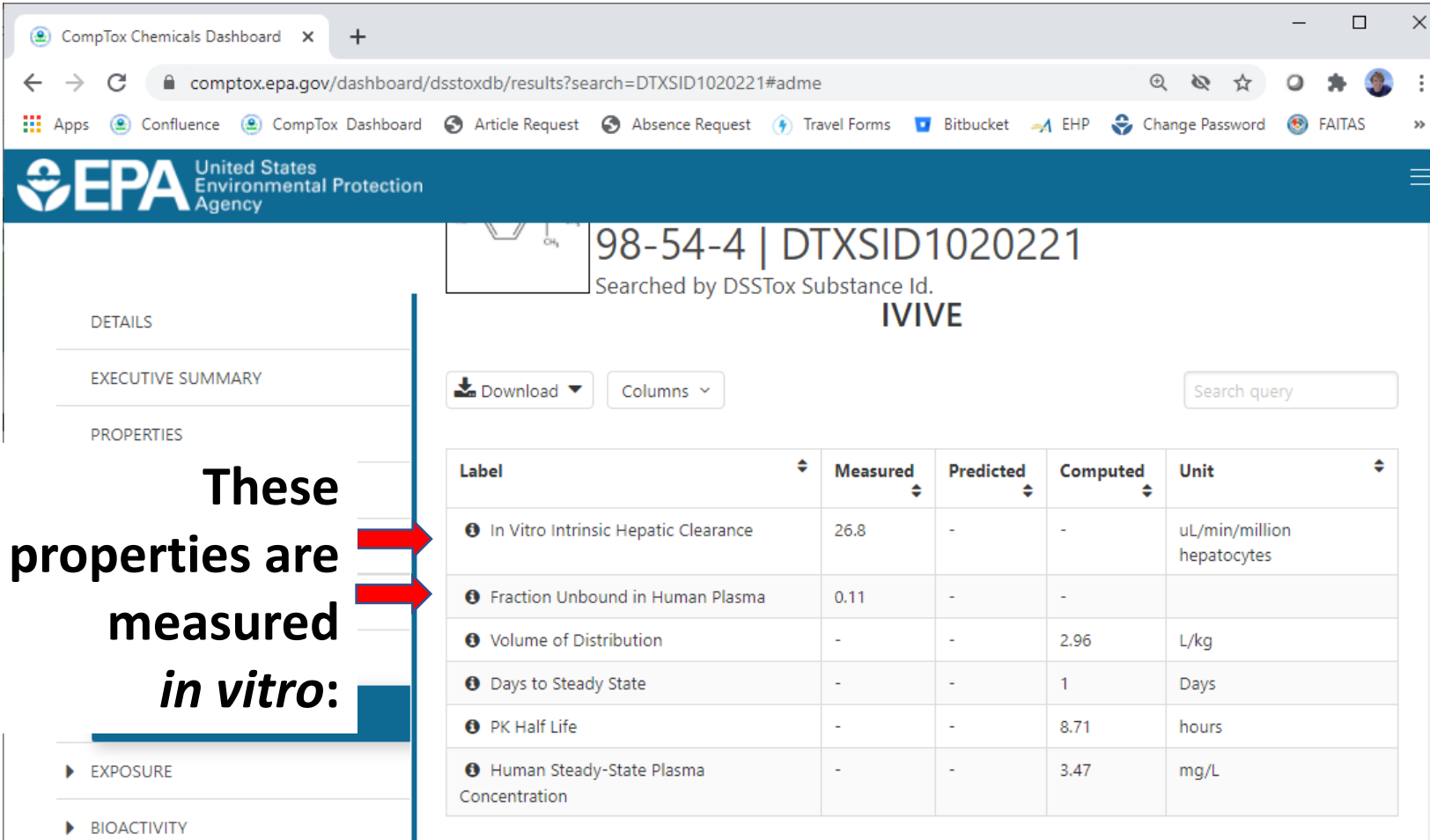


The screenshot shows the EPA CompTox Chemicals Dashboard interface. The browser address bar displays the URL: `comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1020221#adme`. The dashboard header includes the EPA logo and navigation links. The main content area displays the chemical name **4-tert-Butylphenol** with its chemical structure, CAS number **98-54-4**, and DTXSID **DTXSID1020221**. Below this, the text "Searched by DSSTox Substance Id." and the model name **IVIVE** are shown. A sidebar on the left lists various categories, with **ADME** selected and **IVIVE** highlighted. A table below the header provides ADME data for the chemical.

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	26.8	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.11	-	-	
Volume of Distribution	-	-	2.96	L/kg
Days to Steady State	-	-	1	Days
PK Half Life	-	-	8.71	hours

ADME on the CompTox Chemicals Dashboard

- The ADME tab provides any available *in vitro* measured determinants of toxicokinetics



The screenshot shows the CompTox Chemicals Dashboard for substance 98-54-4 (DTXSID1020221). The left sidebar contains navigation tabs: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, EXPOSURE, and BIOACTIVITY. The main content area displays the substance name and a table of ADME properties. A text overlay with red arrows points to the first two rows of the table, indicating they are measured *in vitro*.

98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

IVIVE

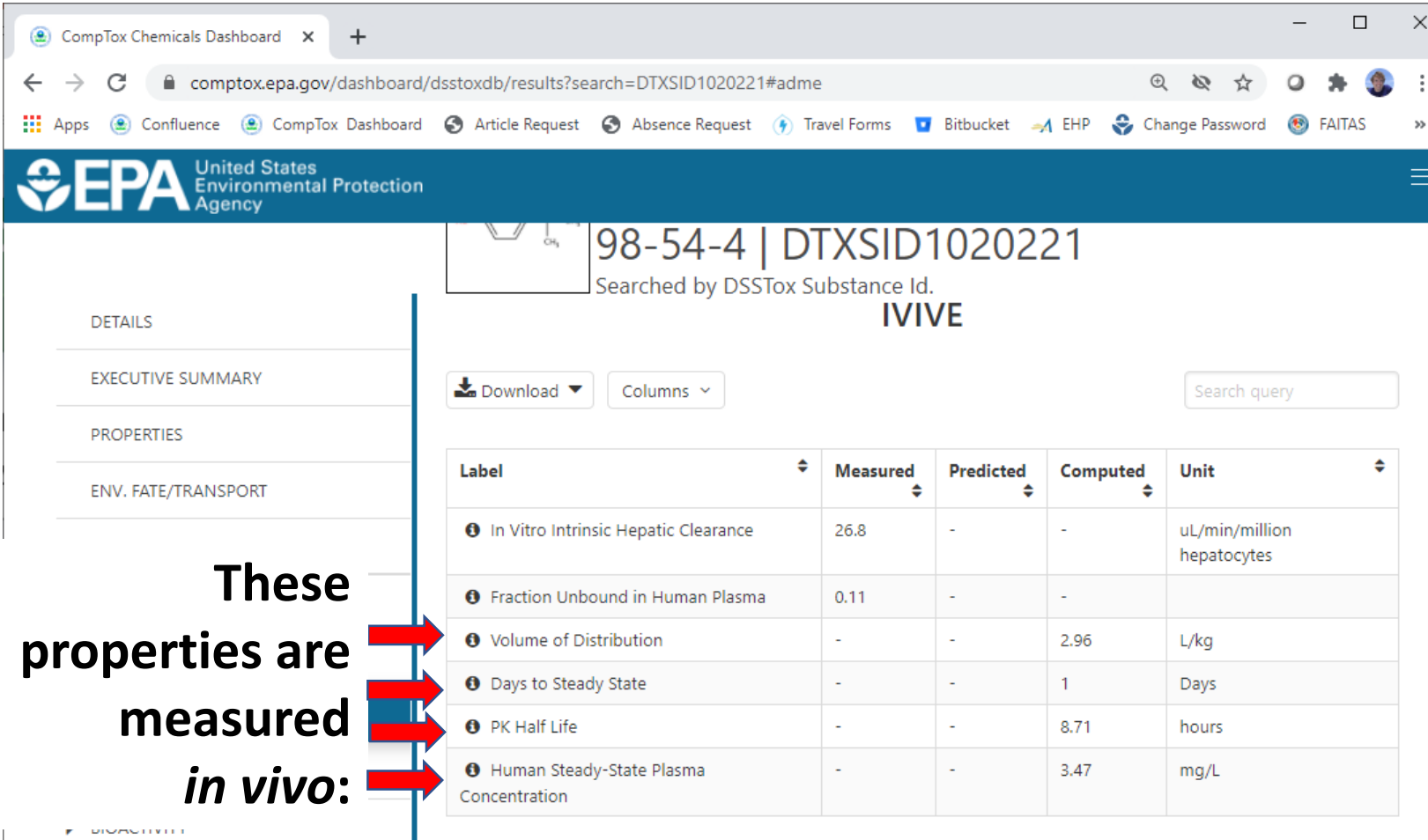
Download Columns Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	26.8	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.11	-	-	
Volume of Distribution	-	-	2.96	L/kg
Days to Steady State	-	-	1	Days
PK Half Life	-	-	8.71	hours
Human Steady-State Plasma Concentration	-	-	3.47	mg/L

These properties are measured *in vitro*:

ADME on the CompTox Chemicals Dashboard

- Eventually *in vivo*-derived values will be available from CvTdb (Sayre et al., 2020)



98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

IVIVE

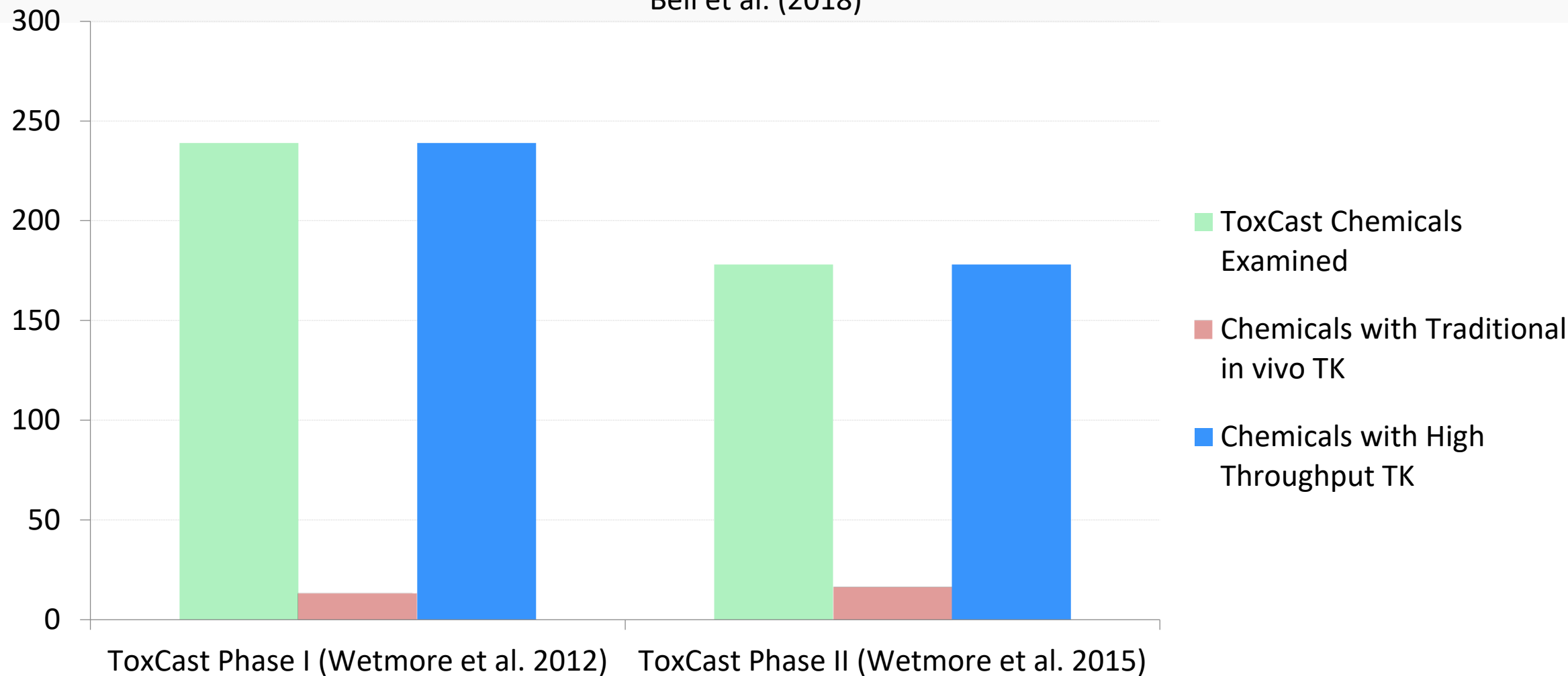
Download Columns Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	26.8	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.11	-	-	
Volume of Distribution	-	-	2.96	L/kg
Days to Steady State	-	-	1	Days
PK Half Life	-	-	8.71	hours
Human Steady-State Plasma Concentration	-	-	3.47	mg/L

These properties are measured *in vivo*:

