

# high-throughput toxicokinetics (httk) training

## Pre-Workshop Information

This document provides guidance and resources to prepare for the NAMs Tools Training Workshop session on httk. We recommend that you review this document and take appropriate action *prior* to the start of the workshop.

Httk is a package in R. To access it, users must install two things on their computers: R and R Studio. Prior to the workshop, please ensure that both R and RStudio are on your machine, or that you have an account in RStudio Cloud. Note: RStudio Cloud accounts require internet access and due to potential accessibility issues via internet, we strongly recommend downloading both R and RStudio on your laptop prior to the workshop.

# R & RStudio

## Download

RStudio is an Integrated Development Environment (IDE) designed for the programming language R.

This training uses RStudio for all examples. Instructions for downloading and installing R and RStudio are below, but additional instructions for downloading and installing R and RStudio for MAC, Windows, and UNIX are available here: <u>https://rstudio-education.github.io/hopr/starting.html</u>

- If you do not want to or are unable to install R and RStudio, you can use RStudio Cloud:
  - <u>https://web.pdx.edu/~gerbing/R/RStudioCloud.pdf</u>
  - Note that you will need to create a free account before using. This application is usable on a mobile device.

## Installation

R is a programming language and software environment and RStudio is the user-friendly graphical interface we will use to utilize packages in R. RStudio is an application (like Microsoft Word, for example) except used for writing code in R. We will be using the RStudio interface because it looks the same across Windows, Mac, and Linux operating systems. **Note:** <u>You must download both R and RStudio;</u> <u>RStudio requires R to run. RStudio alone does not come with a version of R on its own.</u>

## 1. Install R

- a. Download the R installer from <a href="https://cran.r-project.org/">https://cran.r-project.org/</a>
  - Click on the link for your operating system. Make sure the installer is for R version 4.3.3. If you already have an earlier version of R installed, that is fine as long as the version > 2.1





Figure 1a.

#### ii. Click install R for the first time

		R for Windows			
	Subdirectories:				
	<u>base</u> contrib	Binaries for base distribution. This is what you want $\frac{1}{10000000000000000000000000000000000$			
CRAN	old contrib	Binaries of contributed CRAN packages for outdated versions of R (for $R \le 3.4.x$ ).			
Mirrors What's new?	Rtools	Tools to build R and R packages. This is what you want to build your own packages on Windows, or to build R itself.			
Search CRAN Team	Please do not submit binaries to CRAN. Package developers might want to contact Uwe Ligges directly in case of questions / suggestions related to Windows binaries.				
About R	You may also want to read the <u>R FAQ</u>	and <u>R for Windows FAQ</u> .			
R Homepage The R Journal	Note: CRAN does some checks on the	se binaries for viruses, but cannot give guarantees. Use the normal precautions with downloaded executables.			
Software					
R Sources R Binaries					
Packages Task Views					
Other					
Documentation <u>Manuals</u>					
Contributed					

iii. Use the download link at the top and save the file.



	R-4.3.1 for Windows			
	Download R-4.3.1 for Windows (79 megabytes, 64 bit) ESEAPHE on the Windows binary distribution New features in this version			
Mirrors What's new?	This build requires UCRT, which is part of Windows since Windows 10 and Windows Server 2016. On older systems, UCRT has to be installed manually from here.			
Search CRAN Team	If you want to double-check that the package you have downloaded matches the package distributed by CRAN, you can compare the md2sum of the .exe to the fingerprint on the master server.			
About R	Frequently asked questions			
R Homepage The R Journal	Does R run under my version of Windows?     How do I update packages in my previous version of R?			
Saftware R Sources	Please see the <u>R-FAQ</u> for general information about R and the <u>R-Windows-FAQ</u> for Windows-specific information.			
R Binaries Packages	Other builds			
Disk Views Other Documentation	<ul> <li>Patches to this release are incorporated in the <u>repatched samphot build</u>.</li> <li>A build of the development version (which will eventually become the next major release of R) is available in the <u>relevel samphot build</u>.</li> <li>Previous release:</li> </ul>			
Manuals FAQs Contributed	Note to webmasters: A stable link which will redirect to the current Windows binary release is < <u>CRAN MIRROR&gt; bin windows base release html</u> .			
	Last change: 2023-06-16			

**b.** Run the installer (double click). Default settings are fine. If you do not have administrative rights on your computer, then ask IT for help (they must give you full permissions to the R directories, else, you will not be able to install packages).

