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EPA United States Environmental Protection Agency

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

High Throughput Toxicokinetic Modeling

Physicians Committee for Responsible Medicine

NURA™

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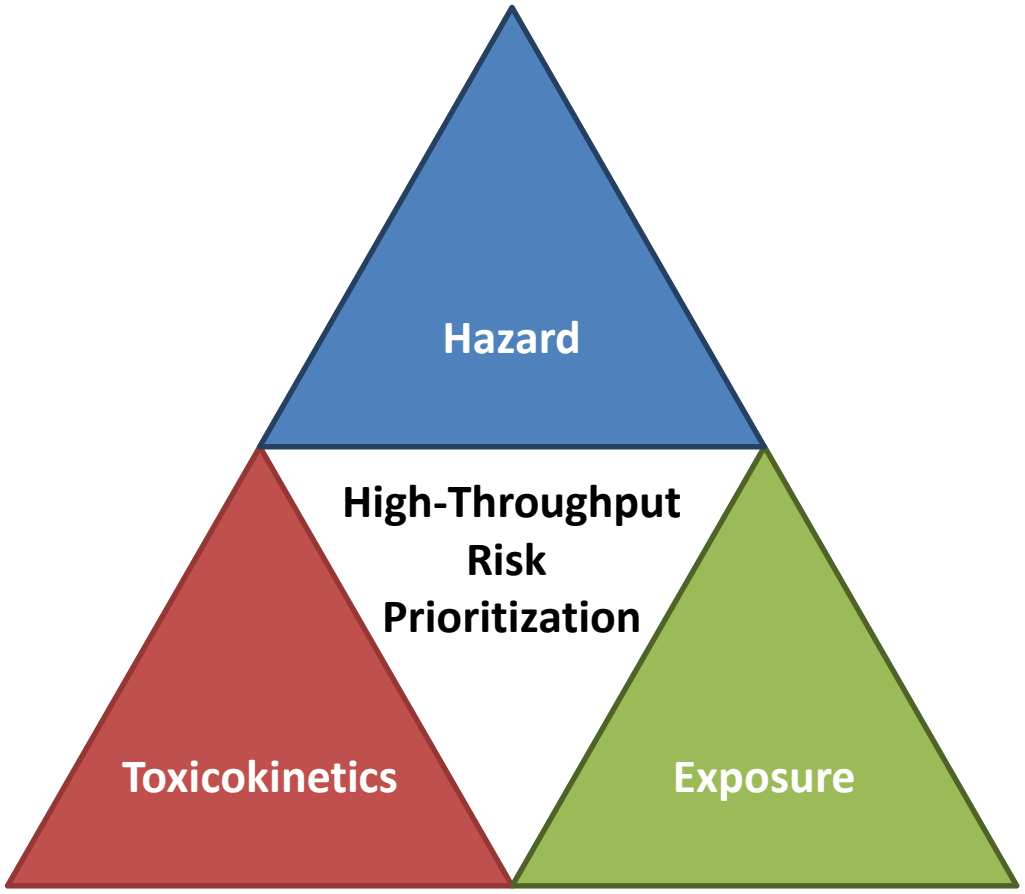
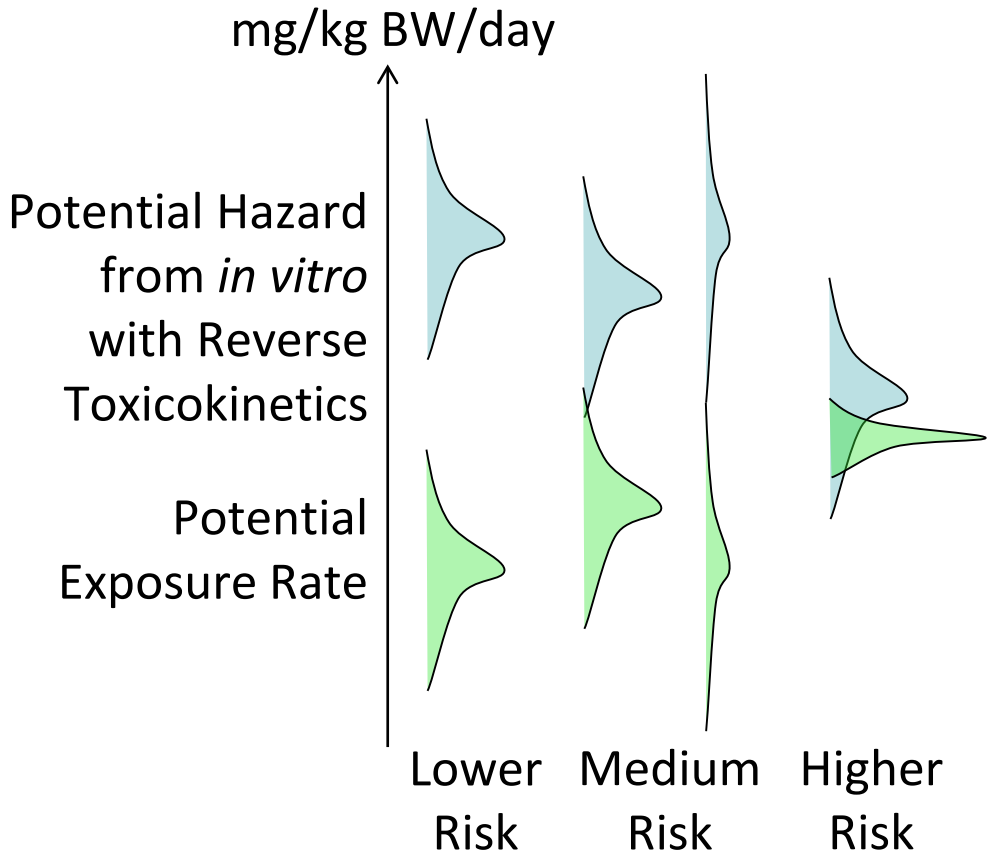
The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

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)

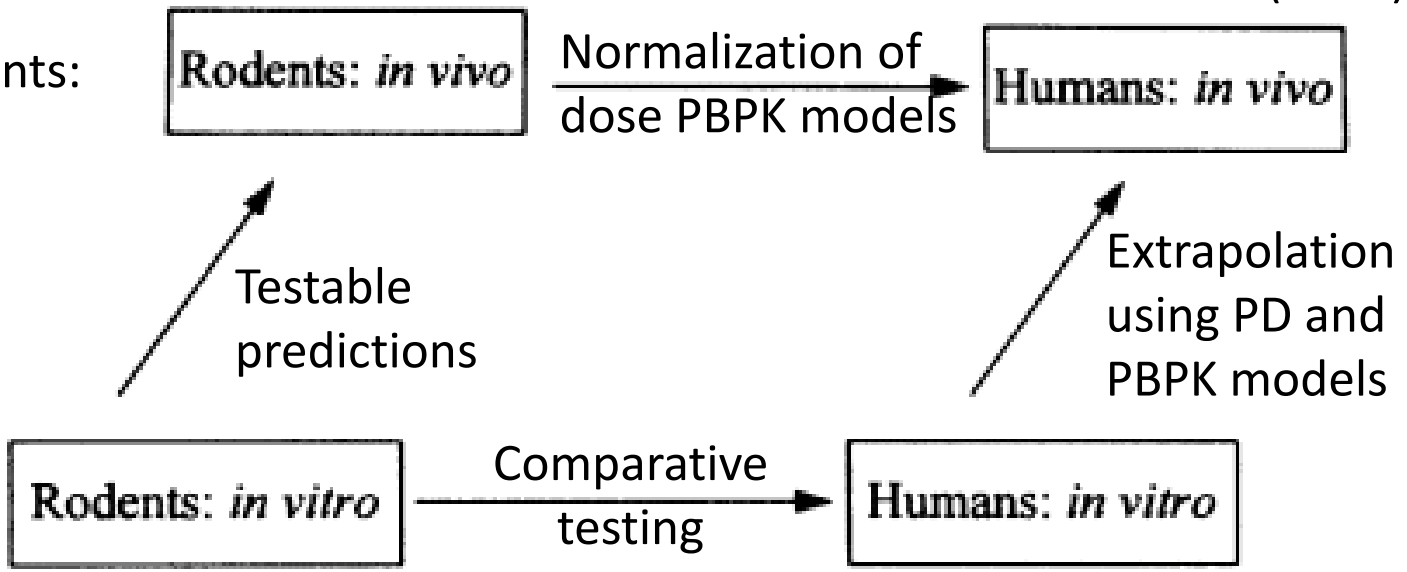




In Vitro - In Vivo Extrapolation (IVIVE)

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

NRC (1998)



"The Parallelogram Approach" (Sobels, 1982)

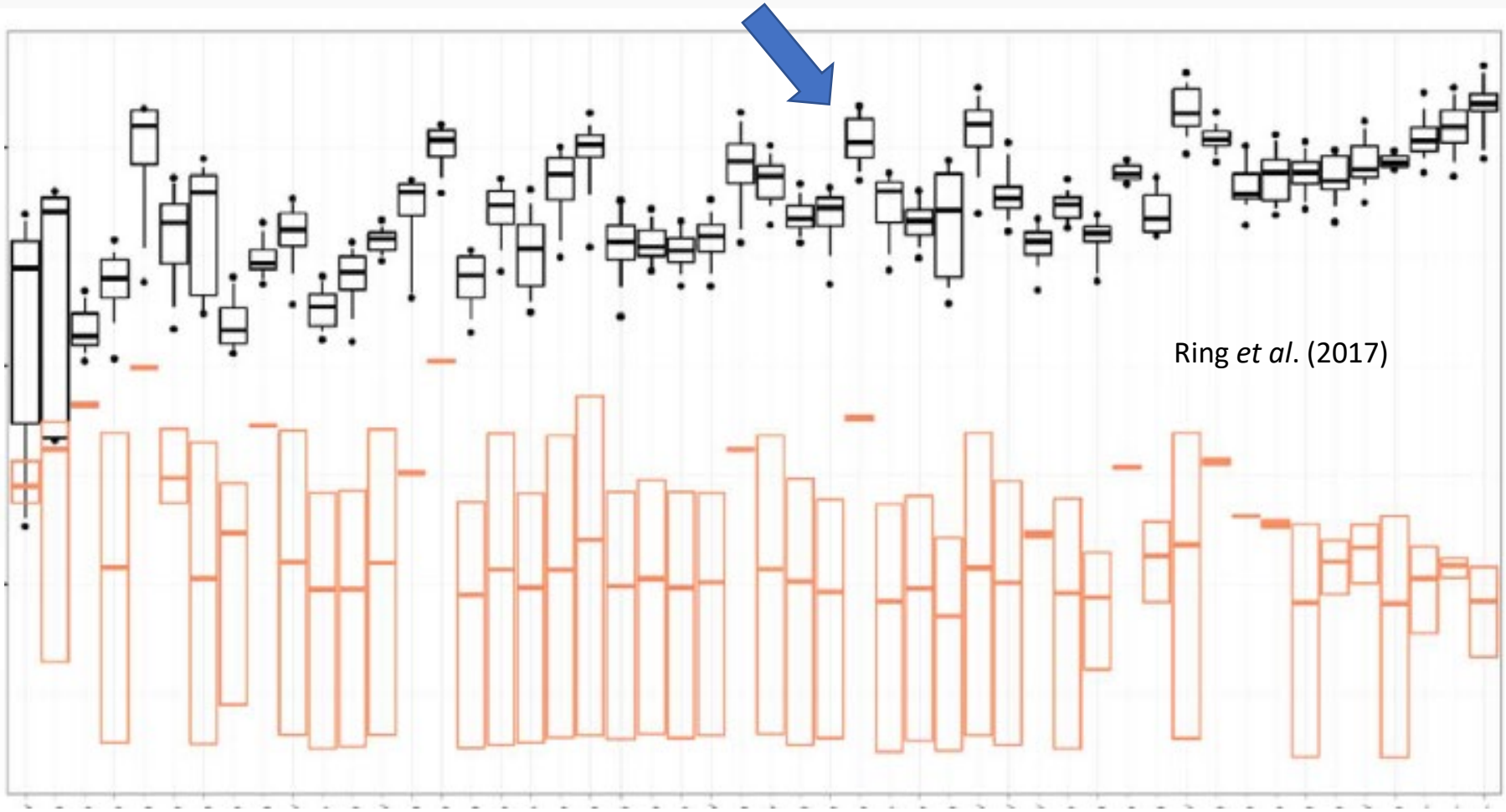
- IVIVE-PK/TK (**Pharmacokinetics/Toxicokinetics**):
  - Fate of molecules/chemicals in body
  - Considers absorption, distribution, metabolism, excretion (ADME)
  - Can use empirical PK or physiologically-based (PBPK)

- 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

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)



Chemicals Monitored by CDC NHANES

IVIVE Allows Chemical Prioritization

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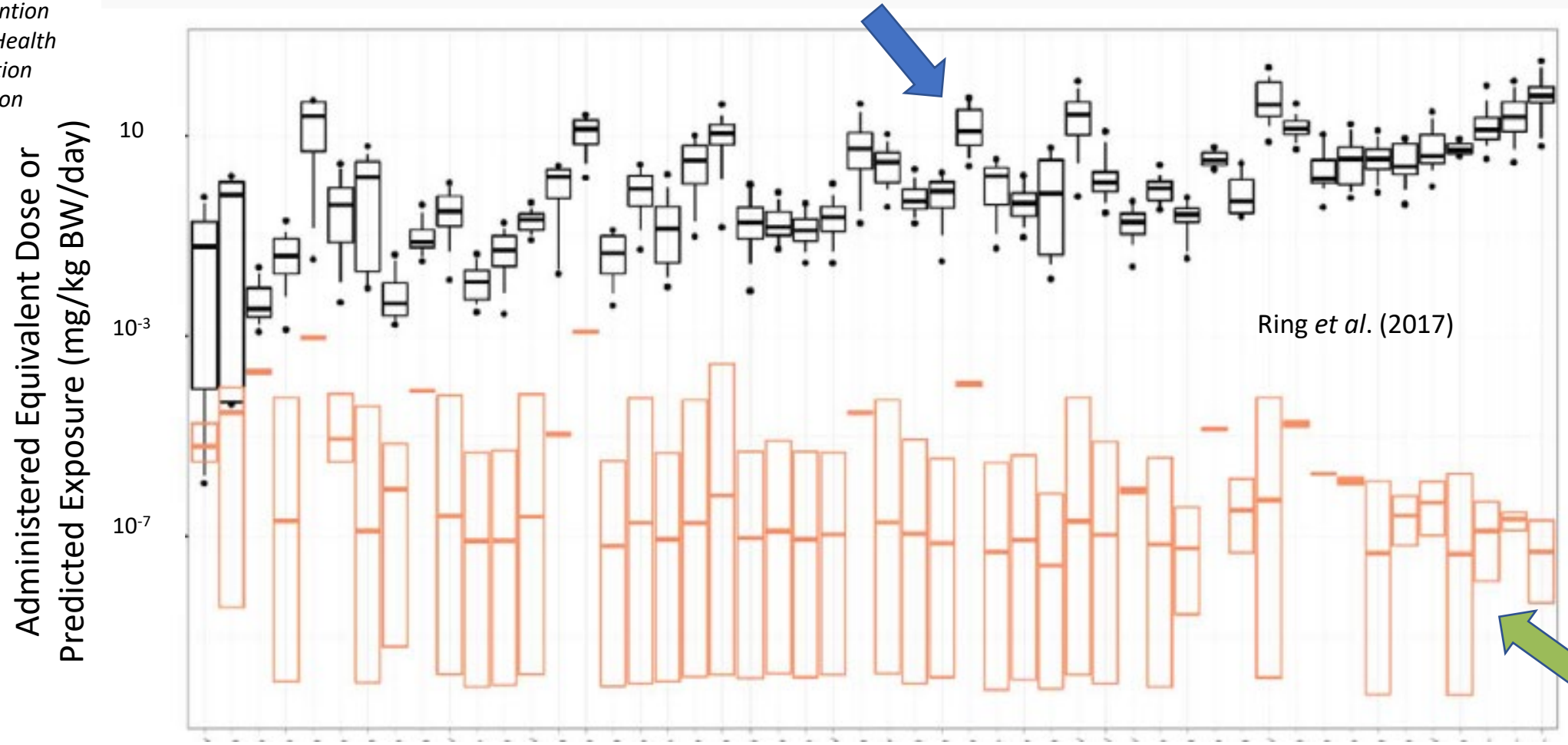

Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

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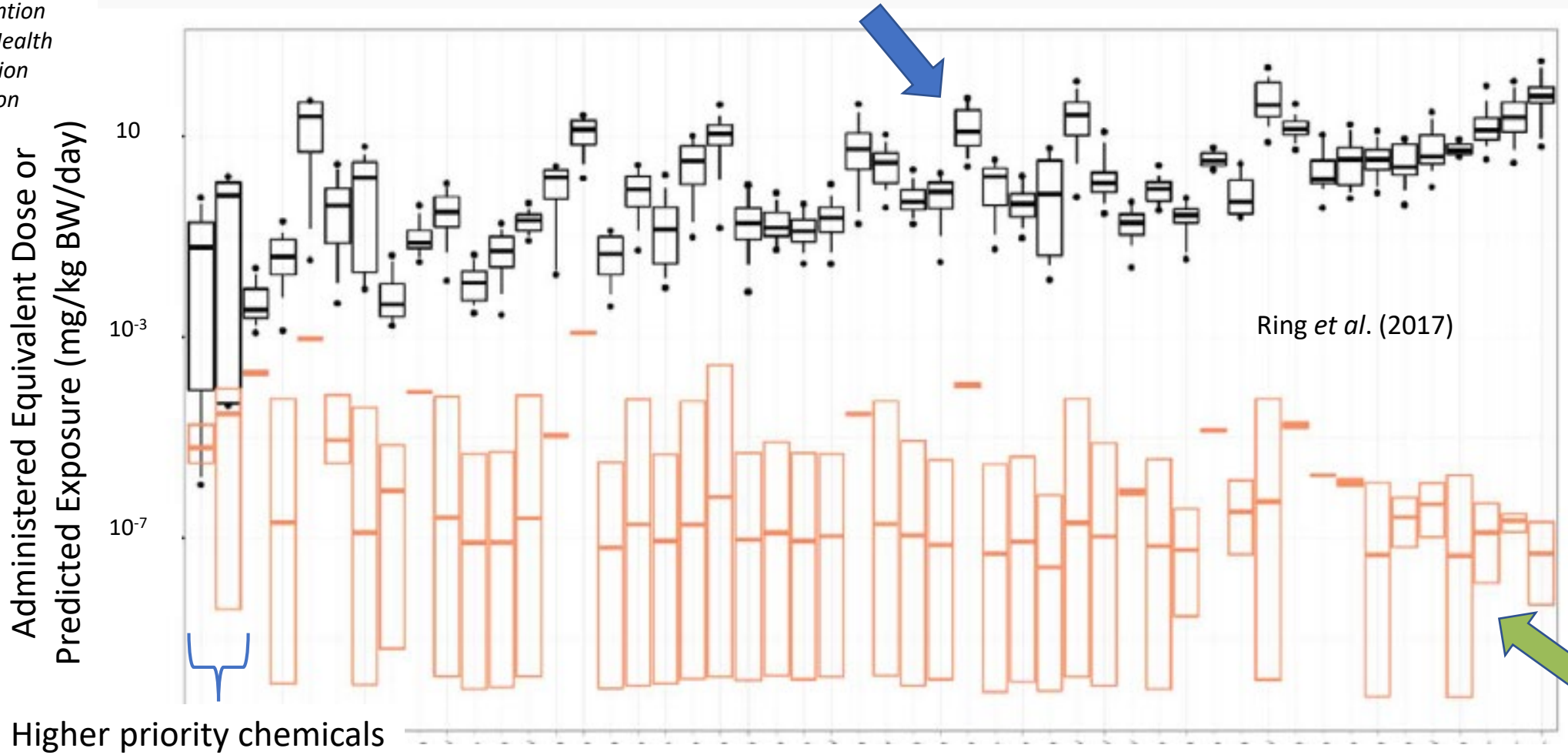


Exposure intake rates can be inferred from biomarkers (Wambaugh et al., 2014)

IVIVE by Scaling Factor

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

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

- **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

IVIVE by Scaling Factor

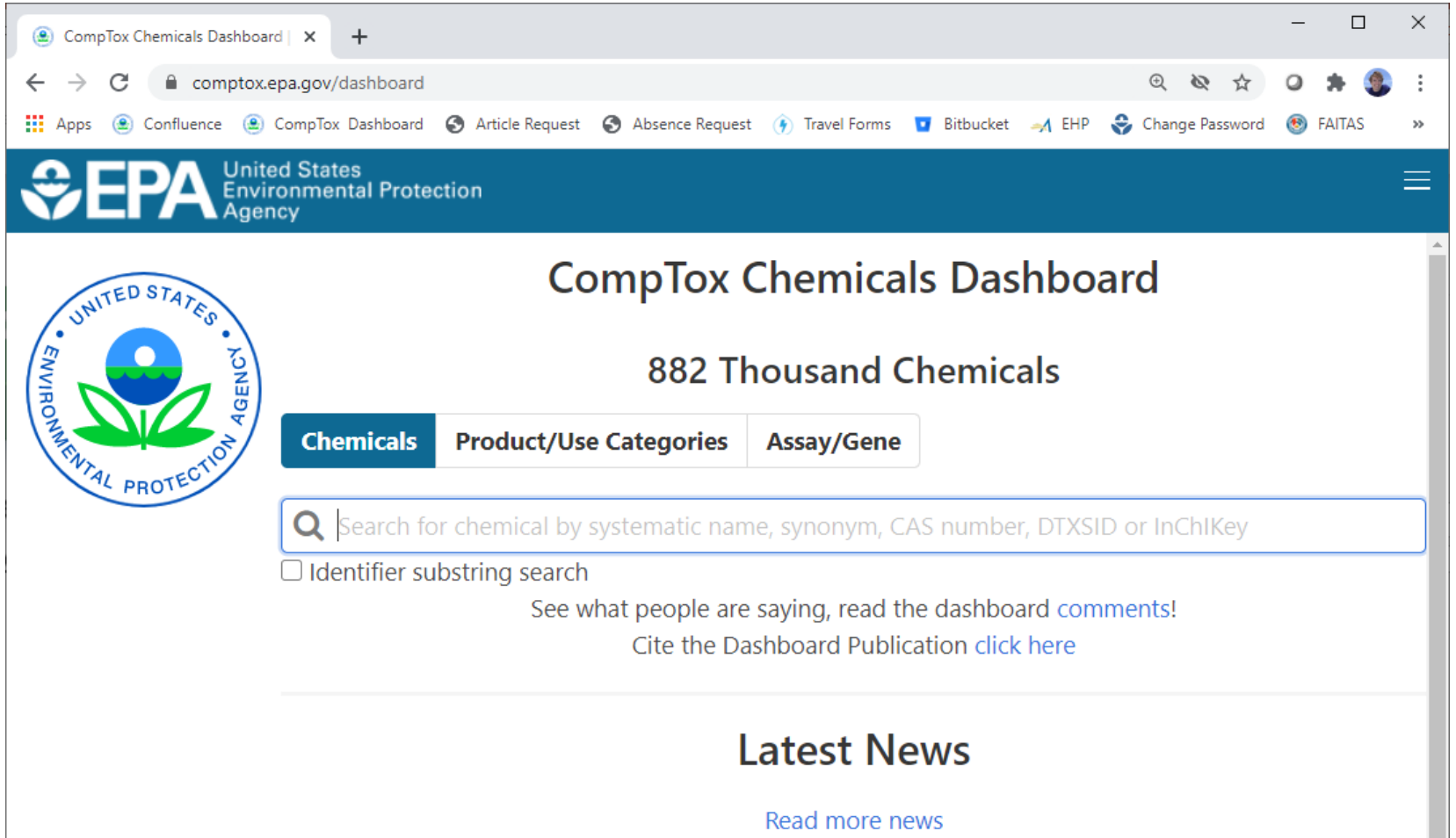
- For a given chemical, $F_{IVIVE} = 1 / C_{ss,95}$
- $C_{ss,95}$ is the steady-state plasma concentration as the result of a 1 mg/kg/day exposure

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

- 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



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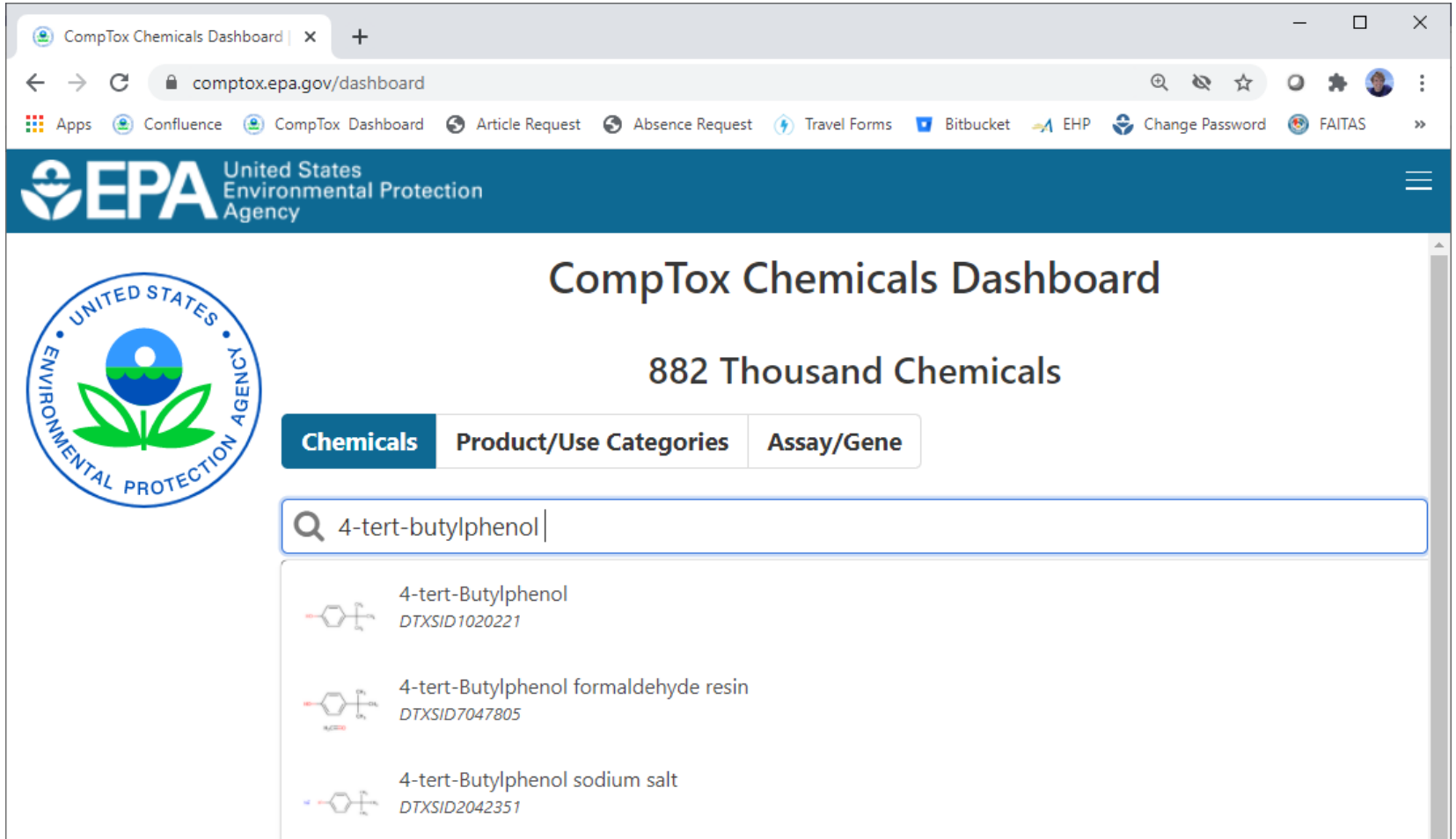

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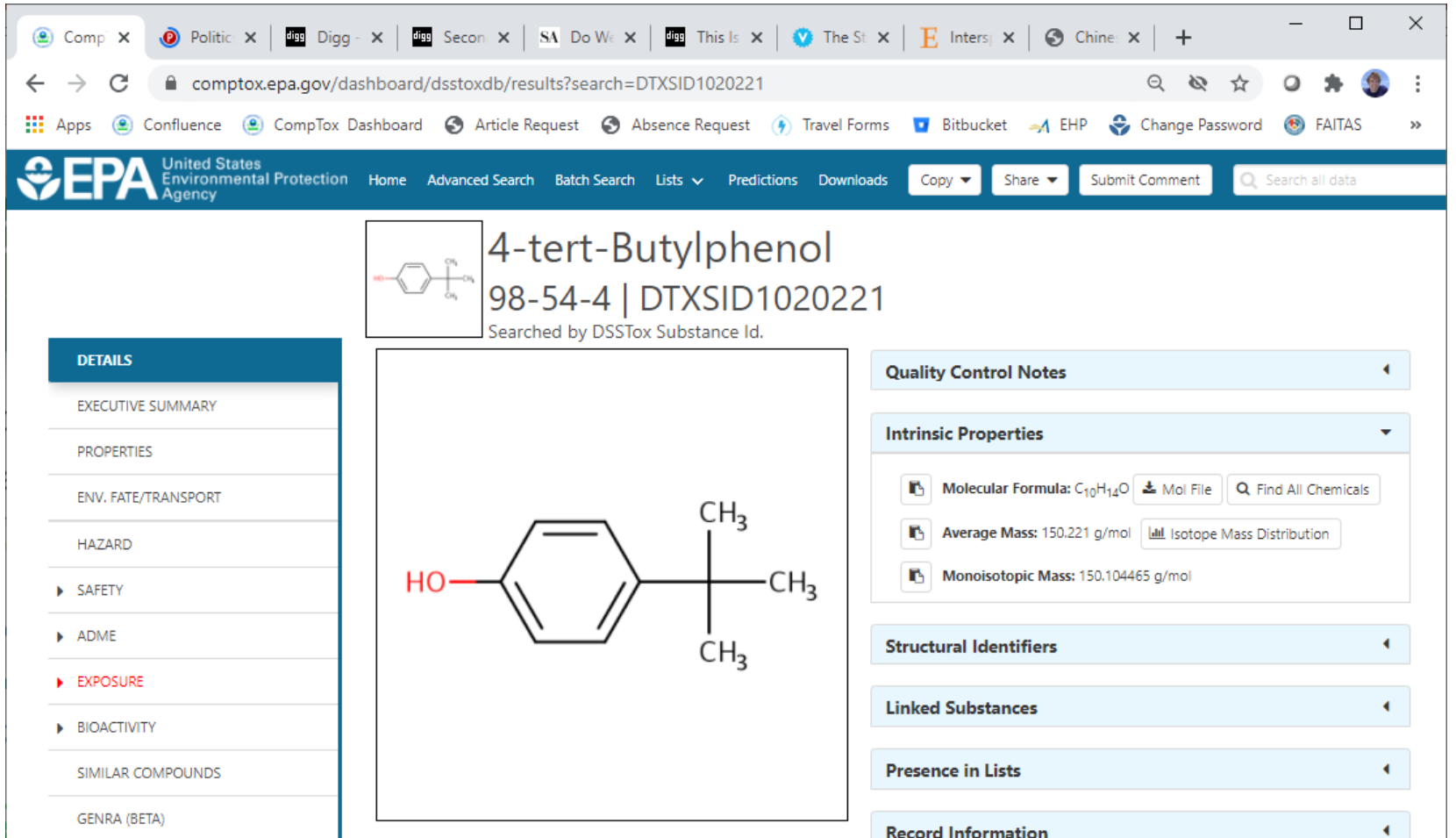

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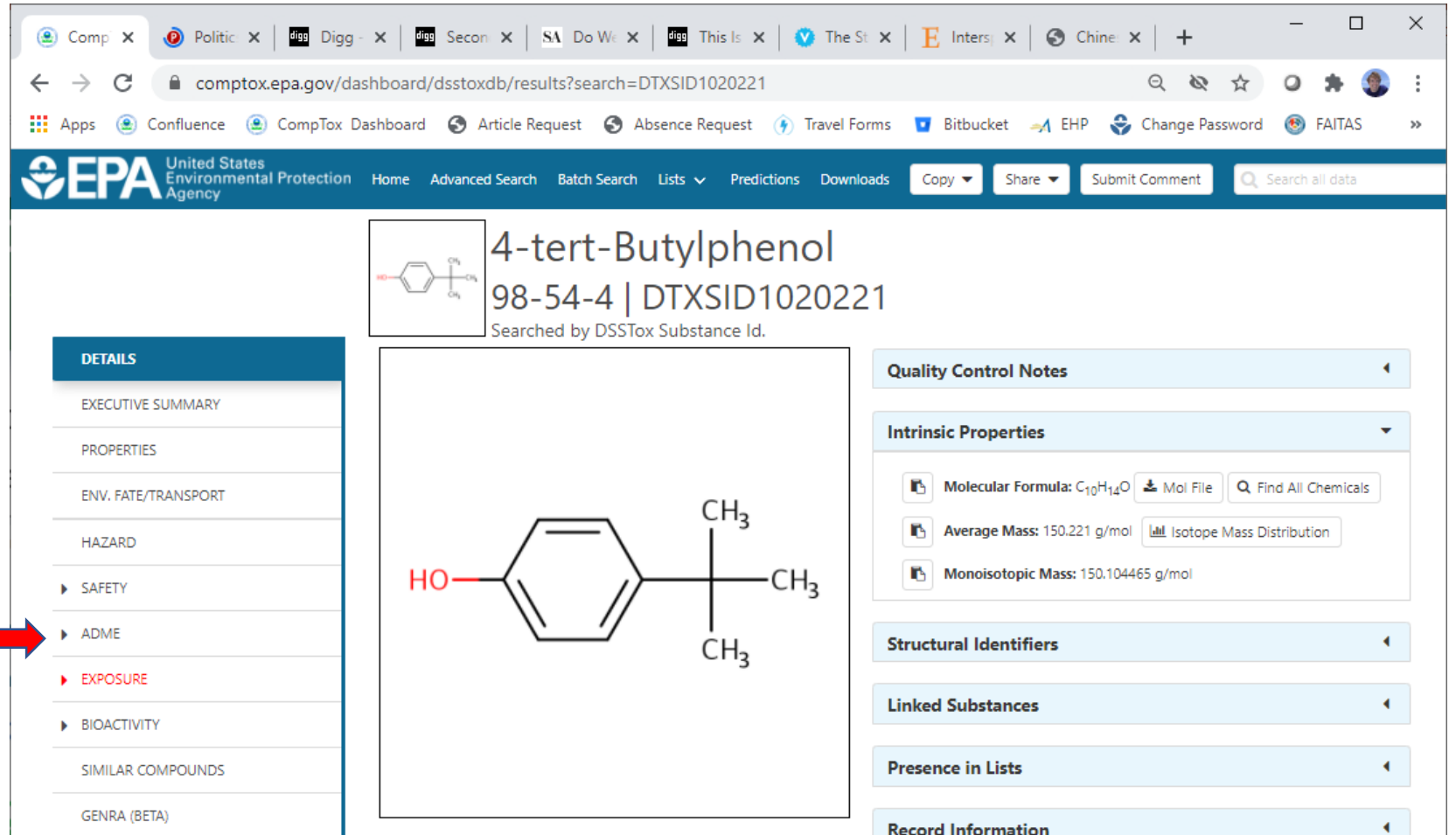
Click here for ADME information