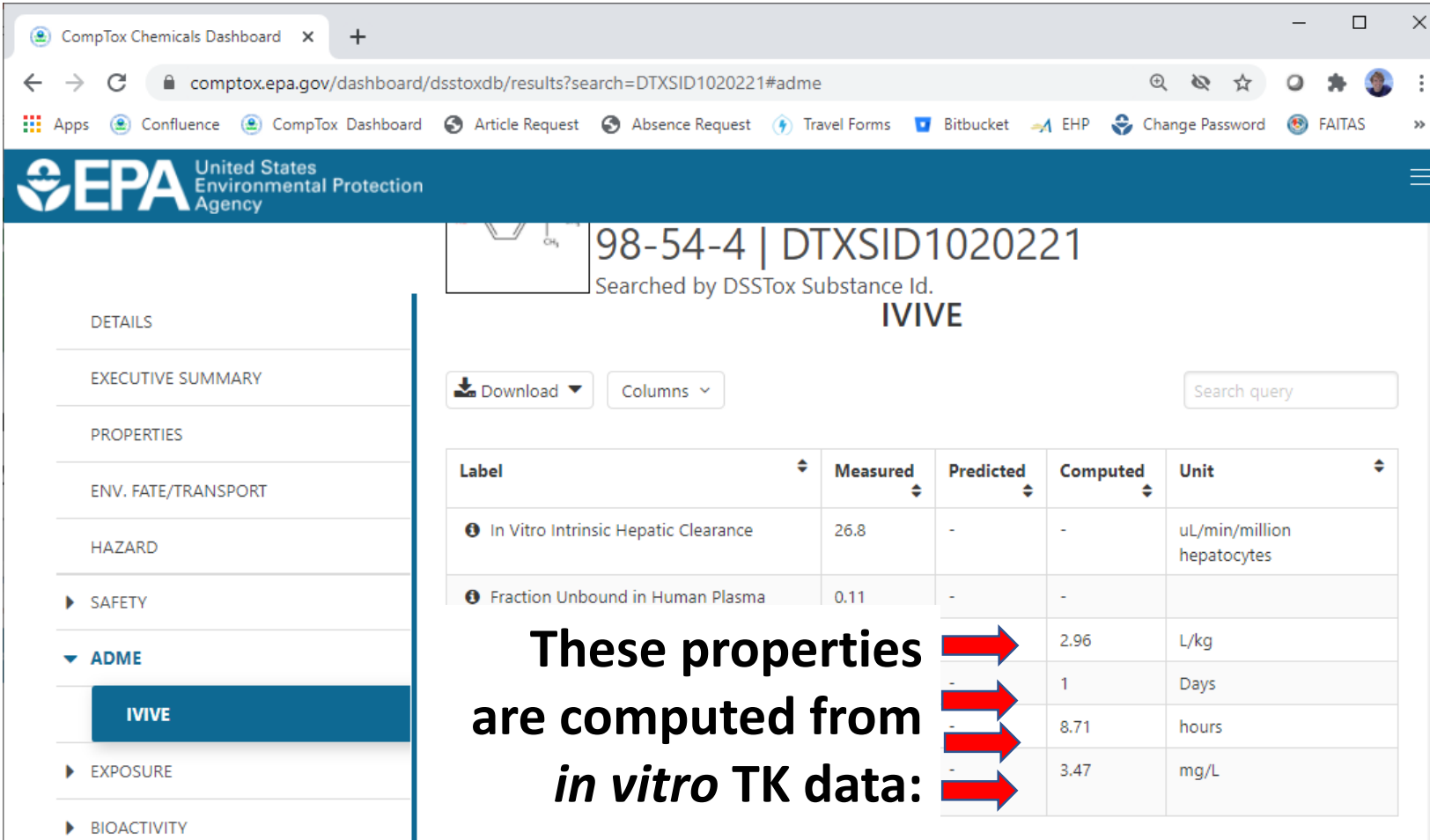
Most chemicals do not have TK Data

Bell et al. (2018)



ADME on the CompTox Chemicals Dashboard

- We use the R package “httk” (Pearce et al., 2017) to make predictions about TK from *in vitro*-measured TK data



CompTox Chemicals Dashboard

comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1020221#adme

EPA United States Environmental Protection Agency

98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

IVIVE

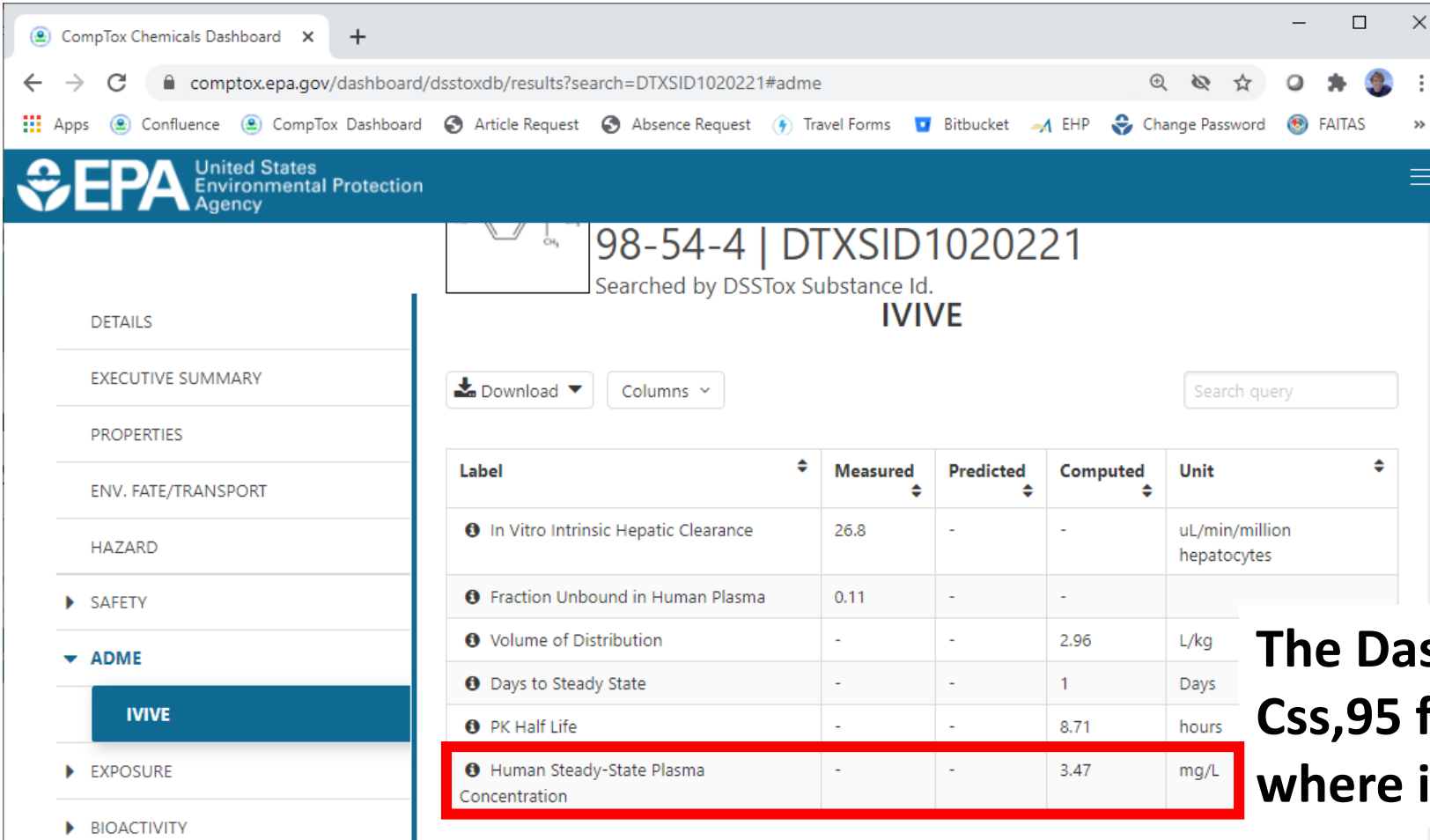
Download Columns Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	26.8	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.11	-	-	
			2.96	L/kg
			1	Days
			8.71	hours
			3.47	mg/L

These properties are computed from *in vitro* TK data:

ADME on the CompTox Chemicals Dashboard

- We use the R package “httk” (Pearce et al., 2017) to make predictions about TK from *in vitro*-measured TK data



CompTox Chemicals Dashboard

comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1020221#adme

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EPA United States Environmental Protection Agency

98-54-4 | DTXSID1020221
Searched by DSSTox Substance Id.

IVIVE

Download Columns Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	26.8	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.11	-	-	
Volume of Distribution	-	-	2.96	L/kg
Days to Steady State	-	-	1	Days
PK Half Life	-	-	8.71	hours
Human Steady-State Plasma Concentration	-	-	3.47	mg/L

The Dashboard provides C_{ss,95} for every chemical where it is available

Does My Chemical Have HTTK Data?



- The “HTTKHUMAN” list will take you to the landing page for a chemical with HTTK data

CompTox Chemicals Dashboard

882 Thousand Chemicals

Chemicals Product/Use Categories Assay/Gene

Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey

☐ Identifier substring search

See what people are saying, read the dashboard [comments!](#)
Cite the Dashboard Publication [click here](#)

Latest News

[Read more news](#)

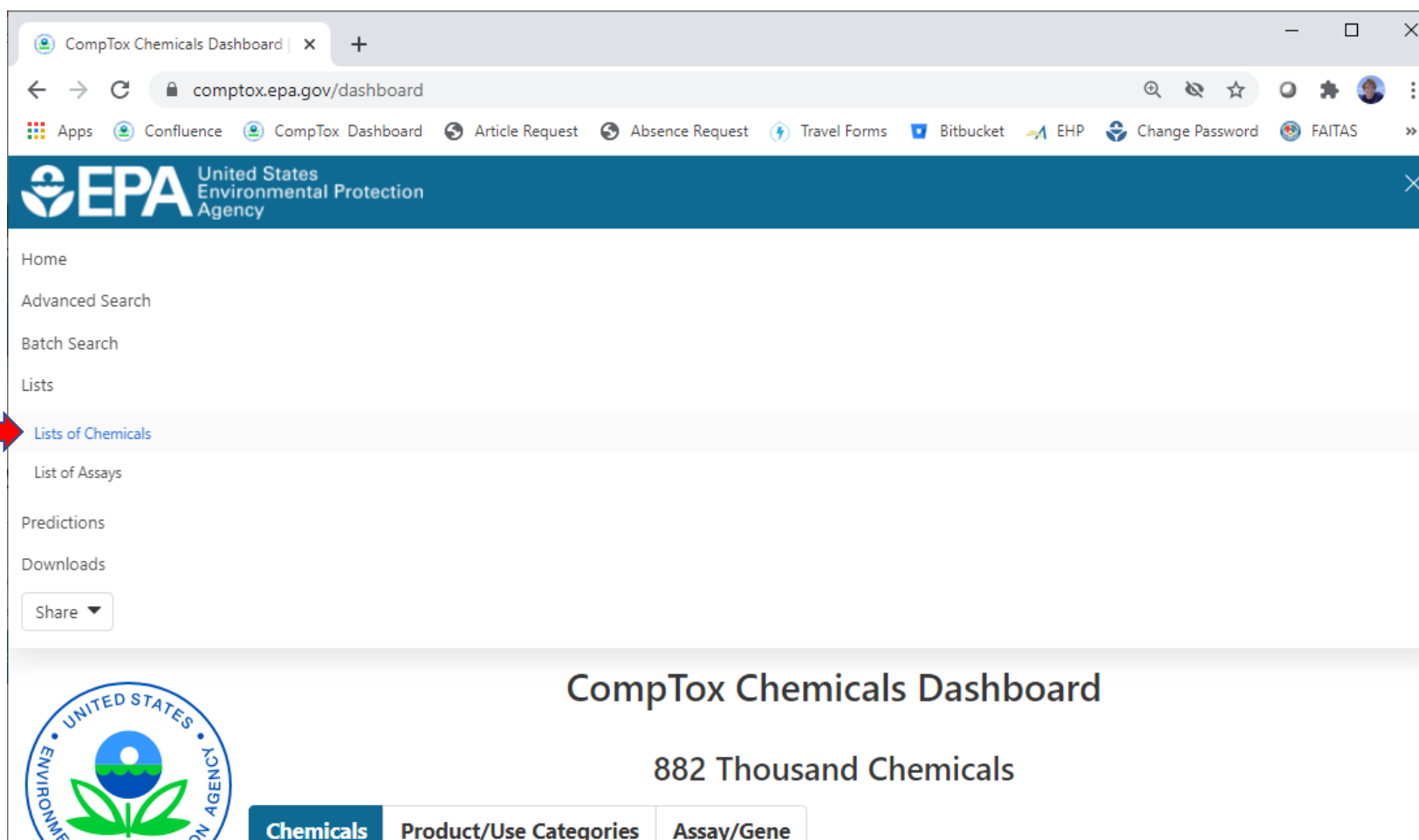
PARIS III Database list added

Click here to
bring up
Dashboard
Options

Does My Chemical Have HHTK Data?

- The “HHTKHUMAN” list will take you to the landing page for a chemical with HHTK data

Select “Lists
of Chemicals”



The screenshot shows a web browser window with the URL `comptox.epa.gov/dashboard`. The page features the EPA logo and a navigation menu on the left. A red arrow points to the "Lists of Chemicals" link in the menu. The main content area displays the "CompTox Chemicals Dashboard" with the text "882 Thousand Chemicals" and three tabs: "Chemicals", "Product/Use Categories", and "Assay/Gene".

