



Users Guide for the FORTRAN Version of the All Ages Lead Model

Excel User Interface and FORTRAN
Model Executable

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I. A Brief History of the Leggett Model and an Introduction to the FORTRAN All Ages Lead Model

The Leggett biokinetic model (Leggett, 1993) simulates the intake, exchange, and excretion of lead in humans from birth through adulthood using a series of body compartments with mass exchange between them. When the model was originally coded, it synthesized a wide variety of sometimes disparate sources of information related to the biokinetics of lead in humans. The Leggett model was informed by:

- Lead tracer studies of injection, ingestion, and inhalation in healthy adult humans,
- Measurements of lead in environmentally exposed men, women, and children at autopsy,
- Lead mass-balance studies on adult humans,
- Bioassay and autopsy measurements on occupationally exposed subjects,
- Lead studies in laboratory animals at different life stages
- Experimental, occupational, environmental, and medical data on the biokinetics of elements that serve as physiological analogues of lead, and
- Basic physiological information on the human body.

As such, the Leggett model structure is a minimal system of body compartments and mass exchange terms needed to synthesize all these data sets. The modular form of the model allows investigators to modify specific parameter values to address special problems in lead toxicology or to incorporate new information related to lead biokinetics. The original Leggett model included:

- **Input file:** an ASCII input file containing information describing the lead exposure scenario and the age-dependent lead transfer rates for each compartment, and
- **Model code:** an executable FORTRAN program which reads the input file, performs the prescribed calculations, and writes the outputs to an ASCII file.

This approach was designed to provide maximum flexibility and versatility rather than user-friendliness.

1. The All Ages Lead Model and an Exposure Interface

The original Leggett model has, on several occasions, been translated onto other software platforms or into other programming languages. One notable example is the inclusion of the Leggett model in the Environmental Protection Agency's (EPA) All Ages Lead Model (AALM). In collaboration with EPA, SRC, Inc. recoded the model in the acslX programming language. Unlike FORTRAN, this programming language comes with off-the-shelf differential equation solvers supporting variable time steps, along with other functions (such as "TABLE") that easily allow input parameters to vary in time during the simulation.

SRC also added an Excel user interface that expanded the Leggett model to incorporate exposure estimation. The original Leggett model accepts inputs of inhalation and total oral intake in units of μg lead/day. The Excel user interface allows the user to enter in time-varying air concentrations (μg lead/ m^3 air); dust concentrations (μg lead/g dust); soil concentrations (μg lead/g soil); water concentrations (μg lead/L water); inhalation rates (m^3 air/day); total (soil plus dust) ingestion rates (g dust/day); water ingestion rates (L water/day); and food and "other"

intake rates (μg lead/day). The total (soil plus dust) ingestion rate and the fraction of total coming from soil are entered in the “Soil” tab. The user can also specify relative absorption factors for air, dust, soil, water, food, and “other” sources. The Excel interface writes input files for the acslX code and the acslX code incorporates the different media concentrations, media intake rates, and relative absorption factors to estimate total inhalation and total ingestion uptakes at each model time step. This feature greatly improved the user-friendliness of the model, since users could record and run a wide variety of exposure scenarios in a transparent way.

As part of coding and testing the AALM, EPA and SRC simulated a number of datasets, including adult and childhood datasets used during the original Leggett code calibration and validation as well as additional datasets identified during a literature search. Based on these tests, parameters were adjusted to ensure the best overall fit against all datasets. A full report documenting the datasets and parameter changes was provided to EPA and serves as a technical background document for this user guide.

