PBPK Model Template Project

Instructions for using source code and data files.

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1. Install R, RStudio, the R packages "deSolve" and "readxl", Rtools, and GNU MCSim on your system. Instructions can be found in "R\_and\_MCSim\_installation\_instructions.pdf".
2. Open RStudio.
3. Within RStudio, open the R source code file "PBPK\_PFAS\_manuscript\_scripts.R"
4. Set the working directory to the location of the file. This can be done by selection "Session" -> "Set Working Directory" -> "To Source Files Location" from the menu bar while the file is open in RStudio.
5. Use the "Run" button to run lines 4-6 of the file. This will "source" the necessary R functions in order to run the included examples.
6. Each example can be run to create the listed figure from the manuscript and the corresponding accuracy calculations by highlighting the code in the chosen example and using the "Run" button. For example, to create Figure 2 in the manuscript, highlight lines 10-24, and select the "Run" button. Figures will print to the figure pane in the lower right area of RStudio.

Description of files:

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**PBPK\_PFAS\_manuscript\_scripts.R**

This R source code file contains the scripts needed to produce the figures included in the PBPK model template manuscript as applicable to PFAS and the scripts to perform the accuracy calculations. It requires the R files "run\_PFAS\_template\_model.R" and "plot\_PFAS\_template\_man.R" to be sourced. This file is used as described in the instructional steps listed above.

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**run\_PFAS\_template\_model.R**

This R source code file includes functions to run the PBPK model template. It requires the R libraries readxl (for importing parameter values) and deSolve (for methods of solving ordinary differential equations) and the R file RMCSim.R. The included functions are:

unload.model(mName)

Unloads the dll file mName if it is currently loaded.

PFAS\_compile(mName = "PFAS\_template")

Uses the compile\_model(mName) function in RMCSim.R to translate the MCSim .model file given in mName into the C language (".c" file) and compile, creating a C object code (.o) file and a dynamic linked library (".dll") file. It also creates an R script ("\_inits.R") containing several R functions used for initializing model states and parameters. Note the “.c”, “.o”, “.dll”, and “\_inits.R” files for each of the models are included in this distribution, so it should not be necessary for Windows users to run this function unless they wish to modify and re-build the output files for any of the models.

PFAS\_run(mName = "PFAS\_template", param.filename = NULL, sheetname = NULL, adj.parms = NULL, BW.table = NULL, data.times = NULL)

Runs a simulation using the compiled MCSim model given in mName using the input parameters specified in the Excel file "param.filename" listed on the sheet "sheetname". adj.parms optionally contains a list of parameters to be adjusted from those given in param.filename/sheetname. BW.table optionally gives the name of a table of body weight values (possible tables are defined within the function). data.times optionally allows the user to specify the times they want to run the simulation; otherwise, the simulation defines the times based on the number of simulation days specified in param.filename/sheetname.

This function returns a data frame containing all state variables and output variables. Values are given using standard units of (mg, L, h) except time (days) and BW\_out (kg).

run\_sim(mName = "PFAS\_template", parms, times = NULL, BW.table = NULL, Free.parms = NULL, input.parms = NULL, BW\_constant = NULL, Free\_constant = NULL, Kf\_constant = NULL, Kbilec\_constant = NULL)

This function is used by PFAS\_run to run the simulation using the compiled MCSim model mName, a list of parameters parms, and a list of simulation times times. BW.table optionally gives the name of a table of body weight values defined within the function. Free.parms provides parameters related to the free fraction. input.parms provides parameters related to the other input parameters (K\_f and K\_bilec). BW\_constant tells whether body weight is constant ("Y") or not ("N"). Free\_constant tells whether the free fraction is constant ("Y") or not ("N"). Kf\_constant tells whether the fecal excretion parameter K\_f is constant ("Y") or not ("N"). Kbilec\_constant tells whether the biliary excretion parameter K\_bilec is constant ("Y") or not ("N").

This function returns a data frame containing all state variables and output variables.

load.parameters(filename, sheetname = NULL)

This function is used by PFAS\_run to import the parameter values given in the Excel file param.filename/sheetname. The file should be located in a folder called "Inputs". After file information is read, several internal variables are created in order to run simulations.

perc.diff(model, data)

This function takes model values and data values and returns the percent difference between them: 100\*((data-model)/data)

perc.diff.scale(model, data, fig.scale)

This function takes model values and data values and returns the percent difference between them relative to the value of fig.scale: 100\*((data-model)/fig.scale)

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**plot\_PFAS\_template\_man.R**

This R source code file contains functions to create the plots shown in the PBPK model template manuscript as applied to PFAS. The included functions are:

plot.Kim(out, out.inc = NULL, chem, sex, dose, img.name = NULL)

This function creates the plots reproducing the results from Kim et al. 2018 and Kim et al. 2019 for PFHxS, PFNA, and PFDA. out is a data frame containing the simulation results from the model template using the corrected blood flow leaving the liver; out.inc is a data frame containing the simulation results from the model template using the published (incorrect) blood flow leaving the liver. chem is a string with the name of the chemical, sex is a string specifying male or female, and dose is a numerical value of the applied dose in mg/kg. img.name is an optional parameter for the name of the image file to be saved which must end in ".tif"; if not provided, the plot prints to the default location (in RStudio, the plot viewer). Data is stored in the folder "Data/Digitized\_Data\_X" where X is the chemical name.