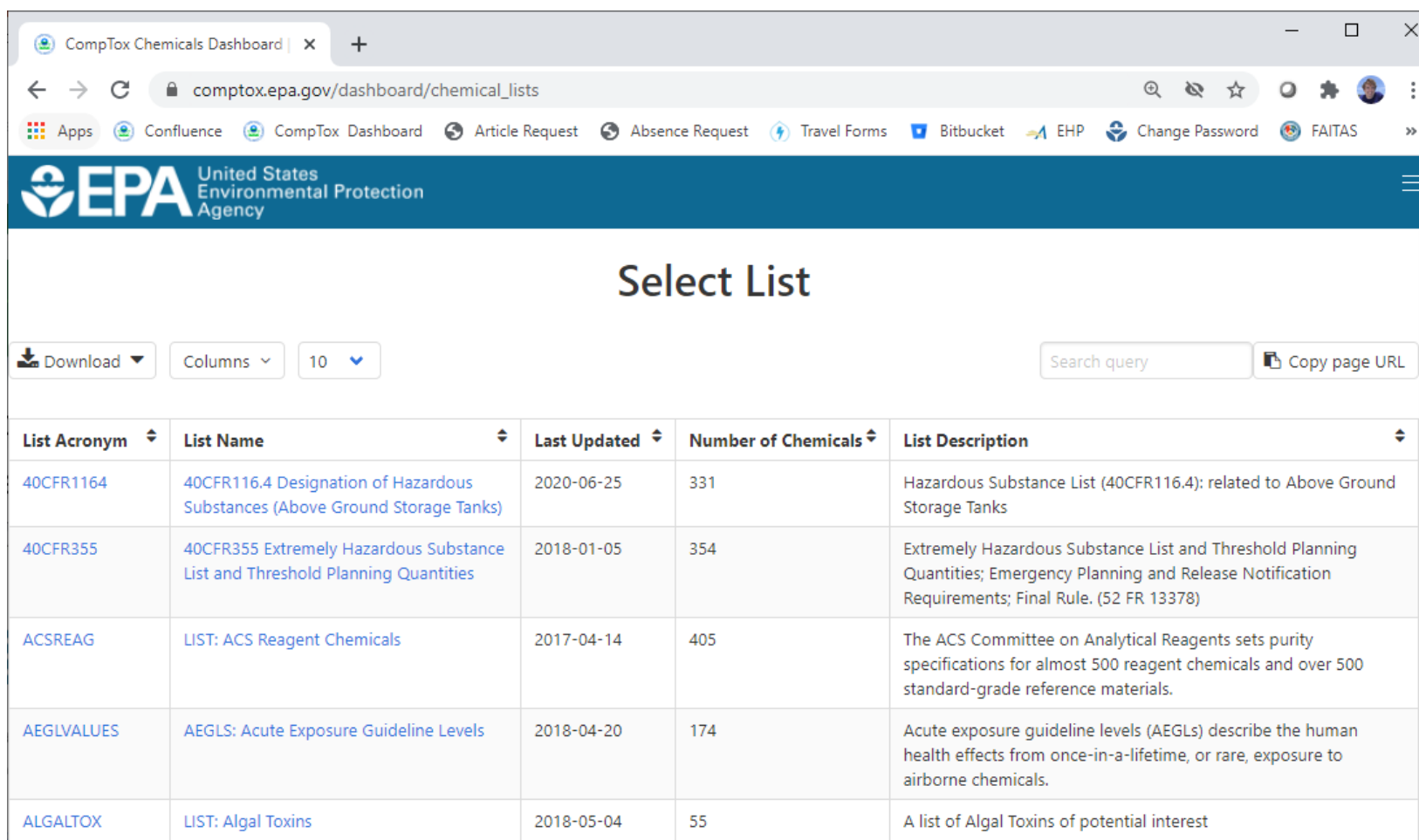
CompTox Chemicals Dashboard

882 Thousand Chemicals

Chemicals Product/Use Categories Assay/Gene

Does My Chemical Have HHTK Data?

- The “HHTKHUMAN” list will take you to the landing page for a chemical with HHTK data



CompTox Chemicals Dashboard | x +

comptox.epa.gov/dashboard/chemical_lists

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EPA United States Environmental Protection Agency

Select List

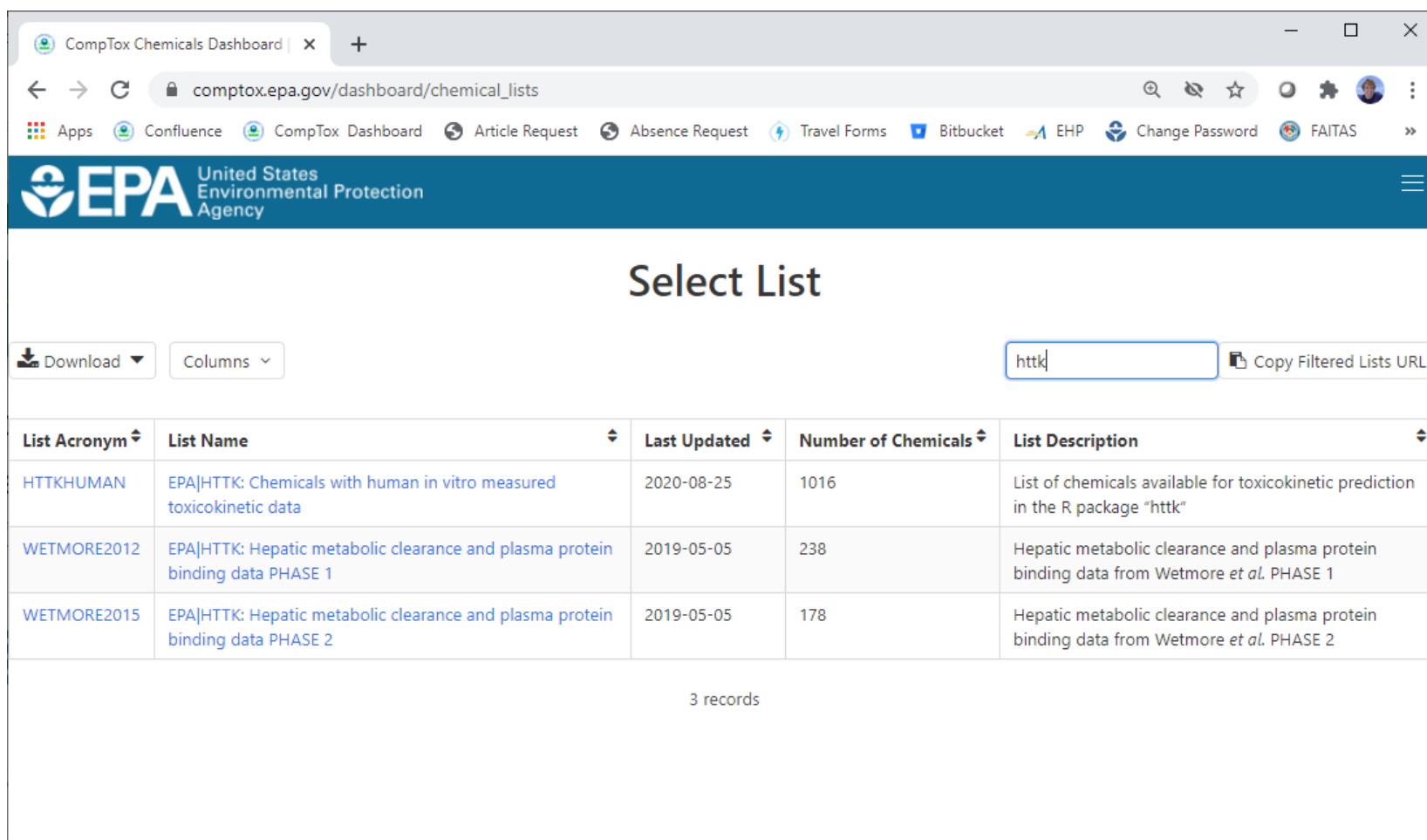
Download Columns 10 Search query Copy page URL

List Acronym	List Name	Last Updated	Number of Chemicals	List Description
40CFR1164	40CFR116.4 Designation of Hazardous Substances (Above Ground Storage Tanks)	2020-06-25	331	Hazardous Substance List (40CFR116.4): related to Above Ground Storage Tanks
40CFR355	40CFR355 Extremely Hazardous Substance List and Threshold Planning Quantities	2018-01-05	354	Extremely Hazardous Substance List and Threshold Planning Quantities; Emergency Planning and Release Notification Requirements; Final Rule. (52 FR 13378)
ACSREAG	LIST: ACS Reagent Chemicals	2017-04-14	405	The ACS Committee on Analytical Reagents sets purity specifications for almost 500 reagent chemicals and over 500 standard-grade reference materials.
AEGLVALUES	AEGLs: Acute Exposure Guideline Levels	2018-04-20	174	Acute exposure guideline levels (AEGLs) describe the human health effects from once-in-a-lifetime, or rare, exposure to airborne chemicals.
ALGALTOX	LIST: Algal Toxins	2018-05-04	55	A list of Algal Toxins of potential interest

← Enter “hhtk”
in search box

Does My Chemical Have HTK Data?

- The “HTTKHUMAN” list will take you to the landing page for a chemical with HTK data



CompTox Chemicals Dashboard | x +

comptox.epa.gov/dashboard/chemical_lists

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EPA United States Environmental Protection Agency

Select List

Download Columns

httk Copy Filtered Lists URL

List Acronym	List Name	Last Updated	Number of Chemicals	List Description
HTTKHUMAN	EPA HTTK: Chemicals with human in vitro measured toxicokinetic data	2020-08-25	1016	List of chemicals available for toxicokinetic prediction in the R package “httk”
WETMORE2012	EPA HTTK: Hepatic metabolic clearance and plasma protein binding data PHASE 1	2019-05-05	238	Hepatic metabolic clearance and plasma protein binding data from Wetmore <i>et al.</i> PHASE 1
WETMORE2015	EPA HTTK: Hepatic metabolic clearance and plasma protein binding data PHASE 2	2019-05-05	178	Hepatic metabolic clearance and plasma protein binding data from Wetmore <i>et al.</i> PHASE 2

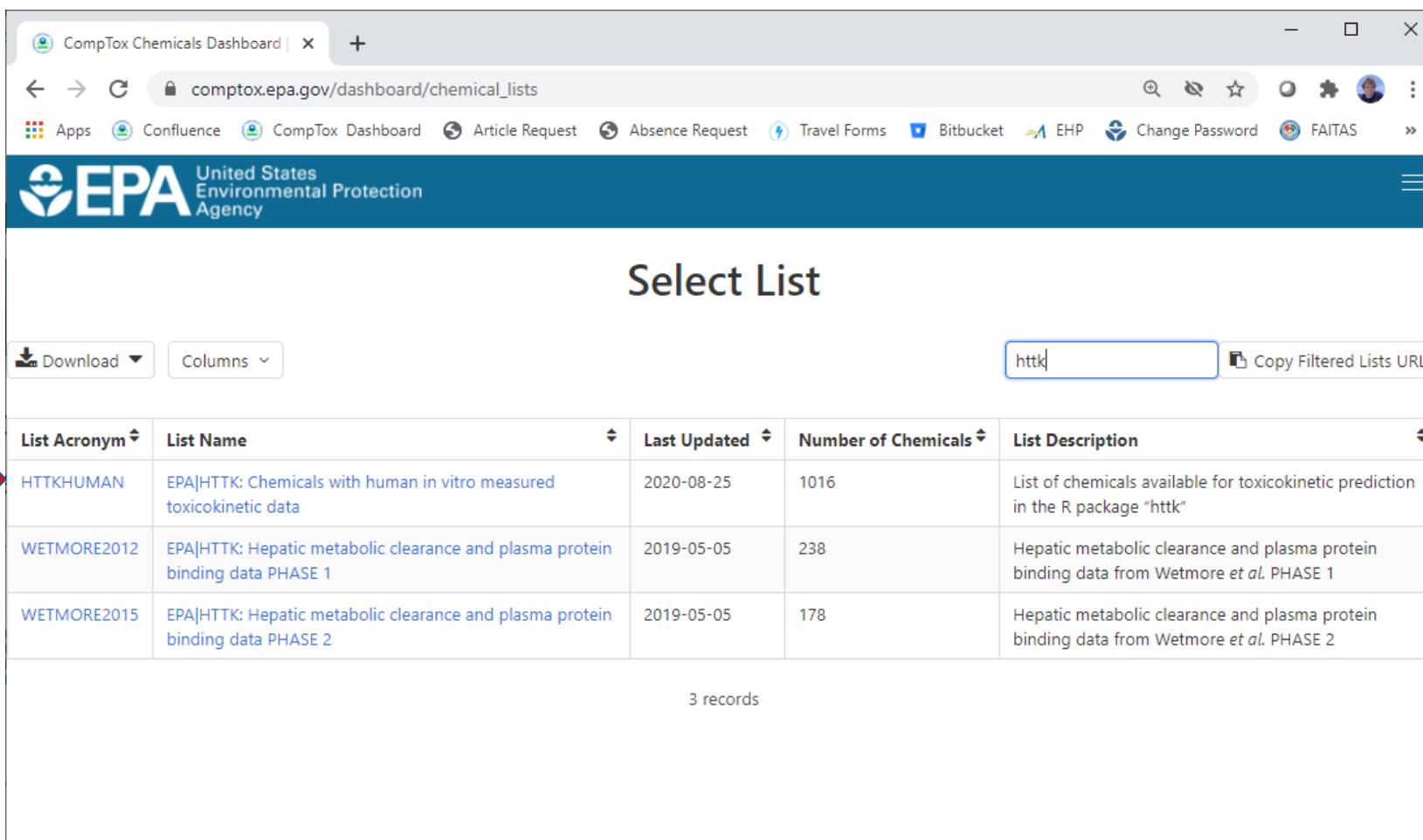
3 records

Enter “httk”
in search box

Does My Chemical Have HTTK Data?