2. Adapting the Exposure Interface for AALM.FOR

As noted above, acslX provides a number of benefits compared with a FORTRAN executable, and the AALM Excel interface improved user-friendliness for estimating exposure profiles. However, acslX is proprietary software, limiting the availability to some stakeholders. Then, in 2015, makers of the acslX simulation language announced the language would be “sunsetting”, meaning no new licenses would be sold. The EPA Office of Pollution Prevention and Toxics was already using the FORTRAN version as part of the Lead Renovation, Repair, and Painting analyses for public and commercial buildings; because of the number of simulations needed for this Monte Carlo analysis, acslX was not practical and EPA required the speed and efficiency inherent in the FORTRAN language to complete the analysis. As part of that project, EPA OPPT worked with EPA ORD to evaluate the differences between the AALM and the Leggett FORTRAN code and to harmonize the inputs. They reevaluated the parameters against all datasets and also demonstrated that the acslX and FORTRAN versions, when configured with the same growth algorithms and input parameters, returned results to within +/- 5% of each other for a range of exposure scenarios in both children and adults. The final product included an acslX version of the All Ages Lead Model (AALM.CSL) and a harmonized FORTRAN version (AALM.FOR).

To help allow other researchers and regulators to use the FORTRAN version, particularly in the face of the acslX “sunsetting”, EPA and ICF have created this Excel user interface. The goals of this user interface are:

- 1) To maintain the format and functionality of the AALM.CSL Excel interface, particularly with respect to exposure estimation,
- 2) To adapt the tool to create the input files for the AALM.FOR and to call the FORTRAN executable directly to allow the user to run the Leggett AALM algorithms without acslX, and
- 3) To provide a rudimentary user’s guide to help users to understand how to setup and run the simulations in this version, given the more extensive AALM.CSL documentation as a resource.

II. Overview of the Excel User Interface and FORTRAN Model

The Excel user interface to AALM.FOR model consists of the following pieces:

- The Excel user interface file:
 - A ReadMe tab with instructions for setting up a run (blue)
 - Main simulation control input tab (purple)
 - Exposure input tabs (green)
 - Biokinetic parameter input tabs (orange)
 - Output tabs (red)
 - Reference tabs (gold)
- An input file template
 - The Excel file uses the information in the tabs to fill in the template and create an input file
- The Leggett executable:
 - This is a 32-bit executable that is called by the Excel file to run the model
- Supplementary files:
 - The user's guide (this file)
 - The Leggett model text file that was compiled to create the Leggett executable. It is not needed to run the model but may be needed by some researchers who wish to make future changes to the model algorithms.

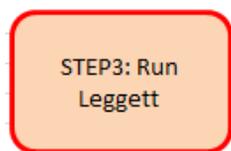
Exhibit 1 outlines the process the tool uses to run AALM.FOR. The steps include:

STEP1: Setup Timestep
Input Zone (use only if
NDELTA is changed)

Configure the **Simulation Control** tab variables. Press the button **“STEP 1. Setup Timesteps”** to complete the configuration. STEP 1 does not need to be completed unless the number of time steps during a simulation is changed. It is recommended that the default of 1 be used.

STEP2: Update
Leggett
Variable Tab

Enter/edit inputs for the exposure inputs and biokinetic inputs in the **exposure input tabs** ("Air", "Dust", "Soil", "Water", "Food", "Other", "RBA") and the **biokinetic input tabs** ("Lung", "Systemic" and "Sex"). Press the **“STEP 2. Update Leggett Variable Tab”** button on the “Simulation Control” tab to complete the configuration. The Excel interface generates the input file using the provided text template file.