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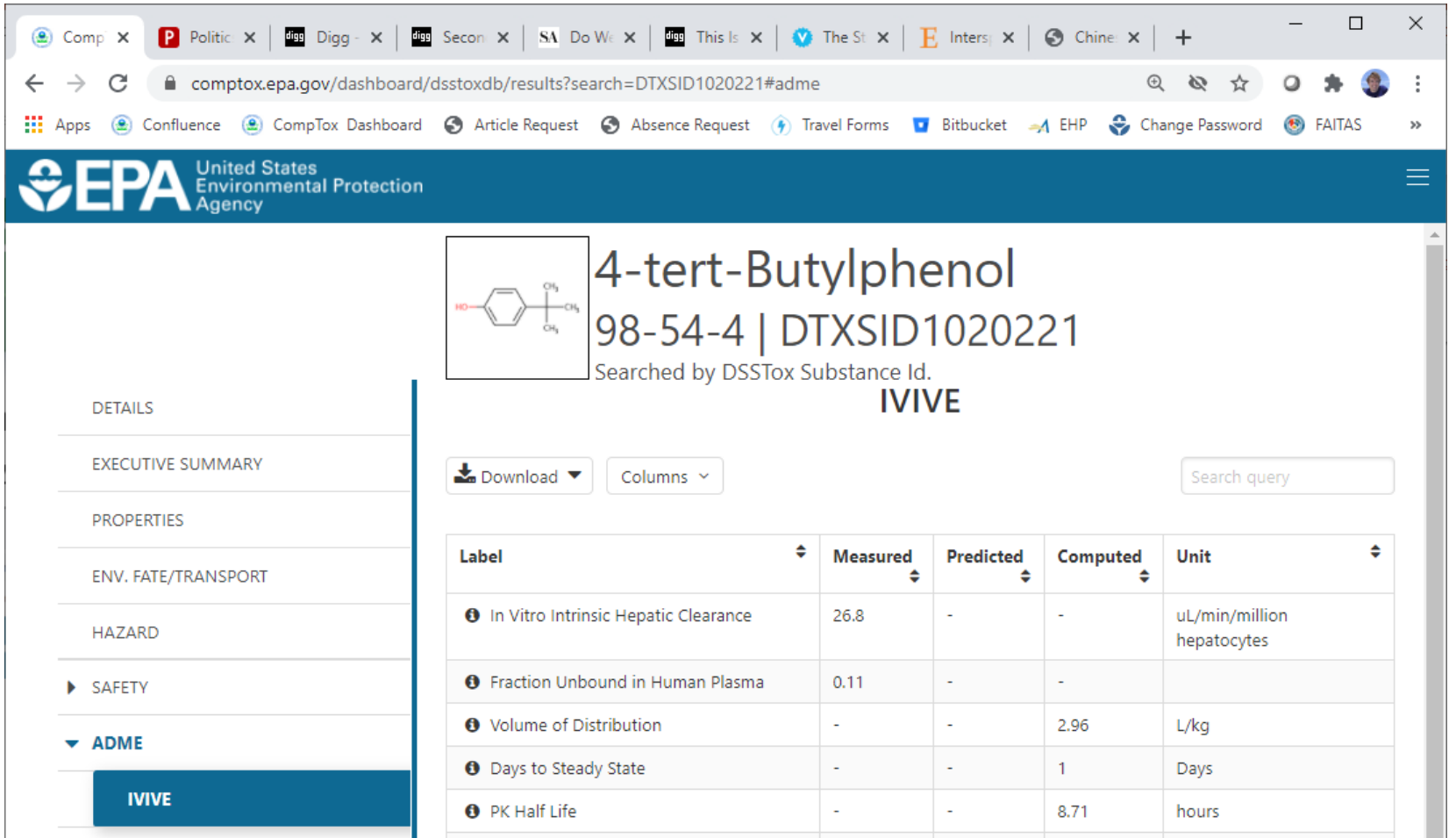
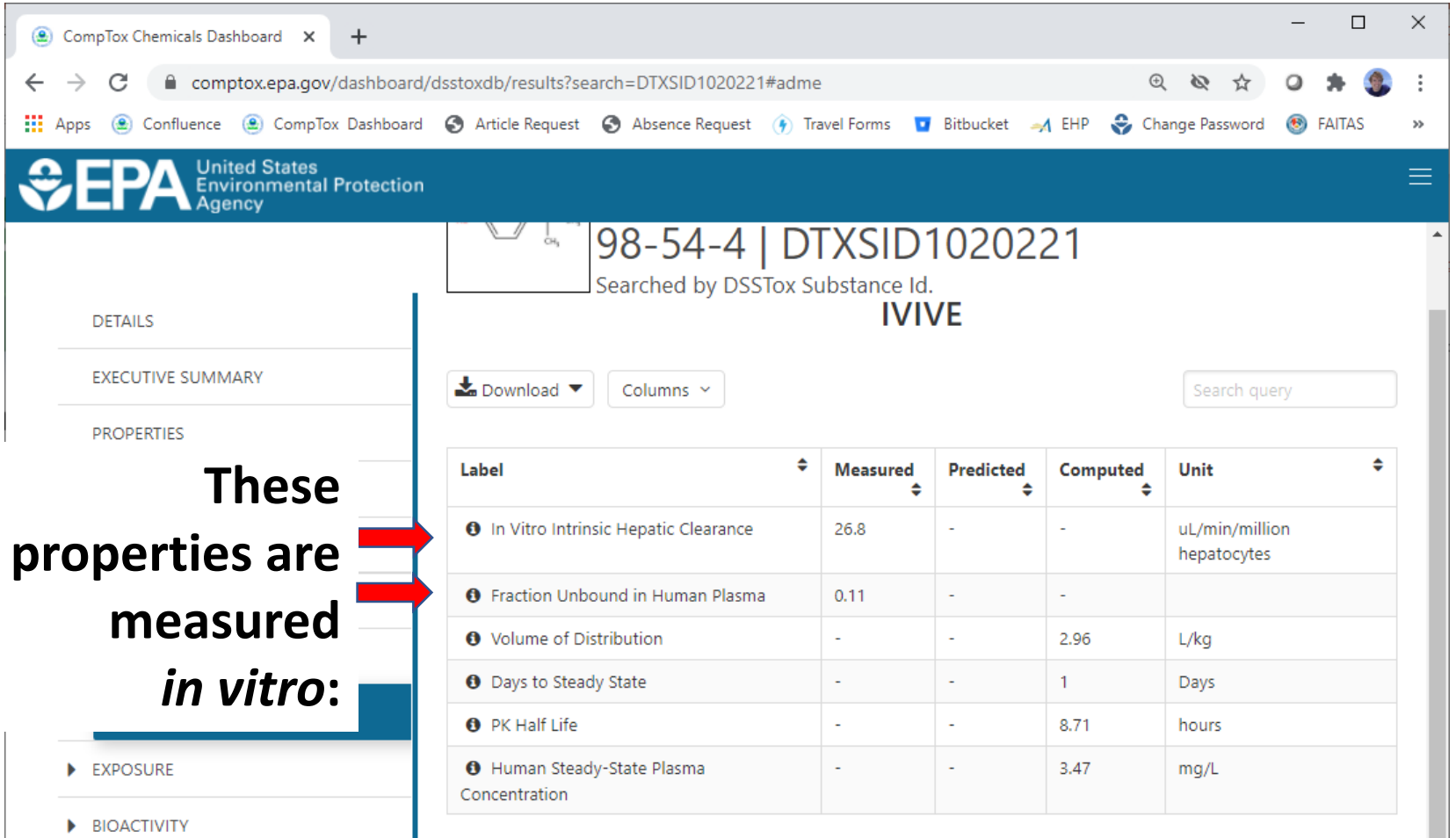


