

Using the U.S. EPA's Lifestage Perchlorate PBPK models

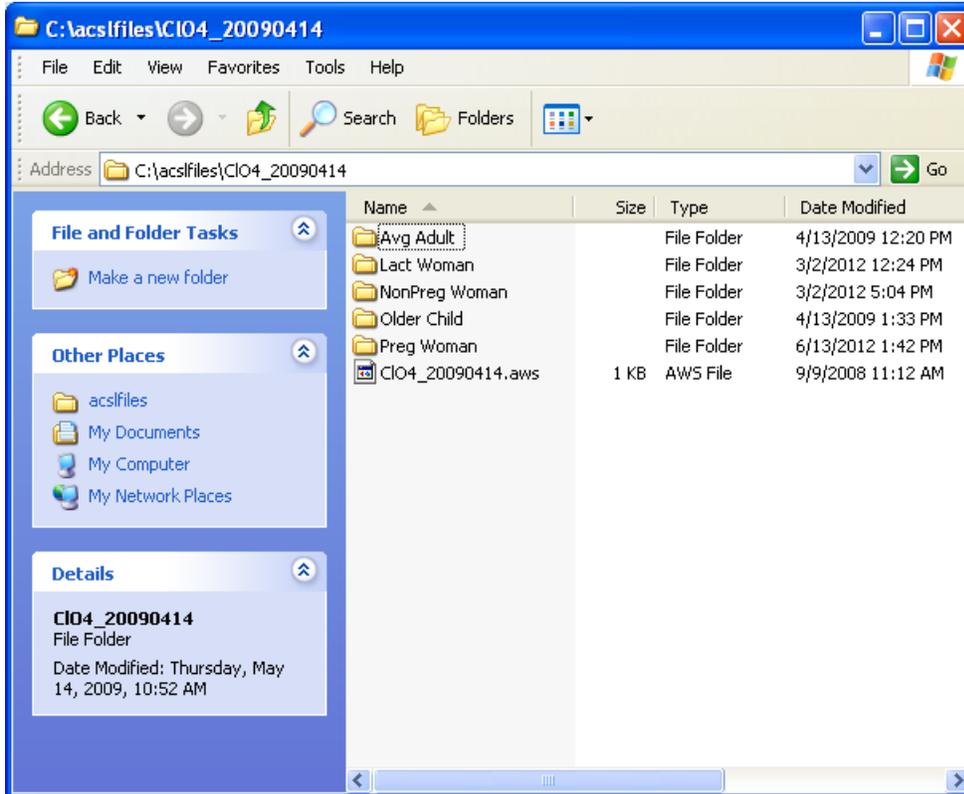
This document provides basic information to assist individuals in running the U.S. EPA versions of the lifestage perchlorate (ClO₄⁻) PBPK models. This is not intended to be a comprehensive “how to” document, and the user will require general knowledge of acslX and PBPK model programming in order to reproduce the results found in the ORD Support Document (U.S. EPA, 2009) and the external peer review draft of the White paper (U.S. EPA, 2012).

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File Management

- 1) Create a top-level folder on your 'C' drive called 'acsfiles'; i.e., C:\acsfiles
- 2) Unzip the workspace in that directory. This creates a folder called 'CLO4_20090414', and when opened it should appear as (note the directory structure in the Address bar):



Note: If you get a folder-within-a-folder, select this set of items from the inner folder, 'cut', move up a folder level, and 'paste'. (Keep the original .zip file as back-up!)

- 3) From within acslX choose "open existing workspace" and browse to this folder. Select CLO4_20090414.aws.

After opening the acslX workspace in acslX, the menu/"tree" on the left will indicate the projects below (first level of the tree), one of which is highlighted red as the active project. By default this will be the first project (NonPreg Woman). To activate a different project, right-click the project name (or little icon to the left of the name) and use the pull-down menu to "Set as active project."

Within each project exists a primary model code (.csl) file which defines the model and one or more "script" (.m) files which perform different analyses. Basic familiarity with acslX is suggested to work with these. Activate a project by right-clicking on the project name and selecting "Set as active project."

