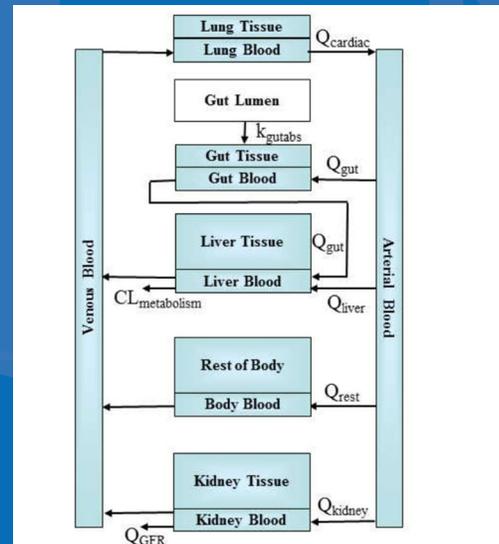


High Throughput Toxicokinetics (httk) Modeling Virtual Training



Marina V Evans and Celia Schacht

EPA NAMs Pilot Training Program

- New Approach Methodologies (NAMs) Training Program is a deliverable in the Agency's Work Plan, first released in 2019 and updated in 2021.
 - Previous trainings include ECOTOX, CompTox Chemicals Dashboard, and GenRA.
- Goal: Develop, implement and maintain an engaging training program.
 - Interactive case studies to encourage active learning
 - Train the trainer
 - Obtain feedback
- The EPA NAMs training website includes existing training resources, including recordings and guidance documents.



AGENDA

- Welcome and Introductions
- Background of httk
 - Why use generic models?
- Introduction to PBPK
 - Why do different routes matter?
- Introduction to httk package and Rstudio
 - Which constants and parameters are needed?
- httk specific R functions for chemical descriptors
- Summary followed by Q&A session

Conflict of Interest Statement

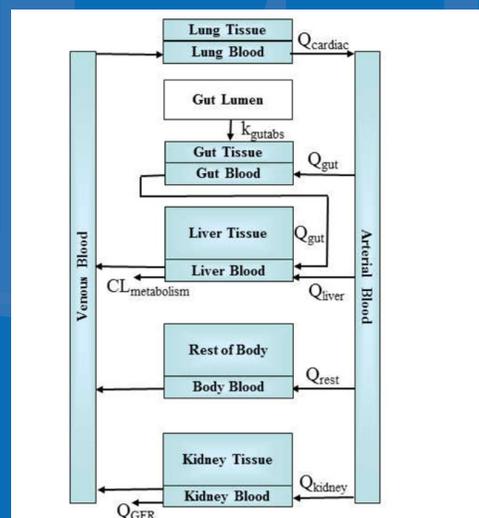
- No conflicts of interest to declare.

- Disclaimer:

The views expressed herein are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

EPA Center for Computational Toxicology and Exposure (CCTE)

High Throughput Toxicokinetics (httk) Modeling Virtual Training



Marina V Evans and Celia Schacht

Httk Project Team

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Dr. Caroline Ring*

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Contributors

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Dr. Greg Honda

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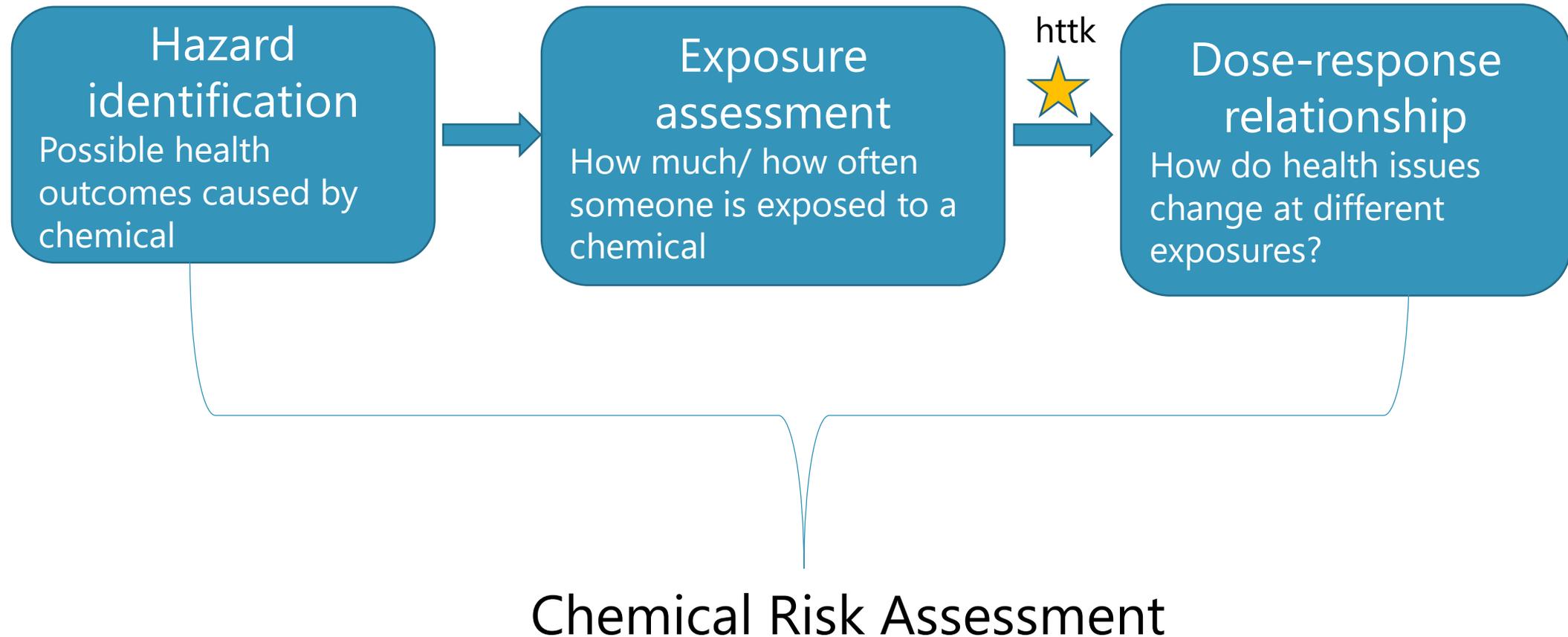
Dr. Annabel Meade

Risa Sayre*

*current

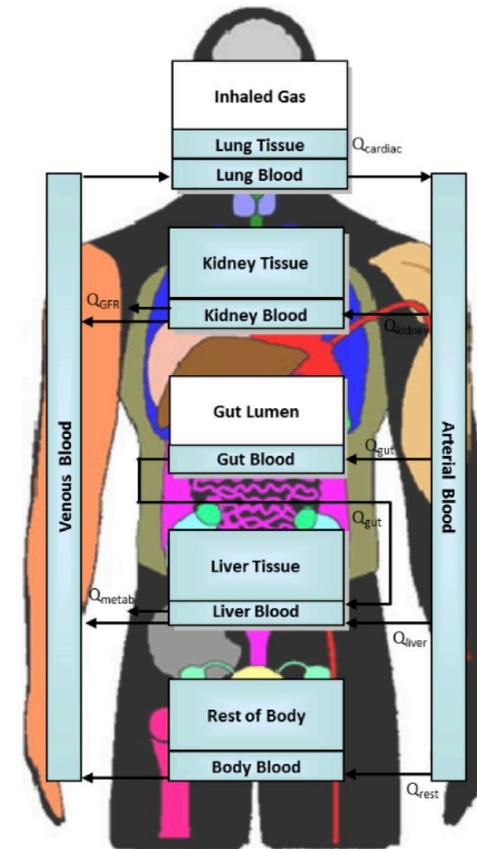
Background: Chemical Risk Assessment

How is toxicity studied and how is risk characterized?



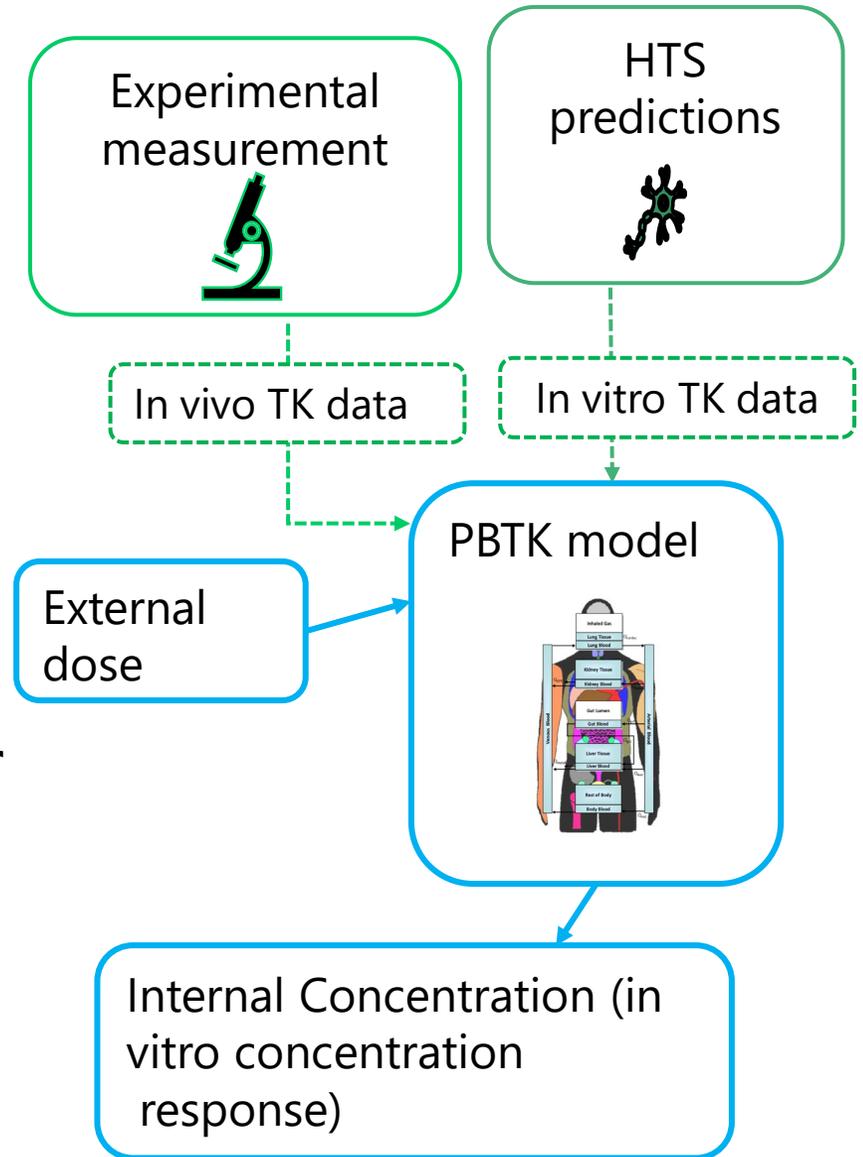
Tools to Estimate Risk: Toxicokinetics

- Toxicokinetics (TK) describes Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body.
 - TK helps prediction of tissue concentrations resulting from chemical exposures → inform dose-response relationship
- Physiological Based Toxicokinetic (PBTK) Models are Used to simulate kinetics of ADME
 - Constructed with a series of ODEs
 - Parameterized by anatomical and physiological variables
 - Estimate human exposure levels from internal doses
- But TK models require chemical-specific parameters commonly found in vivo.
 - Very little in vivo data!



What is httk?

- R package
 - Created with systems of ODEs developed in MCSim, solved using compiled C code
- Goal: provide human dose information for bioactive in vitro concentrations from HTS (i.e. IVIVE)
- **Generic** models can be rapidly customized for thousands of chemicals/numerous species.



