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

- If you do not want to or are unable to install R and RStudio, you can use RStudio Cloud:
    - https://web.pdx.edu/~gerbing/R/RStudioCloud.pdf
    - 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:** You must download both R and RStudio; RStudio requires R to run. RStudio alone does not come with a version of R on its own.
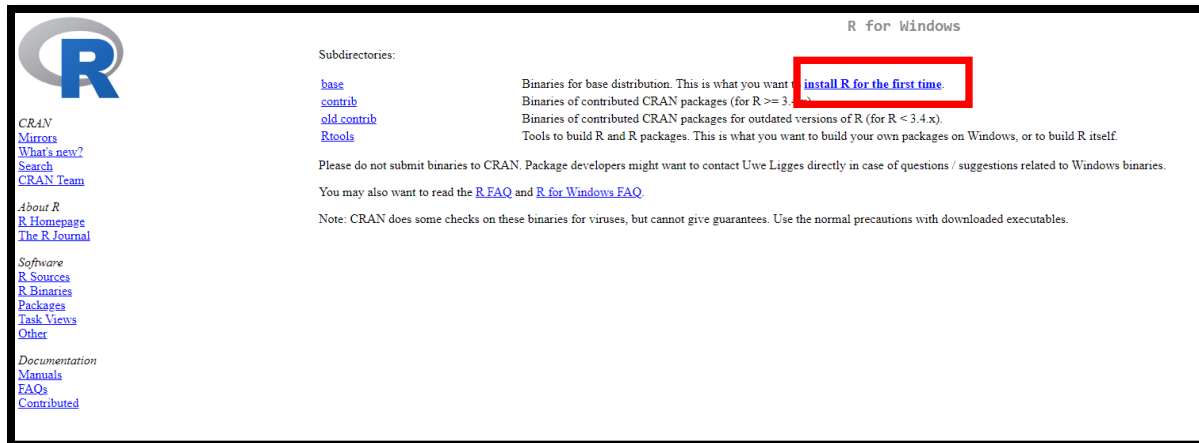
1. **Install R**
    a. Download the R installer from https://cran.r-project.org/
        i. Click on the link for your operating system. Make sure the installer is for R version 4.3.3. If you already have an earlier version of R installed, that is fine as long as the version > 2.1
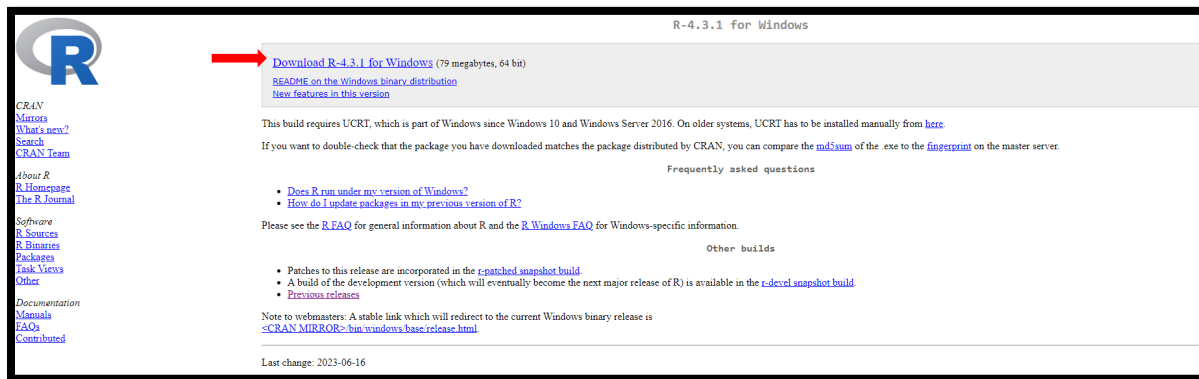
Figure 1a.