- The “HTTKHUMAN” list will take you to the landing page for a chemical with HTTK data

Select list
“HTTKHUMAN”



CompTox Chemicals Dashboard | x +

comptox.epa.gov/dashboard/chemical_lists

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EPA United States Environmental Protection Agency

Select List

Download Columns

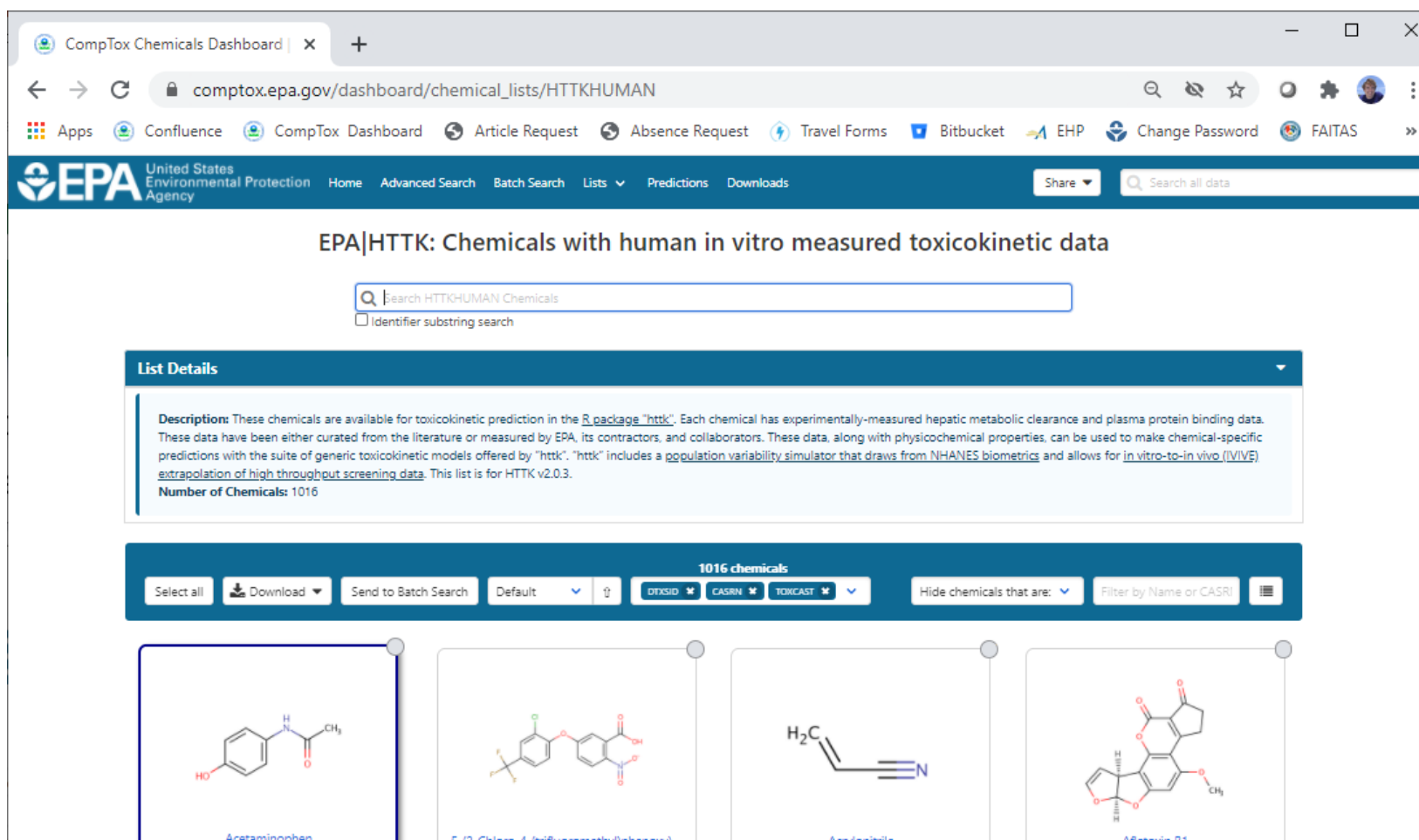
httk Copy Filtered Lists URL

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3 records

Does My Chemical Have HHTK Data?

- The “HHTKHUMAN” list will take you to the landing page for a chemical with HHTK data



The screenshot displays the EPA CompTox Chemicals Dashboard in a web browser. The address bar shows the URL `comptox.epa.gov/dashboard/chemical_lists/HHTKHUMAN`. The dashboard header includes the EPA logo, navigation links (Home, Advanced Search, Batch Search, Lists, Predictions, Downloads), and a search bar. The main content area is titled "EPA|HHTK: Chemicals with human in vitro measured toxicokinetic data". Below the title is a search bar and a checkbox for "Identifier substring search". A "List Details" section provides a description of the chemicals and their availability for toxicokinetic prediction, along with the number of chemicals (1016). Below this, a toolbar offers options to "Select all", "Download", "Send to Batch Search", and "Default", along with filters for "DTXSID", "CASRN", and "TOXCAST". The bottom of the image shows four chemical structures: Acetaminophen, 5-(2-Chloro-4-(trifluoromethyl)phenoxy)-2-nitrobenzoic acid, Acrylonitrile, and Aflatoxin B1.

CompTox Chemicals Dashboard | x +

comptox.epa.gov/dashboard/chemical_lists/HHTKHUMAN

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EPA United States Environmental Protection Agency Home Advanced Search Batch Search Lists Predictions Downloads

Share Search all data

EPA|HHTK: Chemicals with human in vitro measured toxicokinetic data

Search HHTKHUMAN Chemicals

☐ Identifier substring search

List Details

Description: These chemicals are available for toxicokinetic prediction in the R package "httk". Each chemical has experimentally-measured hepatic metabolic clearance and plasma protein binding data. These data have been either curated from the literature or measured by EPA, its contractors, and collaborators. These data, along with physicochemical properties, can be used to make chemical-specific predictions with the suite of generic toxicokinetic models offered by "httk". "httk" includes a [population variability simulator that draws from NHANES biometrics](#) and allows for [in vitro-to-in vivo \(IVIVE\) extrapolation of high throughput screening data](#). This list is for HHTK v2.0.3.

Number of Chemicals: 1016

1016 chemicals

Select all Download Send to Batch Search Default DTXSID CASRN TOXCAST Hide chemicals that are: Filter by Name or CASRN

Acetaminophen

5-(2-Chloro-4-(trifluoromethyl)phenoxy)-2-nitrobenzoic acid

Acrylonitrile

Aflatoxin B1

How Does AED Work?

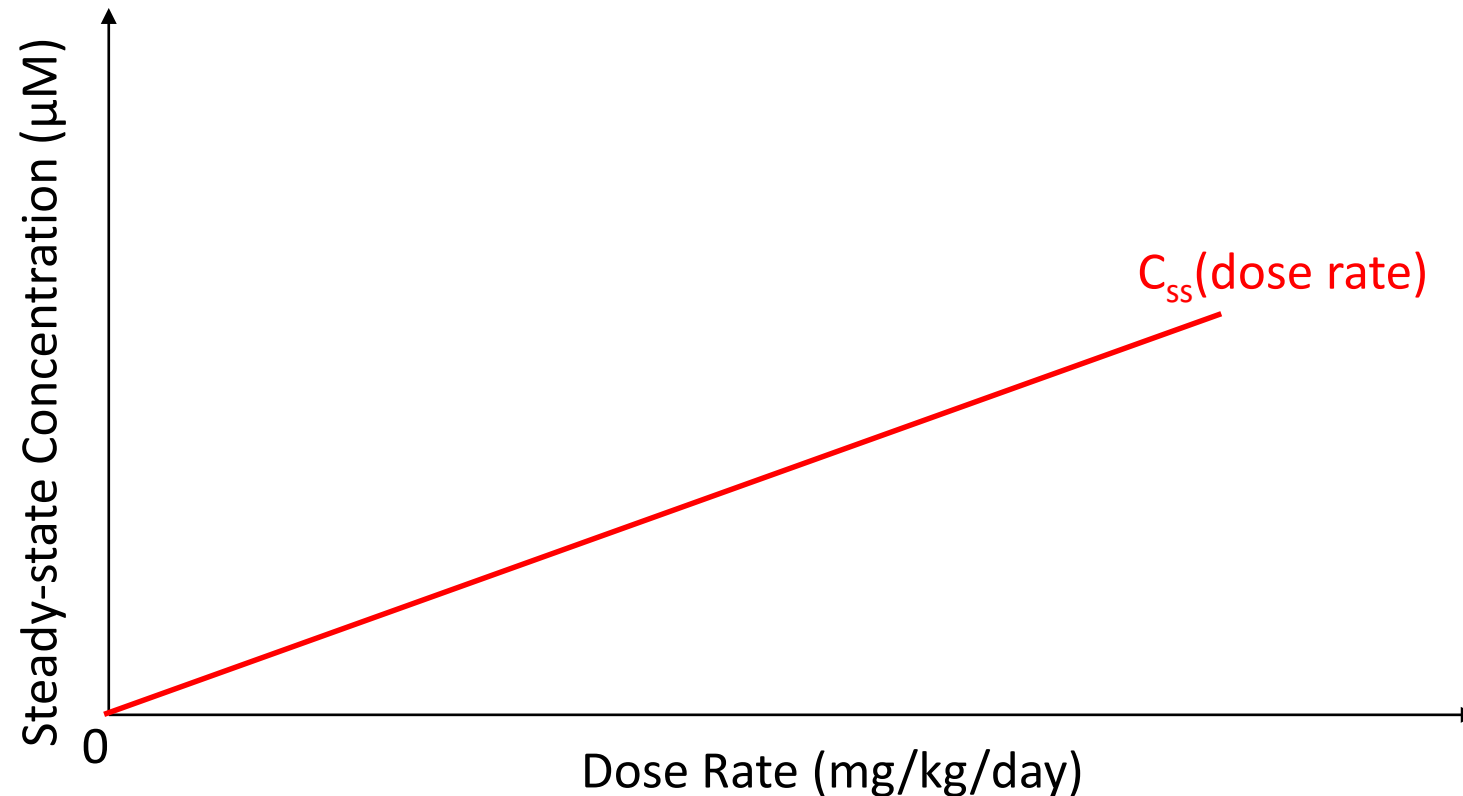
- AED is the administered equivalent dose for an *in vitro* concentration

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

- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure
- The dashboard provides $C_{ss,95}$ values for >1000 chemicals
- The “95” refers to the upper 95th percentile – due to human variability and measurement uncertainty there are a range of possible C_{ss} values
- All of this assumes that the individual has had enough time to come to “steady-state” with respect to their daily exposures
 - Here that means that their average plasma concentration is unchanged 24 hours later

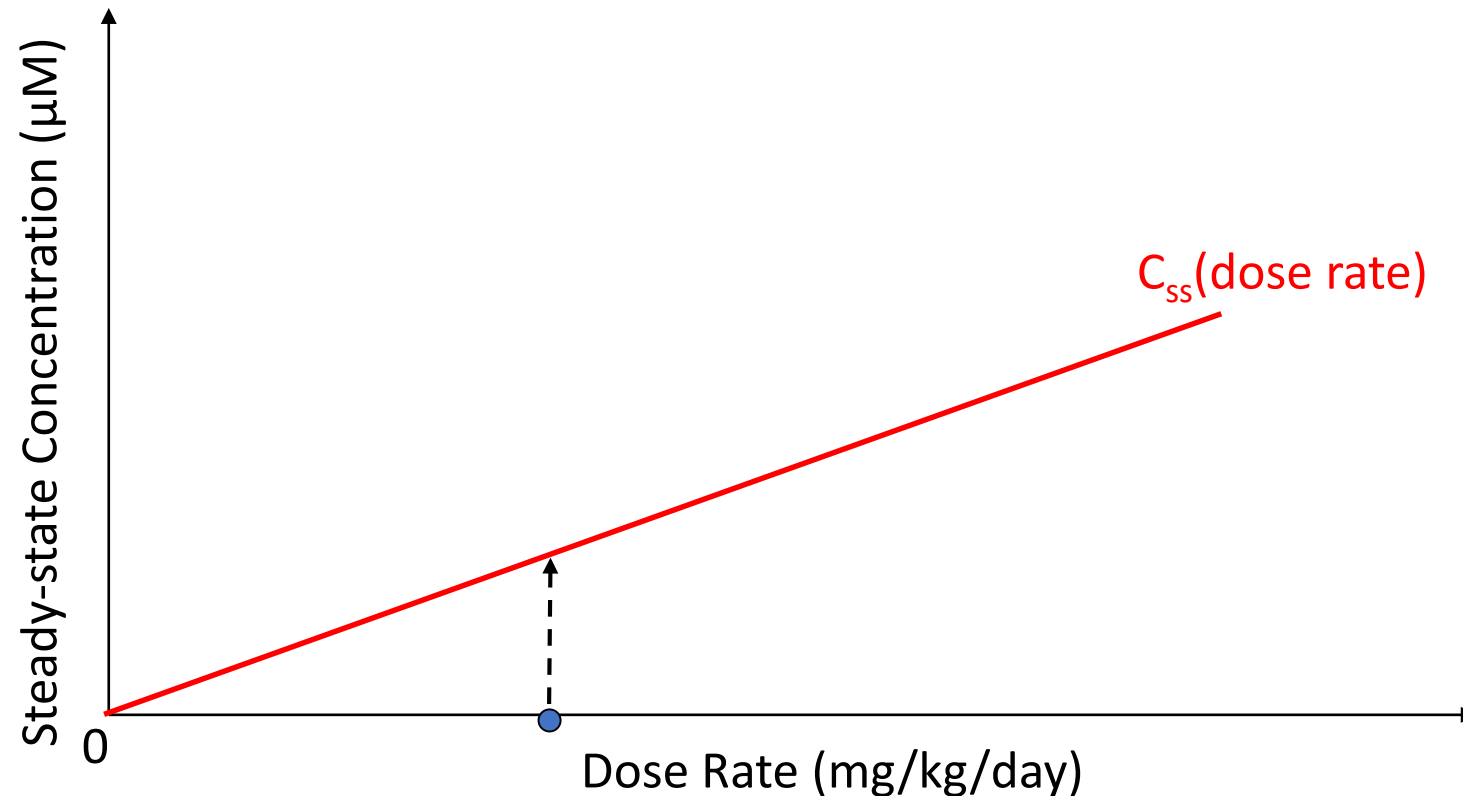
Steady-State Plasma Concentration

- C_{ss} (dose rate) is the steady-state plasma concentration as the result of a fixed daily dose rate (mg/kg/day)
- Because of limitations on the data available, we use a linear model