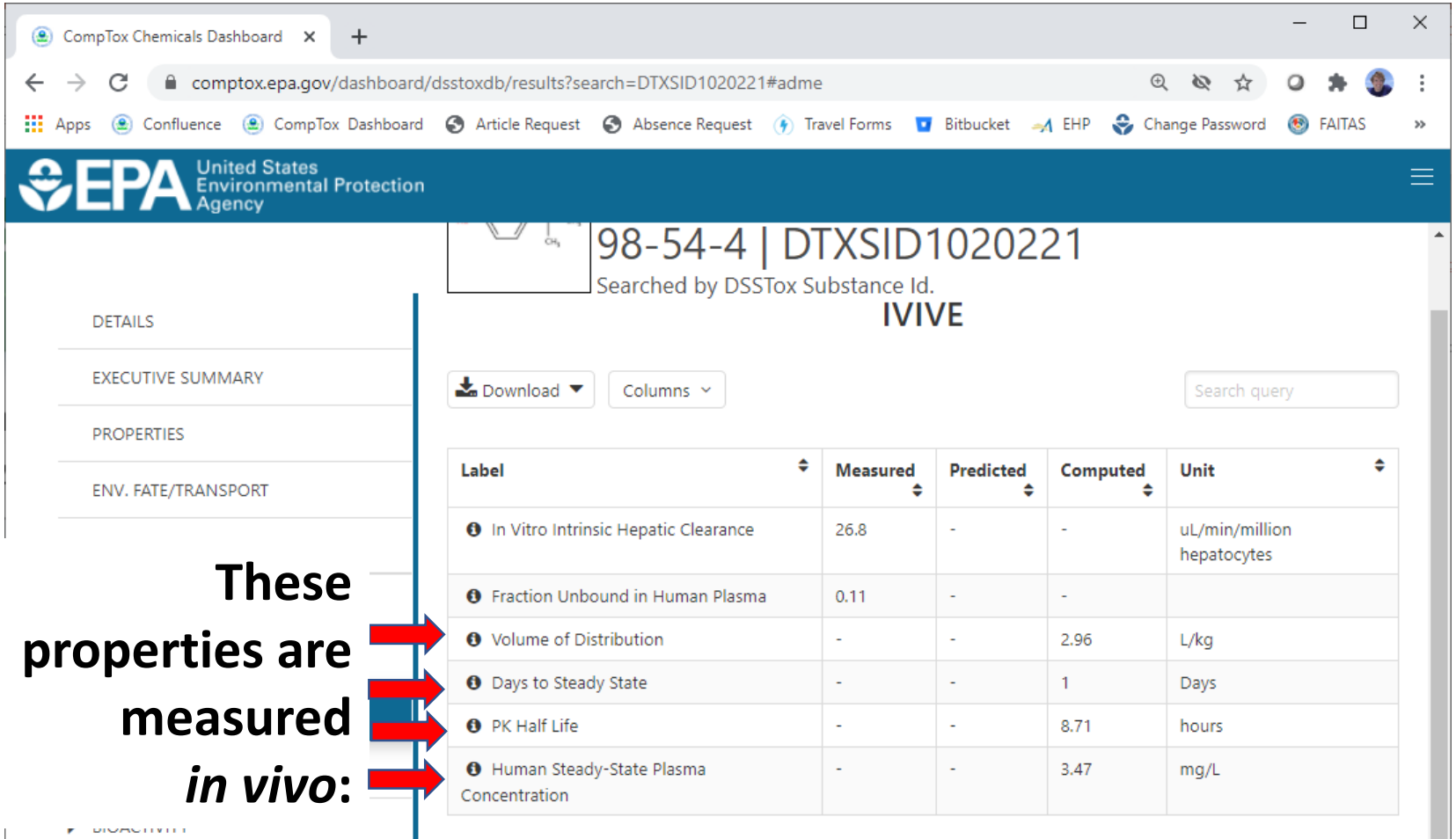
ADME on the CompTox Chemicals Dashboard

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

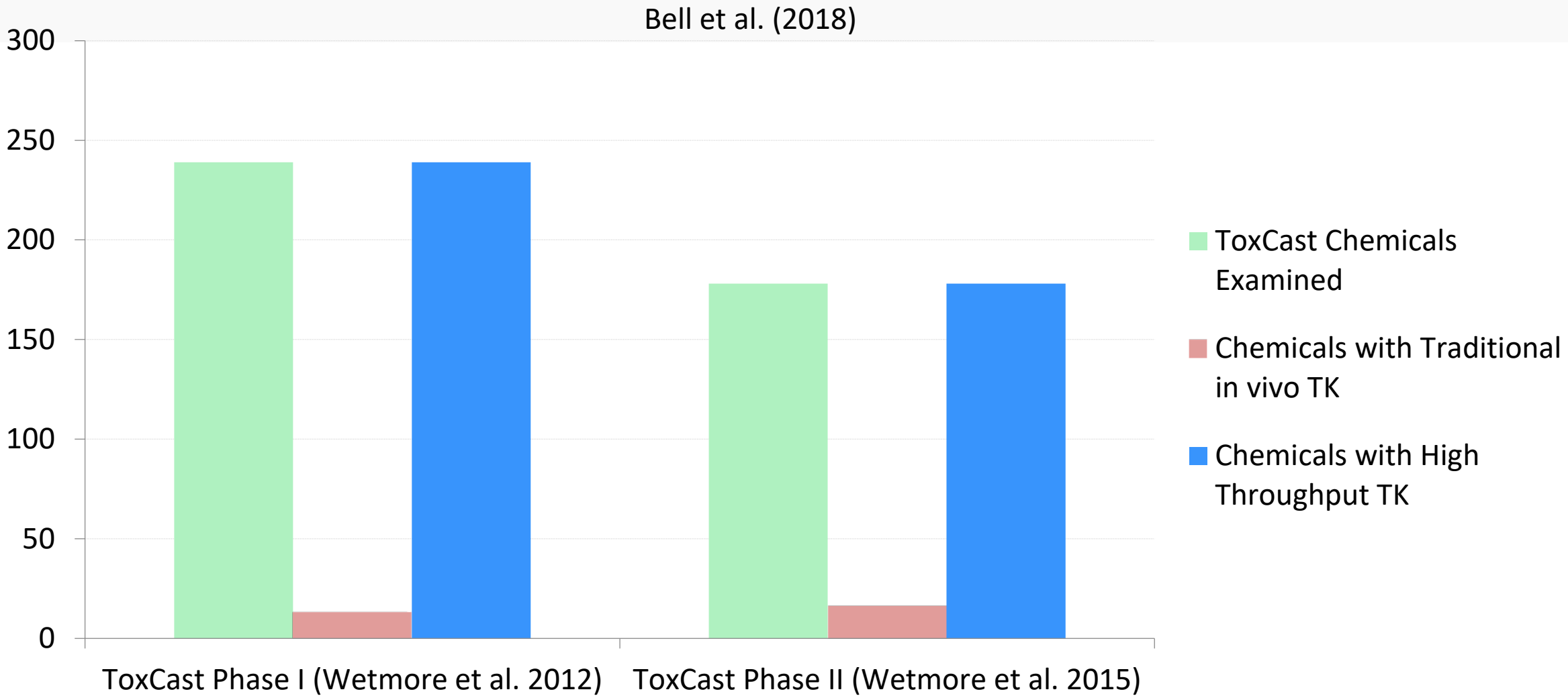


ADME on the CompTox Chemicals Dashboard

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

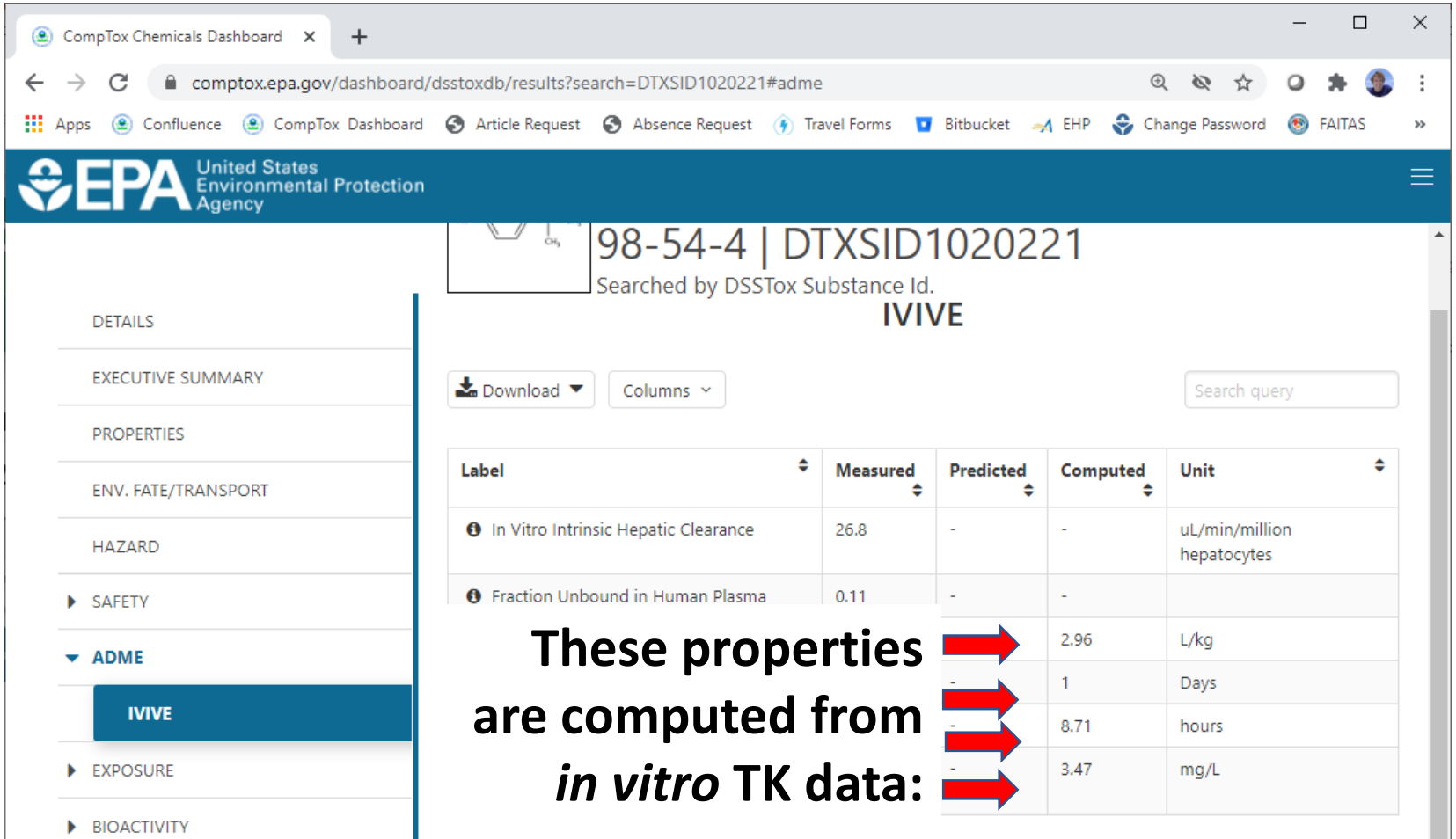


Most chemicals do not have TK Data



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



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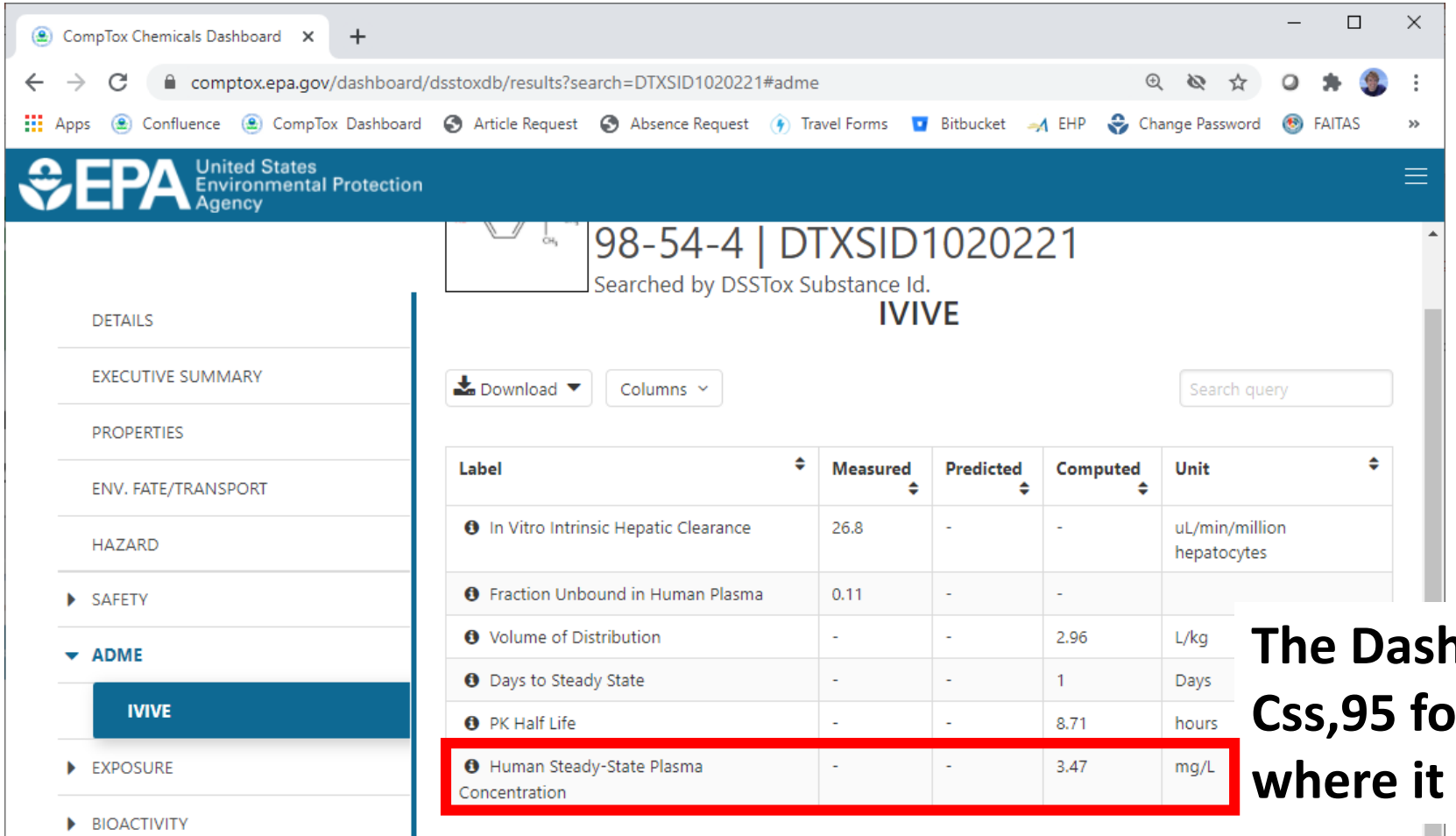
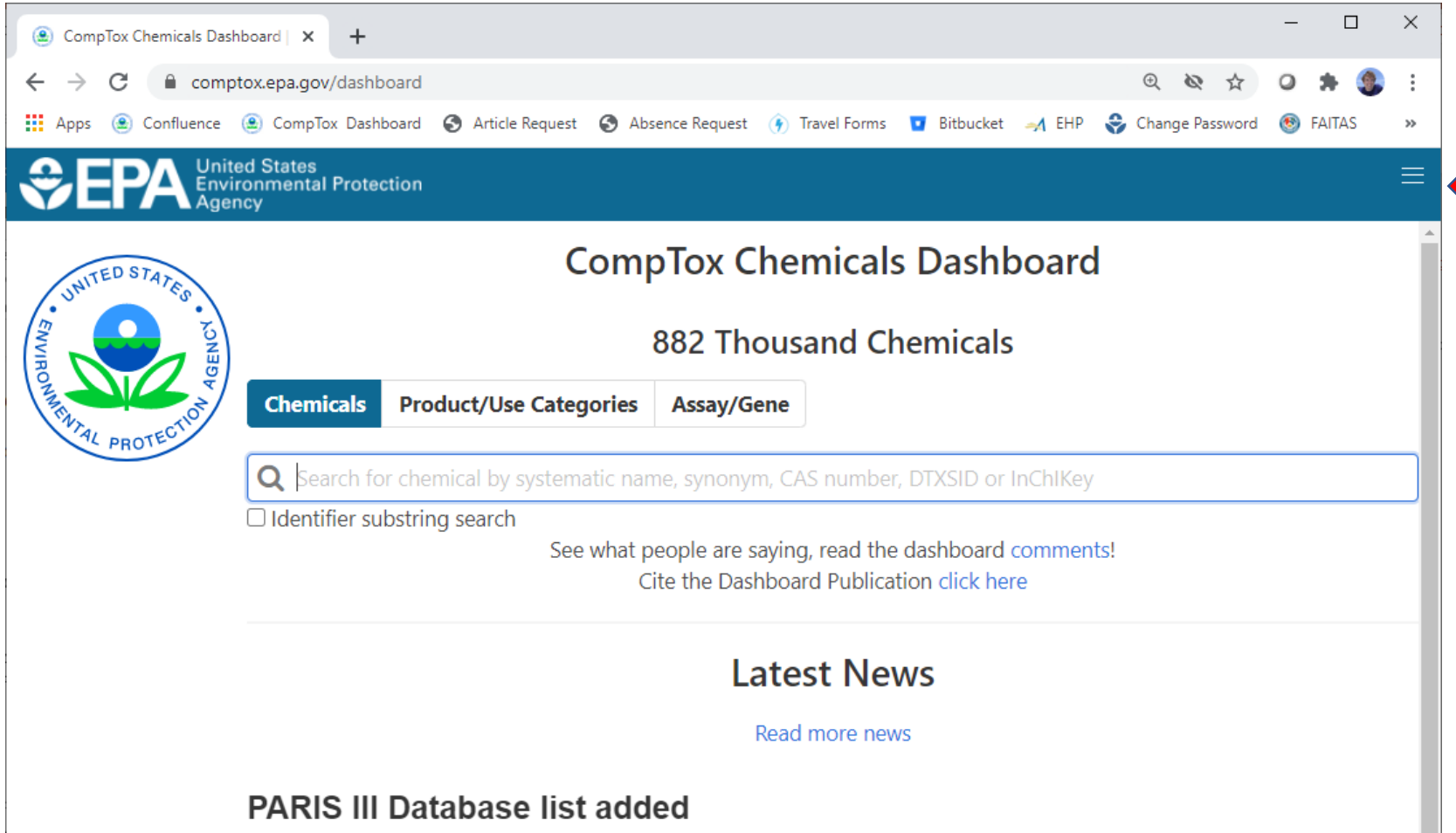


The Dashboard provides Css,95 for every chemical where it is available

Does My Chemical Have HTTK Data?

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



Click here to bring up Dashboard Options

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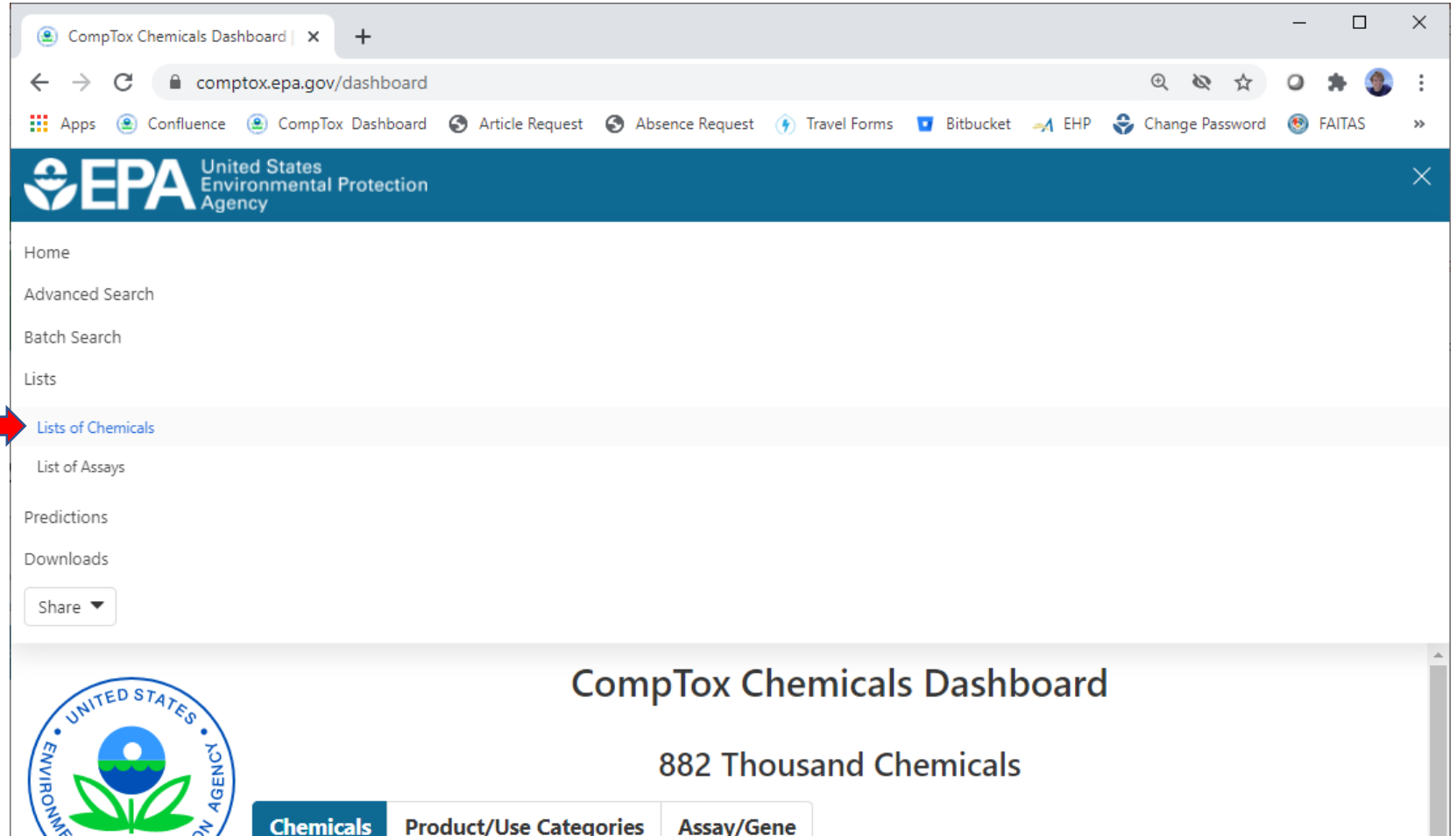
Select “Lists of Chemicals”



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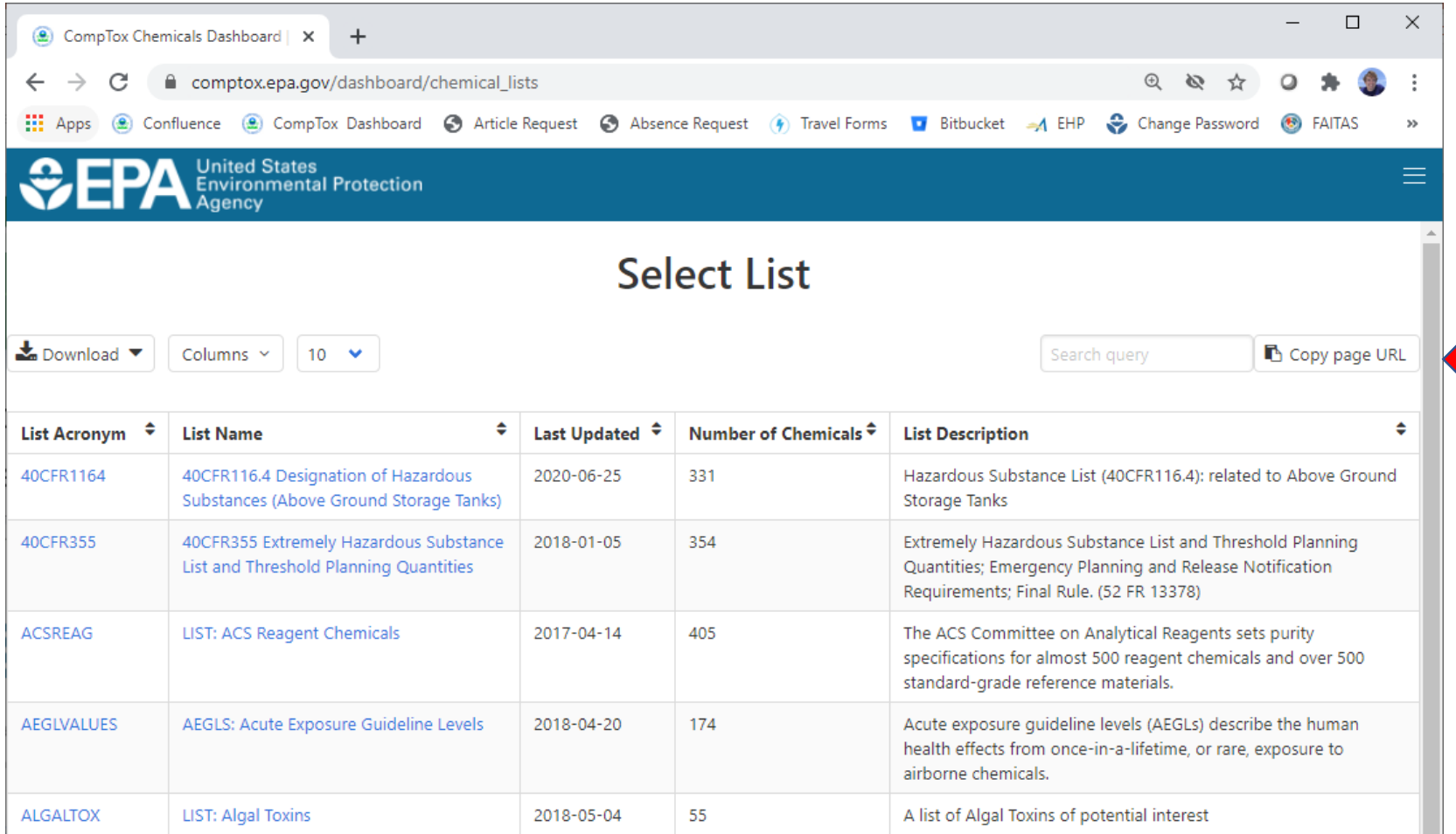

Enter “httk” in search box

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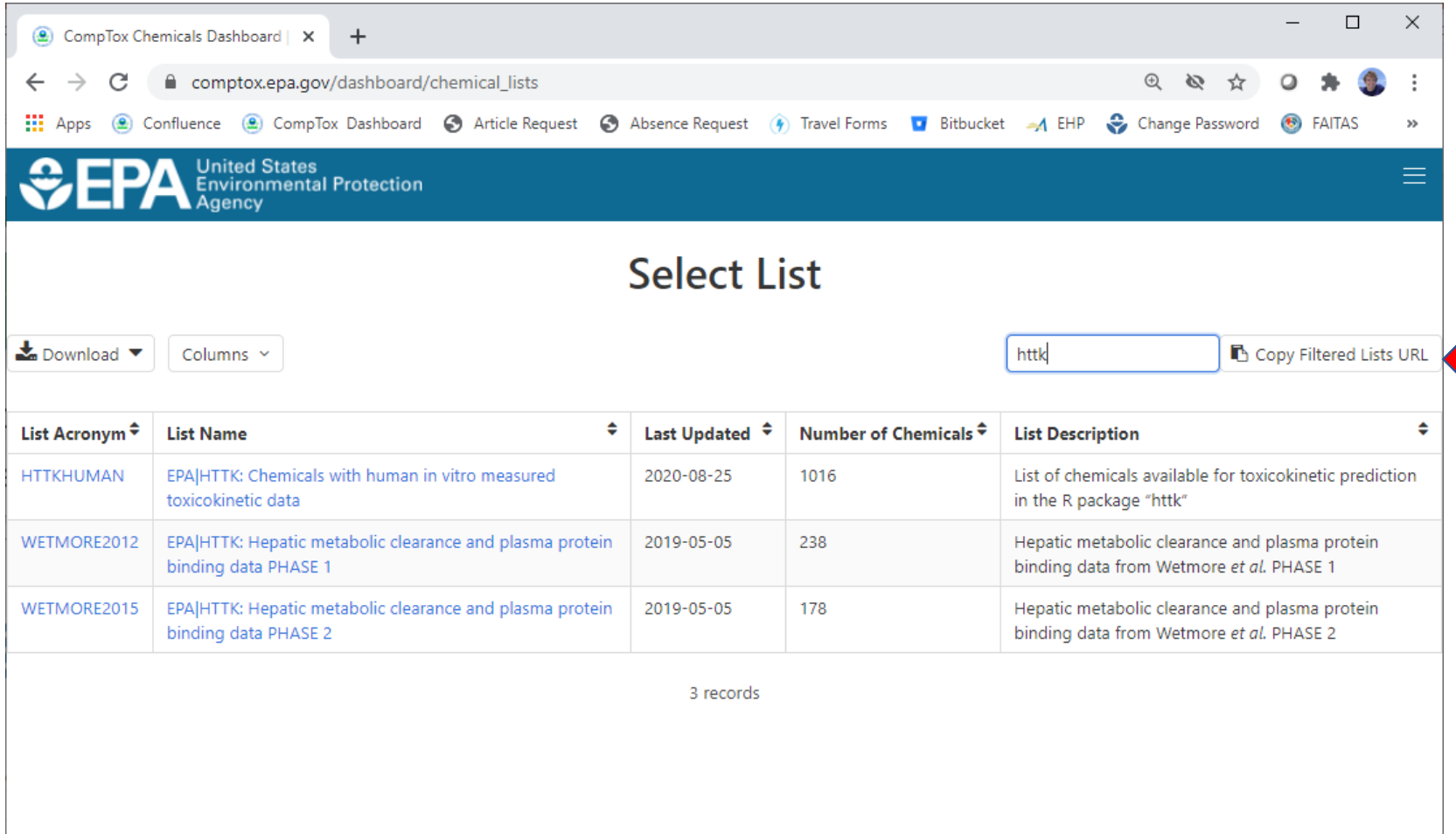

