Instructions for using source code and data files

Dustin Kapraun, US EPA, 5/31/2022

1. Unzip the file "Kapraun2022_LPEC_PK_model.zip" to a folder on your C drive. For example, you could unzip to C:\Users\[username]\Documents to create a folder with the path "C:\Users\[username]\Documents\Kapraun2022_LPEC_PK_model".
2. Install R, RStudio, the R package "deSolve", Rtools (optional), and MCSim (optional) on your system by following the instructions in the provided document "R_and_MCSim_installation_instructions.pdf".
3. Open RStudio.
4. Within RStudio, open one of the R source code files in the "Kapraun2022_LPEC_PK_model" directory. See "Description of files" below for information on the content and uses of each source code files.
5. Use the button in the upper right-hand corner of the window to "source" the file. Note that the "source" command causes a script to be read and interpreted by an R session instance (i.e., the "source" command "runs" a script).

Description of files:

- **build_lipophilic_tk.R**: This R source code file reads the file "lipophilic_tk.model" (described below) and creates the files "lipophilic_tk_model.c" (a C implementation of the model), "lipophilic_tk_model.o", (a C object file), "lipophilic_tk_model_inits.R" (an R source code file that defines initialization functions for the model), and a compiled version of the model called either "lipophilic_tk_model.dll" (on a Windows system) or "lipophilic_tk_model.so" (on a Unix system) that can be used by the R package "deSolve". This source code file reads and depends upon "RMCSim.R". The files "lipophilic_tk_model.c", "lipophilic_tk_model.o", "lipophilic_tk_model_inits.R", and "lipophilic_tk_model.dll" are included in this distribution, so it should not be necessary for Windows users to run "build_lipophilic_tk.R" unless they wish to modify and re-build the output files for "lipophilic_tk.model".
- **compare_verner2013.R:** This R source code file performs a simulation of continuous exposure of a human mother to 1 mg/kg/d of PCB 153 from her birth until she reaches 28 years of age. The simulation provides the same exposure to the infant after weaning (once the woman reaches 26 years of age). It then generates figures that compare model-predicted mother and offspring concentrations with those generated using the Verner et al. (2013) model ("compare_verner_pcb153.tif" and "compare_verner_pcb153_zoom.tif"). It also generates figures that show the total amount that has entered the system ("amount_test.tif") and mass balance ("kapraun_balance_pcb153.tif"). These figures are saved in the "Output" directory. By changing the comments on Lines 35 and 36, one can generate similar figures for a simulation of exposure to HCB. Results from the Verner et al. (2013) model simulations that are used for comparison can be found in the files "Verner_Kapraun_predictions_hcb.csv" and "Verner_Kapraun_predictions_pcb153.csv".

- **hcb_nakashima1997_study1_mc.R**: This R source code file performs simulations of an experiment involving rat dams exposed to HCB (Nakashima et al., 1997) using the model "lipophilic_tk" as described in the manuscript associated with this set of files (Kapraun et al., 2022). It then generates figures showing HCB concentrations in rat dams ("nakashima1997_exp1_maternal_concentration_mc.tif"), HCB concentrations in rat fetuses and pups ("nakashima1997_exp1_filial_concentration_mc.tif"), total HCB amount in the system ("nakashima1997_exp1_amount_in_mc.tif"), maternal body mass ("nakashima1997_exp1_maternal_mass_mc.tif"), filial body mass ("nakashima1997_exp1_filial_mass_mc.tif"). These figures are saved in the "Output" directory.
- **hed_nakashima1997.R**: This R source code file computes human equivalent doses (HEDs) for the rat HCB exposure scenario of Nakashima et al. (1997) using the model "lipophilic_tk" as described in the manuscript associated with this set of files (Kapraun et al., 2022). One HED is computed for each of the five dose metrics described in the manuscript.
- **hed_vodicnik1980.R:** This R source code file computes human equivalent doses (HEDs) for the mouse PCB 153 exposure scenario of Vodicnik et al. (1980) using the model "lipophilic_tk" as described in the manuscript associated with this set of files (Kapraun et al., 2022). One HED is computed for each of the five dose metrics described in the manuscript.
- **human_female_mass_0_to_20.csv:** This comma-separate-values (CSV) file contains time-course average body mass data for human females between the ages of 0 and 20 years. The data was extracted from Kuczmarski et al. (2002) as described in the manuscript associated with this set of files (Kapraun et al., 2022).
- **human_female_mass_20_to_25_pregnancy.csv:** This comma-separate-values (CSV) file contains time-course average body mass data for human females between the ages of 20 and 25 years, assuming they conceive at age 24.25 years and give birth at age 25 years. The data were taken from Table 3 of the manuscript associated with this set of files (Kapraun et al., 2022).
- **human_female_mass_20_to_75.csv:** This comma-separate-values (CSV) file contains time-course average body mass data for human females between the ages of 20 and 75 years, assuming they do not become pregnant. The data were taken from Table 8-5 of Chapter 8 of U.S. EPA (2011) as described in the manuscript associated with this set of files (Kapraun et al., 2022).
- **human_female_mass_25_to_26.csv:** This comma-separate-values (CSV) file contains time-course average body mass data for human females between the ages of 25 and 26 years, assuming they become pregnant and give birth at age 25 years. The data were taken from Table 3 of the manuscript associated with this set of files (Kapraun et al., 2022).
- **lipophilic_tk.model:** This MCSim source code file defines the ordinary differential equation (ODE) pharmacokinetic (PK) model for lipophilic persistent environmental

chemicals described in the manuscript associated with this set of files (Kapraun et al., 2022).