"Build" the model prior to running a script. Scripts within each project can be run by right-clicking on the script name and selecting "Run." You will get an error message if you try to run a script in a project that is not the "active" project.

Details and Usage of Model Files

The text below provides basic information on the model files and instructions on how to run these models. For the first model, the “average” adult, we point the user to the specific comparisons of model results with the EPA documents to provide some further orientation.

Average Adult (“Avg Adult”) Project

This will come up as the very last project on the tree – you may have to scroll down to see it.

- **human10.csl** – model code for an “average” adult. Standard 70 kg BW.
- **TEST_ADULT.m** - model script to estimate %RAIU for the average adult at a constant dose (PDOSE_P) or for specific drinking water (PPB) and food (FOOD) intake levels.

When the script is run:

- First output is the plasma/whole blood volume ratio (PBRAT) being used.
- Second output is % RAIU at the fixed dose rate set on line 28; currently PDOSE_P=7000 (ng/kg) for the POD. Result should be 1.6498 which rounds to 1.6 – the “Average Adult” value in Table A-3.
- It then sequentially builds a table, ‘adulth’ with the following columns:
- BW, PPB (water), FOOD (other ingestion), TDOSE (resulting total ng/kg-day), INH (% RAIU) – the resulting values for 15, 20, and 24.5 ppb should match Table A-4 (values for 100 ng/kg-day FOOD are those in parentheses in A-4)

Non-Pregnant Woman (“NonPreg Woman”) Project

- **adult_woman_edm.csl** – model code for non-pregnant adult woman created by removing the fetus and placenta sub-models from the pregnancy code and otherwise setting the physiological variables to those for day 1 of pregnancy from that code. In particular, BW = BWinit = 66 kg. It also includes the mammary with active transport of iodide and perchlorate, which is not in the “average adult” model.
- **inh_rels_woman.m** - model script to estimate %RAIU for the non-pregnant adult woman using constant dose (PDOSE) or drinking water (PPB) and food (FOOD) intake
 - Similar to ‘TEST_ADULT.m’ – see notes above – except
 - The last column in the table reports concentration in plasma (CA_P)
 - The data output after the table ‘woman_inhres’ is built are (output should match Table A-3):
 - The %RAIU at the POD (7000 ng/kg)
 - The ratio of non-pregnant woman %RAIU to the average adult %RAIU at the POD are given at the end

Pregnant Woman and Fetus (“Preg Woman”) Project

- **HPregF_Y_pms2.csl** – model code for pregnant woman and fetus
- **fetal_dose_calcs_pms2.m** - model script to estimate %RAIU for the pregnant woman and fetus using constant dose (PDOSE) or drinking water (PPB) and food (PDOSE) intake
 - PDOSE and PPB are set in the ‘for’ statements on lines 60 and 61. Here, food intake is included by simply adding the ingestion to PDOSE.
 - IVSTART_I, set on line 35, is the time in hours (hr) after the beginning of perchlorate exposure when the radioiodide tracer IV exposure is given; 336 hr is 2 weeks.
 - On line 36, gwk, is the gestation week at which this happens and the %RAIU is calculated. The simulation is then started at time IVSTART_I *before* gwk.
- **store_endpreg.m** – stores the end of pregnancy values to be used as initial values in lactation model
 - To estimate the %RAIU in the mother or infant shortly after birth using lactation model code (see below), a set of “initial” value scripts for the end of pregnancy/gestation needs to be used (e.g., ‘ffet_###_###.m’ and ‘fpreg_###_###.m’ files). The scripts used to create the tables in the White Paper (CITE) are included in the Lactating Woman project folder.
 - This script create and store two files, ‘fpreg_###_###.m and ‘ffet_###_###.m’, in the ‘lactation’ folder, where the first ‘###’ is 10x the water (PPB) exposure level (so 24.5ppb is ‘245’), then ‘_’ and the last ‘###’ is the total dietary/fixed dose in ng/kg-day.
 - On line 4 there is a ‘cd’ (change directory) command. The directory\folders in the command should be ‘C:\acslfiles\CIO4_20090414\Lact Woman’, unless you unzipped your workspace in a different sub-directory, in which case this should be edited appropriately.
 - On line 56, the PPB value(s) tested is defined. To test a range of values, delete the ‘0; %’, so the line reads:

```
for PPB=[15 20 24.5];           %ppb water concentrations to test
```

Similar changes should be made to line 55 for PDOSE if different dietary/fixed doses are tested.
 - The script does not write anything to the screen, only creates/saves the initial value scripts.