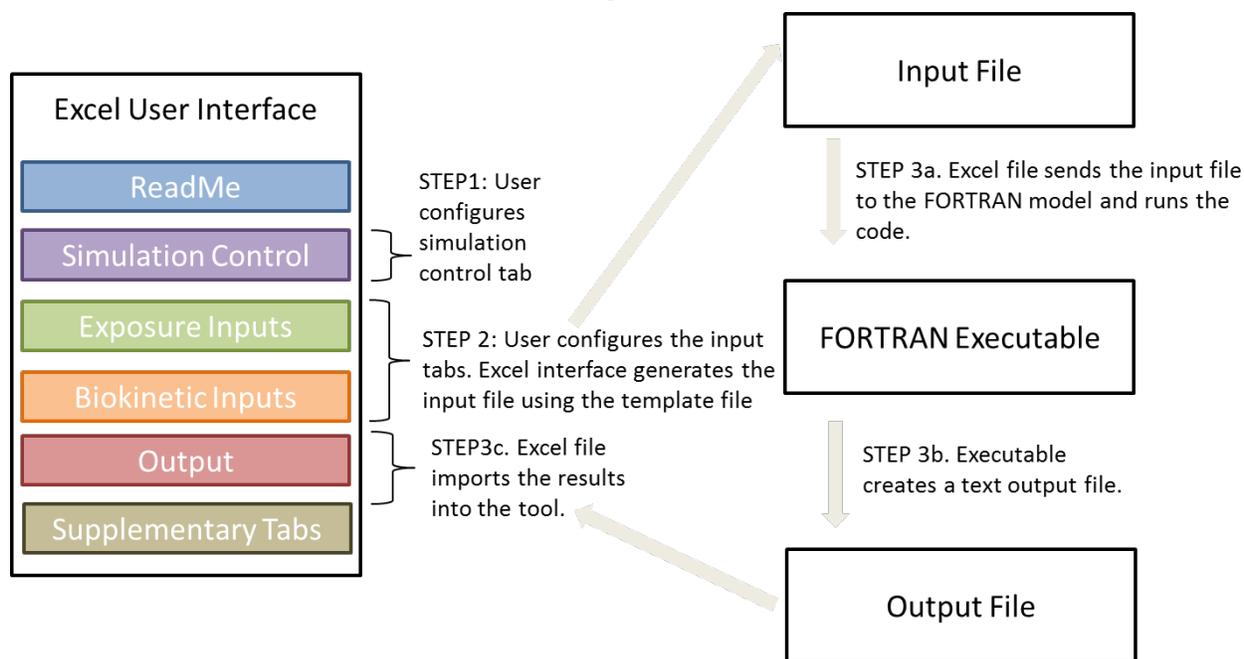


Press the “**STEP 3: Run Leggett**” button on the “Simulation Control” tab.

- a. The code then sends the input file to the FORTRAN model and calls the FORTRAN executable to run the model.
- b. The executable creates the output text file.
- c. Excel then imports the results into the **Output tab** of the tool.

Please note: to create the 32-bit executable, ICF used the proprietary Intel FORTRAN compiler. As such, the compiler itself is not provided as part of the package. This compiler version was needed to get the model to properly compile. ICF also attempted to compile the model using free FORTRAN compilers, including the GNU compiler. However, the code returned errors in the compilation during our testing.

Exhibit 1. Overview of the Excel Interface Configuration and Run Process



III. How to Setup and Run the Leggett Model Using the Excel Interface

This final section of the User’s Guide provides a brief description of how to configure the user interface and run AALM.FOR.

1. Unzip the Model File Package and add the Appropriate Runtime Library

To begin to use the model, unzip the zip file and place the contents in any folder on your computer. On some systems, if the files are placed in the “Documents” folder or subfolder, a Microsoft Visual Basic “Run-time error ‘5’: Invalid procedure or call or argument” will occur when the STEP3 macro tries to determine the file path. Should this error occur, try placing the folder on a part of the C: drive where you have read/write permissions. You can save different Excel files for each of your different simulations, and these can be in different folders on your computer. The only restriction is that each time you run the Excel file, the following files must be in the same folder as the Excel file:

1. ICRPv008d_aalm_32bit.exe (the model executable)
2. Intermediate Exposure Time Series.csv (an optional diagnostic file to save intermediate exposure time series, see page 12)

Next you can open the Excel file. For the file to work, you must add a runtime library to Excel if you have never done so in the past. To do this:

Step 1: Load the VB Editor (ALT+F11)