Why generic PBTK modeling?

- Generic vs. customized PBTK models.
- Model types are available within R package “httk”, which is open source.
- PBTK Model parameterization
 - Physiologic parameters – different species are included.
 - Chemical-specific parameters
 - httk functions use information from the Dashboard for multiple chemicals.

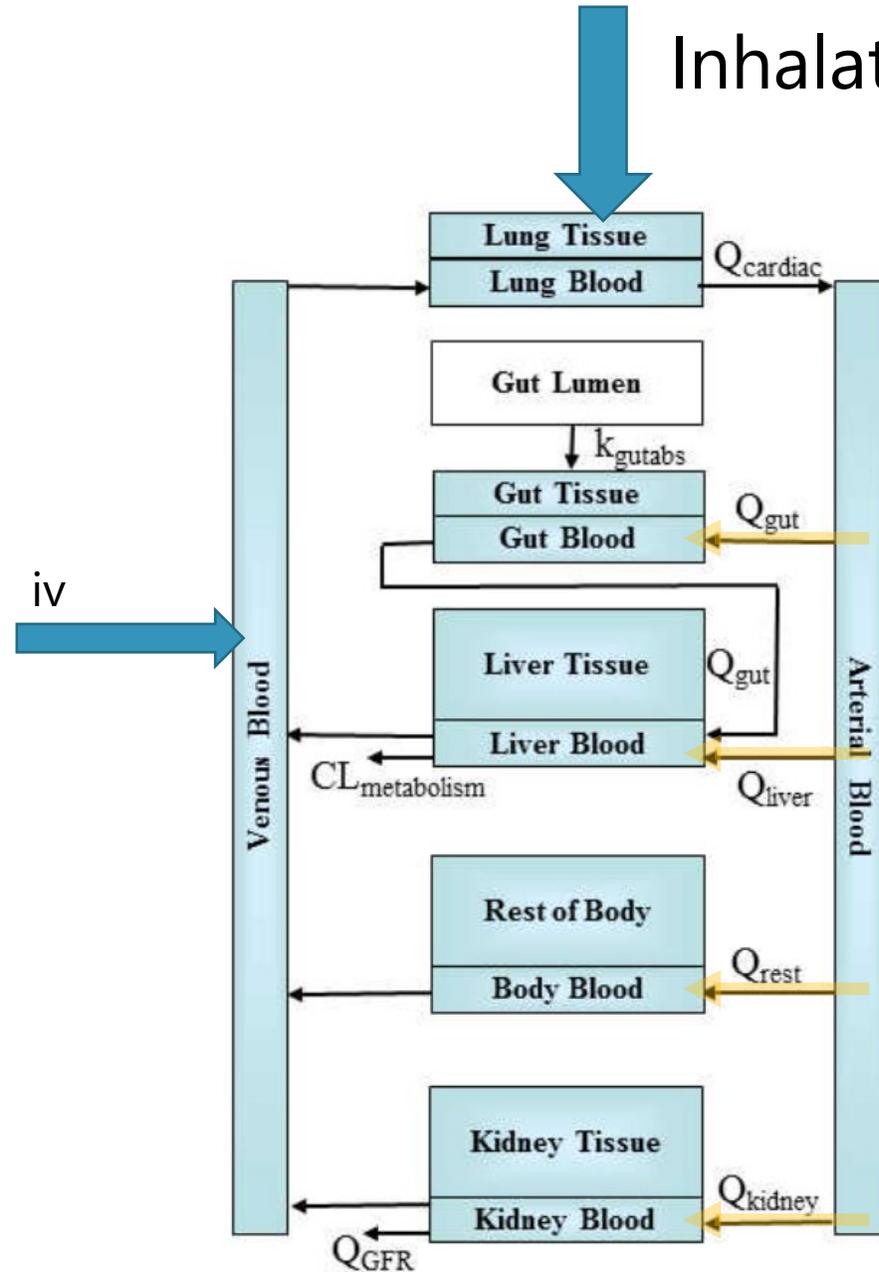
Why generic PBTK modeling (cont)?

- The core model equations can be checked once and re-used for multiple chemicals.
- Estimates are needed for PBTK parameters –
 - Partition coefficients for blood and tissues
 - Clearance values
- Experimental values for PBTK parameters are not available.
 - Can be predicted using basic physico-chemical descriptors
 - Partition coefficients are based on logKow
 - Fraction unbound – only free chemical moves into tissue
 - Clearance estimation makes use of fraction unbound.

Summary

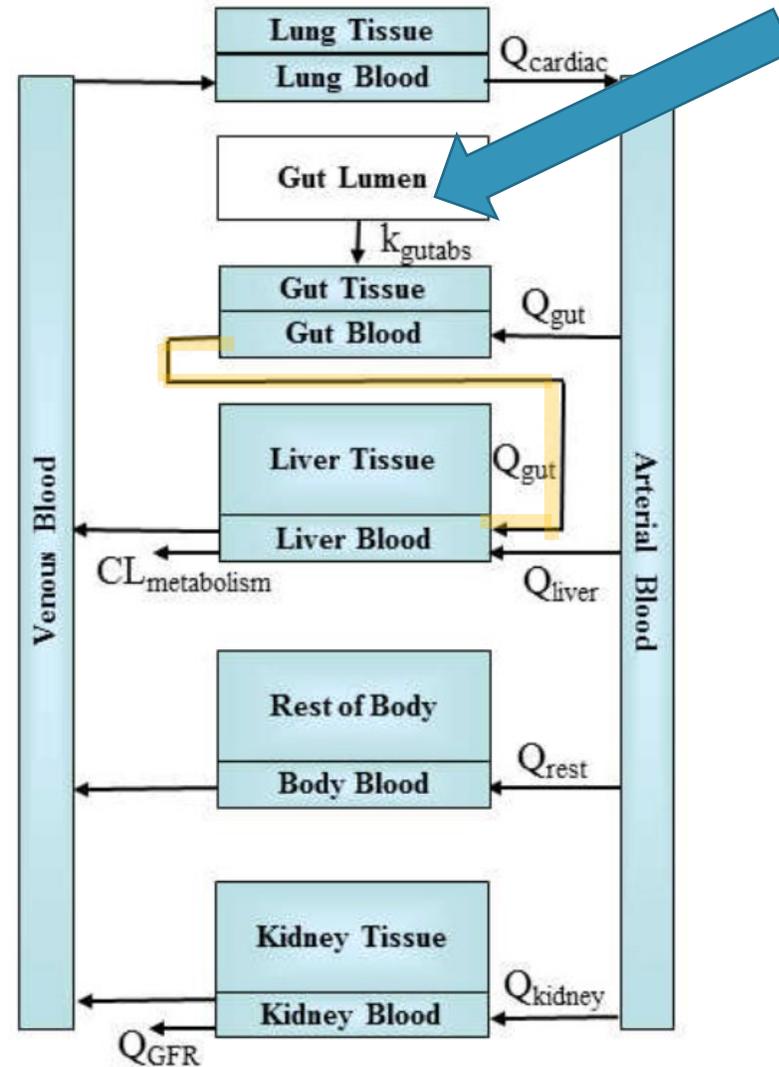
- Each of the models provided by the R package “httk” is a generic model
 - Each model is designed to use standardized chemical-specific *in vitro* measurements (fraction unbound in plasma, intrinsic hepatic clearance)
- Standardized physiology is assumed, regardless of chemical:
 - The same parameters such as volumes, flows, and rates are used
 - The same processes are included (hepatic metabolism, glomerular filtration) or omitted
- The generic model is a hypothesis
 - If we have evaluation data then we can check if we need to elaborate the model - CvTdb
- We can estimate the accuracy of a generic model for a new chemical using performance across multiple chemicals where data happen to exist

**highthrought
toxicokinetics =**
***In vitro* toxicokinetic data +
generic toxicokinetic model**



Inhalation

Inhalation and iv are similar in that same amount is distributed by arterial blood in parallel to each tissue by each organ's blood flow.



Oral dosing is different in that the full dose is seen by the liver first, then a fraction is cleared by the liver. The remaining amount returns to the body via venous blood.

This concept is known as **first pass effect** due to clearance by the liver.

Difference between R and RStudio

R is a programming language. <https://www.r-project.org/>

Rstudio is an Integrated Development Environment (IDE) designed for R.

<https://rstudio-education.github.io/hopr/starting.html>

Instructions included for MAC, Windows and UNIX

This course will make use of Rstudio for all examples.

If you do not have Rstudio installed, you can use:

<https://web.pdx.edu/~gerbing/R/RStudioCloud.pdf>

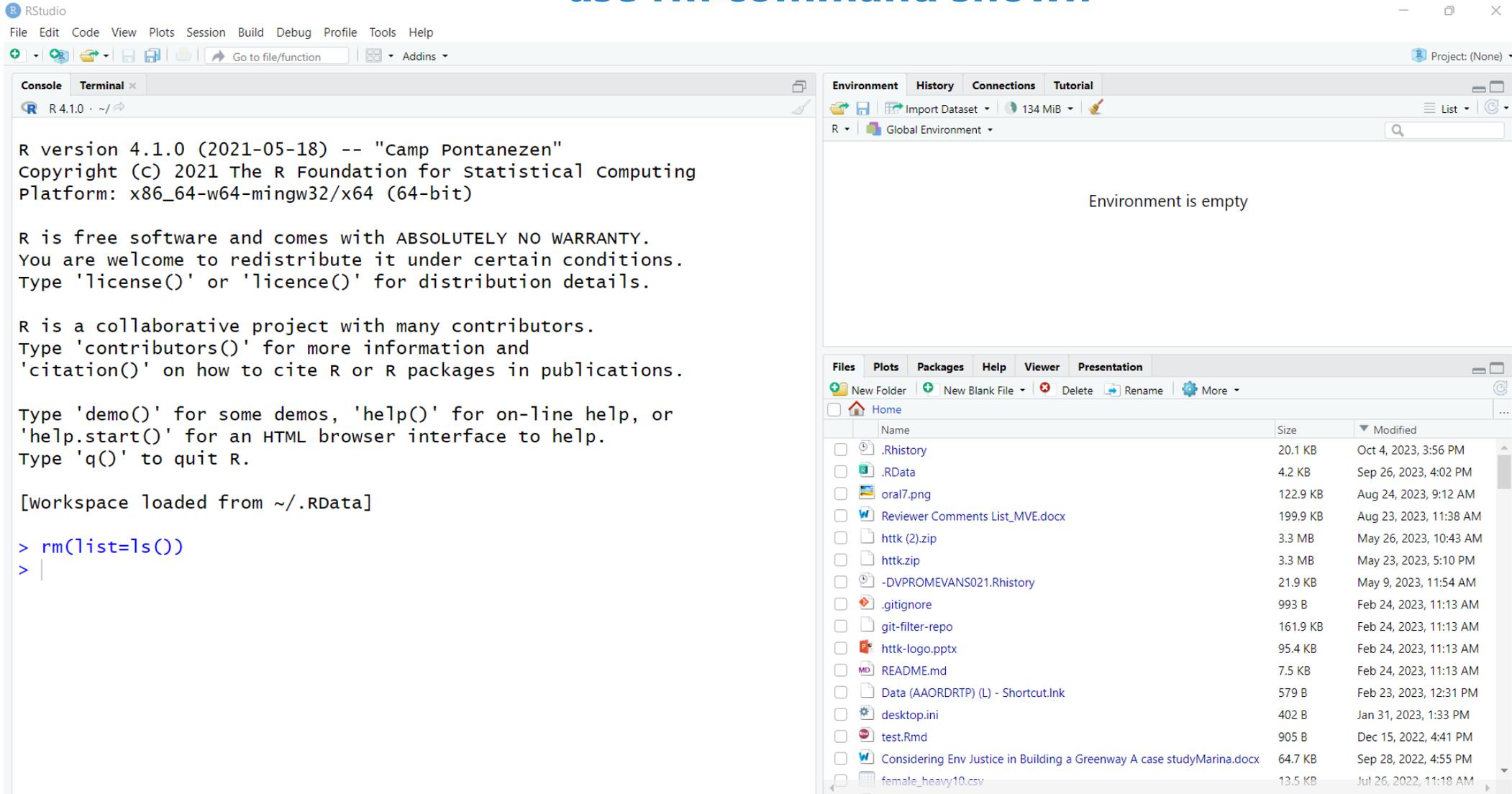
Note that you will need to create a free account before using.