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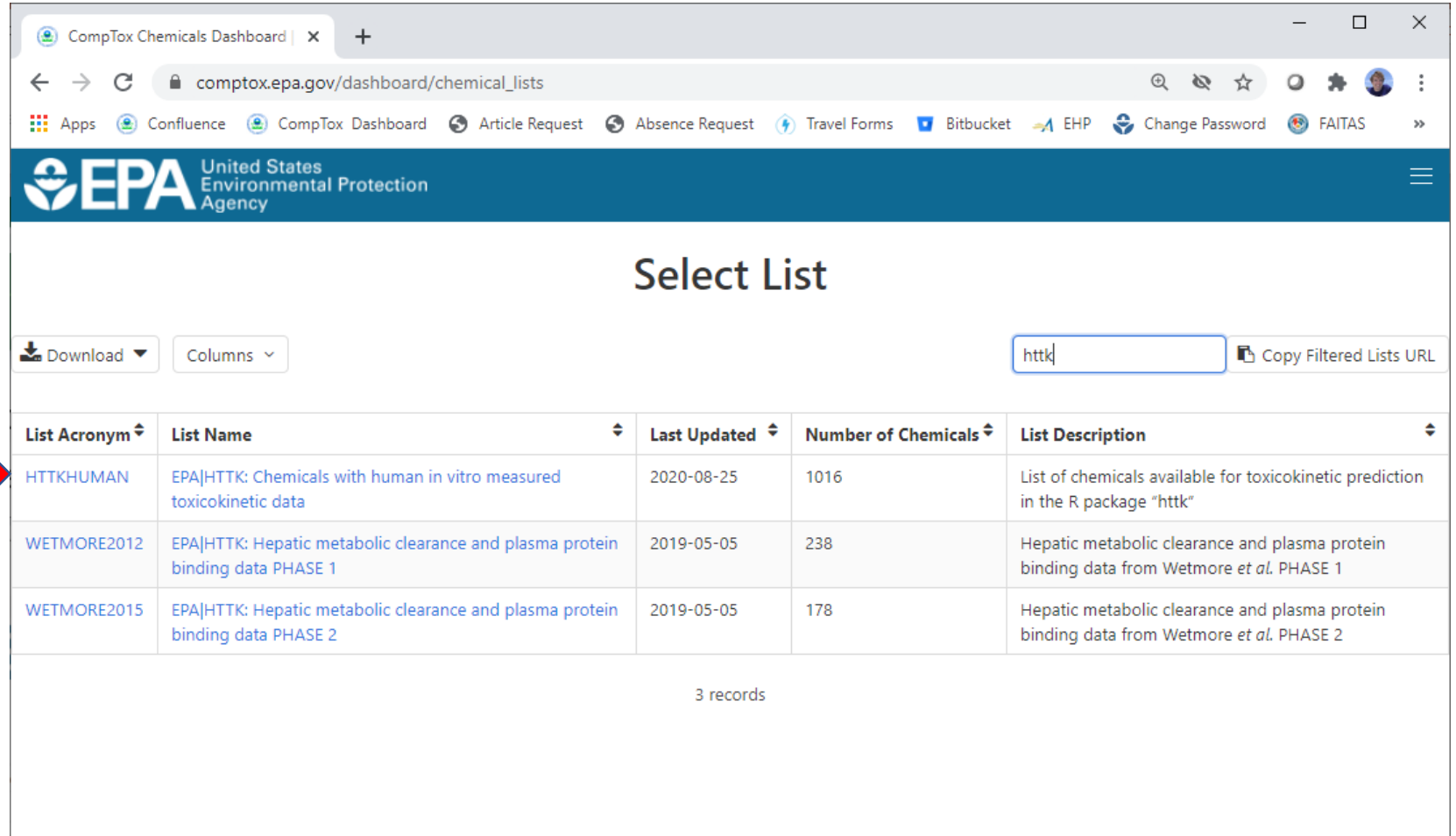
Select list “HTTKHUMAN”



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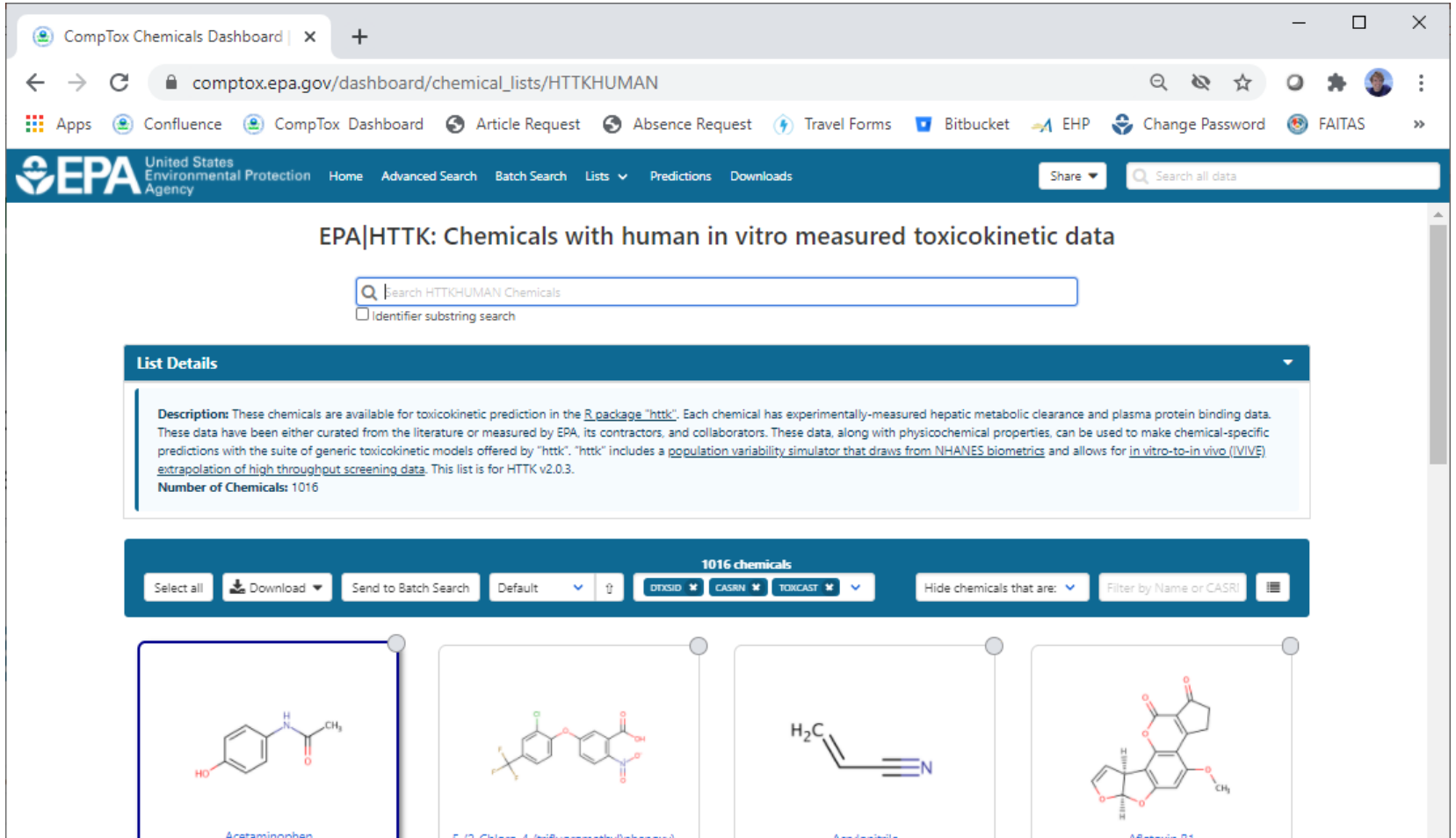


How Does AED Work?

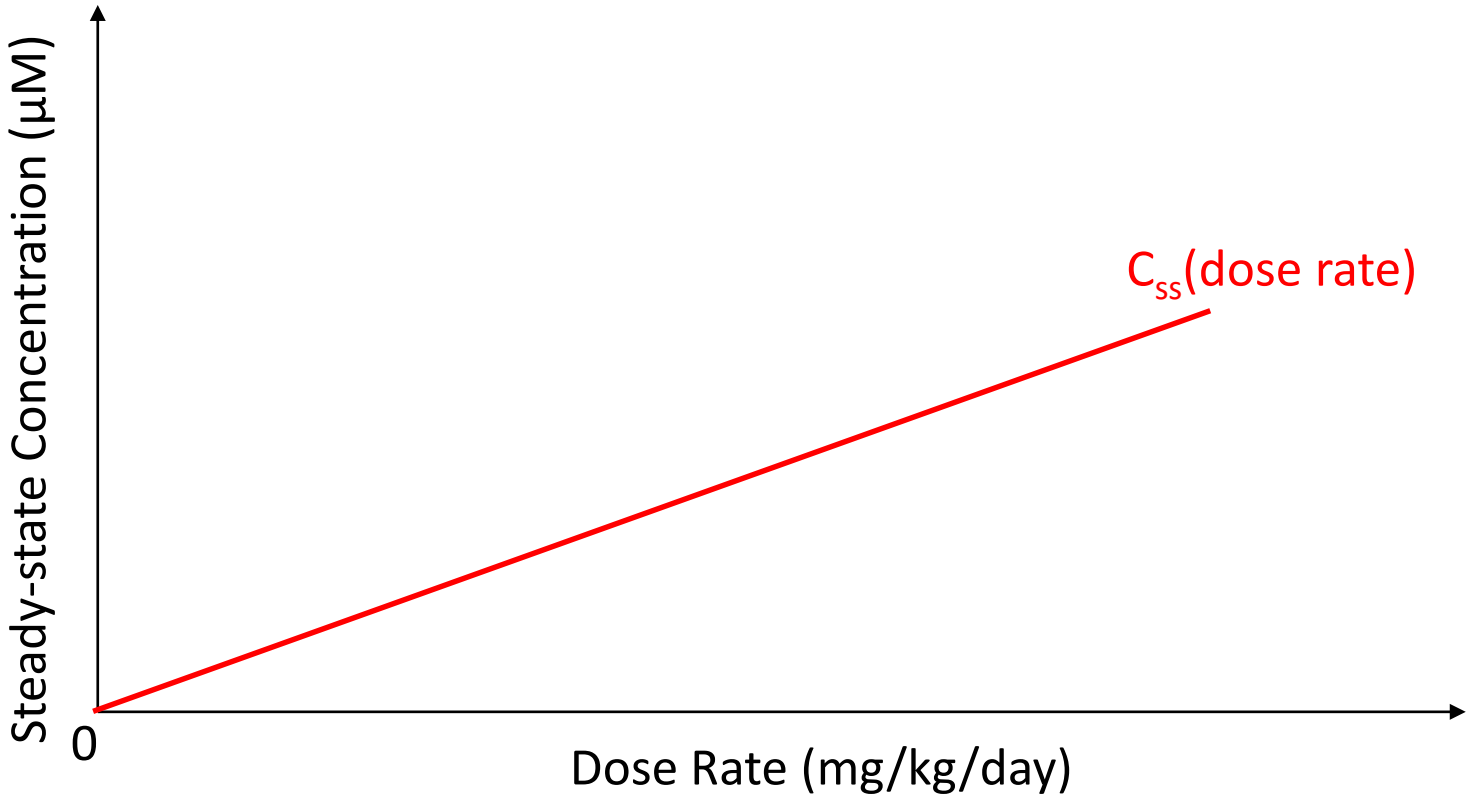
- AED is the administered equivalent dose for an *in vitro* concentration

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

- $C_{ss,95}$ 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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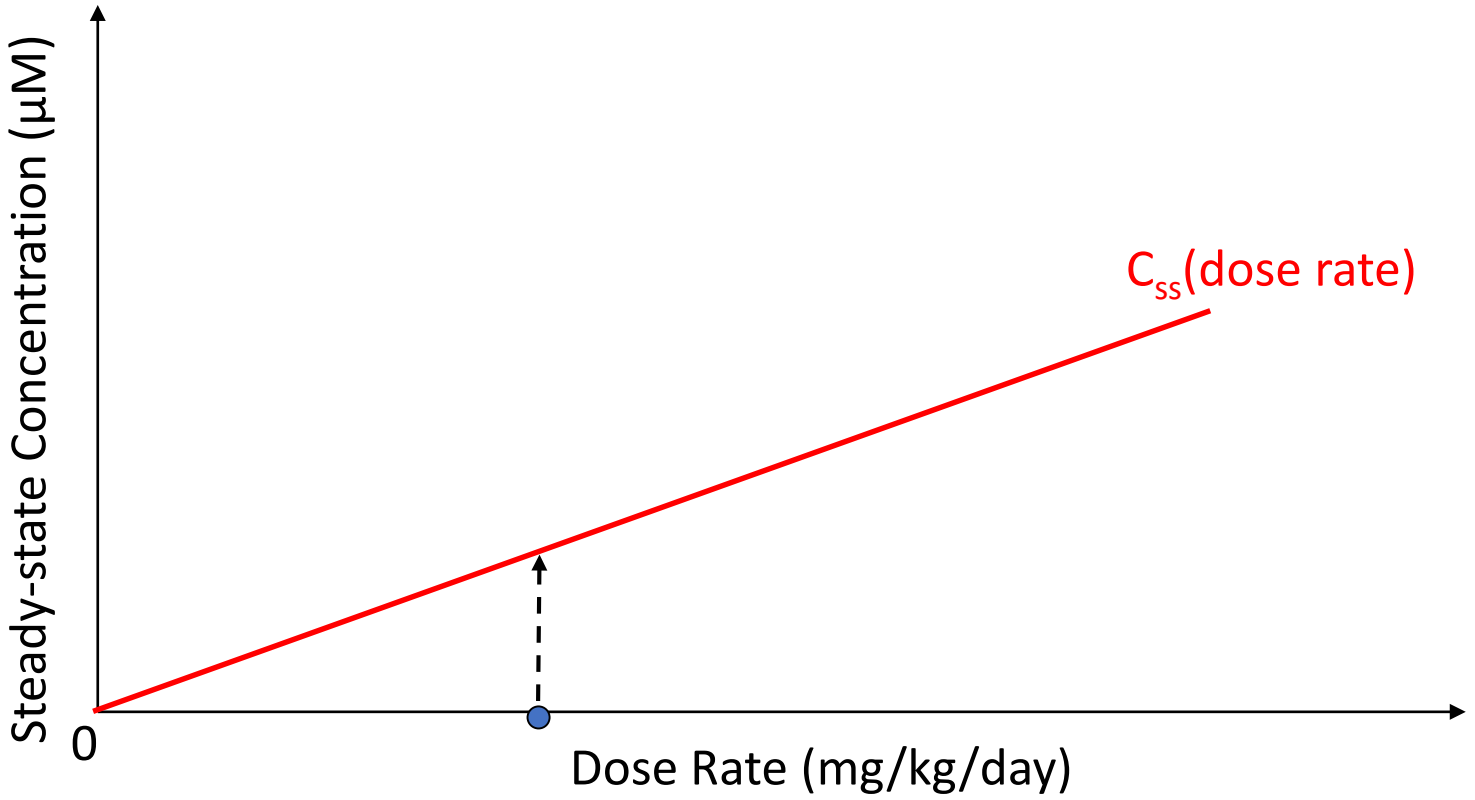