#### 2. Install RStudio

a. Once the R installer has finished, download Rstudio: https://rstudio.com/products/rstudio/download/#download.

RStudio Desktop - Posit

The page should recommend the right file for your OS. If not, scroll down to "All installers and Tarballs" and choose the option that for your system.





#### 3. Check that R and RStudio are working

**a.** Open RStudio (you can open it like any other program by clicking the icon on your desktop). It should look like the following image.



When you open RStudio, you will see a window with three panes. The largest pane is the console window, which is where you can run code and see results. The pane on the top right shows your environment (any variables or functions you use will appear there). The pane on the bottom has the following tabs: Files, Plots, Packages, Help, Viewer, and Presentation.



- b. Go to File -> New File -> R Script. This will open a fourth pane (the Source pane). Here you can create and edit R scripts. You can write code in this pane and click the "Run" button, which will show what you ran down in the console.
- **c.** Notice that the bottom right panel now has the "Files" tabs open. Here, you can access any necessary files, such as excel sheets you want to read into R.



- **d.** Make sure you are in the correct working directory. If you want to load an excel file (or another file of some kind), you must be located in the same directory as that file (unless you call to it with a path, which is also fine).
  - Go to Session -> Set Working Directory -> Choose Directory to choose your working directory from a file explorer. You can also do Session -> Set Working Directory -> To Files Pane Location if the Files pane you see on your bottom right is the one you want to be in.



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#### How to Install R and RStudio (R Studio bundle) for EPA Employees

US EPA employees can use the pre-approved RStudio package included in the Software Center:

<ul> <li>version</li> &lt;</ul>	D Software Center		- 🗆 X
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EISD – R Suite 4.2.2 is the most recent version available.

If you have administrative privileges, you can install R and RStudio yourself. If you need assistance, contact EISD.

# **Publications and References**

Httk:

Breen M., Ring C. L., Kreutz A., Goldsmith M. & Wambaugh (2021) J. F. 'High-throughput PBTK models for in vitro to in vivo extrapolation', *Expert Opinion on Drug Metabolism & Toxicology*, 17:8, 903-921.



Linakis, M. W., et al. (2020). "Development and Evaluation of a High Throughput Inhalation Model for Organic Chemicals " *Journal of Exposure Science & Environmental Epidemiology*, *30*(*5*):866-877.

Pearce RG, Setzer RW, Strope CL, et al. (2017a) 'Httk: R package for high-throughput toxicokinetics', *Journal of Statistical Software*.;79(1):1-26.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF. (2017b) 'Evaluation and calibration of high-throughput predictions of chemical distribution to tissues', *J Pharmacokinet Pharmacodyn.*,44(6):549-65.

Ring, C., Sipes, N. S., Hsieh, J. H., Carberry, C., Koval, L. E., Klaren, W. D., ... & Rager, J. E. (2021). Predictive modeling of biological responses in the rat liver using in vitro Tox21 bioactivity: Benefits from high-throughput toxicokinetics. *Computational Toxicology*, *18*, 100166.

Wambaugh, J. F., Wetmore, B. A., Pearce, R., Strope, C., Goldsmith, R., Sluka, J. P., ... & Setzer, R. W. (2015). Toxicokinetic triage for environmental chemicals. *Toxicological Sciences*, *147*(1), 55-67.

Wambaugh, J. F., Hughes, M. F., Ring, C. L., MacMillan, D. K., Ford, J., Fennell, T. R., ... & Thomas, R. S. (2018). Evaluating in vitro-in vivo extrapolation of toxicokinetics. *Toxicological Sciences*, *163*(1), 152-169.

Resources to learn more:

httk package access via CRAN:

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

httk Reference manual:

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

R for httk:

https://uncsrp.github.io/Data-Analysis-Training-Modules/toxicokinetic-modeling.html

General introduction to R:

https://uncsrp.github.io/Data-Analysis-Training-Modules/introduction-to-coding-in-r.html#introduction-to-coding-in-r

Self-guided R training interactive modules:

swirl: <u>https://swirlstats.com/</u>

Access chemical information:

CompTox Dashboard URL: <u>https://comptox.epa.gov/dashboard/</u>