## Instructions for the Carbaryl life stage PBPK/PD 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 “R submission**

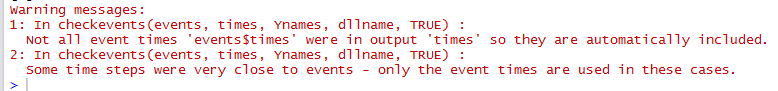
This is the current version of the Carbaryl human model in R as of July 28th, 2017. Model file (model. R) is saved in the folder named ‘Model’ and parameter files for Carbaryl simulations are saved in the folders named ‘Carbaryl’. R files are included in the folder named ‘Scenarios’ to simulate POD (10% AChE inhibition in RBC and brain) for Carbaryl at a given exposure scenario in human at specific ages using pre-populated default parameters. Any parameters can be changed to examine the impact of the change on model outputs. All together there are a total of 57 model files, and their file extensions have been changed to .txt. In order to run these model files in R, the file extensions need to be changed back to R:

1. Copy the whole model folder (R submission) on your computer.
2. **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, therefore after copying all the R files, they need to be organized into subfolders as suggested below:**
   1. Copy the whole model folder (R submission) on your computer
   2. Make 3 subfolders under this main folder as “Model”, “Carbaryl” and “Scenarios”.
   3. Save the “model-new-annotated” as “.R” in a folder named “model”. Note as this file is provided as txt, therefore need to be saved as R to be able to run in R-studio.
   4. Save all parameter files names starting with “params” in folder called “Carbaryl” by “.R”. Note as these files are provided as txt, therefore need to be saved as R to be able to run in R-studio.
   5. Save all scenario files in folder called “Scenarios” by “.R”. Note as these files are provided as txt, therefore need to be saved as R to be able to run in R-studio.
3. **Running Scenarios in “R”**

To run the scenarios, click on “Source”, not “run” in RStudio. There are 29 files for scenario (Note 2) simulations and 1file named “Oral-ParaHuman-standard” to simulate single oral dose of 1mg/kg for human carbaryl model validation with May et al. data.

* 1. Exposure values need to be changed (as per cited in table 2 and 3 in white paper) in respective scenario files to simulate either 10% AChE inhibition in RBC or brain.
  2. If different scenario is desired to be simulated, then you need to change the chemical, the gender and the age in #get paramFile accordingly with the scenario needed. If you want to change parameters that are in the parameter files, don’t change them in these parameter files but in the scenario files. Copy this new line: params[["NAME OF THE PARAMETER"]] <- x.

1. **Note 1:**
2. While running the R version of the models, in case of few scenarios, you may come across the message below. The first message indicates that some dosing events were triggered at times that were originally not a part of timepoints that the model was asked to output. So, they were automatically added to the output vector. The second message indicates that in this simulation the dosing events occurred very close to a model timepoint, and so the model time point was ignored (eg. Dosing began at 0.09 hr and model was supposed to print an output at 0.1 hr. In this case only the output at 0.09 hr was printed)



1. The exposure related parameters in scenario files are setup such that the result provides a POD for brain. To obtain the correct POD value for RBC, please update the parameters to match the values provided in this report.
2. **Note 2: Description of each scenario in the R Scenario folder**