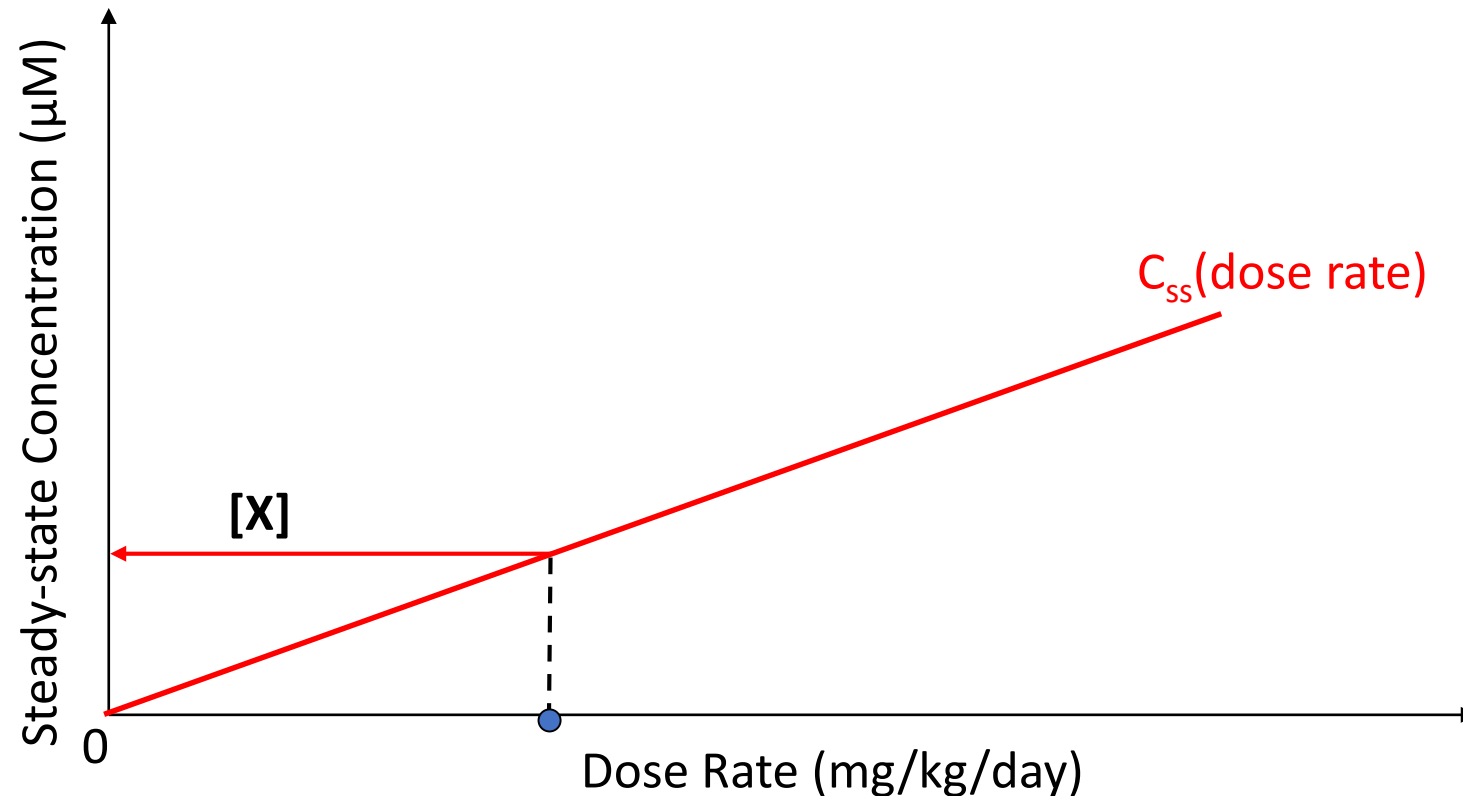
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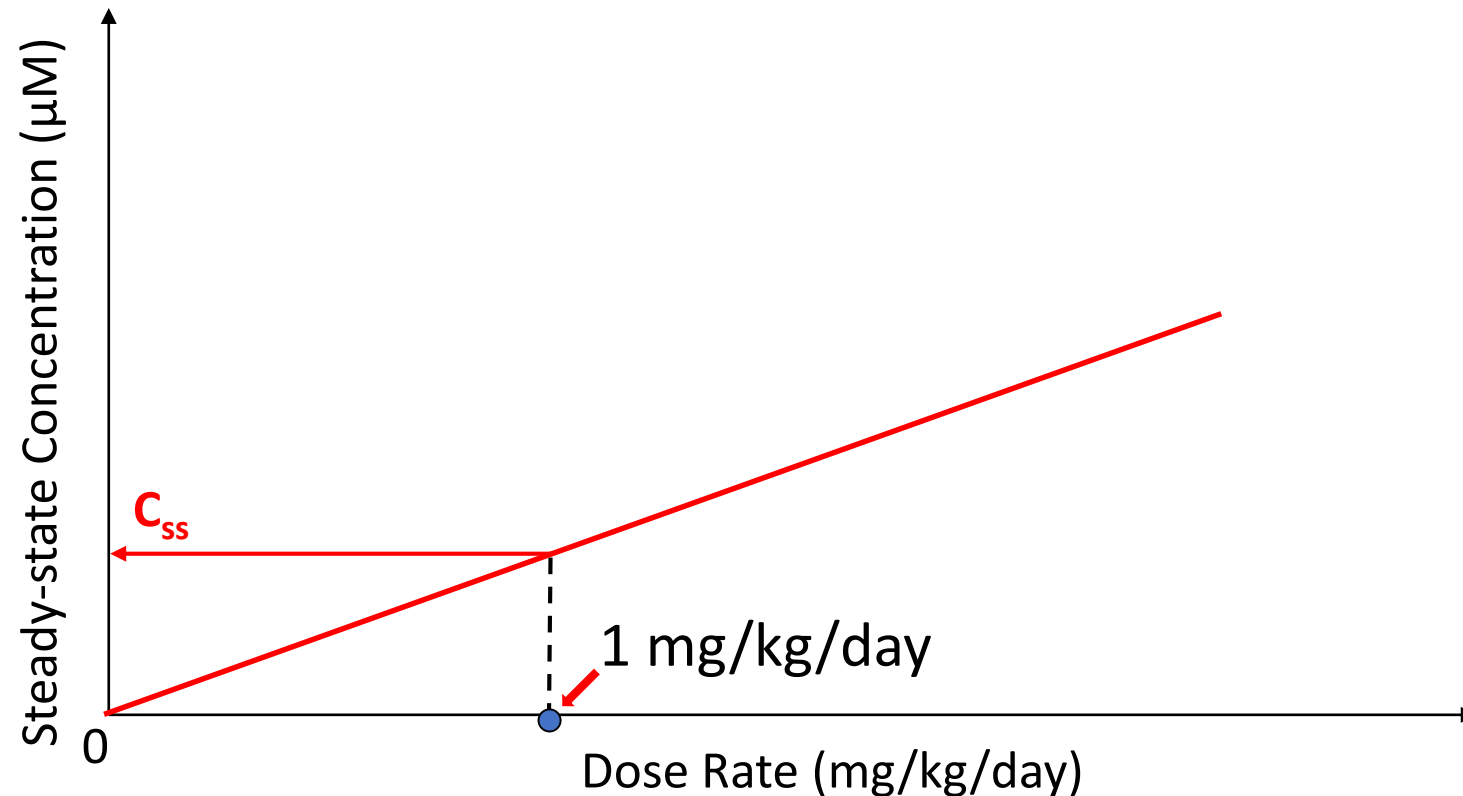
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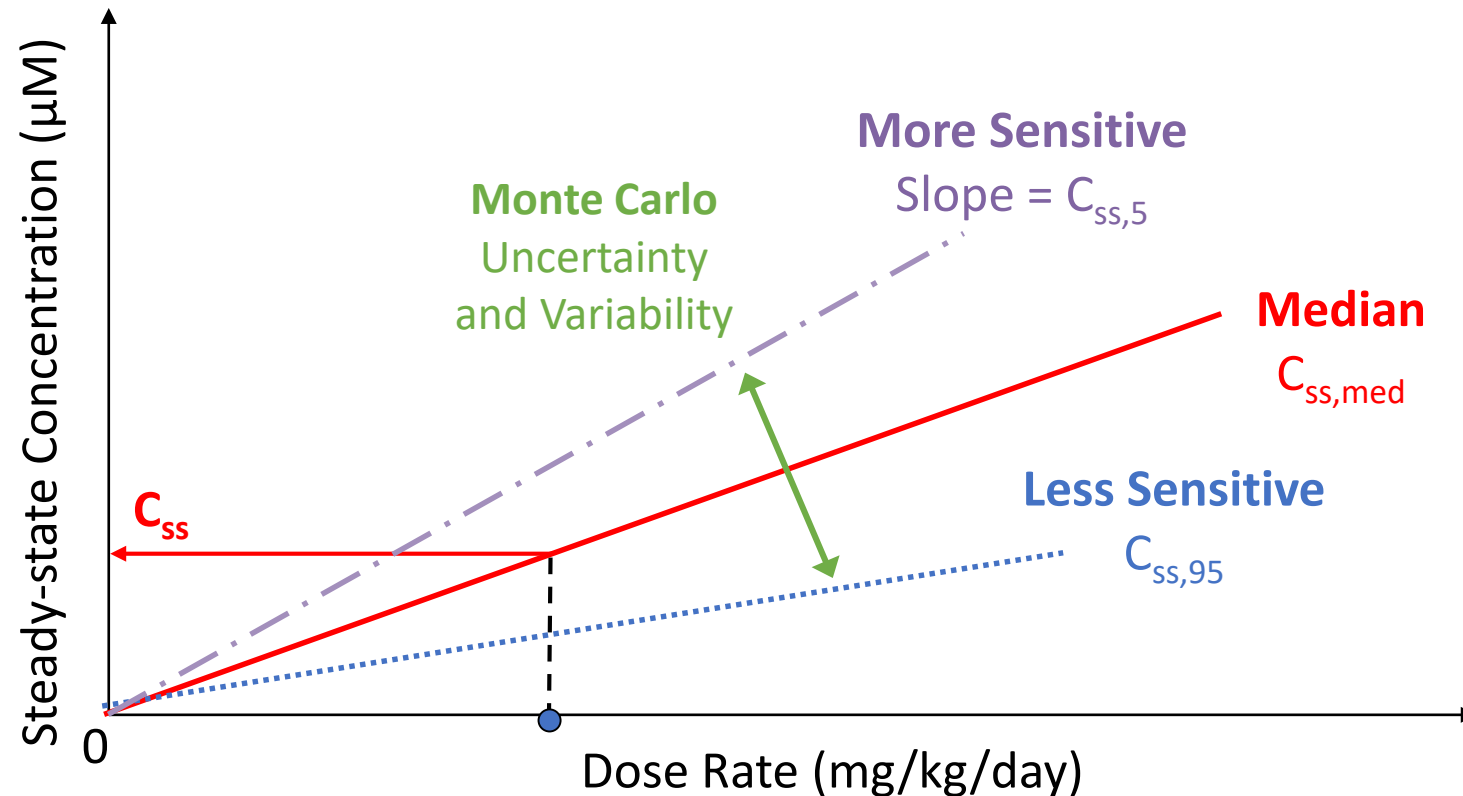
Steady-State Plasma Concentration

- Because of limitations on the data available, we use a linear model
- We calculate " C_{ss} " for the case of 1 mg/kg/day



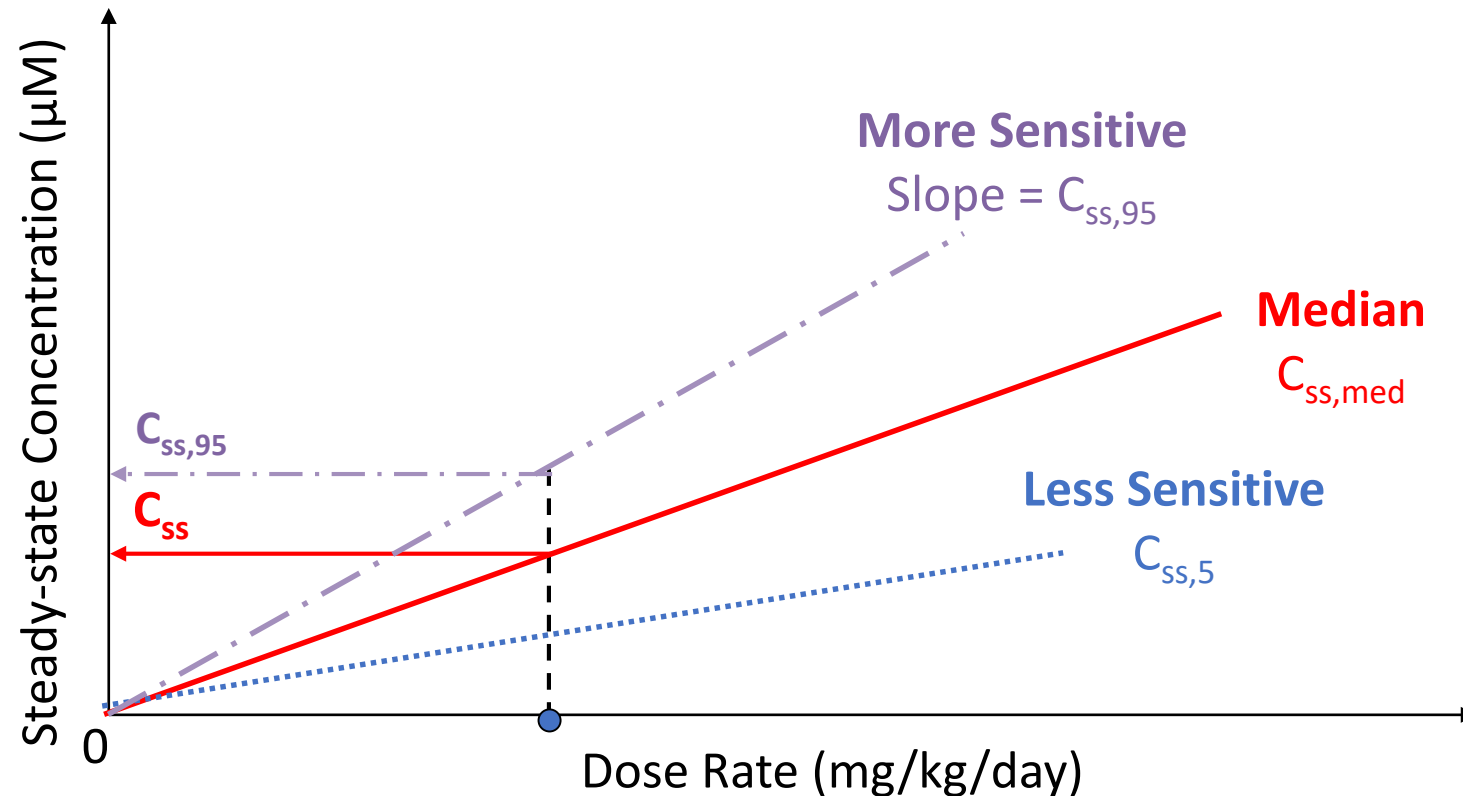
Monte Carlo Simulation

- We use Monte Carlo simulation to propagate measurement uncertainty (Wambaugh et al., 2019) and characterize human physiological variability (Ring et al., 2017)
- This produces a range of C_{ss} values



