## Instructions for the rat model in R

1. **Installing R, R studio and packages needed to run models**

Installing R

1. In a web-browser, navigate to https://cran.r-project.org/

2. Select “Download R for Windows” under “Download and Install R”

3. Select “Install R for the first time”

4. Select “Download R 3.(version) for Windows “

5. Save and run the installer file

Installing Rstudio

1. In a web-browser navigate to https://www.rstudio.com/

2. On the homepage select Download Rstudio

3. Download the open source license version of Rstudio (first from left)

4. Select windows installer (Under Installers -> RStudio 1.(ver) – Windows Vista /7/8/10

5. Save and Run the executable file

Installing Packages:

1. Run Rstudio

2. Select Packages tab from the bottom right panel in RStudio

3. Select Install in the packages tab

4. Under packages enter deSolve and select install

This will setup the environment needed to run the models

1. **Model folder “Rsubmission\_Rat”**
2. All files in the docket are provided as .txt files. Please follow the steps below to convert the file format to appropriate R files in order to be able to run the PBPK model in RStudio:

**Important:** The name of the folders where you will copy the files from the docket is very important to run the PBPK model in RStudio.

* 1. “model\_rat.txt” needs to be renamed to “model.R” and placed in a folder named “model”. Simple replace the ‘\_rat.txt’ part of the file name by ‘.R’.
  2. Parameter files names starting with “params”: Place the params files in 3 different folders called DLM, CPM and TPM. Replace “\_CPM.txt”, “\_DLM.txt” and “\_TPM.txt” by “.R”.

Example: “params\_Oral\_15d\_CPM.txt” will become “params\_Oral\_15d.R” and will be in the folder named “CPM”.

* 1. Copy all the scenario files in a folder named “Scenarios” and replace “.txt” by “.R”.

1. This is the current version of the pyrethroid growing rat model in R as of July 24th, 2017. Model file (model. R) is saved in the folder named ‘Model’ and parameter files for DLM, CPM, and TPM simulations in PND15 and PND90 rats following oral or IV exposures are saved in the folders named ‘DLM’, ‘CPM’, or ‘TPM’ respectively. R files are included in the folder named ‘Scenarios’ to simulate plasma and tissue concentration profiles of DLM, CPM, or TPM at a given exposure scenario in rats at specific age.

c. Open a specific file in the folder named ‘Scenarios’ in RStudio. In all scenario files, appropriate paramFile from DLM, CPM, and TPM folders corresponding to the selected exposure scenario is currently defined. To run the scenario file selected, click on Source. There are 25 scenario files for simulations of DLM, CPM, and TPM *in vivo* PK data in rats at specific age as described as below:

|  |  |
| --- | --- |
| Scenario file in R | Note |
| DLM\_Oral\_Scenario1\_90d | It is to simulate new *in vivo* DLM PK in PND90 rats after oral dose at 0.5 mg/kg |
| DLM\_Oral\_Scenario2\_90d | It is to simulate new *in vivo* DLM PK in PND90 rats after oral dose at 0.25 mg/kg |
| DLM\_Oral\_Scenario3\_90d | It is to simulate new *in vivo* DLM PK in PND90 rats after oral dose at 0.1 mg/kg |
| DLM\_Oral\_Scenario4\_15d | It is to simulate new *in vivo* DLM PK in PND15 rats after oral dose at 0.5 mg/kg |
| DLM\_Oral\_Scenario5\_15d | It is to simulate new *in vivo* DLM PK in PND15 rats after oral dose at 0.25 mg/kg |
| DLM\_Oral\_Scenario6\_15d | It is to simulate new *in vivo* DLM PK in PND15 rats after oral dose at 0.1 mg/kg |
| DLM\_Oral\_Scenario\_PUB1\_90d | It is to simulate published DLM PK in PND90 rats after oral dose at 2 mg/kg |
| DLM\_Oral\_Scenario\_PUB2\_90d | It is to simulate published DLM PK in PND90 rats after oral dose at 10 mg/kg |
| DLM\_Oral\_Scenario\_PUB3\_10d | It is to simulate published DLM PK in PND10 rats after oral dose at 0.4 mg/kg |
| DLM\_Oral\_Scenario\_PUB4\_10d | It is to simulate published DLM PK in PND10 rats after oral dose at 2 mg/kg |
| DLM\_Oral\_Scenario\_PUB5\_10d | It is to simulate published DLM PK in PND10 rats after oral dose at 10 mg/kg |
| DLM\_IV\_Scenario1\_90d | It is to simulate new *in vivo* DLM PK in PND90 rats after IV dose at 0.5 mg/kg |
| DLM\_IV\_Scenario2\_90d | It is to simulate published DLM PK in PND90 rats after IV dose at 1.75 mg/kg |
| CPM\_Oral\_Scenario1\_90d | It is to simulate new *in vivo* CPM PK in PND90 rats after oral dose at 60 mg/kg |
| CPM\_Oral\_Scenario2\_90d | It is to simulate new *in vivo* CPM PK in PND90 rats after oral dose at 90 mg/kg |
| CPM\_Oral\_Scenario3\_90d | It is to simulate new *in vivo* CPM PK in PND90 rats after oral dose at 120 mg/kg |
| CPM\_Oral\_Scenario4\_15d | It is to simulate new *in vivo* CPM PK in PND15 rats after oral dose at 15 mg/kg |
| CPM\_Oral\_Scenario5\_15d | It is to simulate new *in vivo* CPM PK in PND15 rats after oral dose at 30 mg/kg |
| CPM\_Oral\_Scenario6\_15d | It is to simulate new *in vivo* CPM PK in PND15 rats after oral dose at 45 mg/kg |
| TPM\_Oral\_Scenario1\_90d | It is to simulate new *in vivo* TPM PK in PND90 rats after oral dose at 120 mg/kg |
| TPM\_Oral\_Scenario2\_90d | It is to simulate new *in vivo* TPM PK in PND90 rats after oral dose at 150 mg/kg |
| TPM\_Oral\_Scenario3\_90d | It is to simulate new *in vivo* TPM PK in PND90 rats after oral dose at 300 mg/kg |
| TPM\_Oral\_Scenario4\_15d | It is to simulate new *in vivo* TPM PK in PND15 rats after oral dose at 300 mg/kg |
| TPM\_Oral\_Scenario5\_15d | It is to simulate new *in vivo* TPM PK in PND15 rats after oral dose at 450 mg/kg |
| TPM\_Oral\_Scenario6\_15d | It is to simulate new *in vivo* TPM PK in PND15 rats after oral dose at 600 mg/kg |

d. Model outputs include simulation results named ‘SimResults.csv’ which will be saved in the same folder named ‘RSubmission\_Rat’. In addition, brain max concentration and plasma max concentration as well as CLINT\_VIVO\_ESTIMATED and *in vivo* hepatic clearance (Clh) will be provided.