Live Demonstration

R Studio

This portion of the training will be presented live. The following slides are meant to be a guide, but may not be the exact content presented during the training.

To clear previous calculations shown in the environment panel use rm command shown



The screenshot shows the RStudio interface. The console window on the left displays the R version information and the command `rm(list=ls())` being entered. The environment panel on the right shows that the environment is empty.

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"  
Copyright (C) 2021 The R Foundation for Statistical Computing  
Platform: x86_64-w64-mingw32/x64 (64-bit)  
  
R is free software and comes with ABSOLUTELY NO WARRANTY.  
You are welcome to redistribute it under certain conditions.  
Type 'license()' or 'licence()' for distribution details.  
  
R is a collaborative project with many contributors.  
Type 'contributors()' for more information and  
'citation()' on how to cite R or R packages in publications.  
  
Type 'demo()' for some demos, 'help()' for on-line help, or  
'help.start()' for an HTML browser interface to help.  
Type 'q()' to quit R.  
  
[workspace loaded from ~/.RData]  
  
> rm(list=ls())  
> |
```

Environment is empty

Name	Size	Modified
.Rhistory	20.1 KB	Oct 4, 2023, 3:56 PM
.RData	4.2 KB	Sep 26, 2023, 4:02 PM
oral7.png	122.9 KB	Aug 24, 2023, 9:12 AM
Reviewer Comments List_MVE.docx	199.9 KB	Aug 23, 2023, 11:38 AM
httk (2).zip	3.3 MB	May 26, 2023, 10:43 AM
httk.zip	3.3 MB	May 23, 2023, 5:10 PM
-DVPROMEVANS021.Rhistory	21.9 KB	May 9, 2023, 11:54 AM
.gitignore	993 B	Feb 24, 2023, 11:13 AM
git-filter-repo	161.9 KB	Feb 24, 2023, 11:13 AM
httk-logo.pptx	95.4 KB	Feb 24, 2023, 11:13 AM
README.md	7.5 KB	Feb 24, 2023, 11:13 AM
Data (AAORDRTP) (L) - Shortcut.lnk	579 B	Feb 23, 2023, 12:31 PM
desktop.ini	402 B	Jan 31, 2023, 1:33 PM
test.Rmd	905 B	Dec 15, 2022, 4:41 PM
Considering Env Justice in Building a Greenway A case studyMarina.docx	64.7 KB	Sep 28, 2022, 4:55 PM
female_heavy10.csv	13.5 KB	Jul 26, 2022, 11:18 AM

RStudio

File Edit Code View Plots Session Build Debug Profile Tools Help

Go to file/function Addins Project: (None)

Environment History Connections Tutorial

Import Dataset 159 MiB

R Global Environment

Environment is empty

Files Plots Packages Help Viewer Presentation

Install Update

Name	Description	Version
System Library		
<input type="checkbox"/> abind	Combine Multidimensional Arrays	1.4-5
<input type="checkbox"/> alabama	Constrained Nonlinear Optimization	2022.4-1
<input type="checkbox"/> askpass	Safe Password Entry for R, Git, and SSH	1.1
<input type="checkbox"/> assertthat	Easy Pre and Post Assertions	0.2.1
<input type="checkbox"/> backports	Reimplementations of Functions Introduced Since R-3.0.0	1.4.1
<input checked="" type="checkbox"/> base	The R Base Package	4.1.0
<input type="checkbox"/> base64enc	Tools for base64 encoding	0.1-3
<input type="checkbox"/> BH	Boost C++ Header Files	1.78.0-0
<input type="checkbox"/> BiocGenerics	S4 generic functions used in Bioconductor	0.40.0
<input type="checkbox"/> BiocManager	Access the Bioconductor Project Package Repository	1.30.16
<input type="checkbox"/> BiocVersion	Set the appropriate version of Bioconductor packages	3.14.0
<input type="checkbox"/> bit	Classes and Methods for Fast Memory-Efficient Boolean Selections	4.0.4
<input type="checkbox"/> bit64	A S3 Class for Vectors of 64bit Integers	4.0.5
<input type="checkbox"/> bitops	Bitwise Operations	1.0-7
<input type="checkbox"/> blob	A Simple S3 Class for Representing Vectors of Binary Data ('BLOBS')	1.2.2
<input type="checkbox"/> boot	Bootstrap Functions (Originally by Angelo Canty for S)	1.3-28

Install Packages

Install from: Repository (CRAN) [? Configuring Repositories](#)

Repositories (separate multiple with space or comma):

httk

httk to Library: C:/Program Files/R/R-4.1.0/library [Default]

Install dependencies

Install Cancel

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"
Copyright (C) 2021 The R Foundation for Statistical Computing
Platform: x86_64-w64-mingw32/x64 (64-bit)

R is free software and comes with ABSOLUTELY NO WARRANTY.
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Type 'license()' or 'licence()' for distribution details

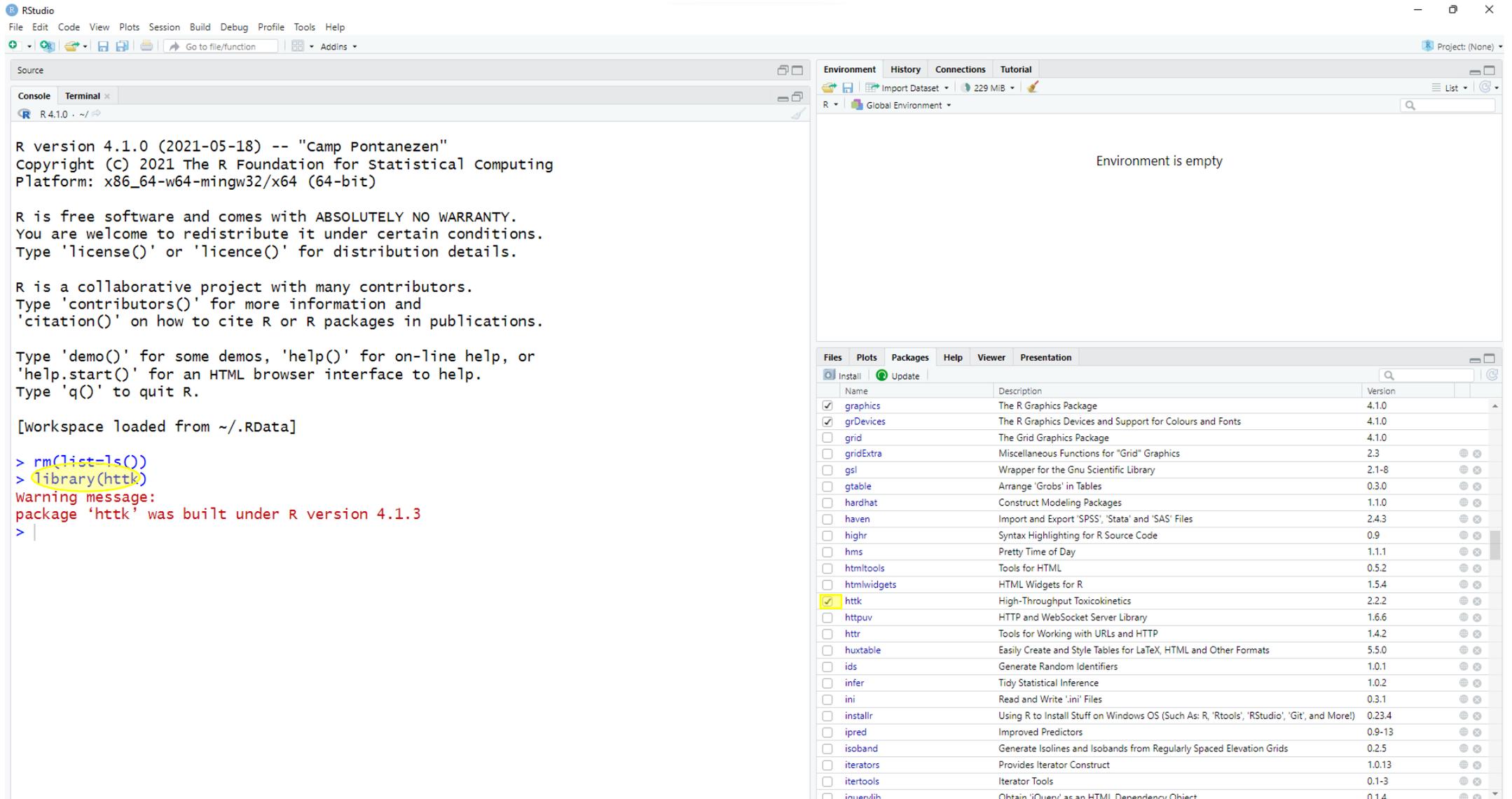
R is a collaborative project with many contributors.
Type 'contributors()' for more information and
'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

[workspace loaded from ~/.RData]

> rm(list=ls())
>
```

Packages are listed alphabetically inside package tab. Look for httk and check the box