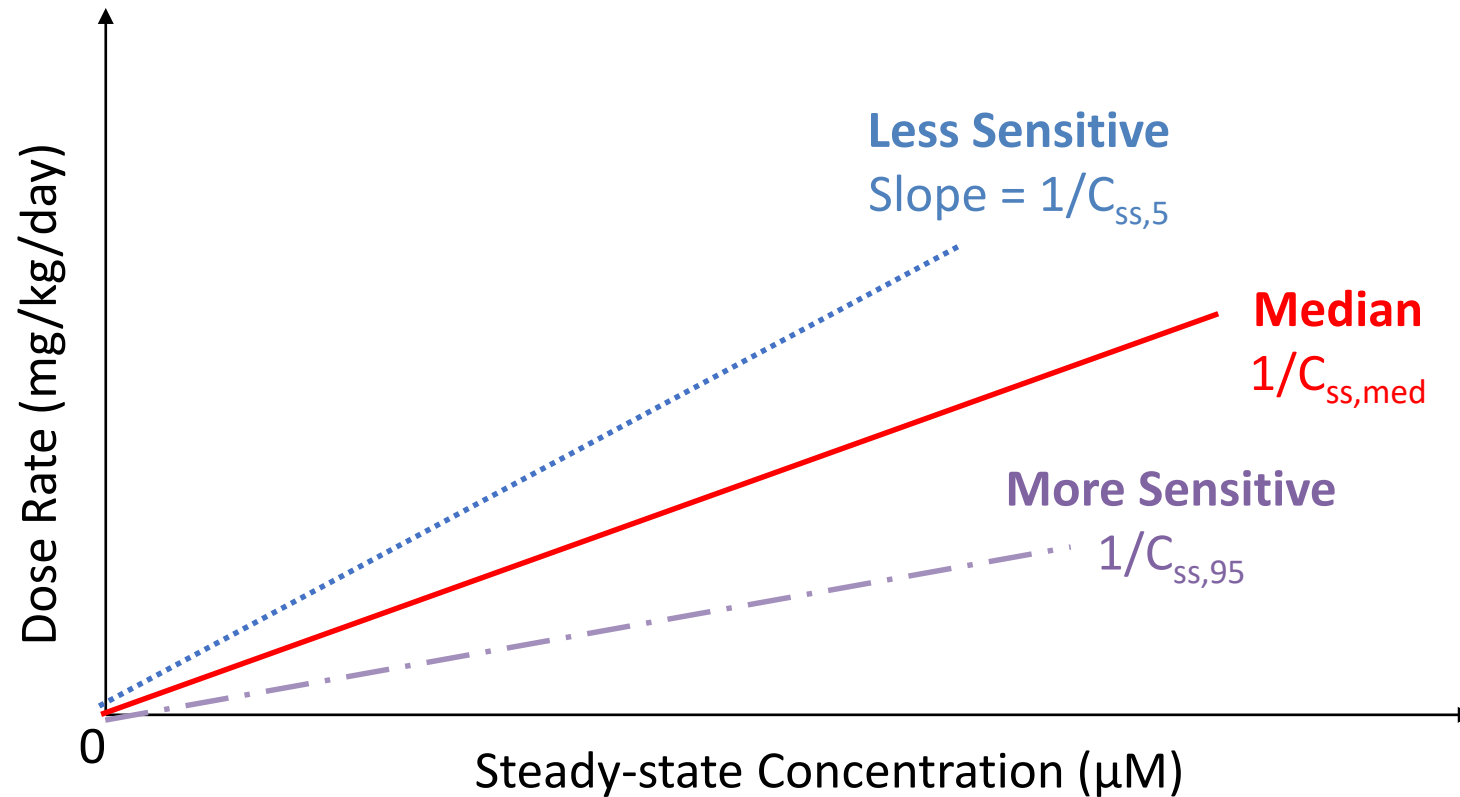
Monte Carlo Simulation

- We typically consider the median and highest (most sensitive) 95th percentile for the same dose rate
- The $C_{ss,95}$ corresponds to higher plasma concentrations for 1 mg/kg/day



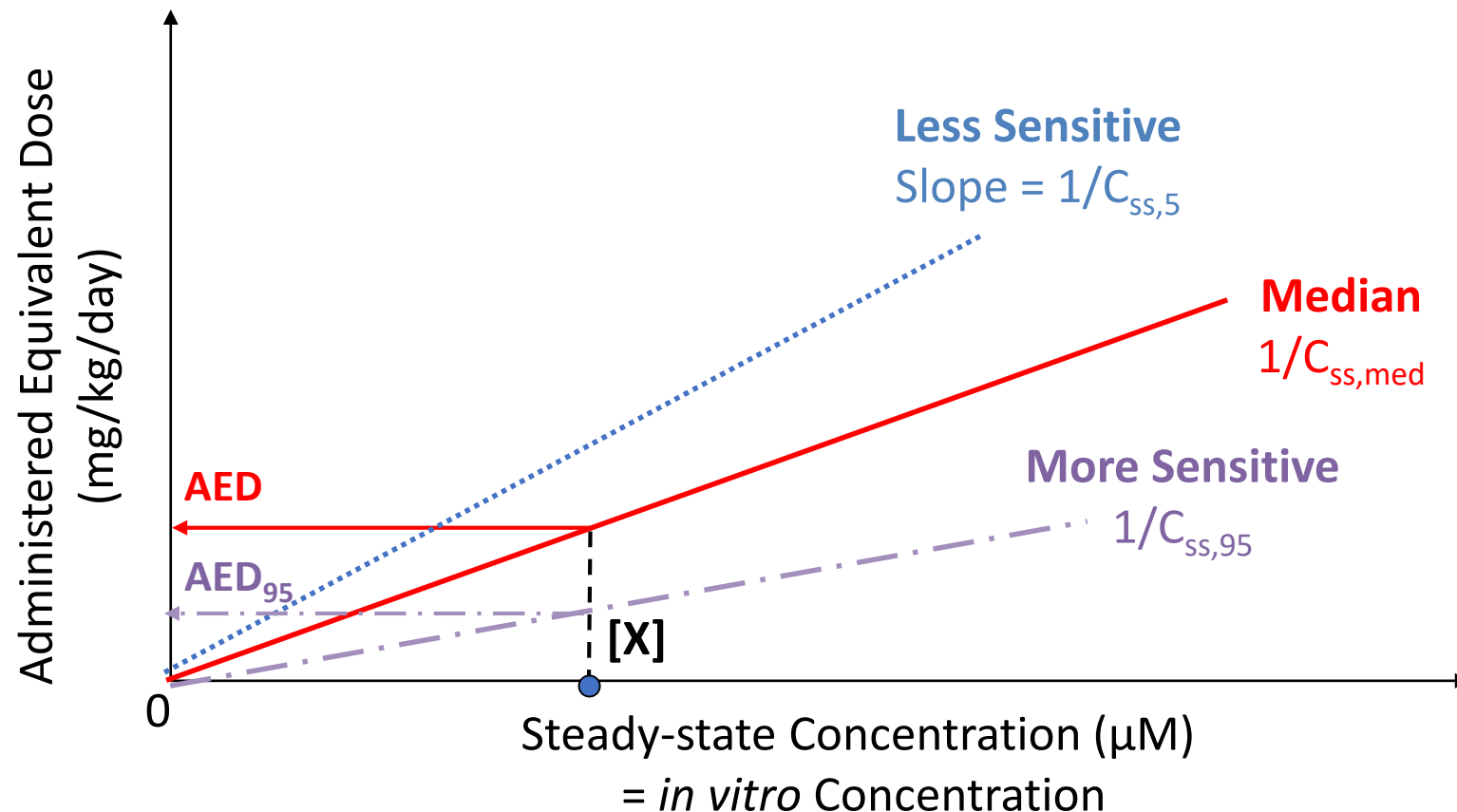
Steady-State Reverse Dosimetry IVIVE

- For “reverse dosimetry” (Tan et al., 2007) we **swap the x- and y-axes**:



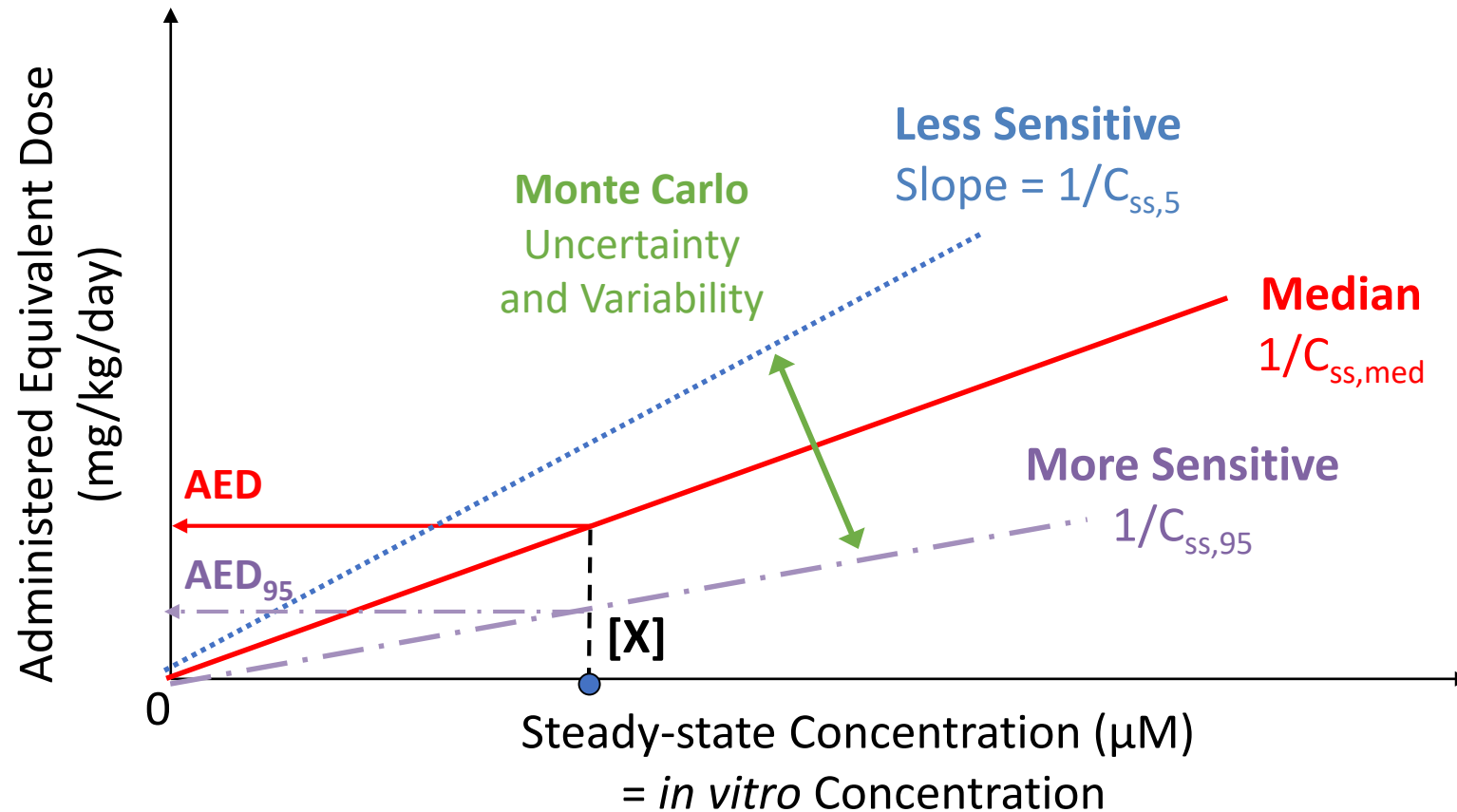
Administered Equivalent Dose (AED)

- We can then calculate a dose rate that would cause steady-state plasma concentrations equal to an *in vitro* concentration
- The AED_{95} is lower than the median AED, because the individuals are more sensitive



Administered Equivalent Dose (AED)

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



Check Your Units!