plot.Kudo.Loccisano(out, dose = NULL, img.name = NULL)

This function creates the plots reproducing the results from Loccisano et al. 2012 (Figure 8) for PFOA using data from Kudo et al. 2007. out is a data frame containing the simulation results from the model template. dose is a string specifying whether this is the "high" or "low" dose case. img.name is an optional parameter for the name of the image file to be saved which must end in ".tif"; if not provided, the plot prints to the default location (in RStudio, the plot viewer). Data is stored in the folder "Data/Digitized\_Data\_PFOA".

plot.Kemper.Loccisano(out, dose.type = NULL, dose = NULL, sex = NULL, img.name = NULL)

This function creates the plots reproducing the results from Loccisano et al. 2012 (Figure 9) for PFOA using data from Kemper 2003. out is a data frame containing the simulation results from the model template. dose.type is a string specifying whether this is the "oral" or "iv" exposure case. dose is a numerical value of the applied dose in mg/kg. sex is a string specifying male or female. img.name is an optional parameter for the name of the image file to be saved which must end in ".tif"; if not provided, the plot prints to the default location (in RStudio, the plot viewer). Data is stored in the folder "Data/Digitized\_Data\_PFOA".

plot.3M.Loccisano(out, sex = "male", img.name = NULL)

This function creates the plots reproducing the results from Loccisano et al. 2012 (Figure 4) for PFOS using data from 3M 2009. out is a data frame containing the simulation results from the model template. sex is a string specifying male or female. img.name is an optional parameter for the name of the image file to be saved which must end in ".tif"; if not provided, the plot prints to the default location (in RStudio, the plot viewer). Data is stored in the folder "Data/Digitized\_Data\_PFOS".

load\_PlasmaData(chem = NULL, species = NULL, sex = NULL, dose.type = NULL, dose = NULL)

load\_LiverData(chem = NULL, species = NULL, sex = NULL, dose.type = NULL, dose = NULL)

load\_KidneyData(chem = NULL, species = NULL, sex = NULL, dose.type = NULL, dose = NULL)

load\_UrineData(chem = NULL, species = NULL, sex = NULL, dose.type = NULL, dose = NULL)

This set of functions load the data digitized from Kim et al. 2018 and Kim et al. 2019 for PFHxS, PFNA, and PFDA. chem, species, sex, and dose.type are strings which specify the chemical name, species, sex, and exposure route (oral or IV), respectively. dose is a numerical value of the applied dose in mg/kg. Data is stored in the folder "Data/Digitized\_Data\_X" where X is the chemical name.

The functions load the concentration data corresponding to the tissue given in the function name.

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**PFAS\_template.model**

This MCSim source code file defines the model template as applicable to PFAS.

**PFAS\_template\_model.c**

This C source code file defines the model template as applicable to PFAS.

**PFAS\_template\_model.dll**

This DLL file defines the model template as applicable to PFAS and can be used directly by functions in the R package “deSolve”.

**PFAS\_template\_model.o**

This C object code file defines the model template as applicable to PFAS.

**PFAS\_template\_model\_inits.R**

This R source code file defines initialization functions for the model template as applicable to PFAS.

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**PFAS\_template\_GI.model**

This MCSim source code file defines the model template as applicable to PFAS. It is the same as PFAS\_template.model except it includes the error in the published models from Kim et al. 2018 and Kim et al. 2019 of the incorrect blood flow leaving the liver.

**PFAS\_template\_GI\_model.c**

This C source code file defines the model template as applicable to PFAS and includes the error in the published models from Kim et al. 2018 and Kim et al. 2019 of the incorrect blood flow leaving the liver.

**PFAS\_template\_GI\_model.dll**

This DLL file defines the model template as applicable to PFAS and includes the error in the published models from Kim et al. 2018 and Kim et al. 2019 of the incorrect blood flow leaving the liver and can be used directly by functions in the R package “deSolve”.

**PFAS\_template\_GI\_model.o**

This C object code file defines the model template as applicable to PFAS and includes the error in the published models from Kim et al. 2018 and Kim et al. 2019 of the incorrect blood flow leaving the liver.

**PFAS\_template\_GI\_model\_inits.R**

This R source code file defines initialization functions for the model template as applicable to PFAS and includes the error in the published models from Kim et al. 2018 and Kim et al. 2019 of the incorrect blood flow leaving the liver.

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**RMCSim.R**

This R source code file defines functions for compiling, loading, and running an ODE model encoded in the GNU MCSim model specification language. The “mod.exe” utility must be available in the user’s PATH for the “compile\_model” function to work properly.

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**Data**

This is a directory containing data files for each of the chemicals and example models. The directory contains sub-folders for each chemical named “Digitized \_Data\_X” where X is the name of the chemical. The sub-folders contain .csv and .xlsx files containing data digitized from the source publications.

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**Inputs**

This is a directory containing input data files for each chemical. The files are named “PFAS\_template\_parameters\_X.xlsx” where X is the name of the chemical. Each file contains one sheet per model simulation listing the model parameters.