The screenshot displays the Microsoft Visual Basic for Applications editor. The main window shows the VBA code for the 'Interop' module. The code includes a loop for processing input arrays and a function for interpolating values between ages. The Properties window shows the 'Sheet13' worksheet.

```

Dim time_length As Long, value_length As Long
Dim time_ind As Long
Dim time_three_1 As Double, time_three_2 As Double
Dim value_1 As Double, value_2 As Double

time_length = UBound(input_array, 1) + 1
value_length = UBound(input_array, 2) + 1
time_ind = 0

Do While (time_ind < time_length)
    If input_array(time_ind, 1) < Time_to_est Then
        time_ind = time_ind + 1
    ElseIf input_array(time_ind, 1) >= Time_to_est Then
        If time_ind = 0 Then
            time_three_1 = input_array(time_ind, 1)
            time_three_2 = input_array(time_ind + 1, 1)
            value_1 = input_array(time_ind, 2)
            value_2 = input_array(time_ind + 1, 2)
        ElseIf time_ind > 0 And time_ind < time_length Then
            time_three_1 = input_array(time_ind - 1, 1)
            time_three_2 = input_array(time_ind, 1)
            value_1 = input_array(time_ind - 1, 2)
            value_2 = input_array(time_ind, 2)
        End If
        Exit Do
    Else
        time_three_1 = 0
        time_three_2 = 0
        value_1 = input_array(time_ind - 1, 2)
        value_2 = value_1
    End If
    Loop
    Debug.Print "matched=" & time_ind & ", time_three_1=" & time_three_1 & ", time_three_2=" & time_three_2 & ", value_1=" & value_1 & ", value_2=" & value_2 & ", Time_to_est=" & Time_to_est
    ' Interpolate value rates between ages
    Interop = value_1 + ((value_2 - value_1) / (time_three_2 - time_three_1)) * (Time_to_est - time_three_1)
End Function

Function ts_array(pulse_start As Long, pulse_stop As Long, pulse_wid As Long, pulse_pd As Long, ENDDAY As Long) As Integer()
    ' =====
    ' This function is used to translate pulse exposure parameters to a vector of 0s (without exposure) and 1s (with exposure)
    ' To use it, one will specify
    '   pulse_start: first day of pulse exposure
    '   pulse_stop: the last day of pulse exposure
    '   pulse_wid: consecutive pulse exposure days
    ' =====

```

The Properties window shows the 'Sheet13' worksheet with the following properties:

Property	Value
AlphaNumeric	Categorized
Always	Sheet13
DisplayPageBreaks	False
DisplayRightToLeft	False
EnableAutoFilter	False
EnableCalculation	True
EnableFormatConditionsCalculation	True
EnableOutlines	False