Lactating Woman and Neonate (“Lact Woman”) Project

- **HlactFrev.csl** - model code for lactating woman and neonate
- **clearance_set.m** - sets values for infant and lactating woman clearance. The basis for this script file is provided in the ORD Support Document (U.S. EPA, 2009).
 - This script is used in v-urine-neonate-GFR.m (see below) and sets specific clearance parameters based on the descriptor (text) values of infant clearance (infclr) and maternal clearance (matclr) in that file. If they have not been set then it assumes infclr = “low” and matclr = “middle”.
 - This script sets the VMXC_TNI table function which defines kidney excretion (GFR) changes with age in the neonate.
 - This script also sets values of exposure to the mother (variable *pds*) such that the breast-fed infant will receive the POD exposure, for each maternal clearance value.
- **table_GFR.m** – model script to estimate %RAIU resulting from different drinking water concentrations [in PPB] (set with ‘conc = [...]’) for the lactating mother and neonate (breast- and bottle-fed) with and without dietary exposure (tdsMOM and tdsKID), or for fixed exposure levels (set by assigning values to *pds*).
- **v-urine-neonate-GFR.m** – model script to determine the impact of different assumptions for urinary clearance on the estimated %RAIU for the lactating woman and neonate (breast- and bottle-fed) for a constant dose to the mom (PDOSE) or directly to the infant (for bottle-fed simulation – PDOSE_N). Code also used for estimating %RAIU for the lactating woman and neonate using water concentration (CONC).
 - The ‘ffet_###_###.m’ and ‘fpreg_###_###.m’ scripts referenced in this file that set the initial concentrations should correspond to the scenario being tested. This sets the initial tissue concentrations for the neonate and lactating mother equal to that at the end of pregnancy.
- **Initial concentration script (.m) files**
 - No perchlorate dose (food or water)
 - ffet_0_0.m
 - fpreg_0_0.m
 - Perchlorate dose of 7000 ng/kg (7ug/kg)
 - ffet_0_7000.m
 - fpreg_0_7000.m
 - Perchlorate dose of 15 ppb in water and 0 in food
 - ffet_150_0.m
 - fpreg_150_0.m
 - Perchlorate dose of 15 ppb in water and 100 ng/kg in food

- ffet_150_100.m
 - fpreg_150_100.m
- Perchlorate dose of 20 ppb in water and 0 in food
 - ffet_200_0.m
 - fpreg_200_0.m
- Perchlorate dose of 20 ppb in water and 100 ng/kg in food
 - ffet_200_100.m
 - fpreg_200_100.m
- Perchlorate dose of 24.5 ppb in water and 0 in food
 - ffet_245_0.m
 - fpreg_245_0.m
- Perchlorate dose of 24.5 ppb in water and 100 ng/kg in food
 - ffet_245_100.m
 - fpreg_245_100.m

Older Children (“Older Child”) Project

- **HkidF_X_edm.csl** – model code for older child
- **Inh_rels_kid.m** - model script to estimate %RAIU for the older child using constant dose (PDOSE) or drinking water (PPB) and food (FOOD) intake. This operates similar to the average adult above. The parameters used in the EPA documents are included in this script file.

References

U.S. EPA (2009). Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity using Physiologically-Based Pharmacokinetic (PBPK) Modeling. (August 2009) Final. EPA/600/R-08/106F.

U.S. EPA (2012). White Paper: Life stage considerations and interpretation of recent epidemiological evidence to develop a maximum contaminant level goal for perchlorate. *External Peer Review Draft*. <http://yosemite.epa.gov/sab/sabproduct.nsf/0/d3bb75d4297ca4698525794300522ace!OpenDocument&TableRow=2.0>