|  |  |
| --- | --- |
| **Exposure scenarios** | **Description** |
|
| Dermal-Residential Handler-80kg-half SKcontact-1hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 0.41 ug/cm2/hr for 180 days and 100% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #1) |
| Dermal-Residential post-app-11kg-half SKcontact-1\_5hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 1Y Male, exposed to carbaryl through dermal route at a rate of 1.17 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 11 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 1Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #12) |
| Dermal-Residential post-app-32kg-half SKcontact-1\_5hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 6Y Female, exposed to carbaryl through dermal route at a rate of 1.17 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 32 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 6Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #11) |
| Dermal-Residential post-app-57kg-half SKcontact-1\_5hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 13Y Female, exposed to carbaryl through dermal route at a rate of 1.17 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 57 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 13Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #10) |
| Dermal-Residential post-app-80kg-half SKcontact-1\_1hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 1.48 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #15) |
| Dermal-Residential post-app-80kg-half SKcontact-1\_5hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 1.17 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #9) |
| Dermal-Residential post-app-80kg-half SKcontact-2\_2hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 1.17 ug/cm2/hr for 180 days and 50% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #14) |
| Dermal-Worker-Applicator-80kg-full SKcontact-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 0.41 ug/cm2/hr for 180 days and 100% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #2) |
| Dermal-Worker-mix loader-80kg-full SKcontact-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 0.41 ug/cm2/hr for 180 days and 100% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #1) |
| Dermal-Worker-PHED-80kg-full SKcontact-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 16Y Female, exposed to carbaryl through dermal route at a rate of 0.41 ug/cm2/hr for 180 days and 100% of skin comes in contact to the carbaryl exposure. Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 16Y Female was most sensitive, we report the corresponding PODs in Table-2 (Scenario #3) |
| Inhalation-Worker-Applicator-80kg-1730RESPR-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 25Y Male, exposed to carbaryl through inhalation for 8hr/day over 180 days at breathing rate of 1730L/hr (1.73 m3/hr). Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 25Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #5) |
| Inhalation-Worker-Loader-80kg-1730RESPR-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 25Y Male, exposed to carbaryl through inhalation for 8hr/day over 180 days at breathing rate of 1730L/hr (1.73 m3/hr). Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 25Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #4) |
| Inhalation-Worker-PHED-80kg-640RESPR-1hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 25Y Male, exposed to carbaryl through inhalation for 8hr/day over 180 days at breathing rate of 640L/hr (0.64 m3/hr). Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 25Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #8) |
| Inhalation-Worker-PHED-80kg-1730RESPR-8hr | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 25Y Male, exposed to carbaryl through inhalation for 8hr/day over 180 days at breathing rate of 1730L/hr (1.73 m3/hr). Note: EPA provided BW as 80 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 25Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #6) |
| Oral turf-Residential Post-app-11kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 1Y Male, exposed to carbaryl orally for 1.5 hrs as 6 replenishments per day over 180 days. Note: EPA provided BW as 11kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 1Y Male was most sensitive, we report the corresponding PODs in Table-2 (Scenario #13) |
| Drinking water-4\_8Kg-6 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 6 months Female, exposed to carbaryl through drinking water. Total water consumption is 0.7L/day as 6 times a day. Note: EPA provided BW as 4.8 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 6-month Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #2). |
| Drinking water-12\_6Kg-6 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 1Y Male, exposed to carbaryl through drinking water. Total water consumption is 0.7L/day as 6 times a day. Note: EPA provided BW as 12.6 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 1Y male was most sensitive, we report the corresponding PODs in Table-3 (Scenario #4). |
| Drinking water-18\_7Kg-6 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 3Y female, exposed to carbaryl through drinking water. Total water consumption is 0.7L/day as 6 times a day. Note: EPA provided BW as 18.7 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 3Y female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #6). |
| Drinking water-37\_1Kg-6 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 6Y male, exposed to carbaryl through drinking water. Total water consumption is 0.7L/day as 6 times a day. Note: EPA provided BW as 37.1 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 6Y male was most sensitive, we report the corresponding PODs in Table-3 (Scenario #8). |
| Drinking water-67\_3Kg-4 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 13Y female, exposed to carbaryl through drinking water. Total water consumption is 1.7L/day as 4 times a day. Note: EPA provided BW as 67.3 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 13Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #10). |
| Drinking water-81\_2Kg-60Y-4 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 60Y female, exposed to carbaryl through drinking water. Total water consumption is 1.7L/day as 4 times a day. Note: EPA provided BW as 81.2 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 60Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #14). |
| Drinking water-81\_5Kg-4 doses | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 20Y female, exposed to carbaryl through drinking water. Total water consumption is 1.7L/day as 4 times a day. Note: EPA provided BW as 81.5 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 20Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #12). |
| Food-Single-4\_8Kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 6 months Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 4.8 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 6-month Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #1). |
| Food-Single-12\_6 kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in1Y Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 12.6 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 1Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #3). |
| Food-Single-18\_7 kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 3Y Male, exposed to carbaryl through food once a day. Note: EPA provided BW as 18.7 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 3Y Male was most sensitive, we report the corresponding PODs in Table-3 (Scenario #5). |
| Food-Single-37\_1 kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 6Y Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 37.1 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 6Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #7). |
| Food-Single-67\_3 kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 19Y Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 67.3 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 19Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #9). |
| Food-Single-81\_2 kg - 60Y | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 60Y Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 81.2 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 60Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #13). |
| Food-Single-81\_5 kg | This scenario is used to generate the Carbaryl PODs (10% AChE inhibition in RBC and Brain) in 49Y Female, exposed to carbaryl through food once a day. Note: EPA provided BW as 81.5 kg, so we simulated the lower and upper end of the age range in addition to the age corresponding to the representative BW for both gender. As 49Y Female was most sensitive, we report the corresponding PODs in Table-3 (Scenario #11). |
| Oral-ParaHuman-standard | This scenario is used to generate the time profiles after a single oral dose of carbaryl (1mg/kg) as evaluation of the adult PBPK model performance using May *et al*. data |