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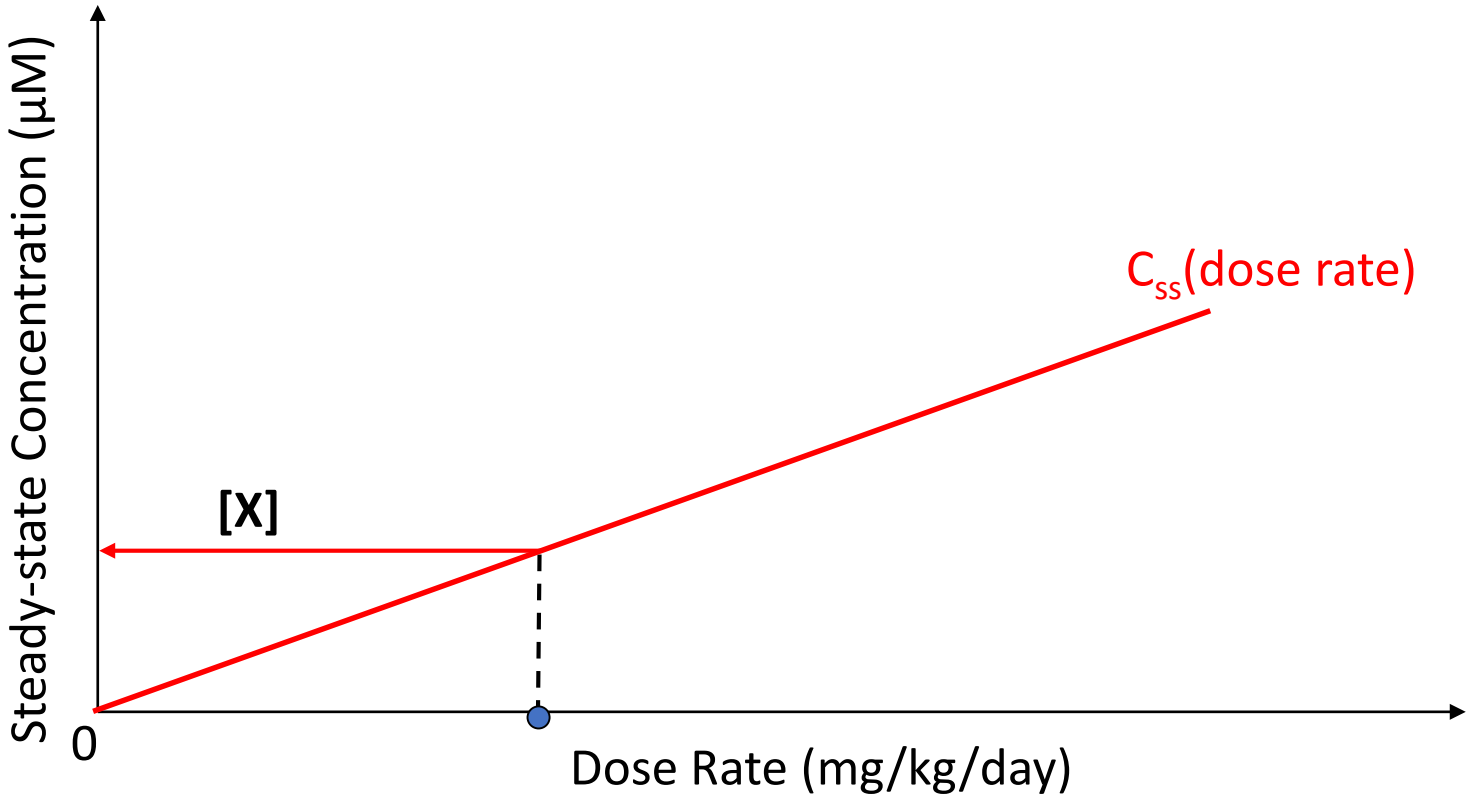
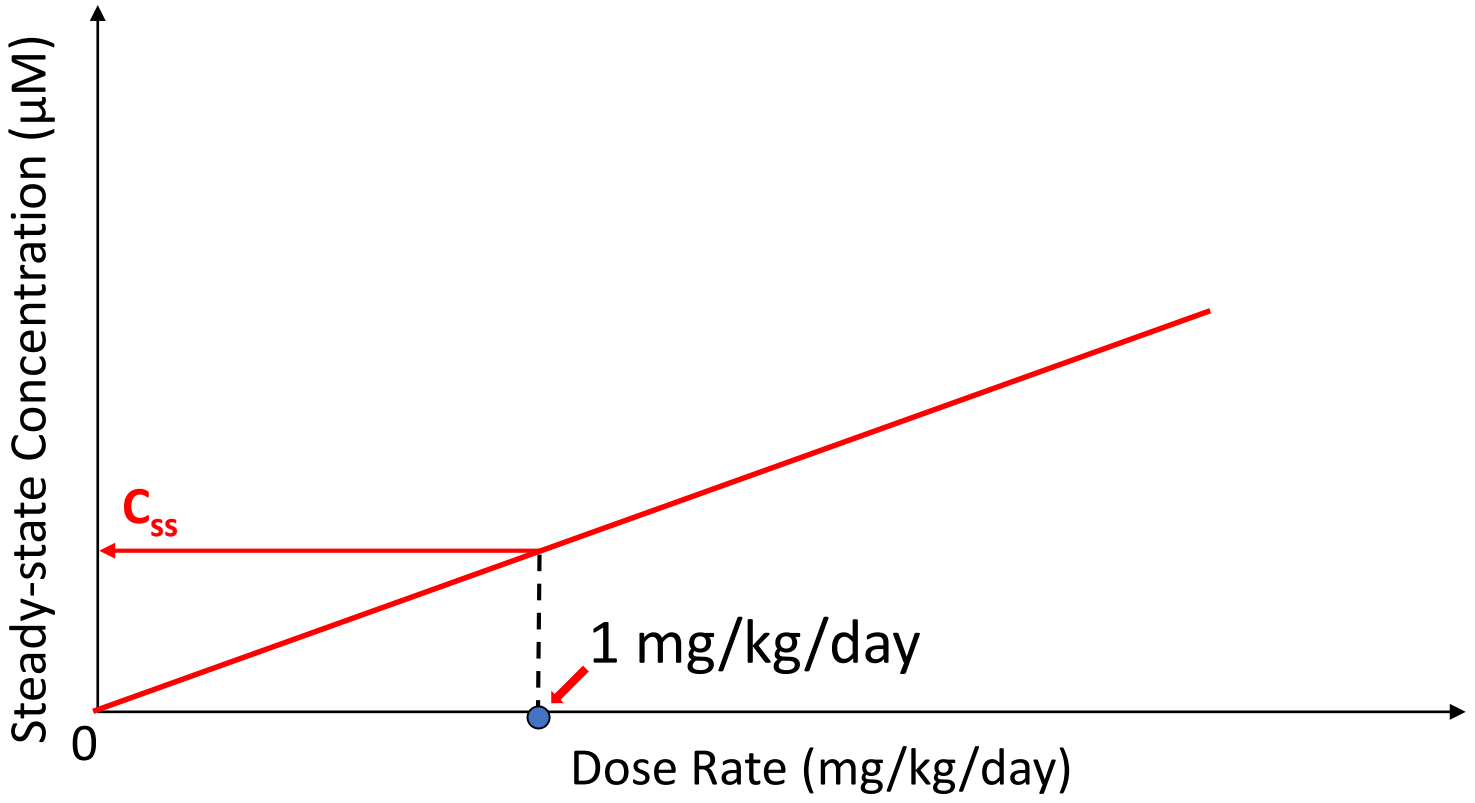