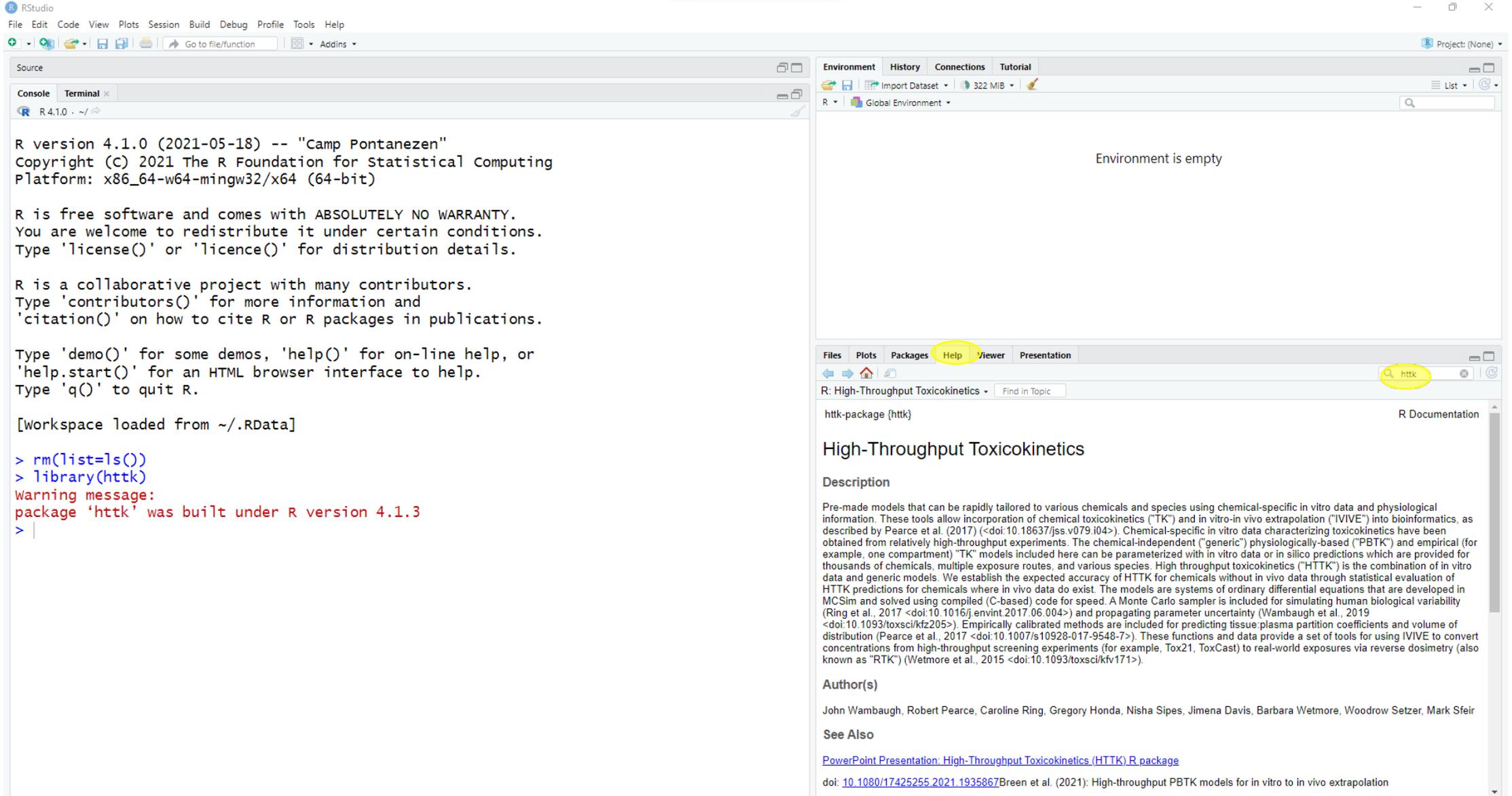


The screenshot shows the RStudio interface. The console on the left displays the R startup message and the execution of the `library(httk)` command, which results in a warning message: "Warning message: package 'httk' was built under R version 4.1.3". The Packages tab on the right shows a list of installed and available packages. The `httk` package is highlighted with a yellow box, and its checkbox is checked.

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"  
Copyright (C) 2021 The R Foundation for Statistical Computing  
Platform: x86_64-w64-mingw32/x64 (64-bit)  
  
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Type 'demo()' for some demos, 'help()' for on-line help, or  
'help.start()' for an HTML browser interface to help.  
Type 'q()' to quit R.  
  
[workspace loaded from ~/.RData]  
> rm(list=ls())  
> library(httk)  
Warning message:  
package 'httk' was built under R version 4.1.3  
> |
```

Name	Description	Version
<input checked="" type="checkbox"/> graphics	The R Graphics Package	4.1.0
<input checked="" type="checkbox"/> grDevices	The R Graphics Devices and Support for Colours and Fonts	4.1.0
<input type="checkbox"/> grid	The Grid Graphics Package	4.1.0
<input type="checkbox"/> gridExtra	Miscellaneous Functions for "Grid" Graphics	2.3
<input type="checkbox"/> gsl	Wrapper for the Gnu Scientific Library	2.1-8
<input type="checkbox"/> gtable	Arrange 'Grobs' in Tables	0.3.0
<input type="checkbox"/> hardhat	Construct Modeling Packages	1.1.0
<input type="checkbox"/> haven	Import and Export 'SPSS', 'Stata' and 'SAS' Files	2.4.3
<input type="checkbox"/> highr	Syntax Highlighting for R Source Code	0.9
<input type="checkbox"/> hms	Pretty Time of Day	1.1.1
<input type="checkbox"/> htmltools	Tools for HTML	0.5.2
<input type="checkbox"/> htmlwidgets	HTML Widgets for R	1.5.4
<input checked="" type="checkbox"/> httk	High-Throughput Toxicokinetics	2.2.2
<input type="checkbox"/> httpuv	HTTP and WebSocket Server Library	1.6.6
<input type="checkbox"/> httr	Tools for Working with URLs and HTTP	1.4.2
<input type="checkbox"/> huxtable	Easily Create and Style Tables for LaTeX, HTML and Other Formats	5.5.0
<input type="checkbox"/> ids	Generate Random Identifiers	1.0.1
<input type="checkbox"/> infer	Tidy Statistical Inference	1.0.2
<input type="checkbox"/> ini	Read and Write '.ini' Files	0.3.1
<input type="checkbox"/> installr	Using R to Install Stuff on Windows OS (Such As: R, 'Rtools', 'RStudio', 'Git', and More!)	0.23.4
<input type="checkbox"/> ipred	Improved Predictors	0.9-13
<input type="checkbox"/> isoband	Generate Isolines and Isobands from Regularly Spaced Elevation Grids	0.2.5
<input type="checkbox"/> iterators	Provides Iterator Construct	1.0.13
<input type="checkbox"/> itertools	Iterator Tools	0.1-3
<input type="checkbox"/> iouenvlib	Obtain 'IOEnv' as an HTML Dependency Object	0.1.4

Help feature inside httk package



The screenshot shows the RStudio interface. The console on the left displays the R startup message and the execution of `rm(list=ls())` and `library(httk)`. A warning message indicates that the `httk` package was built under R version 4.1.3. The Environment pane on the right shows an empty environment. The Help pane on the right displays the help page for the `httk` package, titled "High-Throughput Toxicokinetics". The help page includes a description of the package, which provides pre-made models for various chemicals and species, and lists the authors: John Wambaugh, Robert Pearce, Caroline Ring, Gregory Honda, Nisha Sipes, Jimena Davis, Barbara Wetmore, Woodrow Setzer, and Mark Sfeir. A "See Also" section includes a link to a PowerPoint presentation and a DOI for a related paper.

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"
Copyright (C) 2021 The R Foundation for Statistical Computing
Platform: x86_64-w64-mingw32/x64 (64-bit)

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'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

[Workspace loaded from ~/.RData]

> rm(list=ls())
> library(httk)
Warning message:
package 'httk' was built under R version 4.1.3
> |
```

Environment is empty

Files Plots Packages **Help** Viewer Presentation

R: High-Throughput Toxicokinetics Find in Topic

httk-package (httk) R Documentation

High-Throughput Toxicokinetics

Description

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>).

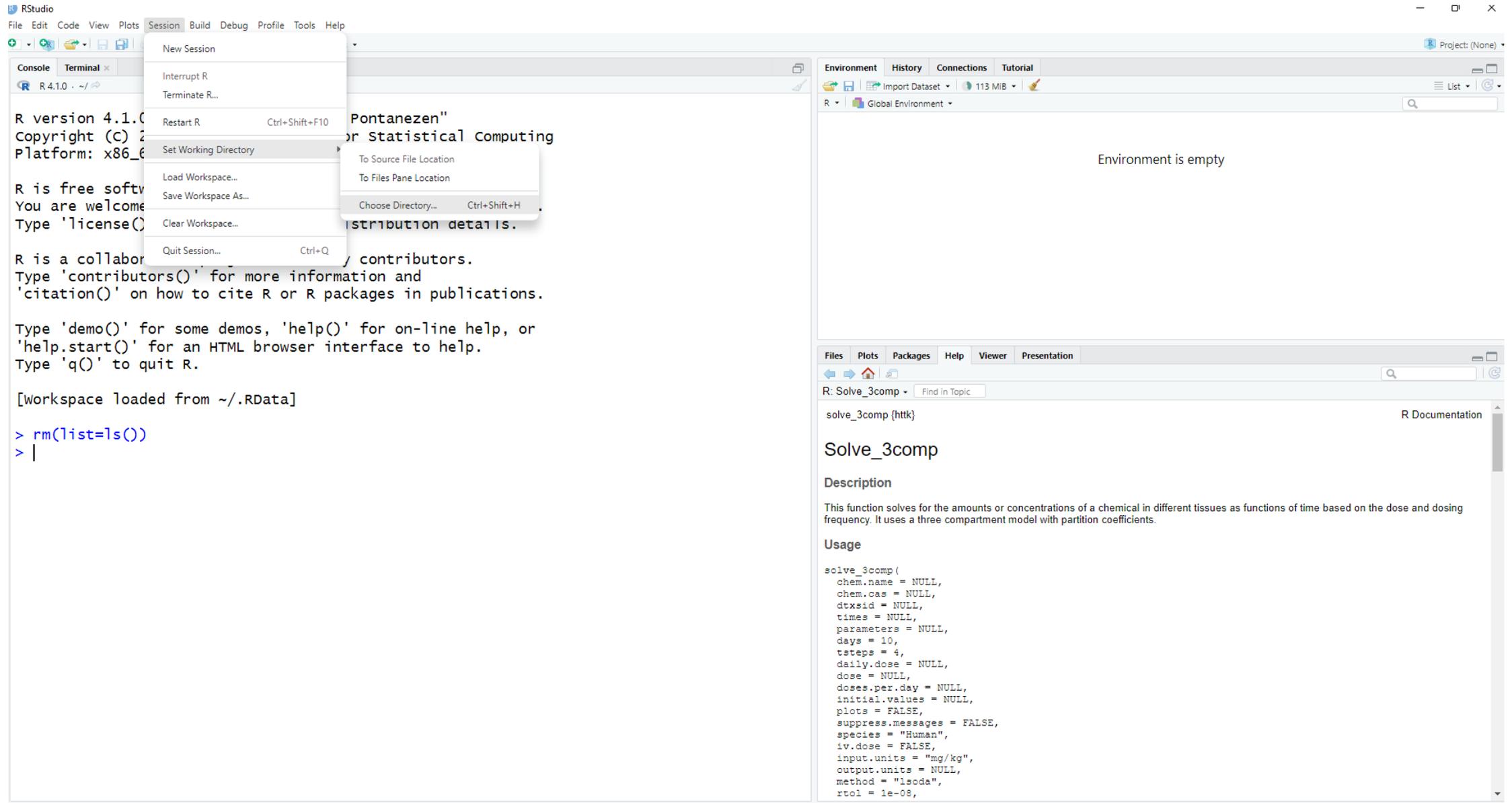
Author(s)

John Wambaugh, Robert Pearce, Caroline Ring, Gregory Honda, Nisha Sipes, Jimena Davis, Barbara Wetmore, Woodrow Setzer, Mark Sfeir

See Also

[PowerPoint Presentation: High-Throughput Toxicokinetics \(HTTK\) R package](#)
doi: [10.1080/17425255.2021.1935867](https://doi.org/10.1080/17425255.2021.1935867) Breen et al. (2021): High-throughput PBTK models for in vitro to in vivo extrapolation

Starting a session and choosing a folder



The screenshot shows the RStudio interface. The 'Session' menu is open, displaying options such as 'New Session', 'Interrupt R', 'Restart R', 'Set Working Directory', 'Load Workspace...', 'Save Workspace As...', 'Clear Workspace...', and 'Quit Session...'. The 'Set Working Directory' sub-menu is also visible, showing options like 'To Source File Location', 'To Files Pane Location', and 'Choose Directory...'. The 'Environment' pane on the right shows 'Environment is empty'. The 'Files' pane at the bottom shows the file 'R: Solve_3comp' selected, with its documentation displayed in the 'Viewer' pane.

```
R version 4.1.0
Copyright (C) 2020
Platform: x86_64-pc-linux-gnu

R is free software; you are welcome to redistribute it under certain
conditions. See the file 'COPYING' for details.

R is a collaborative project with many contributors.
Type 'contributors()' for more information and
'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

[workspace loaded from ~/.RData]
> rm(list=ls())
> |
```