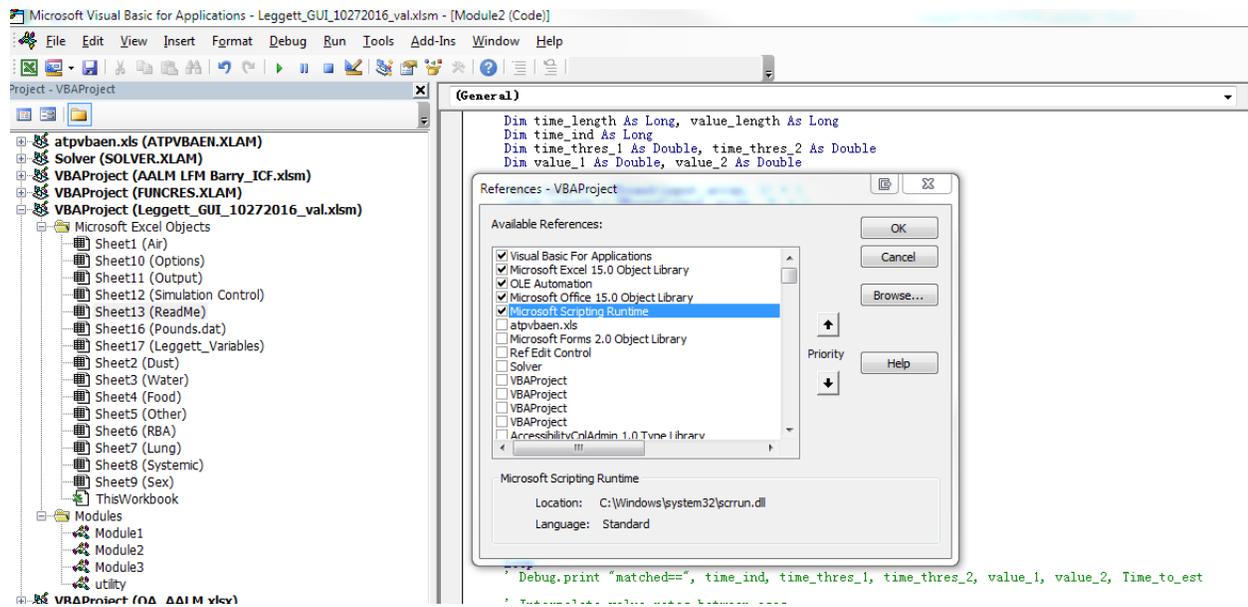
The Immediate window shows the following output:

```

30000 Vent_inter===== 19.91 C_base===== 0 Fpulse===== 0 Pulse_TS_1m===== 0 Pulse_TS_2m===== 0 Disc_inter===== 0
31000 Vent_inter===== 19.91 C_base===== 0 Fpulse===== 0 Pulse_TS_1m===== 0 Pulse_TS_2m===== 0 Disc_inter===== 0
32000 Vent_inter===== 19.91 C_base===== 0 Fpulse===== 0 Pulse_TS_1m===== 0 Pulse_TS_2m===== 0 Disc_inter===== 0

```

Step 2: Select Tools > References from the drop-down menu, and from the list of available references tick the check box next to 'Microsoft Scripting Runtime' and click OK.



Then you can close the VBA editor. You only need to complete this step the first time you run the tool on your computer.

For some versions of Excel, you may also need to enable the macros within the file when you open it as well. When you open the tool, a yellow bar will appear at the top with a button “Enable Content?”. Click the button to enable the macros. If this button does not appear, you can also do the following:

- Click the Microsoft Office Button, and then click Excel Options.
- Click Trust Center, click Trust Center Settings, and then click Macro Settings.
- Click the options to enable the macros.

2. Complete the Simulation Control Tab

To begin a simulation, begin with the simulation control tab. This sheet primarily contains the Leggett input parameters that control:

- 1) Timing in the simulation (age at the start, time step lengths, and ending day of the simulation).
- 2) How often the outputs should be written to the output file (that is, how many time steps there are between each output).
- 3) The sex of the modeled individual (for estimation of growth parameters).
- 4) The name of the output text file.
- 5) Binary switches (“shortcuts”) to indicate which exposure pathways (air, dust, soil, water, food, and other) will be used in the simulation.

Yellow Highlighted Text = Cells That Can Be Edited by the User

Throughout the Excel GUI, yellow cells indicate values that can be adjusted by the user if desired. Other cells should not be edited.

6) A binary switch to indicate whether the user wants to save the intermediate exposure time series.

7) A binary switch to indicate whether the exposure time series should be stepwise or interpolated when implemented in the model.

Other information includes parameters that are currently fixed (not editable) in the user interface:

8) Information about the number of ages at which the biokinetic parameters vary in the model (this is currently fixed at 11) and the ages (0, 3 months, 1, 5, 10, 15, 25, 30, 40, 60, and 90).

9) The route of exposure and how the exposure is entered in the model (set to include all possible routes)

10) Switch for whether the RBC equation is linear or non-linear (set to non-linear)

11) Radiological decay rate and chelation parameters (fixed so there is no decay or chelation)

Timing in the simulation (age at the start, time step lengths, and ending day of the simulation)

The timing setup in the Leggett FORTRAN model is the most nuanced part from a user-perspective. The user has to figure out how long to run the model, what time steps to use, and how many time step “cycles” the model needs in order to reach the specified simulation length. The interplay between these variables is explained in this section. The calculation is straightforward if the user uses a single time step for the full simulation, which is strongly recommended.

