# README Supplementary material for the current work (Ethylbenzene PBPK model)

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# **Overview:**

# The supplementary data include R code (in the folder of \*\*codes\*\*) and datasets (the folder of \*\*datasets\*\*) that can reproduce the modeling and analyze result (in the folder of \*\*outputs\*\*) and visualize plots (in the \*\*plots\*\* folder). Also, the readers can also re-run the whole MCMC analysis (optional) as detailed below.

# **Quick Start:**

# The readers can directly duplicate the current results in a time manner using the generated MCMC outputs by the authors. First, please execute the “*EB.Rproj”* file under the parent directory to set up the correct folder/file path. Once completed, the readers can execute the files under the folder of \*\*codes\*\* in a stepwise fashion to duplicate the current work (e.g., “1\_calibration\_Human.R”, “2\_MCMC\_diagnosis\_Human.Rmd” and so on)

**\*\*MCMC replication analysis (optional – please see the instructions in the last page for details):**

# As an alternative option, the readers can also re-run the MCMC analysis using the files provided in \*\*MCMC replication analysis\*\*. The resultant outputs of MCMC sampling are expected to be the same as those provided by the authors.

# **================= Folder contents =============**

# \*\***codes\*\*:**

# As mentioned above, the R source codes in this folder were organized by species (e.g., human, etc) in a stepwise fashion. As such, the readers can easily duplicate the current work. Using human as an example:

# *“1\_calibration\_Human.R” (Step 1):* The output of this R code script provides the results of model fitting to human calibration data (Figure 4C).

# *2\_MCMC\_diagnosis\_Human.RMD (Step 2):* The output of this R code script provides the results of post-MCMC diagnosis tests, including:

(a) Posterior distribution of population scaling parameters (Supplemental Table S5, S6, and S7 for mouse, rat and human, respectively). In accordance with the scaling relationship (Supplemental Table S1) and the PBPK model parameters were updated (Table 3 and 4) using these updated "scaling parameters". Further details are provided in Supplemental material Section 2.2.

(b) Posterior distributions for model residual errors (Supplemental Table S8, S9 and S10 for mouse, rat and human, respectively).

(c) Traces plot of EB-specific population parameters including the estimated value of Brooks-Gelman Multivariate Shrink Factors (MPSRF) (Supplemental Figure S1, S2 and S3 for mouse, rat and human, respectively).

(d) Probability density function plots of EB-specific population parameters (Figure S4, S5 and S6 for mouse, rat and human, respectively).

(e) Correlation matrix of population metabolism-related parameters for humans (Figure S7, S8 and S9 for mouse, rat and human, respectively).

# *3\_validation\_MAP\_Human3.R (Step 3):*

# The output of this R code script provides the results of model fitting to validation data (Figure 5A, 5B and 5C for mouse, rat and human, respectively).

# *4\_gsa\_Human.R (Step 4):*

# The output of this R code script provides the results of parameter sensitivity analysis for EB-specific parameters (Figure 6A, 6B and 6C for mouse, rat and human, respectively).

# *5\_HEC\_Mouse\_MAP.R and 5\_HEC\_Rat\_MAP.R (Step 5):*

# The output of these two R code scripts (called “Mouse\_HEC.csv” and “Rat\_HEC.csv”, saved in the “outputs” folder) provide the results of estimated human equivalent concentration (HEC) based on mouse and rat models, respectively (Table 5).

# \*\***datasets\*\*:** The datasets provided original data used in the current analysis. These datasets are the same as those embedded in the R source codes.

# \*\***MCSim**\*\*: The source files of GNU MCSim software and the related modeling and input files that can conduct model simulation and prediction.

# \*\***outputs**\*\*: The files in the output folder are generated by the above R code and datasets.

# The readers can replace these output files provided by the authors with the newly generated outputs by the readers themselves from re-running the MCMC analysis (e.g., “*EBHumanMCMC\_3365.out*” for human, one output file for each of 4 chains in each species like human).

# \*\***plots**\*\*: All plots showed in the manuscript were saved in this folder.

# **\*\*MCMC replication analysis\*\* (optional):**

# **!!!Note!!!** Again, the readers can skip this folder and is still able to duplicate the current work by using the outputs provided by the authors.

# The readers can re-run the MCMC analysis by executing the MCMC application file by clicking on the file (e.g., *mcsim.EBAll.model.exe*) and entering the name of MCMC input and output files, respectively such as “*EBHumanMCMC\_3365.in”* and “*EBHumanMCMC\_3365.out”* (one chain for one input file each species).

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