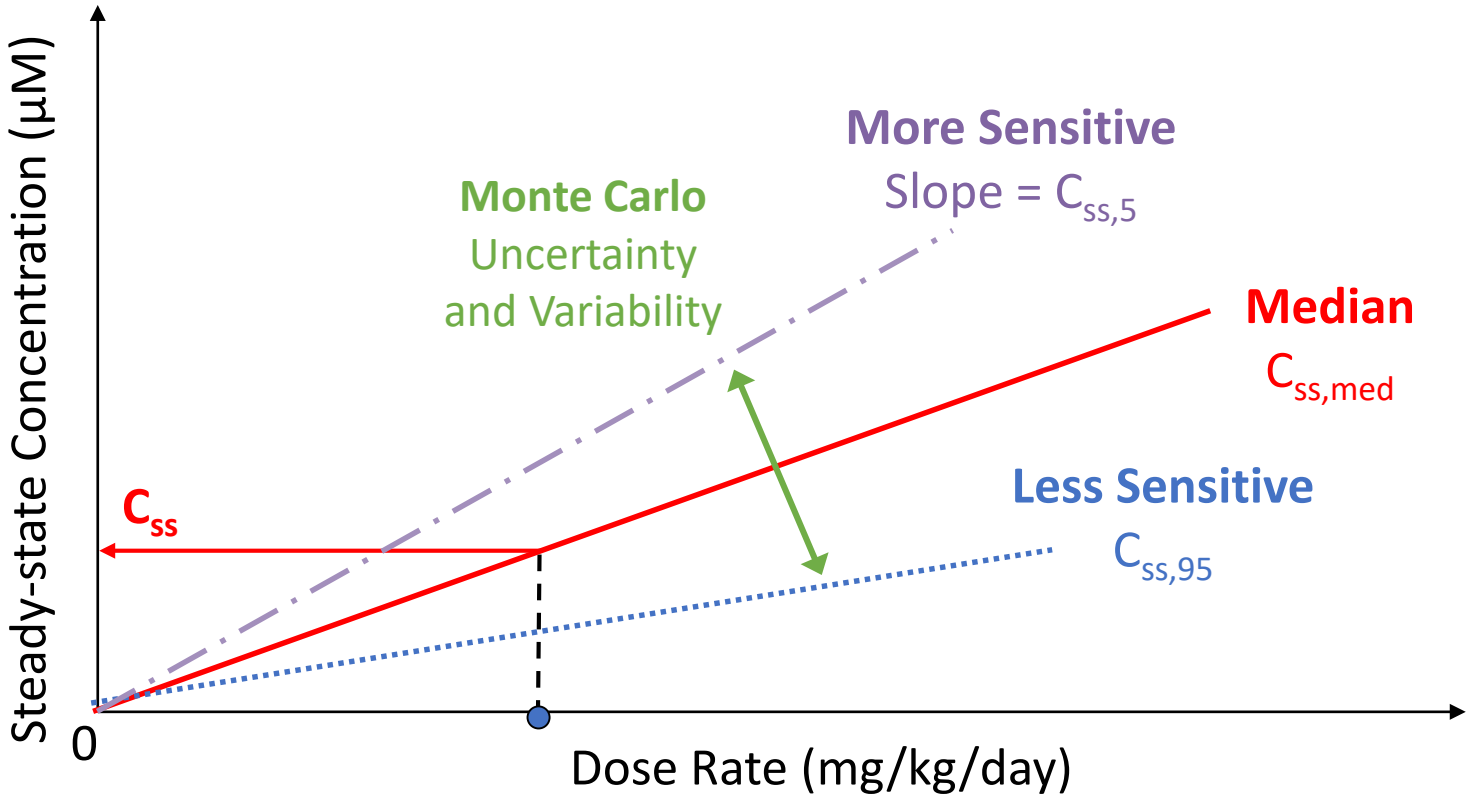
Steady-State Plasma Concentration

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



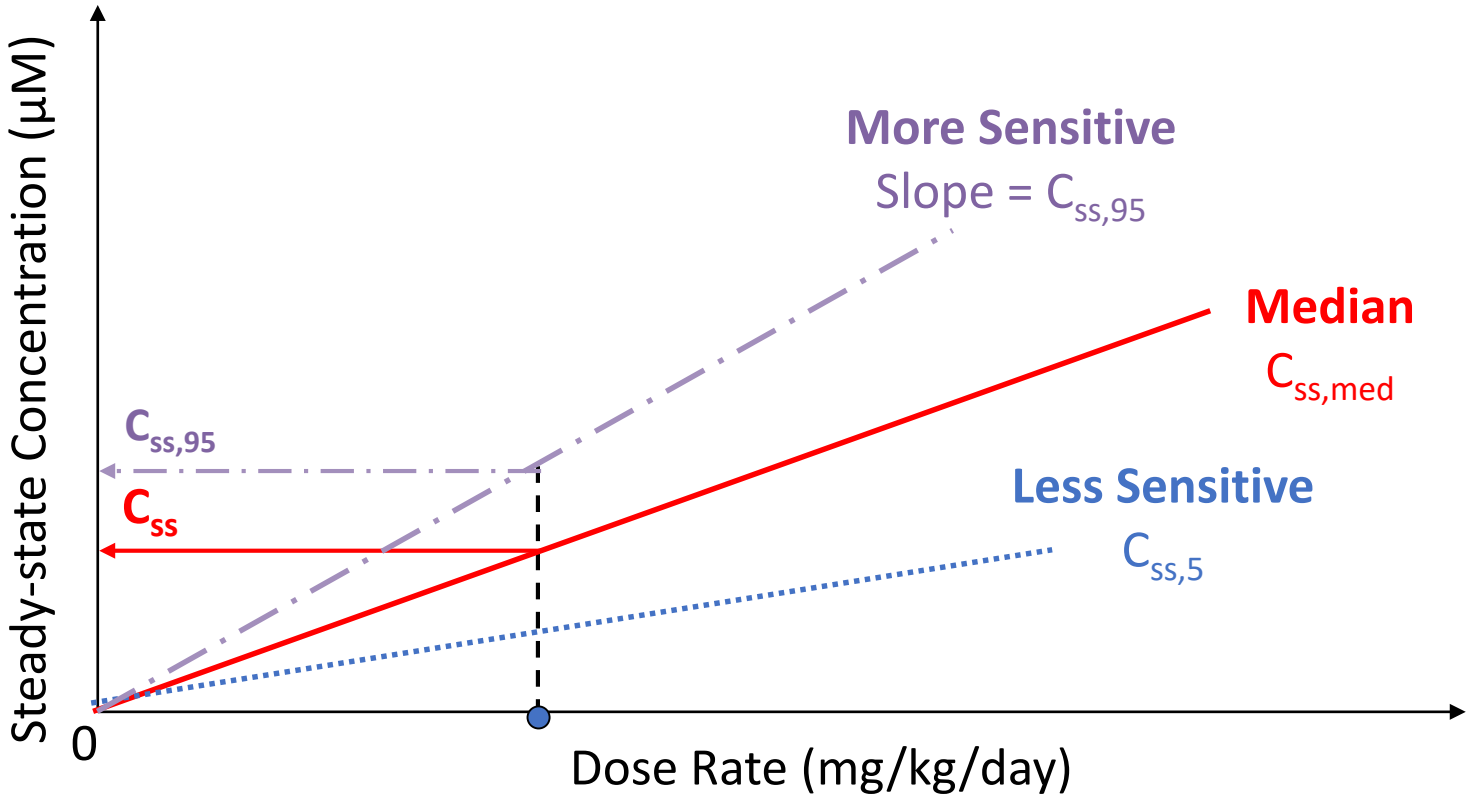
Monte Carlo Simulation

- 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



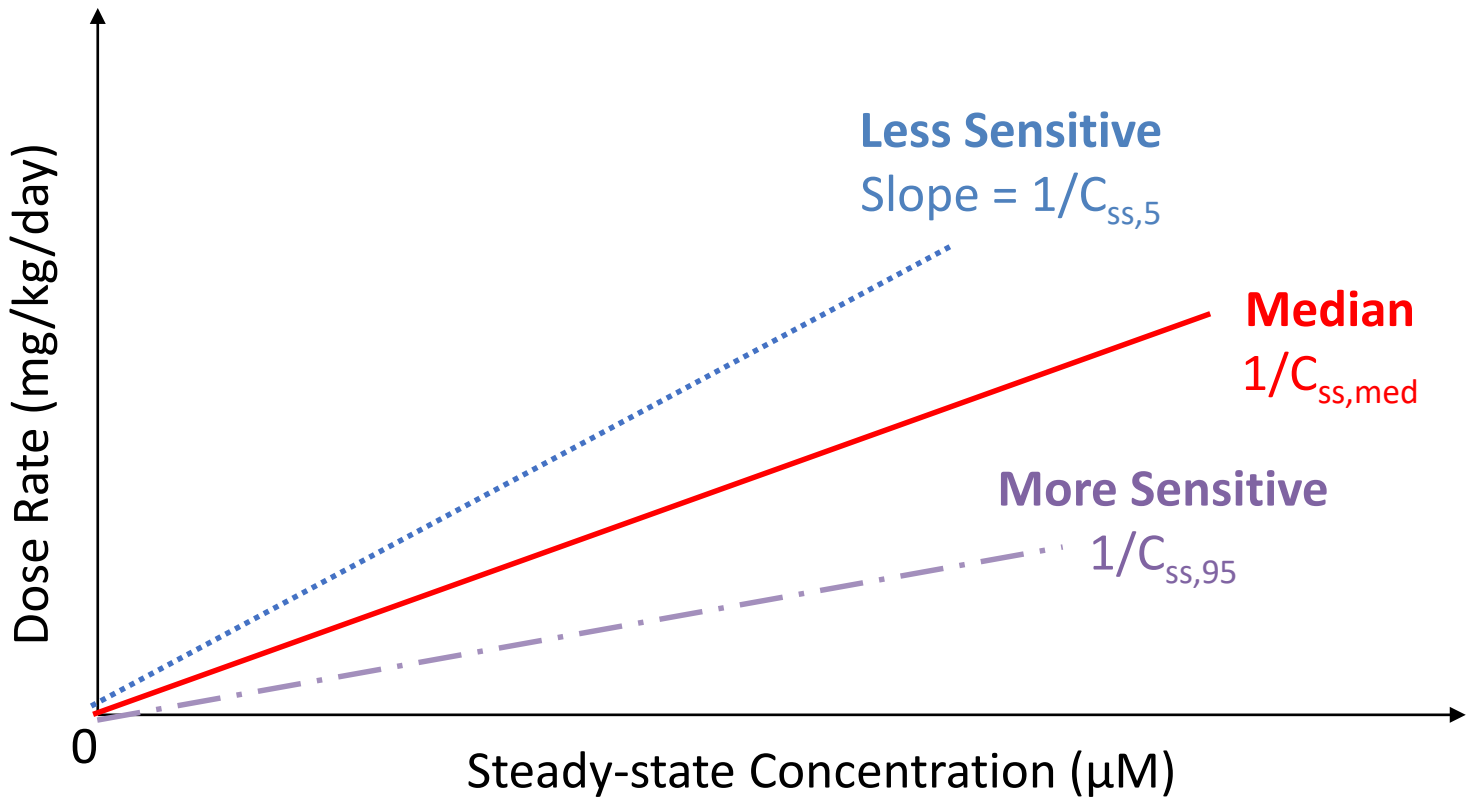
Monte Carlo Simulation

- We typical 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



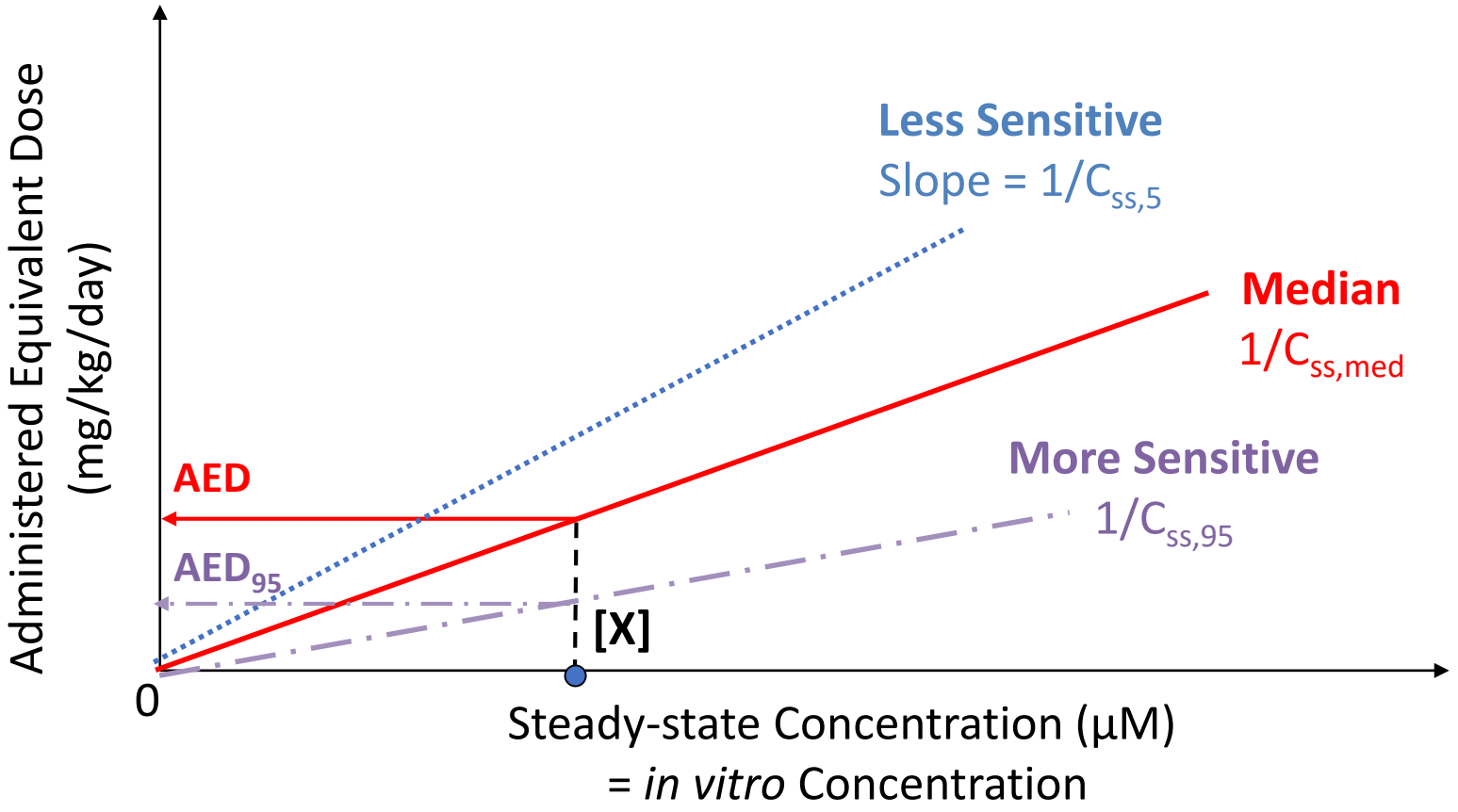
Steady-State Reverse Dosimetry IVIVE

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



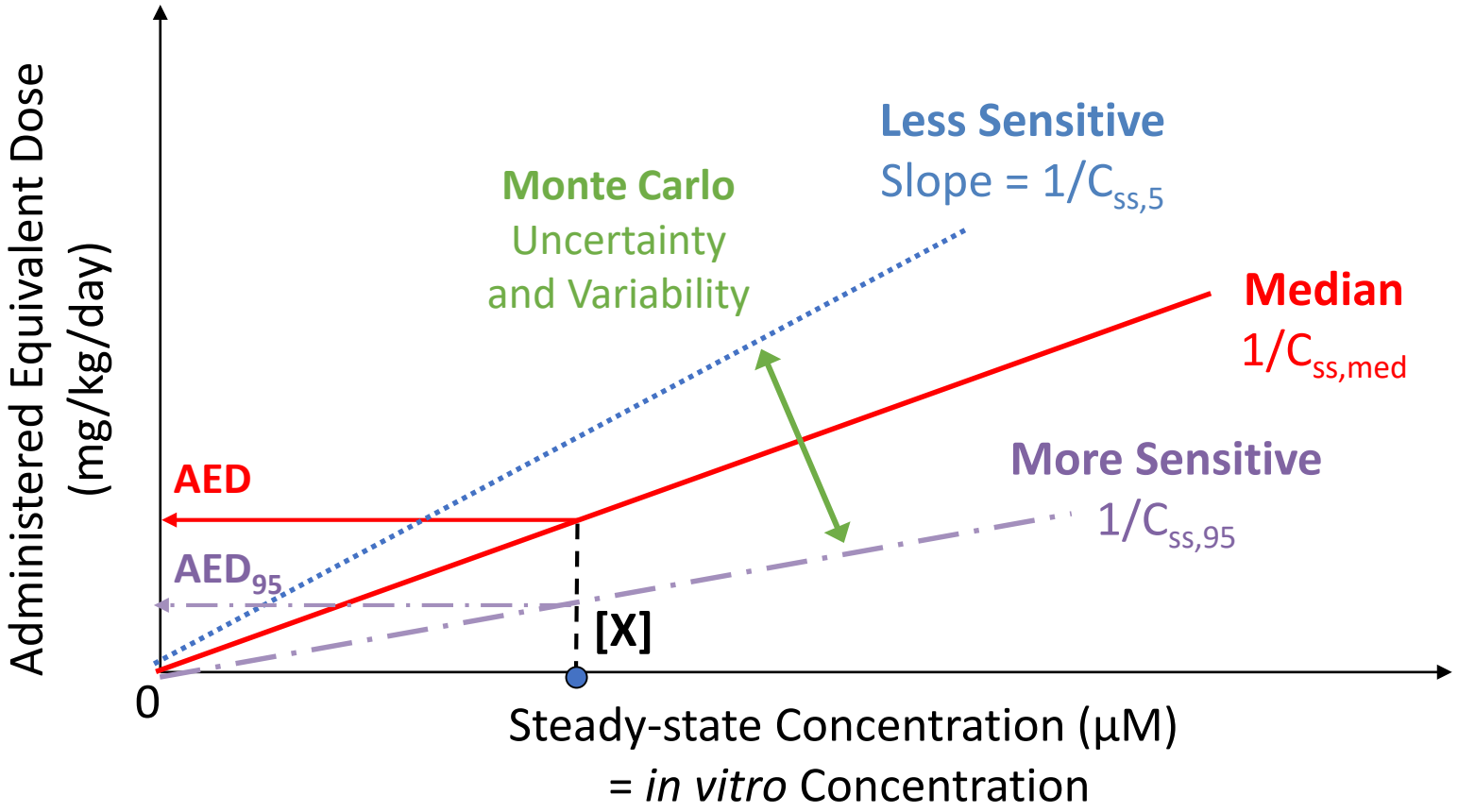
Administered Equivalent Dose (AED)

- 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)

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



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):

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

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)

High Throughput Toxicokinetics (HTTK)

EPA United States Environmental Protection Agency

In vitro toxicokinetic data + generic toxicokinetic model

= high(er) throughput toxicokinetics

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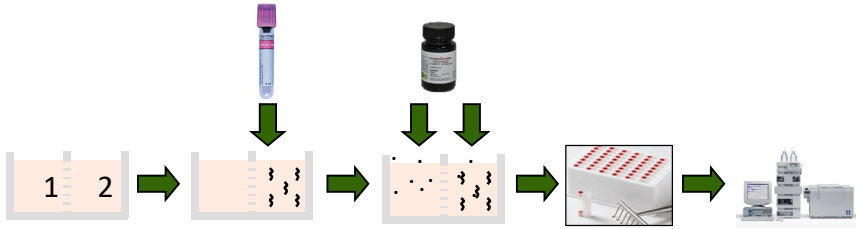

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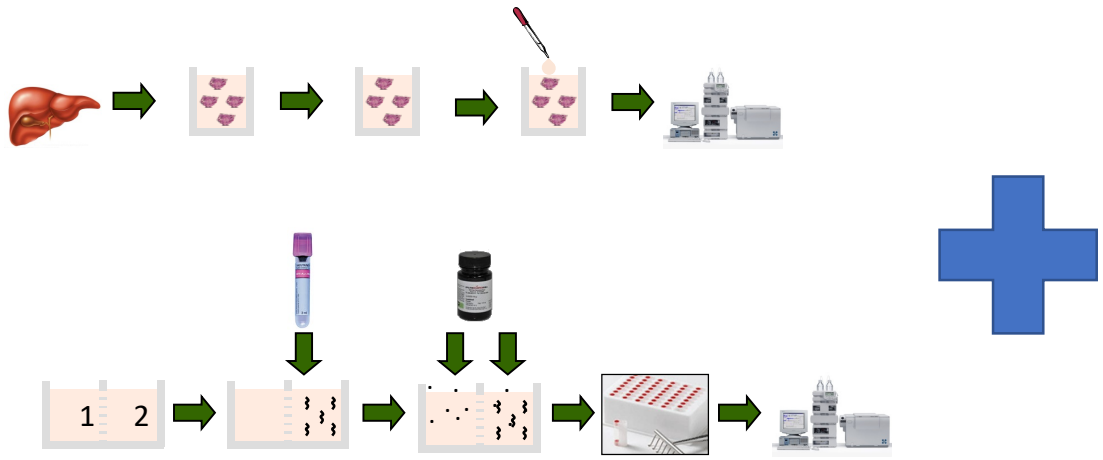

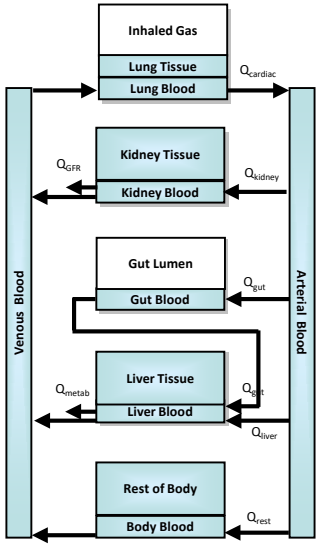

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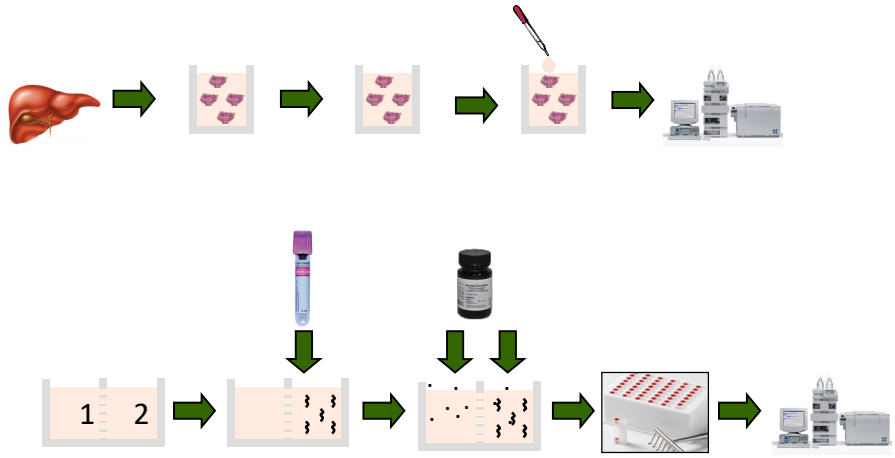
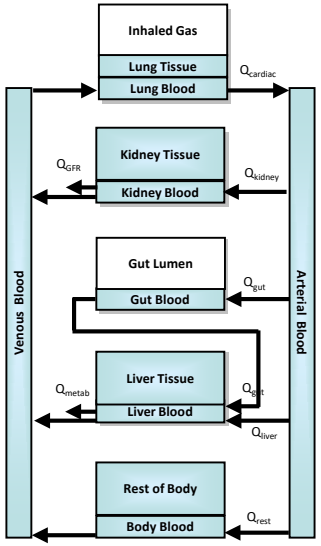
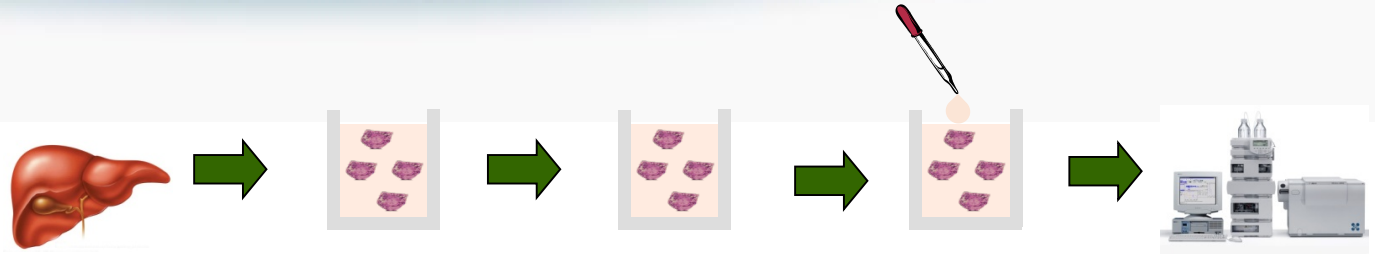




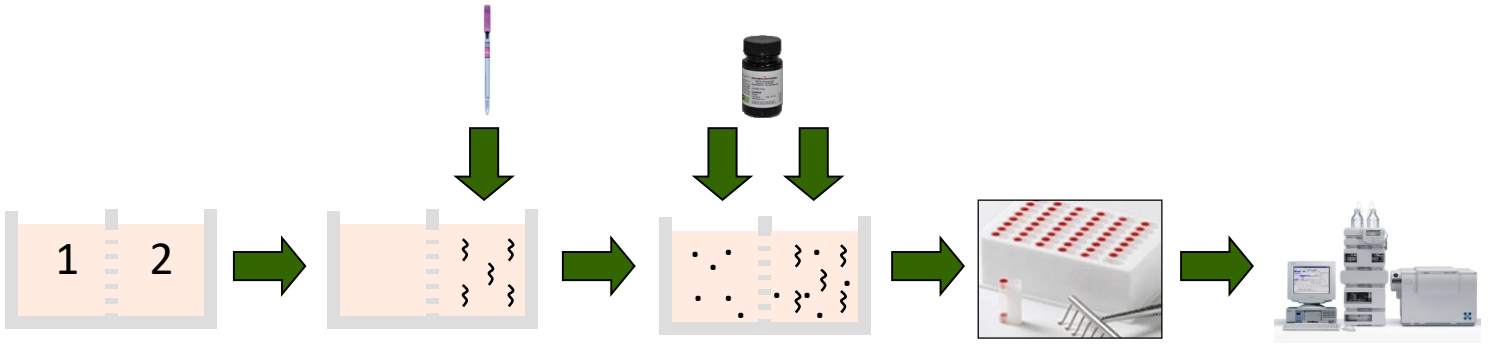
= *httk*

In Vitro Data for HTTK

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

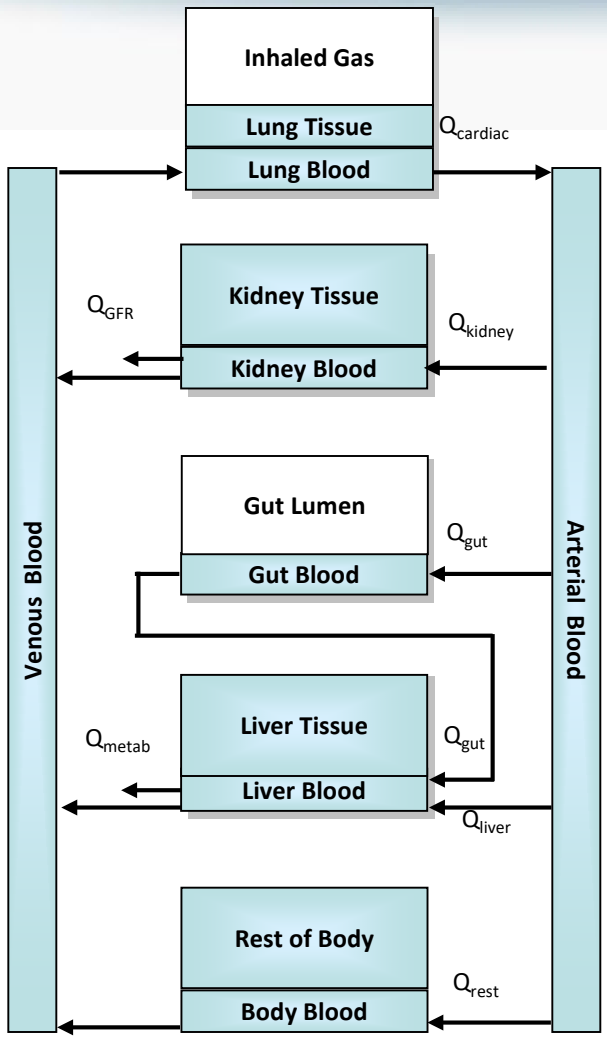


Rapid Equilibrium Dialysis (RED) Waters *et al.* (2008)



- **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)