Environment is empty

R: Solve_3comp {httk}

Solve_3comp

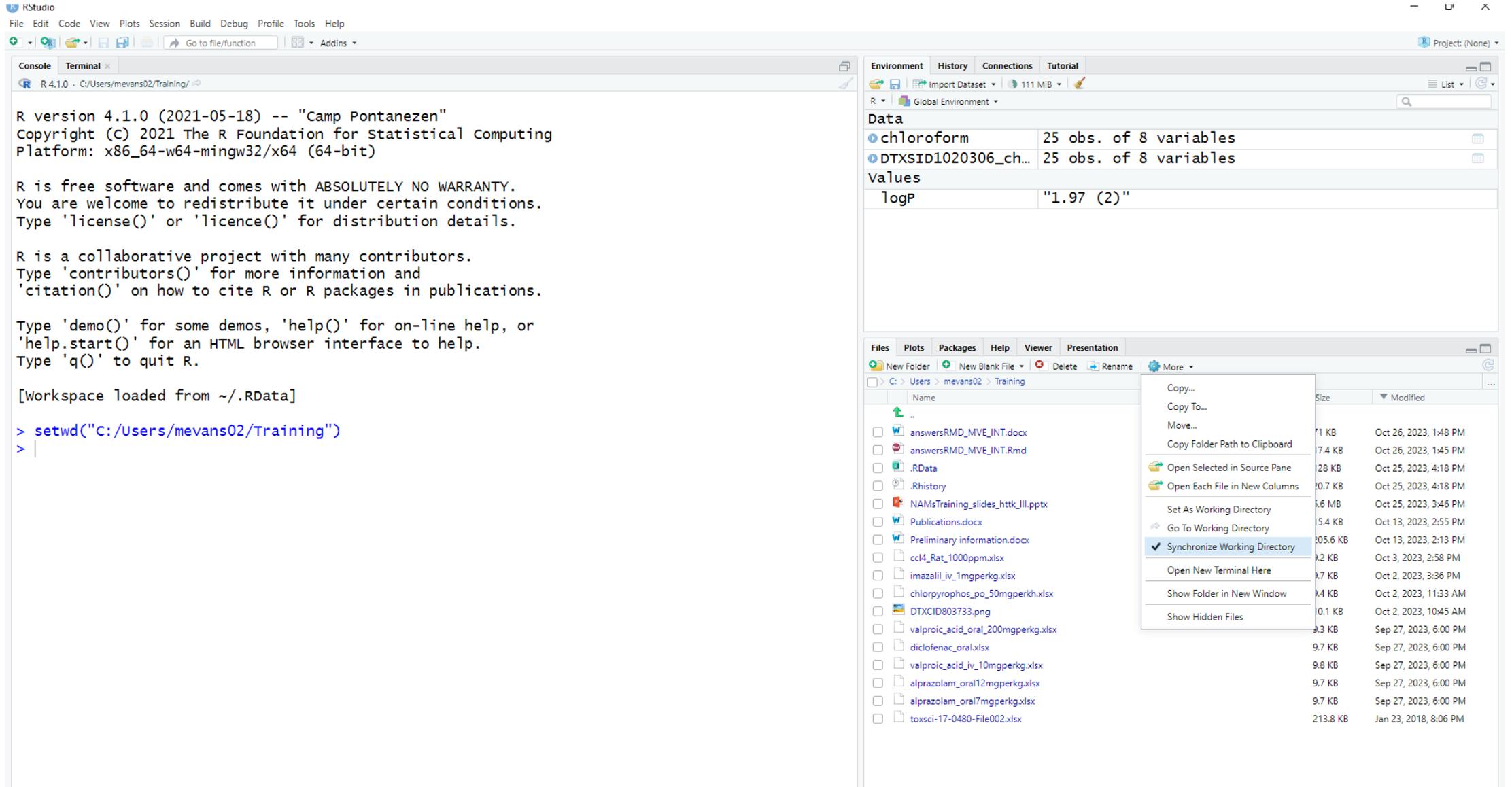
Description

This function solves for the amounts or concentrations of a chemical in different tissues as functions of time based on the dose and dosing frequency. It uses a three compartment model with partition coefficients.

Usage

```
solve_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  method = "lsoda",
  rtol = 1e-08,
```

How to synchronize your files with your R path



The screenshot displays the RStudio environment. The console on the left shows the R version (4.1.0) and the current working directory (C:/Users/mevans02/Training/). The file explorer on the right shows a list of files in the Training directory, with a context menu open over the directory, highlighting the 'Synchronize Working Directory' option.

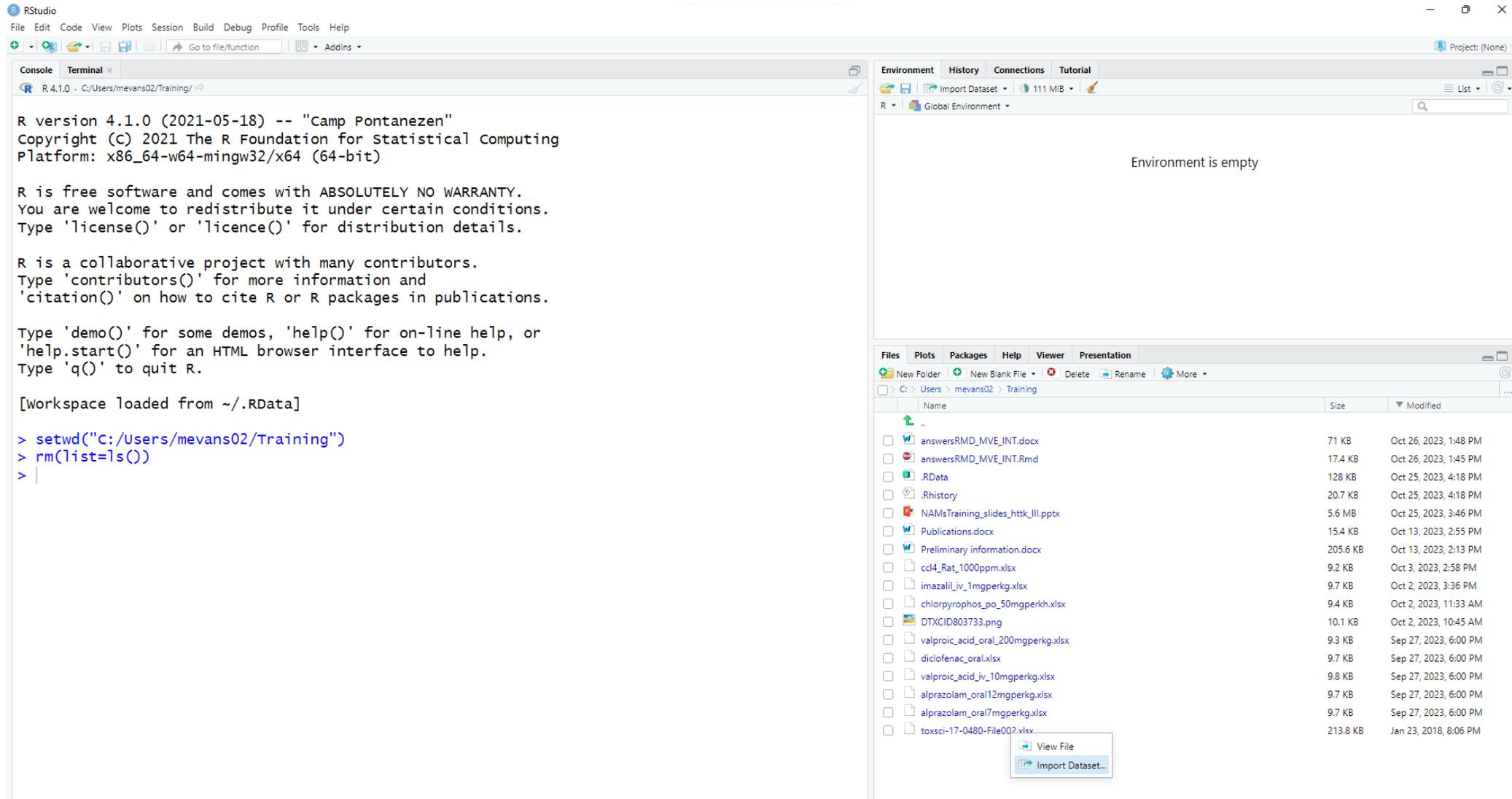
Console Output:

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"  
Copyright (C) 2021 The R Foundation for Statistical Computing  
Platform: x86_64-w64-mingw32/x64 (64-bit)  
  
R is free software and comes with ABSOLUTELY NO WARRANTY.  
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R is a collaborative project with many contributors.  
Type 'contributors()' for more information and  
'citation()' on how to cite R or R packages in publications.  
  
Type 'demo()' for some demos, 'help()' for on-line help, or  
'help.start()' for an HTML browser interface to help.  
Type 'q()' to quit R.  
  
[workspace loaded from ~/.RData]  
  
> setwd("C:/Users/mevans02/Training")  
> |
```

File Explorer Context Menu:

- Copy...
- Copy To...
- Move...
- Copy Folder Path to Clipboard
- Open Selected in Source Pane
- Open Each File in New Columns
- Set As Working Directory
- Go To Working Directory
- Synchronize Working Directory**
- Open New Terminal Here
- Show Folder in New Window
- Show Hidden Files

Reading an .xlsx file using readxl package



The screenshot shows the RStudio interface. The console on the left displays the R version information and the results of the commands `setwd("C:/Users/mevans02/Training")` and `rm(list=ls())`. The Environment pane on the right shows that the environment is empty.

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"  
Copyright (c) 2021 The R Foundation for Statistical Computing  
Platform: x86_64-w64-mingw32/x64 (64-bit)  
  
R is free software and comes with ABSOLUTELY NO WARRANTY.  
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Type 'demo()' for some demos, 'help()' for on-line help, or  
'help.start()' for an HTML browser interface to help.  
Type 'q()' to quit R.  
  
[Workspace loaded from ~/.RData]  
  
> setwd("C:/Users/mevans02/Training")  
> rm(list=ls())  
> |
```

Environment is empty

Name	Size	Modified
..		
answersRMD_MVE_INT.docx	71 KB	Oct 26, 2023, 1:48 PM
answersRMD_MVE_INT.Rmd	17.4 KB	Oct 26, 2023, 1:45 PM
.RData	128 KB	Oct 25, 2023, 4:18 PM
.Rhistory	20.7 KB	Oct 25, 2023, 4:18 PM
NAMsTraining_slides_httk_III.pptx	5.6 MB	Oct 25, 2023, 3:46 PM
Publications.docx	15.4 KB	Oct 13, 2023, 2:55 PM
Preliminary information.docx	205.6 KB	Oct 13, 2023, 2:13 PM
cci4_Rat_1000ppm.xlsx	9.2 KB	Oct 3, 2023, 2:58 PM
imazalil_iv_1mgperkg.xlsx	9.7 KB	Oct 2, 2023, 3:36 PM
chlorpyrifos_po_50mgperkh.xlsx	9.4 KB	Oct 2, 2023, 11:33 AM
DTXCID803733.png	10.1 KB	Oct 2, 2023, 10:45 AM
valproic_acid_oral_200mgperkg.xlsx	9.3 KB	Sep 27, 2023, 6:00 PM
diclofenac_oral.xlsx	9.7 KB	Sep 27, 2023, 6:00 PM
valproic_acid_iv_10mgperkg.xlsx	9.8 KB	Sep 27, 2023, 6:00 PM
alprazolam_oral12mgperkg.xlsx	9.7 KB	Sep 27, 2023, 6:00 PM
alprazolam_oral7mgperkg.xlsx	9.7 KB	Sep 27, 2023, 6:00 PM
toxsci-17-0480-File002.xlsx	213.8 KB	Jan 23, 2018, 8:06 PM