EXPAGE	0
--------	---

To make changes to the editable (yellow) simulation timing variables, begin by entering the age of the individual at the start of the simulation. Because lead accumulates in the body, it is generally necessary to model the entire lifetime exposure of an individual, so this parameter is usually set to 0 (birth).

NDELTA	1
--------	---

Next, decide on the number of different time step lengths to be used in the model. Unlike the AALM.CSL, which can vary the time step as needed during the simulation, AALM.FOR requires the user to specify whether they want to vary the time step by setting “NDELTA” equal to the number of different time step lengths desired. In general, time steps should be shorter than the fastest biological process or the fastest rate of change in exposure. If exposure is varying quickly (e.g., due to an acute exposure scenario), the time step needs to be short and overall runtime becomes longer. The original Leggett code allows the user to specify a longer time step either before the acute exposure or after exposure returns to baseline levels so that portions of the simulation can be run faster. When the original code was built in 1993, this technique could greatly reduce the overall runtime of the model. However, with current computing power, the

Leggett model tends to run in less than a minute for a 90 year simulation with a half-day time step. For this reason, we strongly suggest selecting the shortest necessary time step and using it for the entire simulation (NDELTA=1). In testing, changing the time step mid-run resulted in numerical noise at the time of the change, so using a single time step is preferred.

TSTOP	1500
--------------	------

Next, enter the final day of the simulation using variable “TSTOP”. In the example here, the model will be run for 1,500 days.

STEP1: Setup Timestep
Input Zone (use only if
NDELTA is changed)

Now that you have specified the number of timestep changes you want to use and how many total days you want to simulate, you need to specify details for each time step. If you have changed the number of timesteps (i.e., NDELTA), press the “STEP1: Setup Timestep Input Zone” button. The interface will adjust the size of the table beginning in cell H20 according to the number of time steps you want to use.

# Time step	DELTA (Time step in days)	ICYC (Total number of model cycles using the associated DELTA time step)
1	0.25	6000

Then, enter the specifics about the time step in the table beginning in cell H20. First, specify how long each time step should be (DELTA) in days. As mentioned above, time steps should be shorter than the fastest biological process or the fastest rate of change in exposure included in the model. As a general guide, for chronic lead exposure, time steps on the order of 0.25-1 day are usually sufficient.

The ICYC variable is then the model cycle where the time step changes. For example, if you wanted to use a specific time step of 0.25 days for the first 1500 days of a simulation, then ICYC would be 1500/0.25=6000 cycles.

If you are only using a single time step for the entire simulation, this table is easy to fill out. You specify the DELTA, and the number of cycles is the total number of days in the simulation divided by the time step:

$$ICYC = TSTOP/DELTA$$

If you are using more than one time step, the table is slightly more intricate to fill out. Suppose you want to create a simulation that uses a 0.5 day time step for the 12.5 days, a 1 day time step for the next 25 days, and then a 2 day time step for the final 100 days. Then:

Word to the Wise: Make Sure Years Have an Integer Number of Time Steps
Because the Leggett model accepts inputs for time step lengths in days but for ages in years, it is generally best to keep the number of time steps in the year an integer. For example, using “0.25” will give 6 hours per time step and 1460 time steps per year (365/0.25). If instead you used “0.33” (the truncated version of 1/3), you will get 1106.06060606... time steps per year (365/0.33). This causes the timing in the model to become slightly misaligned.