- At least once a year I make the mistake of failing to convert *in vitro* concentrations to the right units
- The Dashboard provides $C_{ss,95}$ in units of **mg/L**
- For example, if your *in vitro* concentration is in μM , you must convert – factor depends on the chemical-specific molecular weight (MW, g/mol):

$$\mu\text{M} = \frac{1}{1000} \frac{1}{\text{MW}} \frac{\text{mg}}{\text{L}}$$

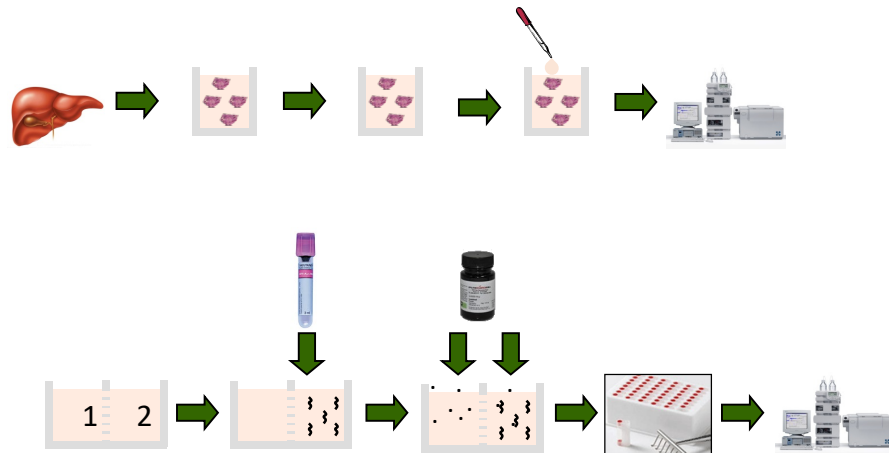
Where Do We Get The TK Predictions?



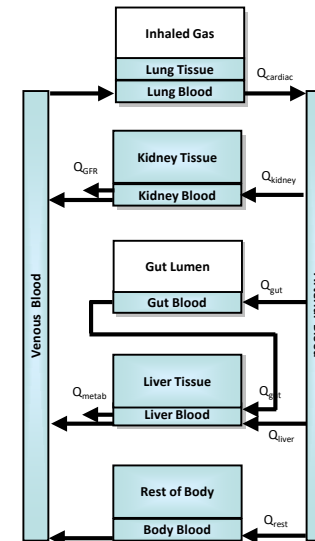
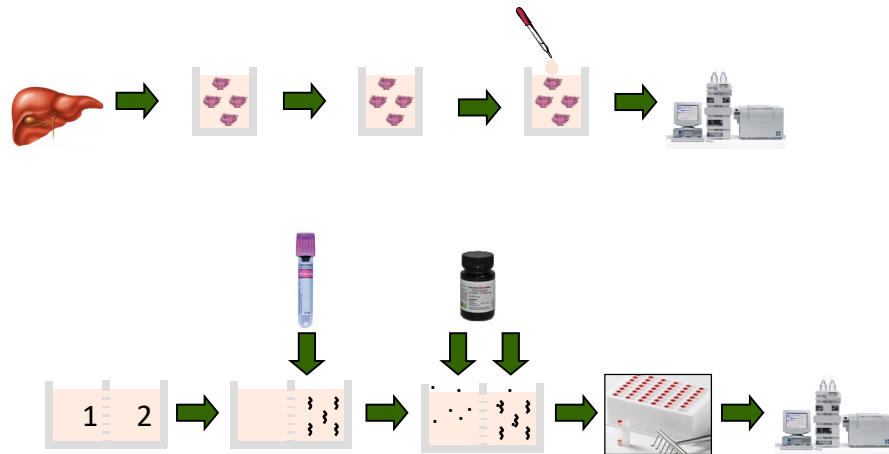
- To provide toxicokinetic data for larger numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data (for example, Rotroff et al., 2010, Wetmore et al., 2012, 2015)
 - This is an example of a New Approach Methodologies (NAM, Kavlock et al. 2018)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
- The **primary goal** of HTTK is to provide a human dose context for bioactive *in vitro* concentrations from HTS (that is, *in vitro-in vivo* extrapolation, or **IVIVE**) (for example, Wetmore et al., 2015)
- A **secondary goal** is to provide **open source data and models** for evaluation and use by the broader scientific community (Pearce et al, 2017)

***In vitro* toxicokinetic data + generic toxicokinetic model
= high(er) throughput toxicokinetics**

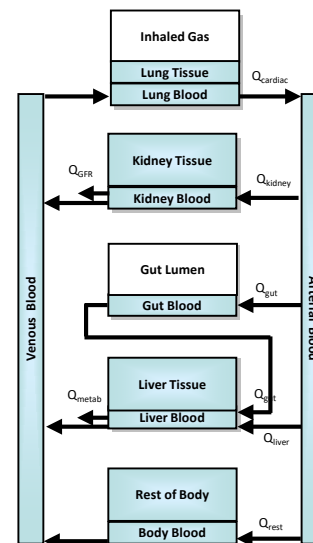
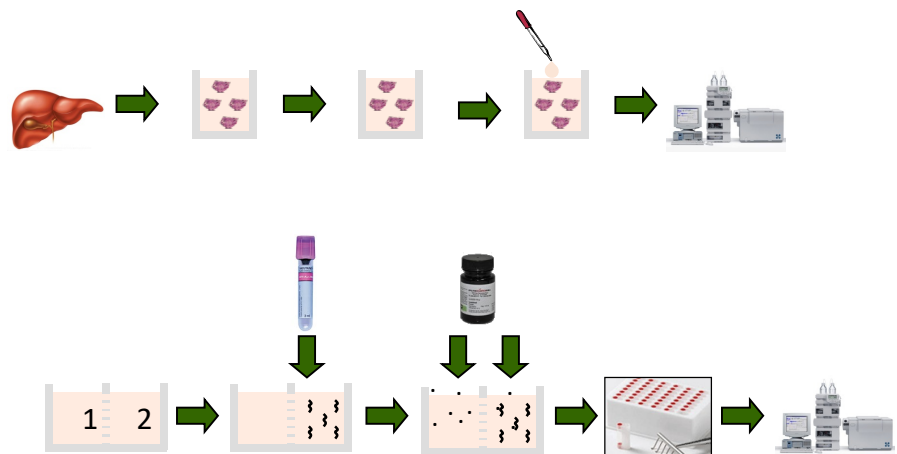
***In vitro* toxicokinetic data + generic toxicokinetic model
= high(er) throughput toxicokinetics**



***In vitro* toxicokinetic data + generic toxicokinetic model
= high(er) throughput toxicokinetics**



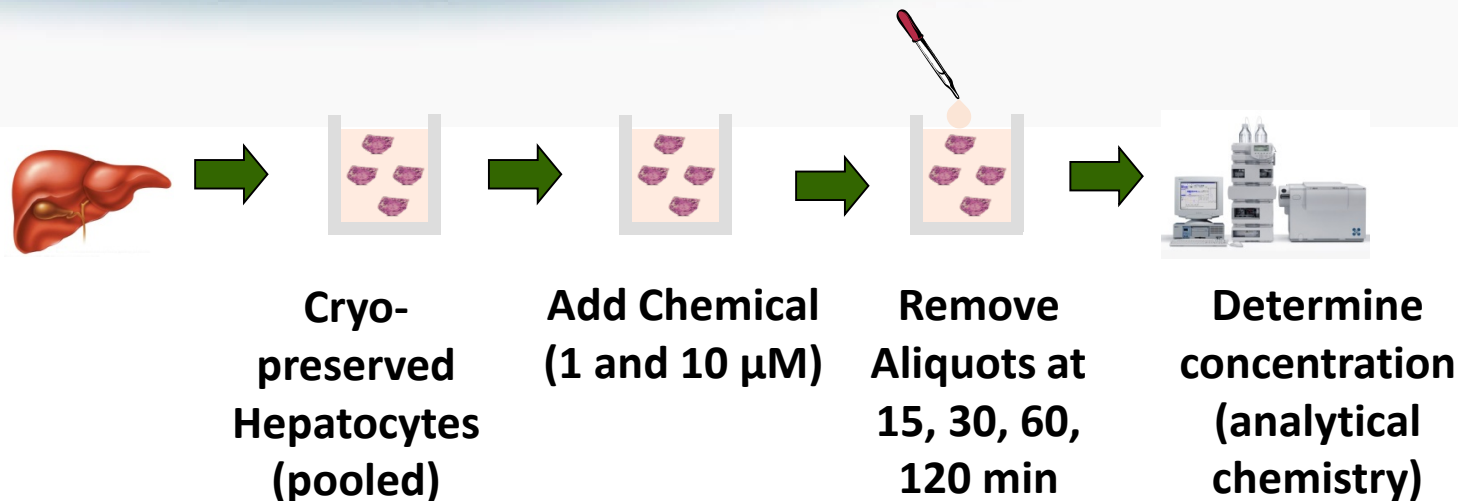
***In vitro* toxicokinetic data + generic toxicokinetic model
= high(er) throughput toxicokinetics**



= *httk*

In Vitro Data for HTTK

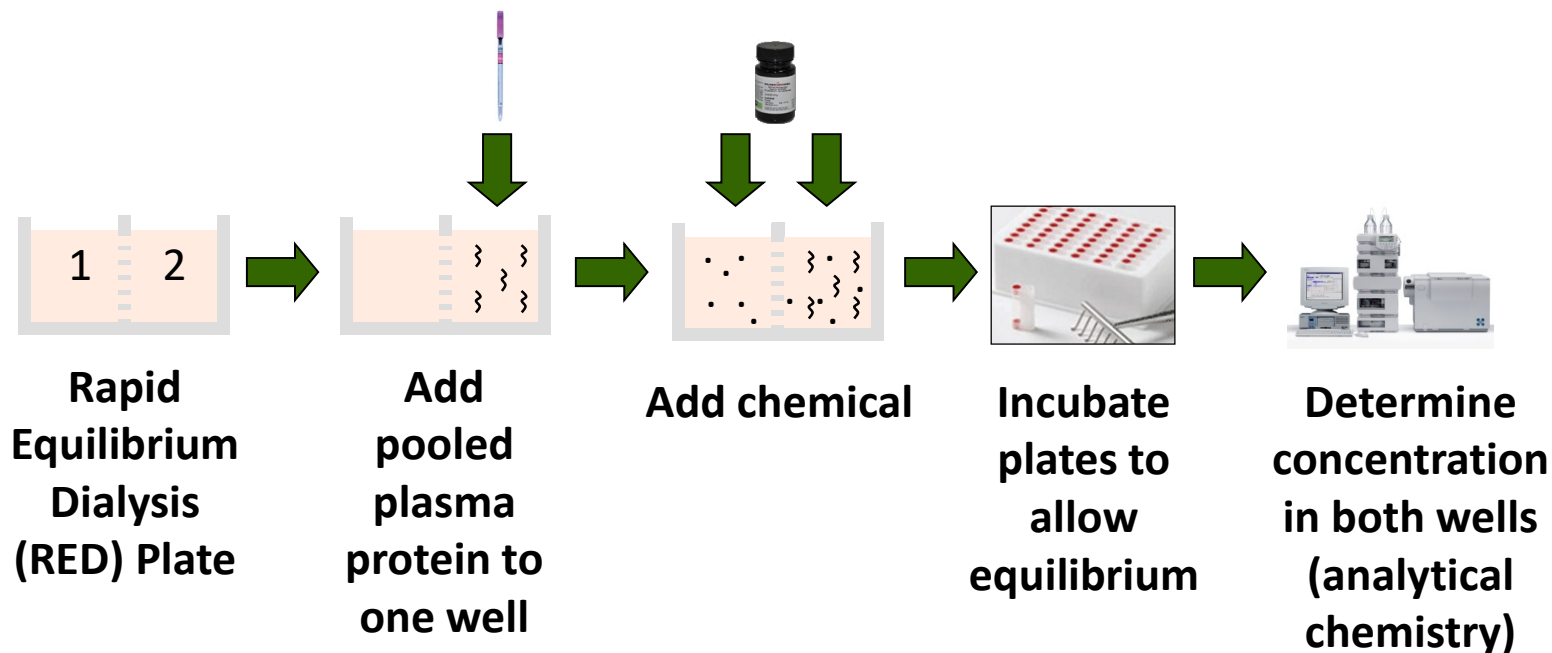
Cryo-
preserved
hepatocyte
suspension
Shibata *et al.*
(2002)

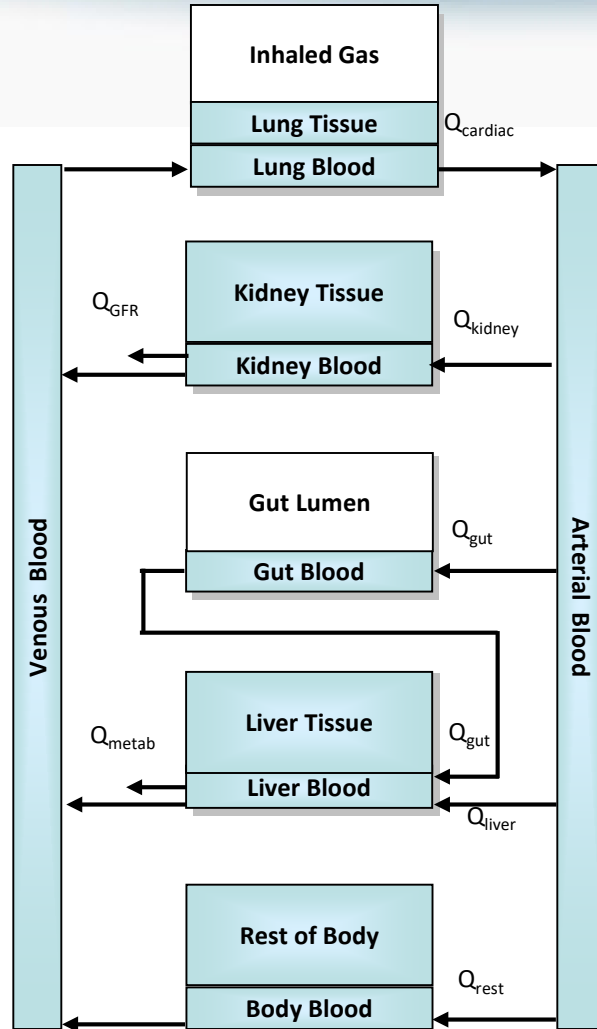


- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps

- In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

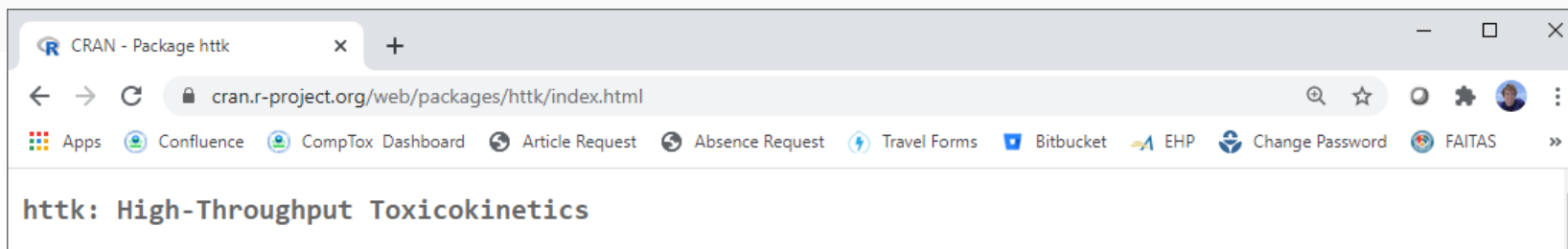
Rapid
Equilibrium
Dialysis
(RED)
Waters *et al.*
(2008)