Import Dataset > From Excel

The readxl package must be installed before importing or you will get an error

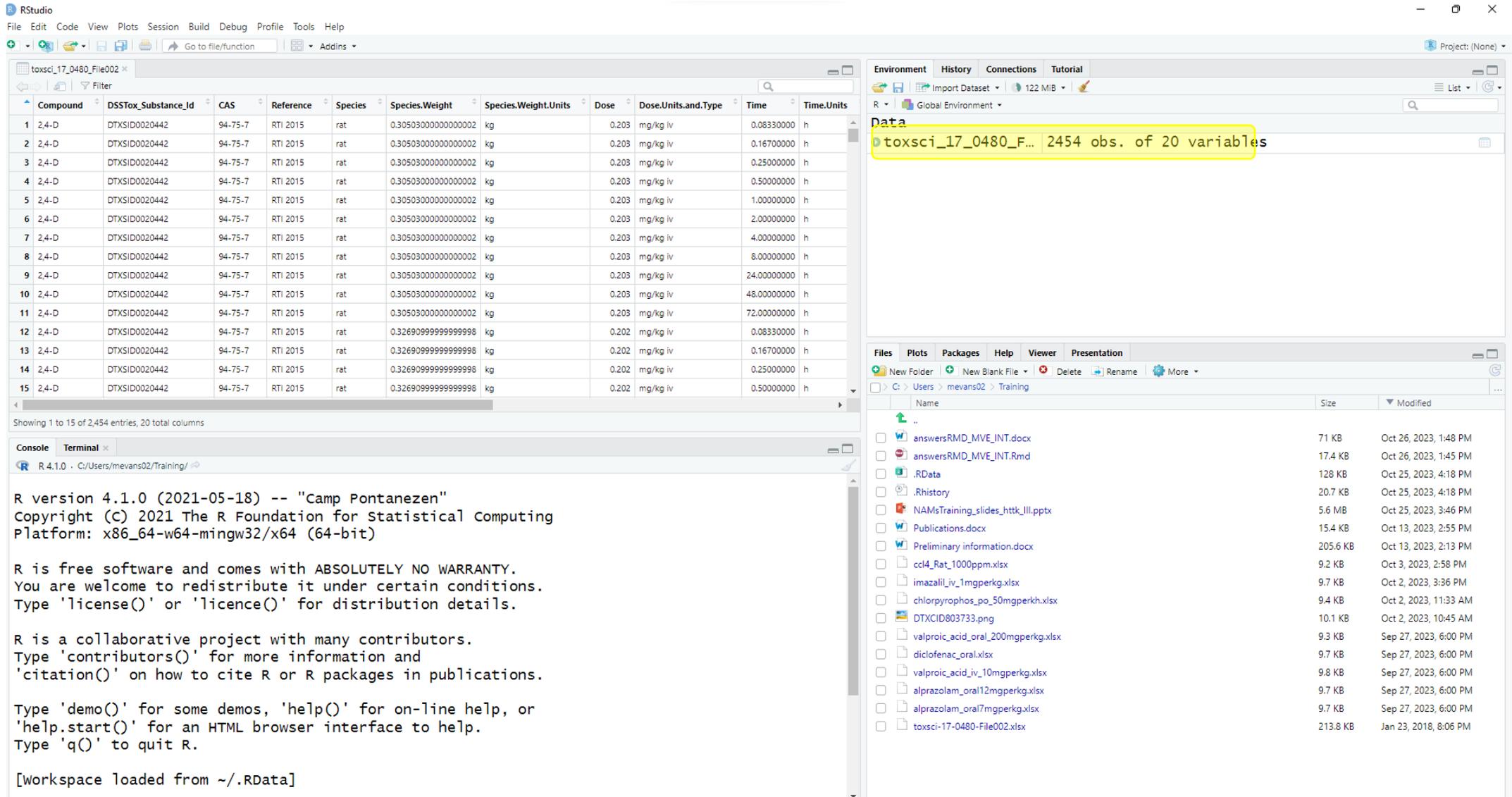
The screenshot shows the RStudio 'Import Excel Data' dialog box. The 'File/URL' field contains the path 'C:/Users/mevans02/Training/toxsci-17-0480-File002.xlsx'. The 'Data Preview' section displays a table with 15 columns: Compound, DSSTox_Substance_Id, CAS, Reference, Species, Species.Weight, Species.Weight.Units, Dose, Dose.Units.and.Type, Time, Time.Units, Media, Media.Units, and Value. The table contains 20 rows of data. Below the table, the 'Import Options' section includes fields for Name (toxsci_17_0480_File002), Sheet (Default), and Range (A1:D10), along with checkboxes for 'First Row as Names' and 'Open Data Viewer'. The 'Code Preview' section shows the following R code:

```
library(readxl)
toxsci_17_0480_File002 <- read_excel("toxsci-17-0480-File002.xlsx")
View(toxsci_17_0480_File002)
```

 At the bottom right, the 'Import' button is highlighted with a yellow circle.

Compound	DSSTox_Substance_Id	CAS	Reference	Species	Species.Weight	Species.Weight.Units	Dose	Dose.Units.and.Type	Time	Time.Units	Media	Media.Units	Value
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	0.0833	h	Plasma concentration	ug/mL	0.709500000000000
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	0.1670	h	Plasma concentration	ug/mL	0.466000000000000
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	0.2500	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	0.5000	h	Plasma concentration	ug/mL	0.1925
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	1.0000	h	Plasma concentration	ug/mL	7.145E-2
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	2.0000	h	Plasma concentration	ug/mL	2.19999999999999
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	4.0000	h	Plasma concentration	ug/mL	1.84500000000000
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	8.0000	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	24.0000	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	48.0000	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.30503000000000002	kg	0.203	mg/kg iv	72.0000	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	0.0833	h	Plasma concentration	ug/mL	0.461000000000000
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	0.1670	h	Plasma concentration	ug/mL	0.25
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	0.2500	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	0.5000	h	Plasma concentration	ug/mL	7.96999999999999
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	1.0000	h	Plasma concentration	ug/mL	3.23000000000000
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	2.0000	h	Plasma concentration	ug/mL	3.075E-2
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	4.0000	h	Plasma concentration	ug/mL	7.74999999999999
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	8.0000	h	Plasma concentration	ug/mL	NA
2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.32690999999999998	kg	0.202	mg/kg iv	24.0000	h	Plasma concentration	ug/mL	NA

Data frame will be shown in the upper left corner – script window



The screenshot shows the RStudio interface with a data frame loaded in the upper left corner. The data frame has 15 rows and 11 columns. The columns are: Compound, DSSTox_Substance_Id, CAS, Reference, Species, Species.Weight, Species.Weight.Units, Dose, Dose.Units.and.Type, Time, and Time.Units. The data shows 15 entries for compound 2,4-D, all with a species of rat and a dose of 0.202 mg/kg iv. The time values range from 0.063300000 h to 0.500000000 h.

Compound	DSSTox_Substance_Id	CAS	Reference	Species	Species.Weight	Species.Weight.Units	Dose	Dose.Units.and.Type	Time	Time.Units	
1	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.063300000	h
2	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.167000000	h
3	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.250000000	h
4	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.500000000	h
5	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	1.000000000	h
6	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	2.000000000	h
7	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	4.000000000	h
8	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	8.000000000	h
9	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	24.000000000	h
10	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	48.000000000	h
11	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	72.000000000	h
12	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.326909999999999998	kg	0.202	mg/kg iv	0.063300000	h
13	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.326909999999999998	kg	0.202	mg/kg iv	0.167000000	h
14	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.326909999999999998	kg	0.202	mg/kg iv	0.250000000	h
15	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.326909999999999998	kg	0.202	mg/kg iv	0.500000000	h

The console window at the bottom shows the R version and copyright information, followed by a message indicating that the workspace was loaded from the .RData file.

```
R version 4.1.0 (2021-05-18) -- "Camp Pontanezen"
Copyright (C) 2021 The R Foundation for Statistical Computing
Platform: x86_64-w64-mingw32/x64 (64-bit)

R is free software and comes with ABSOLUTELY NO WARRANTY.
You are welcome to redistribute it under certain conditions.
Type 'license()' or 'licence()' for distribution details.

R is a collaborative project with many contributors.
Type 'contributors()' for more information and
'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

[workspace loaded from ~/.RData]
```

- We are going to use provided time course data published as supplementary information using excel file.
- All data is specific to rat, route is either iv or oral.
- There are three chemical identifiers used in httk:
 - Chemical name
 - CAS number
 - DTXSID number (US EPA generated these identifiers)

In httk,

Chemical name chem.name=""

CAS number chem.cas=""

DTXSID number dtxsid=""

Please note: **R is case sensitive.**

Live Demonstration

Introduction to R Commands

Basic R commands

- Variables names are called symbols in R and are stored in the environment window.
- Names are case sensitive, must not contain reserved words and can have unlimited length.
- Variable names cannot start with an `_` (underscore).
- You can assign a value to a variable using `<-` operator.
- Example:
`logP <- 2.2` and `LogP <- 2.2` are different variables

How to index a column/matrix of numbers in R

- First, let's create a column of numbers:

```
even<-c(2,4,6,8,10)
```

- The column is indexed from 1 thru 5 in sequential order. R always starts with a number one index.
- To obtain the number 6, we need to refer to the third index. In the Rstudio console type:

```
>even[3]
```

```
[1] 6
```

- Matrices have both rows and columns. Inside the brackets, always start with [row,column]

```
> numbers<-matrix(1:10, nrow=2,ncol=5)
```

```
> numbers
```

	[,1]	[,2]	[,3]	[,4]	[,5]
[1,]	1	3	5	7	9
[2,]	2	4	6	8	10

```
> numbers[2,4]
```

```
[1] 8
```

We can set `y` as a vector of numbers and find its range and its length

```
> y = c(0, 1.1, 2.4, 3, 3.6, 3.4, 3, 2.2)
> y
[1] 0.0 1.1 2.4 3.0 3.6 3.4 3.0 2.2
> min(y); max(y)
[1] 0
[1] 3.6
> range(y)
[1] 0.0 3.6
> tail(y,1)
[1] 2.2
> length(y)
[1] 8
> y[length(y)]
[1] 2.2
```

A vector can also contain characters

```
> variables = c("time", "concentration")
> variables
[1] "time"          "concentration"
```

Set a sequence of numbers: `seq(from, to, step)`

```
> x = seq(1,8,1)
> x
[1] 1 2 3 4 5 6 7 8
```

Combine columns with cbind (or rbind to join by row)

```
> mat = cbind(x,y); colnames(mat) = variables
> mat
      time concentration
[1,]    1           0.0
[2,]    2           1.1
[3,]    3           2.4
[4,]    4           3.0
[5,]    5           3.6
[6,]    6           3.4
[7,]    7           3.0
[8,]    8           2.2
> mat[,"time"]
[1] 1 2 3 4 5 6 7 8
```

Or create a data frame (use the \$ operator to call columns)

```
> df = data.frame(x = x,y = y); colnames(df) = variables
> df$concentration
[1] 0.0 1.1 2.4 3.0 3.6 3.4 3.0 2.2
```

Load and analyze data from an excel file

```
# Install "readxl" if not already installed and load it with "library"  
install.packages("readxl")  
library(readxl)
```

Remember to have the .xlsx file loaded in your same working directory!