ii. Click *install R for the first time*

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

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.
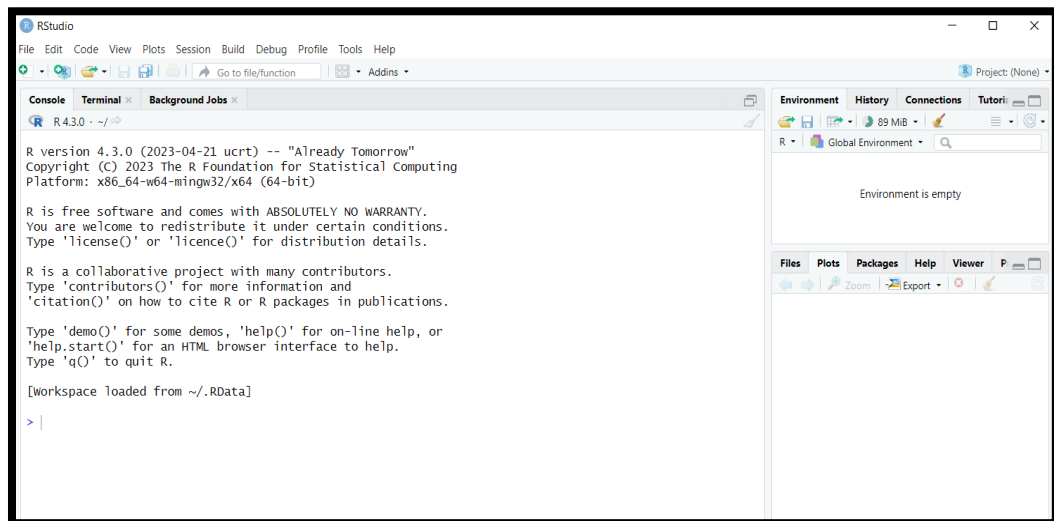

When you open RStudio, you will see a window with three panes. The largest pane is the console window, which is where you can run code and see results. The pane on the top right shows your environment (any variables or functions you use will appear there). The pane on the bottom has the following tabs: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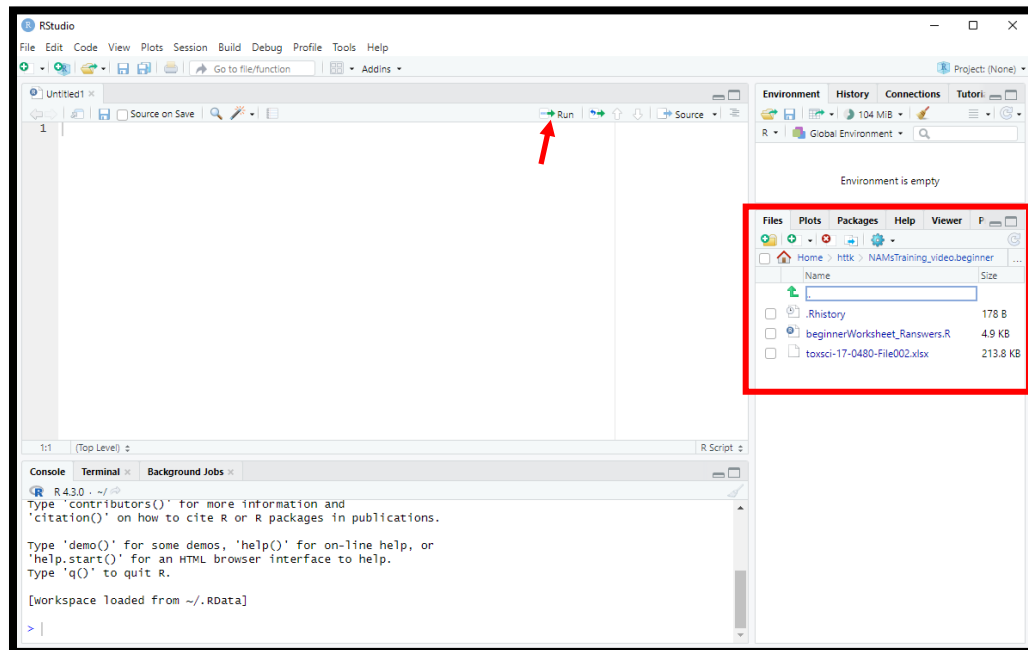

d. Make sure you are in the correct working directory. If you want to load an excel file (or another file of some kind), you must be located in the same directory as that file (unless you call to it with a path, which is also fine).