- Tissues are modeled by compartments:
- Clearance from the body depends on two processes:
 - Metabolism in the liver (estimated from *in vitro* clearance and binding)
 - Excretion by glomerular filtration in the kidney (estimated from *in vitro* binding)
- Model parameters are either:
 - **Physiological:** determined by species and potentially varied via Monte Carlo (including HTTK-pop, Ring et al. 2017)
 - **Chemical-specific:** physico-chemical properties (Mansouri et al., 2018) and equilibrium partition coefficients plus plasma binding and metabolism rates that are determined from *in vitro* measurements or potentially predicted from structure

<https://CRAN.R-project.org/package=httk>



Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics (Pearce et al. (2017) <[doi:10.18637/jss.v079.i04](https://doi.org/10.18637/jss.v079.i04)>). Chemical-specific *in vitro* data have been obtained from *in vitro* experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models are parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A Monte Carlo simulation is included, which allows for simulating human biological variability (Ring et al., 2017 <[doi:10.1016/j.envint.2017.05.014](https://doi.org/10.1016/j.envint.2017.05.014)>), propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and distribution (Pearce et al., 2017 <[doi:10.1007/s10928-017-9548-7](https://doi.org/10.1007/s10928-017-9548-7)>). These functions and data provide a set of *in vivo* extrapolation ("IVIVE") of *in vitro* dosimetry (also known as "RTK")

downloads 1071/month

Version: 2.0.3
Depends: R (≥ 2.10)
Imports: [deSolve](#), [msm](#), [data.table](#), [survey](#), [mvtnorm](#), [truncnorm](#), stats, graphics, utils, [magrittr](#), [ggplot2](#), [knitr](#), [rmarkdown](#), [R.ssp](#), [GGally](#), [gplots](#), [scales](#), [EnvStats](#), [MASS](#), [RColorBrewer](#), [classInt](#), [ks](#), [stringr](#), [reshape](#), [reshape2](#), [gdata](#), [viridis](#), [CensRegMod](#), [gmodels](#), [colorspace](#), [dplyr](#), [forcats](#), [smatr](#), [gtools](#), [gridExtra](#)
Published: 2020-09-25
Author: John Wambaugh  [aut, cre], Robert Pearce  [aut], Caroline Ring  [aut], Greg Sfeir [aut], Matt Linakis  [aut], Jimena Davis [ctb], James Sluka  [ctb], Nisha Siwetmore  [ctb], Woodrow Setzer  [ctb]
Maintainer: John Wambaugh <wambaugh.john@epa.gov>
BugReports: <https://github.com/USEPA/CompTox-ExpoCast-httk>

R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for 987 chemicals
- Described in Pearce et al. (2017a)

Modules within R Package “httk”



Feature	Description	Reference
Chemical Specific <i>In Vitro</i> Measurements	Metabolism and protein binding for ~1000 chemicals in human and ~200 in rat	Wetmore et al. (2012, 2013, 2015), plus others
Chemical-Specific <i>In Silico</i> Predictions	Metabolism and protein binding for ~8000 Tox21 chemicals	Sipes et al. (2017)
Generic toxicokinetic models	One compartment, three compartment, physiologically-based oral, intravenous, and inhalation (PBTK)	Pearce et al. (2017a), Linakis et al. (2020)
Tissue partition coefficient predictors	Modified Schmitt (2008) method	Pearce et al. (2017b)
Variability Simulator	Based on NHANES biometrics	Ring et al. (2017)
<i>In Vitro</i> Disposition	Armitage et al. (2014) model	Honda et al. (2019)
Uncertainty Propagation	Model parameters can be described by distributions reflecting uncertainty	Wambaugh et al. (2019)

Correlated Monte Carlo
sampling of physiological
model parameters built into
R “httk” package:

Sample NHANES biometrics
for actual individuals:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Serum creatinine





Correlated Monte Carlo
sampling of physiological
model parameters built into
R “httk” package:

Sample NHANES biometrics
for actual individuals:

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

Regression equations from
literature (McNally *et al.*, 2014)
(+ residual marginal variability)

(Similar approach used in SimCYP [Jamei *et al.* 2009], GastroPlus,
PopGen [McNally *et al.* 2014], P3M [Price *et al.* 2003], physB
[Bosgra *et al.* 2012], etc.)



Population simulator for HHTK



Correlated Monte Carlo
sampling of physiological
model parameters built into
R “httk” package:

Sample NHANES biometrics
for actual individuals:

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

Regression equations from
literature (McNally *et al.*, 2014)
(+ residual marginal variability)

(Similar approach used in SimCYP [Jamei *et al.* 2009], GastroPlus,
PopGen [McNally *et al.* 2014], P3M [Price *et al.* 2003], physB
[Bosgra *et al.* 2012], etc.)

Predict physiological
quantities for generic
Models:

Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Calculating Dashboard Values in R

- R is freely available from the Comprehensive R Archive Network (CRAN):

<https://cloud.r-project.org/>

- It is often helpful to set an environmental variable that points to a personal library of R packages, for me, on Windows, I have the “user variable” R_LIBS_USER set to “c:/users/jwambaug/Rpackages”

- Many people like to use a graphical user interface (GUI) such as RStudio, which also may be freely available to you:

<https://rstudio.com/>

The Comprehensive R Archive Network

Download and Install R

Precompiled binary distributions of the base system and contributed packages, **Windows and Mac** users most likely want one of these versions of R:

- [Download R for Linux](#)
- [Download R for \(Mac\) OS X](#)
- [Download R for Windows](#)

R is part of many Linux distributions, you should check with your Linux package management system in addition to the link above.

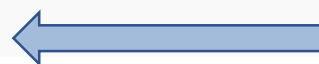
Source Code for all Platforms

Windows and Mac users most likely want to download the precompiled binaries listed in the upper box, not the source code. The sources have to be compiled before you can use them. If you do not know what this means, you probably do not want to do it!

- The latest release (2020-02-29, Holding the Windsock) [R-3.6.3.tar.gz](#), read [what's new](#) in the latest version.
- Sources of [R alpha and beta releases](#) (daily snapshots, created only in time periods before a planned release).
- Daily snapshots of current patched and development versions are [available here](#). Please read about [new features and bug fixes](#) before filing corresponding feature requests or bug reports.
- Source code of older versions of R is [available here](#).
- Contributed extension [packages](#)

Calculating Dashboard Values in R

```
> install.packages("httk")
```



Install HTTK from the
command line
(GUI's like RStudio also provide
menus for this)

```
Installing package into 'c:/Users/jwambaug/Rpackages'
(as 'lib' is unspecified)
--- Please select a CRAN mirror for use in this session ---
trying URL 'https://cloud.r-
project.org/bin/windows/contrib/3.6/httk_2.0.1.zip'
Content type 'application/zip' length 10127063 bytes (9.7 MB)
downloaded 9.7 MB
```

```
package 'httk' successfully unpacked and MD5 sums checked
```

```
The downloaded binary packages are in
```

```
C:\Users\jwambaug\AppData\Local\Temp\Rtmp4STebz\downloaded_packages
```

```
> library(httk)
```



Load the HTTK data,
models, and functions

```
> packageVersion("httk")
```

```
[1] '2.0.1'
```



Check what version you are using

```
> set.seed(12345)

> calc_mc_css(dtxsid="DTXSID1020221",
              which.quantile=0.95,
              output.units="mg/L")
```

Human plasma concentration returned in mg/L units for 0.95 quantile.

95%

2.931

Warning messages:

- 1: In (function (chem.cas = NULL, chem.name = NULL, dtxsid = NULL, :
Funbound.plasma adjusted for in vitro partitioning (Pearce, 2017).
- 2: In calc_rblood2plasma(chem.cas = chem.cas, species = species,
adjusted.Funbound.plasma = adjusted.Funbound.plasma, :
Rblood2plasma has been recalculated.
- 3: In calc_rblood2plasma(hematocrit = parameters.dt\$hematocrit, Krbc2pu =
parameters.dt\$Krbc2pu, :
Rblood2plasma has been recalculated.

Calculating Dashboard Values in R



```
> set.seed(12345)
> calc_mc_css(dt xsid="DTXSID1020221",
              which.quantile=0.95,
              output.units="mg/L")
```

```
Human plasma concentration returned in mg/L units for 0.95 quantile.
95%
2.931
```

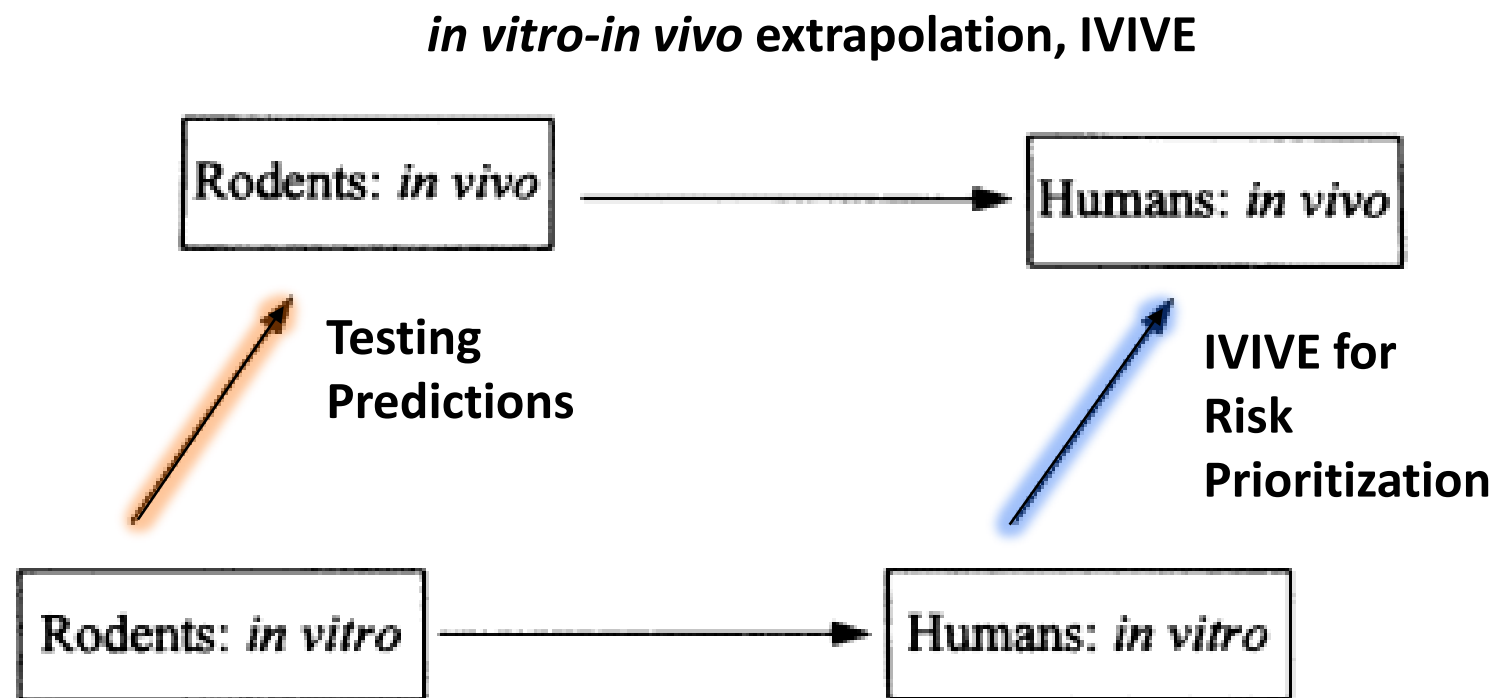
Warning messages:

```
1: In (function (chem.cas = NULL, chem.name = NULL, dt xsid = NULL, :
  Funbound.plasma adjusted for in vitro partitioning (Pearce, 2017).
2: In calc_rblood2plasma(chem.cas = chem.cas, species = species,
  adjusted.Funbound.plasma = adjusted.Funbound.plasma, :
  Rblood2plasma has been recalculated.
3: In calc_rblood2plasma(hematocrit = parameters.dt$hematocrit, Krbc2pu =
  parameters.dt$Krbc2pu, :
  Rblood2plasma has been recalculated.
```

This step sets the random number generator to a specific state, otherwise Monte Carlo (MC) will give you slightly different answers

Conclusions

- For >1000 chemicals, the CompTox Chemicals Dashboard provides information on absorption, distribution, metabolism, and excretion (ADME)
- ADME information allows calculation of administered equivalent doses (AEDs) for *in vitro* bioactivity data
- This information is based upon HTKK, comprising *in vitro* measured chemical-specific data and generic models that can use those data
- These predictions, and much more, can also be accessed via open source, free, and evaluated “httk” software for R



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Absorption**

**Human
Gestation**

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*In Vitro
Measurement*

**Structure-Based
Predictions**

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CvTdb

Inhalation

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References



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