- Read in ToxSci data and convert it to a data frame

```
> toxsci.data <- data.frame(read_excel("toxsci-17-0480-File002.xlsx"))
```

- Find what information is contained in toxsci.data through the column names.
- Find the dimensions of the data frame.

```
> colnames(toxsci.data)  
[1] "Compound"          "DSSTox_Substance_Id" "CAS"          "Reference"  
[5] "Species"           "Species.Weight"     "Species.Weight.Units" "Dose"  
[9] "Dose.Units.and.Type" "Time"              "Time.Units"    "Media"  
[13] "Media.Units"       "Value"             "Units"         "Route"  
[17] "Source"           "LOQ"              "Subject"       "info"  
> nrow(toxsci.data); ncol(toxsci.data)  
[1] 2454  
[1] 20  
> dim(toxsci.data)  
[1] 2454 20
```

This data file has 2454 rows of data and 20 columns to describe each row.

You may notice that there are repeated values in many columns. Find the unique values of elements from a vector with repeats using `unique()`.

Here, we find the unique names of the compounds in the data file.

```
> unique(toxsci.data$Compound)
 [1] "2,4-D"                "Alachlor"           "Alprazolam"
 [4] "Antipyrine"          "Bensulide"         "Bisphenol A"
 [7] "Boscalid"            "Bosentan"         "Carbaryl"
[10] "Carbendazim"        "Chloridazon"      "Chlorpyrifos"
[13] "Cyclanilide"        "Cyclosporin A"   "Diazinon-o-analog"
[16] "Diclofenac"         "Diltiazem"        "Dimethenamid"
[19] "Etoxazole"          "Fenarimol"        "Flufenacet"
[22] "Formetanate hydrochloride" "Hexobarbitone"   "Ibuprofen"
[25] "Imazalil"           "Imidacloprid"    "Imipramine"
[28] "Metoprolol"         "Midazolam"        "Nilvadipine"
[31] "Novaluron"          "Ondansetron"      "Pentadecafluorooctanoic acid"
[34] "Permethrin"         "Phenacetin"       "Phenytoin"
[37] "Propamocarb hydrochloride" "Propyzamide"     "Pyriithiobac sodium"
[40] "Resmethrin"         "S-Bioallethrin"  "Simazine"
[43] "Tolbutamide"        "Triclosan"        "Valproic acid"
```

Subset the data to contain information only for the compound "2,4-D"

```
> chemical_24d = subset(toxsci.data, Compound == "2,4-D")
> head(chemical_24d)
```

	Compound	DSSTox_Substance_Id	CAS	Reference	Species	Species.Weight	Species.Weight.Units	Dose	Dose.Units.and.Type	Time	Time.Units
1	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.0833	h
2	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.1670	h
3	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.2500	h
4	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	0.5000	h
5	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	1.0000	h
6	2,4-D	DTXSID0020442	94-75-7	RTI 2015	rat	0.305030000000000002	kg	0.203	mg/kg iv	2.0000	h

	Media	Media.Units	Value	Units	Route	Source	LOQ	Subject	info
1	Plasma concentration	ug/mL	0.709500000000000002	mg/kg	iv	RTI 2015	0.001	42736	NA
2	Plasma concentration	ug/mL	0.466000000000000003	mg/kg	iv	RTI 2015	0.001	42736	NA
3	Plasma concentration	ug/mL	NA	mg/kg	iv	RTI 2015	0.001	42736	NA
4	Plasma concentration	ug/mL	0.1925	mg/kg	iv	RTI 2015	0.001	42736	NA
5	Plasma concentration	ug/mL	7.145E-2	mg/kg	iv	RTI 2015	0.001	42736	NA
6	Plasma concentration	ug/mL	2.1999999999999999E-2	mg/kg	iv	RTI 2015	0.001	42736	NA

Find the rows that contains a certain element or has a condition (iv route and body weight conditions) and view certain columns

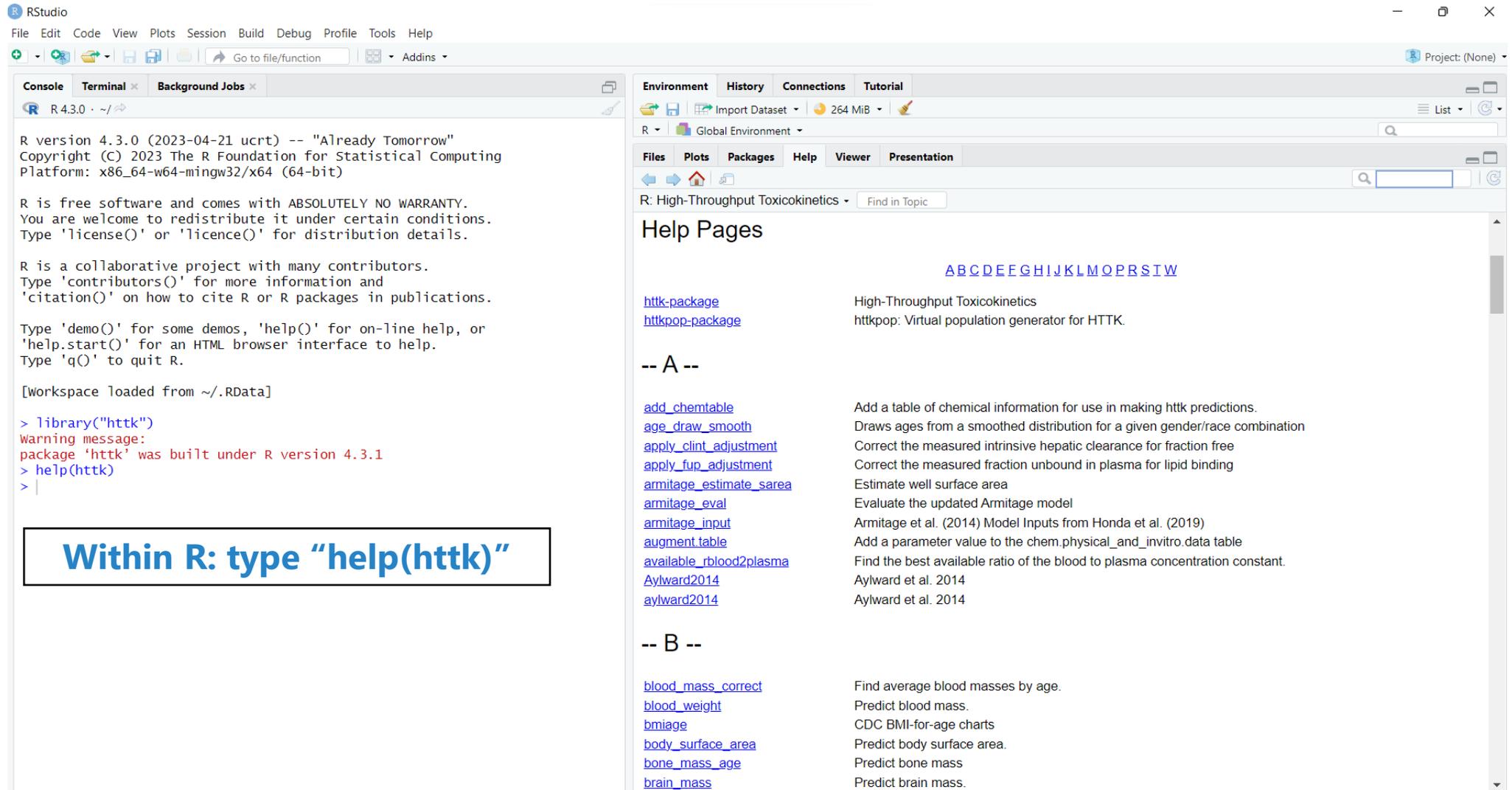
```
> these.rows = which(chemical_24d$Route== "iv" & chemical_24d$Species.Weight < .32)
> these.rows
[1] 1 2 3 4 5 6 7 8 9 10 11
> chemical_24d[these.rows,c("Time","Value")]
```

	Time	Value
1	0.0833	0.709500000000000002
2	0.1670	0.466000000000000003
3	0.2500	NA
4	0.5000	0.1925
5	1.0000	7.145E-2
6	2.0000	2.1999999999999999E-2
7	4.0000	1.84500000000000001E-3
8	8.0000	NA
9	24.0000	NA
10	48.0000	NA
11	72.0000	NA

Live Demonstration

httk-Specific Functions

Visit [httk: High-Throughput Toxicokinetics \(r-project.org\)](https://r-project.org) for a complete guide to httk



The screenshot shows the RStudio interface. The console on the left displays the R version information and the execution of the `library("httk")` command, which results in a warning message: "Warning message: package 'httk' was built under R version 4.3.1". Below the console, a text box contains the instruction: "Within R: type 'help(httk)'".

The right pane shows the "Help Pages" for the "httk" package. The search bar contains "R: High-Throughput Toxicokinetics". The help pages are organized into sections: "A" and "B".

Function Name	Description
httk-package	High-Throughput Toxicokinetics
httkpop-package	httkpop: Virtual population generator for HTTK.
-- A --	
add_chemtable	Add a table of chemical information for use in making httk predictions.
age_draw_smooth	Draws ages from a smoothed distribution for a given gender/race combination
apply_clint_adjustment	Correct the measured intrinsic hepatic clearance for fraction free
apply_fup_adjustment	Correct the measured fraction unbound in plasma for lipid binding
armitage_estimate_sarea	Estimate well surface area
armitage_eval	Evaluate the updated Armitage model
armitage_input	Armitage et al. (2014) Model Inputs from Honda et al. (2019)
augment.table	Add a parameter value to the chem.physical_and_invitro.data table
available_rblood2plasma	Find the best available ratio of the blood to plasma concentration constant.
Aylward2014	Aylward et al. 2014
aylward2014	Aylward et al. 2014
-- B --	
blood_mass_correct	Find average blood masses by age.
blood_weight	Predict blood mass.
bmiage	CDC BMI-for-age charts
body_surface_area	Predict body surface area.
bone_mass_age	Predict bone mass
brain_mass	Predict brain mass.

get_physchem_param {httk}

R Documentation

Get physico-chemical parameters from chem.physical_and_invitro.data table

Description

This function retrieves physico-chemical properties ("param") for the chemical specified by chem.name or chem.cas from the vLiver tables.

Usage

```
get_physchem_param(param, chem.name = NULL, chem.cas = NULL, dtxsid = NULL)
```

Arguments

- `param` The desired parameters, a vector or single value.
- `chem.name` The chemical names that you want parameters for, a vector or single value
- `chem.cas` The chemical CAS numbers that you want parameters for, a vector or single value
- `dtxsid` EPA's 'DSSTox Structure ID (<https://comptox.epa.gov/dashboard>) the chemical must be identified by either CAS, name, or DTXSIDs

```
> get_physchem_param(param="logP", chem.cas = "94-75-7")  
[1] 2.81
```

Physico-chemical properties and in vitro measurements for toxicokinetics

Description

This data set contains the necessary information to make basic, high-throughput toxicokinetic (HTTK) predictions for compounds, including Funbound.plasma, molecular weight (g/mol), logP, logMA (membrane affinity), intrinsic clearance(uL/min/10⁶ cells), and pKa. These data have been compiled from multiple sources, and can be used to parameterize a variety of toxicokinetic models. See variable EPA.ref for information on the reference EPA.