EXPAGE = 0 (start from birth)

NDELTA = 3 (two different time steps)

TSTOP = 137.5 days, and

# Time step	DELTA (Time Step)	ICYC (Model cycle where the time step changes to DELTA)
1	0.5	25
2	1	50
3	2	100

This indicates:

- The first time step (DELTA1) is 0.5, it lasts 25 time steps (ICYC1), corresponding to 12.5 days
- The second time step (DELTA2) is 1, it lasts 25 time steps (ICYC2-ICYC1), corresponding to 25 days
- The third time step (DELTA3) is 2, it lasts 50 time steps (ICYC3-ICYC2), corresponding to 100 days
- In total, those three time steps covers a total of 137.5 days

One final nuance: TSTOP and the total number of cycles may not actually match each other based on user input, and the FORTRAN code will use whichever is shorter. If TSTOP = 80, the actual simulation period will be 80 days. On the other hand, if TSTOP = 180, the actual simulation period will be 137.5 days (the number of cycles specified in the time step input table).

How Often the Outputs should be Written to the Output File

In order to control the frequency of the output, the user decides how often the model should write the output variables to the output file. CINT uses the number of time steps as its unit. If the time step is 0.5 days and the CINT is 730, the outputs will only be written every year (0.5×730). This helps to control the file size of the output file so that every time step is not saved.

CINT implies the time between outputs will vary if you are using different time steps over the course of a run. For example, for the following time step input table, when CINT=1 and TSTOP=7, the time step table and associated output table will be:

# Time step	DELTA (Time Step)	ICYC (Ending Time of Each Time Step)
1	0.5	5
2	1	10

N	DAY	YEAR	INTAKE IV ug/day	INTAKE INH ug/day	INTAKE ING ug/day
1	5.00E-01	1.37E-03	0.00E+00	6.44E+00	6.43E+00
2	1.00E+00	2.74E-03	0.00E+00	6.44E+00	6.43E+00
3	1.50E+00	4.11E-03	0.00E+00	6.44E+00	6.43E+00
4	2.00E+00	5.48E-03	0.00E+00	6.44E+00	6.44E+00

5	2.50E+00	6.85E-03	0.00E+00	6.44E+00	6.44E+00
6	3.50E+00	9.59E-03	0.00E+00	1.43E+00	6.52E+00
7	4.50E+00	1.23E-02	0.00E+00	1.43E+00	6.25E+00
8	5.50E+00	1.51E-02	0.00E+00	1.43E+00	5.97E+00
9	6.50E+00	1.78E-02	0.00E+00	1.43E+00	5.86E+00
10	7.50E+00	2.05E-02	0.00E+00	1.43E+00	5.87E+00

The outputs are written every time step which is every half day for the first 2.5 days and then every day for the remainder of the simulation. When CINT=2 and TSTOP=7, the output table will be

N	DAY	YEAR	INTAKE IV	INTAKE INH	INTAKE ING
			ug/day	ug/day	ug/day
2	1.00E+00	2.74E-03	0.00E+00	6.44E+00	6.43E+00
4	2.00E+00	5.48E-03	0.00E+00	6.44E+00	6.44E+00
6	3.50E+00	9.59E-03	0.00E+00	1.43E+00	6.52E+00
8	5.50E+00	1.51E-02	0.00E+00	1.43E+00	5.97E+00
10	7.50E+00	2.05E-02	0.00E+00	1.43E+00	5.87E+00

Now the outputs are written every day for the first 2.5 days and then every 2 days after that.

The sex of the modeled individual (for estimation of growth parameters)

Next the user specifies whether the modeled individual is a male or a female. The AALM uses growth algorithms that vary for males and females. Thus, the choice of sex does not control any biokinetics in the model, but it does affect the predicted concentrations by altering the volume of the modeled tissues/compartments over which the lead mass is distributed.

The name of the output text file

Finally, the user can type in the name of the text file generated by the Leggett executable.

Binary switches (“shortcuts”) to include or exclude a certain exposure pathways

These switches allow the user to easily include or exclude exposure from a given pathway (air, dust, soil, water, food, and other). Please be aware that if “No” is selected for a certain pathway, the corresponding exposure doses will be considered to be zero no matter what values are listed on its individual exposure tab.