Generic Models for HTTK

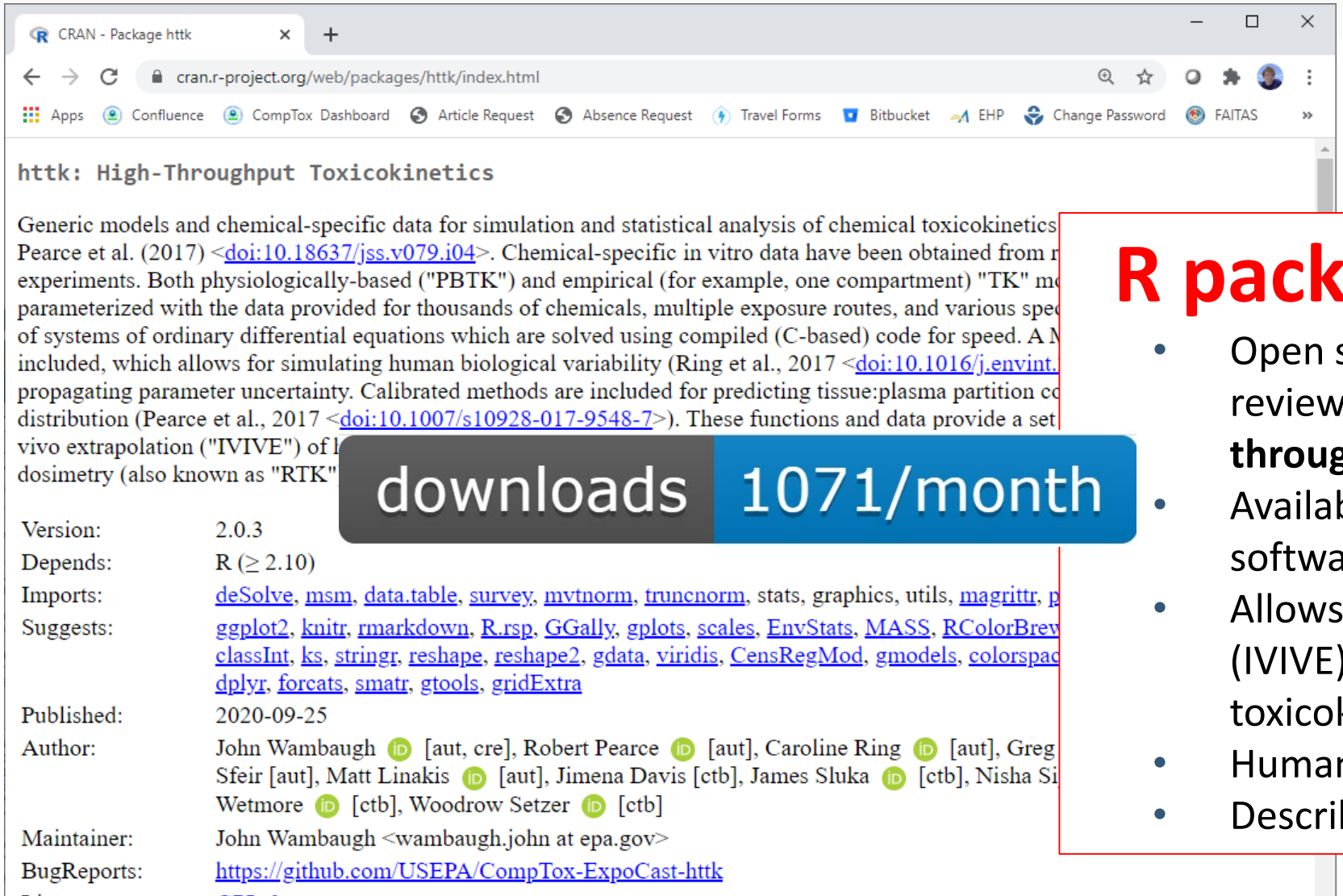


- Tissues are modeled by compartments:
- Clearance from the body depends on two processes:
  - Metabolism in the liver (estimated from *in vitro* clearance and binding)
  - Excretion by glomerular filtration in the kidney (estimated from *in vitro* binding)
- Model parameters are either:
  - **Physiological:** 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

Open Source Tools and Data for HTTK

EPA United States Environmental Protection Agency

https://CRAN.R-project.org/package=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 *In Vitro* Measurements	Metabolism and protein binding for ~1000 chemicals in human and ~200 in rat	Wetmore et al. (2012, 2013, 2015), plus others
Chemical-Specific *In Silico* 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)
In Vitro 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)

Population simulator for HTTK

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

NHANES: US CDC National Health and Nutrition Examination Survey

Ring *et al*. (2017)

Population simulator for HTTK

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

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- Sex
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- Height
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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.)

NHANES: US CDC National Health and Nutrition Examination Survey

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Population simulator for HTTK

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Predict physiological quantities for generic Models:

- Tissue masses
- Tissue blood flows
- GFR (kidney function)
- Hepatocellularity

NHANES: US CDC National Health and Nutrition Examination Survey

Ring *et al.* (2017)

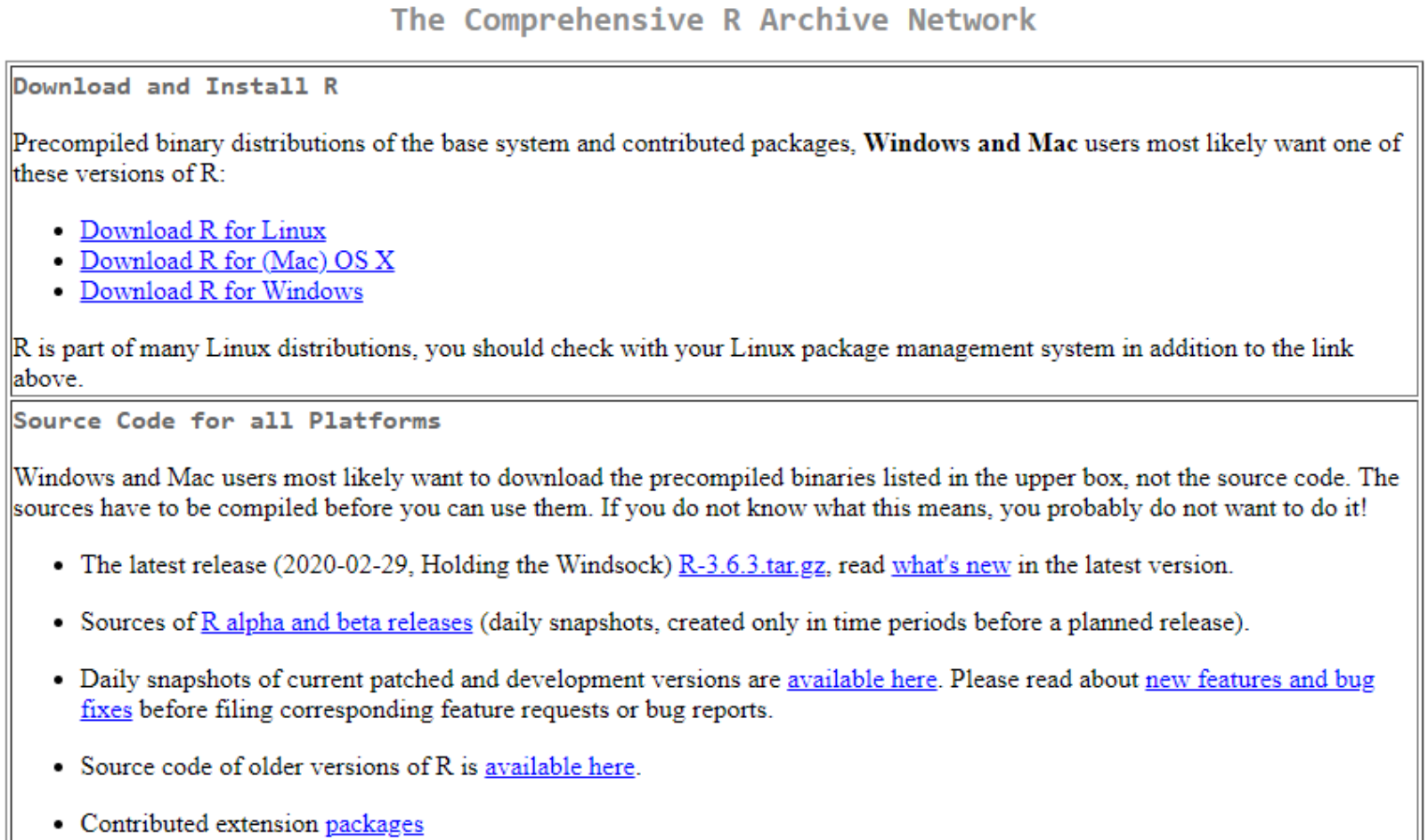
Calculating Dashboard Values in R

EPA United States Environmental Protection Agency

- 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")
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
```

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

```
> library(httk)
```

Load the HTTK data, models, and functions

```
> packageVersion("httk")
[1] '2.0.1'
```

Check what version you are using

Calculating Dashboard Values in R

```
> 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(dtxsid="DTXSID1020221",
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parameters.dt$Krbc2pu,  :
  Rblood2plasma has been recalculated.
```
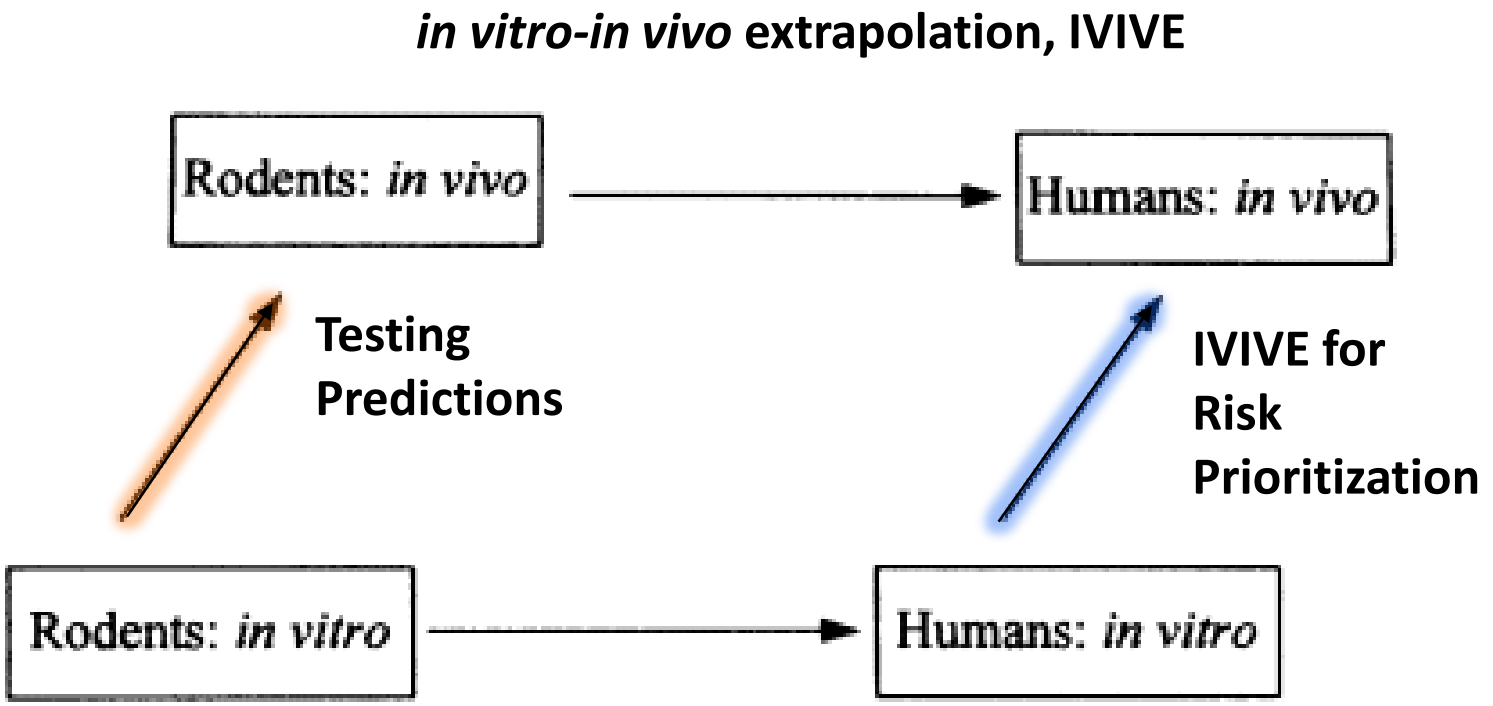
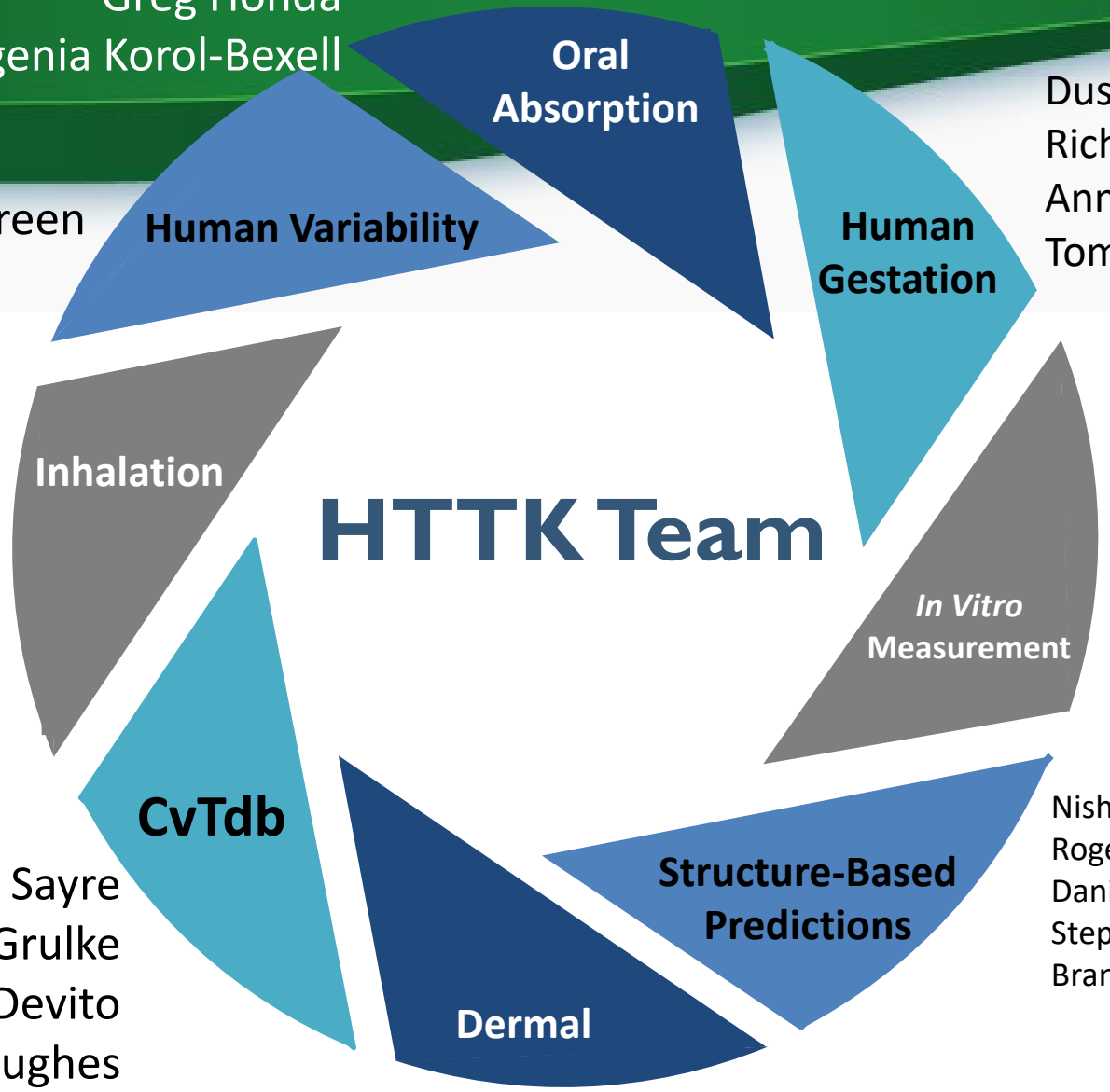

This step sets the random number generator to a specific state, otherwise Monte Carlo (MC) will give you slightly different answers

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 HTTK, 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



HTTK Team



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References

- Bell, Shannon M., et al. (2018) "In vitro to in vivo extrapolation for high throughput prioritization and decision making." Toxicology In Vitro 47 213-227.
- Honda, Gregory S., et al. "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." PloS one 14.5 (2019): e0217564.
- Jamei, Masoud, et al. "The Simcyp® population-based ADME simulator." Expert opinion on drug metabolism & toxicology 5.2 (2009): 211-223.
- Linakis, Matthew et al. “Development of a Generalized Inhalation Model for use with the High-Throughput Toxicokinetics (httk) Package n R”, Journal of Exposure Science & Environmental Epidemiology 2020): 1-12.
- Lukacova, et al.. "Prediction of modified release pharmacokinetics and pharmacodynamics from in vitro, immediate release, and intravenous data." The AAPS journal 11.2 (2009): 323-334.
- Mansouri, Kamel, et al. (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. Journal of cheminformatics, 10(1), 10.
- National Research Council. (1983). Risk Assessment in the Federal Government: Managing the Process Working Papers. National Academies Press.
- National Research Council. (1998). Issues in Potable Reuse: The viability of augmenting drinking water supplies with reclaimed water. National Academies Press.
- Pearce, Robert G,, et al. “httk: R Package for High-Throughput Toxicokinetics.” Journal of Statistical Software, (2017a)
- Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017b): 549-565.
- Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118.
- Rotroff, Daniel M., et al. "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." Toxicological Sciences 117.2 (2010): 348-358.
- Sayre, Risa et al., “Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals”, Scientific data 7.1 (2020): 1-10.
- Schmitt, Walter. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology in Vitro 22.2 (2008): 457-467.
- Shibata, Y., et al. (2002). Prediction of hepatic clearance and availability by cryopreserved human hepatocytes: an application of serum incubation method. Drug Metabolism and Disposition, 30(8), 892-896
- Sipes, Nisha S., et al. "An intuitive approach for predicting potential human health risk with the Tox21 10k library." Environmental science & technology 51.18 (2017): 10786-10796.
- Sobels, F. H. (1982) “The parallelogram; an indirect approach for the assessment of genetic risks from chemical mutagens.” In: Progress in Mutation Research, Vol. 3 (K. C. Bora, G. R. Douglas, and E. R. Nestman, Eds.), Elsevier, Amsterdam, pp. 233-327.
- Tan, Yu-Mei, Kai H. Liao, and Harvey J. Clewell. "Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling." Journal of Exposure Science & Environmental Epidemiology 17.7 (2007): 591-603.
- Thomas, Russell S., et al. "Incorporating Monte Carlo simulation into physiologically based pharmacokinetic models using advanced continuous simulation language (ACSL): a computational method." *Toxicological Sciences* 31.1 (1996): 19-28.
- Wambaugh, John F., et al. "Evaluating In Vitro-In Vivo Extrapolation of Toxicokinetics." Toxicological Sciences 163.1 (2018): 152-169.
- Wambaugh, John F., et al. “Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization” Toxicological Sciences, 172(2), 235-251.
- Wang, Ying-Hong. "Confidence assessment of the Simcyp time-based approach and a static mathematical model in predicting clinical drug-drug interactions for mechanism-based CYP3A inhibitors." Drug Metabolism and Disposition 38.7 (2010): 1094-1104.
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." *Tox. Sciences* (2012)
- Wetmore, Barbara A., et al. "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." toxicological sciences 132.2 (2013): 327-346.
- Wetmore, Barbara A., et al. "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." Toxicological Sciences 148.1 (2015): 121-136.
- Waters, Nigel J., et al. "Validation of a rapid equilibrium dialysis approach for the measurement of plasma protein binding." Journal of pharmaceutical sciences 97.10 (2008): 4586-4595