Usage

```
chem.physical_and_invitro.data
```

Format

A data.frame containing 9411 rows and 54 columns.

```
> subset(chem.physical_and_invitro.data, CAS == "94-75-7")
  Compound CAS CAS.Checksum DTXSID Formula SMILES.desalt
94-75-7 2,4-d 94-75-7 TRUE DTXSID0020442 C8H6Cl2O3 OC(=O)COC1=C(C1)C=C(C1)C=C1
  All.Compound.Names logHenry logHenry.Reference logMA logMA.Reference logP logP.Reference
94-75-7 2,4-d|Dichlorophenoxy|2,4-dichlorophenoxyacetic acid|94-75-7 -8.53 OPERAv2.7 NA <NA> 2.81 OPERAv2.7
  logPwa logPwa.Reference logWsol logWsol.Reference MP MP.Reference MW MW.Reference pKa_Accept pKa_Accept.Reference pKa_Donor
94-75-7 5.84 OPERAv2.7 -2.16 OPERAv2.7 141 OPERAv2.7 221 EPA None Sipes 2017 2.42
  pKa_Donor.Reference All.Species DTXSID.Reference Formula.Reference Human.Clint Human.Clint.pValue Human.Clint.pValue.Reference
94-75-7 OPERAv2.7 Human|Rat EPA EPA 0 0.1488 Wetmore 2012
  Human.Clint.Reference Human.Fgutabs Human.Fgutabs.Reference Human.Funbound.plasma Human.Funbound.plasma.Reference Human.Rblood2plasma
94-75-7 Wetmore 2012 NA <NA> 0.04001 Wetmore 2012 2.11
  Human.Rblood2plasma.Reference Mouse.Funbound.plasma Mouse.Funbound.plasma.Reference Rabbit.Funbound.plasma
94-75-7 TNO <NA> <NA> <NA>
  Rabbit.Funbound.plasma.Reference Rat.Clint Rat.Clint.pValue Rat.Clint.pValue.Reference Rat.Clint.Reference Rat.Fgutabs
94-75-7 <NA> 0 0.1365 Wetmore 2013 Wetmore 2013 NA
  Rat.Fgutabs.Reference Rat.Funbound.plasma Rat.Funbound.plasma.Reference Rat.Rblood2plasma Rat.Rblood2plasma.Reference
94-75-7 <NA> 0.02976 Wetmore 2013 NA <NA>
  SMILES.desalt.Reference Chemical.Class
94-75-7 EPA
```

Simulating concentrations using solve_[model_name] (Example case is solve_pbtck)

Usage

```
solve_pbtck(  
  chem.name = NULL,  
  chem.cas = NULL,  
  dtxsid = NULL,  
  times = NULL,  
  parameters = NULL,  
  days = 10,  
  tsteps = 4,  
  daily.dose = NULL,  
  dose = NULL,  
  doses.per.day = NULL,  
  initial.values = NULL,  
  plots = FALSE,  
  suppress.messages = FALSE,  
  species = "Human",  
  iv.dose = FALSE,  
  input.units = "mg/kg",  
  output.units = NULL,  
  method = "lsoda",  
  rtol = 1e-08,  
  atol = 1e-12,  
  default.to.human = FALSE,  
  recalc.blood2plasma = FALSE,  
  recalc.clearance = FALSE,  
  dosing.matrix = NULL,  
  adjusted.funbound.plasma = TRUE,  
  regression = TRUE,  
  restrictive.clearance = TRUE,  
  minimum.funbound.plasma = 1e-04,  
  monitor.vars = NULL,  
  ...  
)
```

- Make sure to set either chemical name, CAS, or DTXSID
- All other function inputs will default unless otherwise specified
- To set the time sequence:
 - Days: number of days
 - Tsteps: number of steps per hour
 - Times: specified sequence of
- Dosing:
 - Dose = single dose (default mg/kg)
 - Daily.dose = total daily dose
 - Doses.per.day
 - Iv.dose = TRUE or FALSE to simulate iv or oral dosing
- Units
 - Set desired units (default output.units umol or uM)

Simulating concentrations using solve_[model_name] (Example case is solve_pbt)

Use solve_[model_name] with your chosen inputs. Here, we are looking at a 0.203 mg/kg iv dose for a rat over the course of 4 hours

```
> out = solve_pbt(chem.cas = "94-75-7",
+               species = "Rat",
+               dose = 0.203,
+               input.units = "mg/kg",
+               output.units = "mg/L",
+               days = 4/24,
+               iv.dose = TRUE,
+               suppress.messages = TRUE)
> head(out)
```

	time	Aven	Cgut	Cliver	Cven	Clung	Cart	Crest	Ckidney	Cplasma	Atubules	Ametabolized	AUC
[1,]	0.00000	0.050740	0.0000	0.0000	7.028	0.0000	0.000	0.0000	0.0000	3.3300	0.000e+00	0	0.0000000
[2,]	0.00100	0.008813	0.1793	0.6676	1.220	0.1934	1.220	0.1363	0.5580	0.5784	3.768e-05	0	0.0007114
[3,]	0.01042	0.008760	0.1783	0.6650	1.213	0.1923	1.213	0.1354	0.5547	0.5748	3.426e-04	0	0.0061390
[4,]	0.02083	0.008701	0.1771	0.6606	1.205	0.1910	1.205	0.1345	0.5510	0.5711	6.774e-04	0	0.0121100
[5,]	0.03125	0.008643	0.1759	0.6564	1.197	0.1897	1.197	0.1336	0.5474	0.5671	1.010e-03	0	0.0180400
[6,]	0.04167	0.008586	0.1747	0.6520	1.189	0.1885	1.189	0.1327	0.5437	0.5633	1.341e-03	0	0.0239300

Parameterize Function

parameterize_1comp	Parameters for a one compartment (empirical) toxicokinetic model
parameterize_3comp	Parameters for a three-compartment toxicokinetic model (dynamic)
parameterize_fetal_pbtok	Parameterize_fetal_PBTK
parameterize_gas_pbtok	Parameters for a generic gas inhalation physiologically-based toxicokinetic model
parameterize_pbtok	Parameters for a generic physiologically-based toxicokinetic model
parameterize_schmitt	Parameters for Schmitt's (2008) Tissue Partition Coefficient Method
parameterize_steadystate	Parameters for a three-compartment toxicokinetic model at steady-state

```
parameterize_pbtok(  
  chem.cas = NULL,  
  chem.name = NULL,  
  dtxsid = NULL,  
  species = "Human",  
  default.to.human = FALSE,  
  tissuelist = list(liver = c("liver"), kidney = c("kidney"), lung = c("lung"), gut =  
    c("gut")),  
  force.human.clint.fup = FALSE,  
  clint.pvalue.threshold = 0.05,  
  adjusted.funbound.plasma = TRUE,  
  adjusted.clint = TRUE,  
  regression = TRUE,  
  suppress.messages = FALSE,  
  restrictive.clearance = TRUE,  
  minimum.funbound.plasma = 1e-04,  
  million.cells.per.gliver = 110,  
  liver.density = 1.05,  
  kgutabs = 2.18  
)
```

- Make sure to set either chemical name, CAS, or DTXSID
- All other function inputs will default unless otherwise specified
- le: default species is human but can be set to: Rat, Human, Mouse, Rabbit
- Set default.to.human = TRUE to substitute in human values when species data is unavailable
- Parameters include tissue:plasma partition coefficients, organ volumes, and flows for the tissue lumping scheme specified by argument tissue list.

First few parameters produced from parameterize function

```
> parameterize_pbt(chem.cas = "94-75-7", species = "Rat")
$BW
[1] 0.25

$Clint
[1] 0

$Clint.dist
[1] NA

$Clmetabolismc
[1] 0

$Fgutabs
[1] 1

$Fhеп.assay.correction
[1] 0.9563

$Funbound.plasma
[1] 0.02976
```

Parameter values can be changed by the user.
Notice the default value for body weight (BW) for
a rat is 0.25. This parameter can be switched by

```
> parms = parameterize_pbt(chem.cas = "94-75-7",
+   species = "Rat", suppress.messages = TRUE)
> parms$BW = 0.31
> head(parms)
$BW
[1] 0.31
```

The solve_model function can then be run with
only "parameters = parms"

```
> out = solve_pbt(parameters = parms,
+   dose = 0.203,
+   input.units = "mg/kg",
+   output.units = "mg/L",
+   days = 4/24,
+   iv.dose = TRUE,
+   suppress.messages = TRUE)
```

Plotting in base R

Let's plot the htkk solution (for the 0.203 mg/kg iv dose) against the data

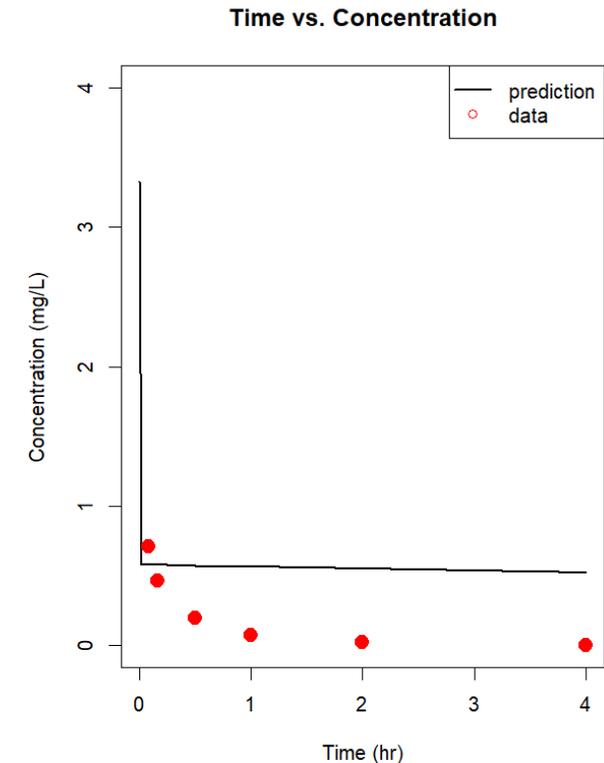
Find your experimental data points

```
experimental.points = subset(chemical_24d, Subject == 42736)[,c("Time","Value")]
experimental.points = data.frame(na.omit(sapply(experimental.points,as.numeric)))
```

```
plot(out[,"time"]*24, out[,"Cplasma"],      # plot x and y values
     type="l",                             # if you are plotting a line, type = "l"
     xlab = "Time (hr)",                   # set x and y axis labels
     ylab = "Concentration (mg/L)",
     main = "Time vs. Concentration",     # set main title
     lwd = 2,                             # set line width
     ylim = c(0,4))                      # specify y (or x) limits

points(experimental.points$Time, experimental.points$Value, # use "points" to overlay points
       col="red",                                           # set color
       pch = 19,                                           # set point shape
       cex=1.5)                                           # set point size

legend("topright",                                       # set legend position
      legend = c("prediction","data"),                 # set text for legend elements
      lwd = c(2,NA),                                   # set lwd for legend (NA if corresponds to points)
      pch = c(NA, 1),                                  # set pch for legend (NA if corresponds to lines)
      col=c("black","red"))                            # set color for each legend element
```



*To overlay another line, use
`lines(x,y)`

Summary

- Introduction to PBTK modeling
- Rstudio basics
- What is httk?
- Basic R commands
- httk specific commands

Tomorrow we will work with concrete PK examples

- Different compartment models available
- How to parameterize a model
- Different routes
- Comparing data and simulations

Please join us for tomorrow's session!

Q&A

We'll see you tomorrow!

Begins at 10:00 AM EST.

Join using the link sent via email.