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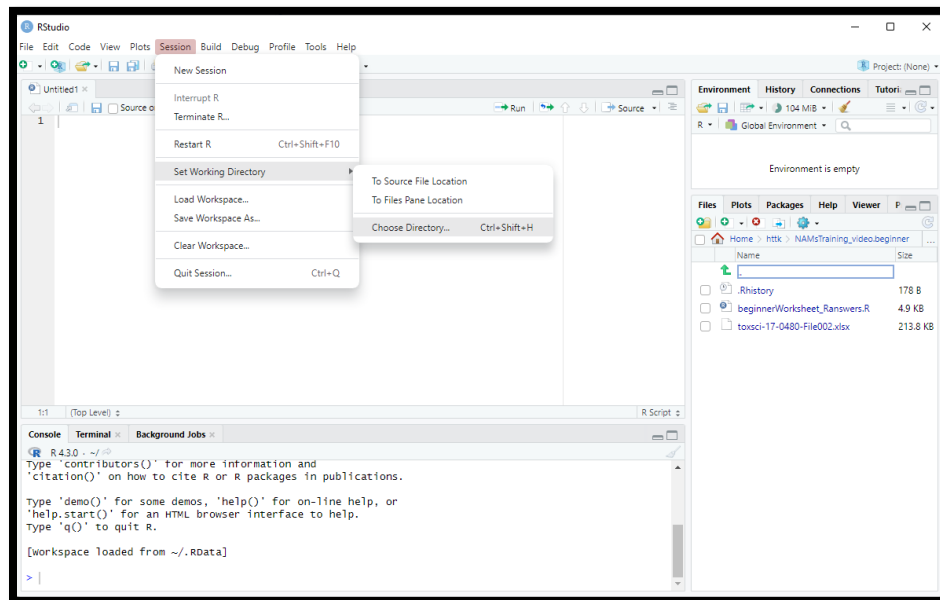
How to Install R and RStudio (R Studio bundle) for EPA Employees

US EPA employees can use the pre-approved RStudio package included in the Software Center:
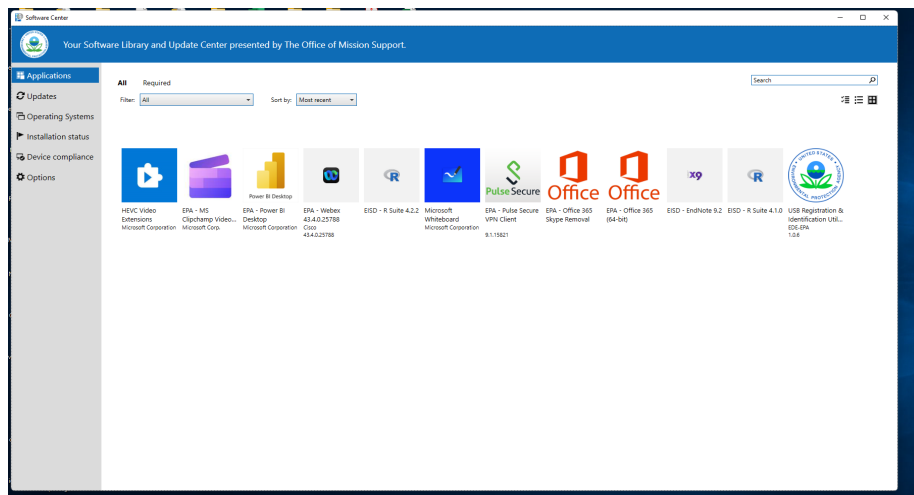
EISD – R Suite 4.2.2 is the most recent version available.

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: https://swirlstats.com/

Access chemical information:

CompTox Dashboard URL: https://comptox.epa.gov/dashboard/