- **lipophilic_tk_model.c**: This C source code file defines the ordinary differential equation (ODE) pharmacokinetic (PK) model for lipophilic persistent environmental chemicals. It is a partial translation of the file "lipophilic_tk.model" into the C language.
- **lipophilic_tk_model.dll**: This DLL file defines the ordinary differential equation (ODE) pharmacokinetic (PK) model for lipophilic persistent environmental chemicals. It can be obtained by compiling the C source code in "lipophilic_tk_model.c" and it can be used directly by functions in the R package "deSolve".
- **lipophilic_tk_model.o**: This C object code file defines the ordinary differential equation (ODE) pharmacokinetic (PK) model for lipophilic persistent environmental chemicals. It can be obtained by compiling the C source code in "lipophilic_tk_model.c".
- **lipophilic_tk_model_inits.R**: This R source code file defines initialization functions for the ordinary differential equation (ODE) pharmacokinetic (PK) model for lipophilic persistent environmental chemicals.
- **pcb153_vodicnik1980_study2_mc.R:** This R source code file performs simulations of an experiment involving mouse dams exposed to PCB 153 (Vodicnik et al., 1980) using the model "lipophilic_tk" as described in the manuscript associated with this set of files (Kapraun et al., 2022). It then generates a figure showing PCB 153 concentrations in mouse dams ("vodicnik1980_maternal_concentration_mc.tif") and another figure showing PCB 153 concentrations in rat fetuses and pups ("vodicnik1980_filial_concentration_mc.tif"). These figures are saved in the "Output" directory.
- **plot_body_mass_defaults.R:** This R source code file generates plots showing body mass vs. time for rat dams and offspring ("rat_body_mass.tif") and human mothers and offspring ("human_body_mass.tif") based on default parameter values described in the manuscript associated with this set of files (Kapraun et al., 2022). These figures are saved in the "Output" directory.
- **plot_milk_consumption_defaults.R:** This R source code file generates plots showing milk consumption vs. time for nursing rat pups ("rat_milk_consumptions.tif") and human infants ("human_milk_consumptions.tif") based on default parameter values described in the manuscript associated with this set of files (Kapraun et al., 2022). These figures are saved in the "Output" directory.
- **posterior_halft_HCB.csv:** This comma-separate-values (CSV) file contains a sample of half-life values for HCB in rats generated using a hierarchical Bayesian model and a Markov chain Monte Carlo sampling method.
- **posterior_halft_PCB153.csv:** This comma-separate-values (CSV) file contains a sample of half-life values for PCB 153 in mice generated using a hierarchical Bayesian model and a Markov chain Monte Carlo sampling method.

- **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.
- **sensitivity_analysis_human.R**: This R source code file performs a local sensitivity analysis for the model “lipophilic_tk”. The sensitivities are calculated based on perturbations about a set of parameter values selected for human simulations of exposure scenarios for HCB. The source code file creates plots and a CSV file that show local sensitivity indices for model parameters. Plots (“sens_all_human.tif” and several others) and the CSV file (“sens_human.csv”) are saved in the “Output” directory.
- **sensitivity_analysis_nakashima1997.R**: This R source code file performs a local sensitivity analysis for the model “lipophilic_tk”. The sensitivities are calculated based on perturbations about a set of parameter values selected for rats exposed to hexachlorobenzene (HCB) in the study of Nakashima et al. (1997). The source code file creates plots and a CSV file that show local sensitivity indices for model parameters. Plots (“sens_all_nakashima1997.tif” and several others) and the CSV (“sens_nakashima1997.csv”) file are saved in the “Output” directory.
- **sensitivity_analysis_vodicnik1980.R**: This R source code file performs a local sensitivity analysis for the model “lipophilic_tk”. The sensitivities are calculated based on perturbations about a set of parameter values selected for mice exposed to PCB 153 in the study of Vodicnik et al. (1980). The source code file creates plots and a CSV file that show local sensitivity indices for model parameters. Plots (“sens_all_vodicnik1980.tif” and several others) and the CSV (“sens_vodicnik1980.csv”) file are saved in the “Output” directory.
- **sim_functions.R:** This R source code file functions for running simulations absorption, distribution, and elimination of a lipophilic substance in various species.
- **Verner_Kapraun_predictions_hcb.csv:** This comma-separate-values (CSV) file contains whole-body concentrations in human mother and her offspring that were generated by using the Verner et al. (2013) model to simulate continuous exposure of the mother to 1 mg/kg/d of PCB 153 from her birth until she reaches 28 years of age.
- **Verner_Kapraun_predictions_pcb153.csv:** This comma-separate-values (CSV) file contains whole-body concentrations in human mother and her offspring that were generated by using the Verner et al. (2013) model to simulate continuous exposure of the mother to 1 mg/kg/d of HCB from her birth until she reaches 28 years of age.
- **Output**: A directory containing output files described in the file descriptions above.