A binary switch to save intermediate exposure time series to a plain text file

An option to save intermediate exposure time series data for further diagnostic is available. If "Yes" is selected, a tab-separated text file "Intermediate Exposure Time Series.csv" will be saved to the working folder. This comma delimited file may be opened in Excel. The column definitions are listed in the following table:

Variable Name	Meaning	Unit
Day	Time series of the simulated outputs in unit of day	µg/day
Air	Intake dose from air pathway (before factoring in RBA)	µg/day
Indoor_Dust	Intake dose from dust pathway (before factoring in RBA)	µg/day
Soil	Intake dose from soil pathway (before factoring in RBA)	µg/day
Water	Intake dose from water pathway (before factoring in RBA)	µg/day
Food	Intake dose from food pathway (before factoring in RBA)	µg/day
Other	Intake dose from other pathway (before factoring in RBA)	µg/day
BRETH	Intake dose from air pathway (before factoring in RBA)	µg/day
EAT	Aggerated intake dose including dust, soil, water, food, and other pathways.	µg/day
Total	Total intake dose.	µg/day

A binary switch to indicate whether the exposure time series should be stepwise or interpolated when implemented in the model

In the data entry section for exposures (see section III.3), exposure values are provided at discrete time points (e.g., intake of 6 µg/day at age 2 and intake of 10 µg/day at age 6). For the biokinetic parameters and media intake rates (e.g., the amount of dust ingested at a given age), the model implements the profiles by interpolating between the discrete time points. This can also be done for exposure. For example, if the intake is 6 µg/day at age 2 and 10 µg/day at age 6, the model would create a smooth line between those points and use the value on the line for each intermediate age (e.g., 7 µg/day at age 3, 7.5 µg/day at age 3 ½, 8 µg/day at age 4, and similarly for every age). This provides a smoother blood lead concentration form the model. However, in some applications, such as discrete acute exposure scenarios, the user may want the exposure to abruptly change rather than interpolating.

Thus, two options are provided to simulate concentrations between two time stamps. For example, if food discrete concentration is 2.25 µg/day at Day 90, and 4.00 at Day 365. When "stepwise" is selected, all of the food discrete exposure concentrations will be set to 2.25 µg/day as long as the modeled person is between 90 days and 365 days old. On the other hand, if "interpolated" is selected, it is assumed that food concentration will be increased gradually between those two time stamps.

ROWN	Age year	Age day	Food_1 ug/day	Food_2 ug/day	Food_3 ug/day	Food_Total ug/d
1	2	3	4	5	6	7
2	0.0	0	1.50	0	0	2
3	0.2	90	2.25	0	0	2
4	1	365	4.00	0	0	4
5	2	730	5.20	0	0	5
6	3	1095	5.20	0	0	5

Other information includes parameters that are currently fixed (not editable) in the user interface

The remaining variables on the simulation control tab are currently fixed in the user interface. Information is given in the interface about the specific assumptions for each one. In general, assumptions are made about each to facilitate user entry of information in the user interface (in the case of “manual” versus “automatic” input and the ages where biokinetic parameters can change), or to make the settings as flexible as possible (such as allowing all routes of exposure to be present).

3. Configure the Exposure Input Tabs

The exposure is separated into air, dust, soil, water, food, and “other” pathways. For air, dust, soil, and water, the user specifies both the media concentration ($\mu\text{g}/\text{m}^3$ for air, $\mu\text{g}/\text{g}$ for dust, $\mu\text{g}/\text{g}$ for soil, $\mu\text{g}/\text{L}$ for water) and the intake rate for that media (m^3/day for air, g/day for totaled for soil and dust, L/day for water). The fraction of soil ingestion out of the total soil plus dust ingestion is set in the Soil tab. Ingestion rates for dust are automatically calculated based on entries in the Soil tab. Then, in each case, the code estimates the intake for that pathway as the media concentration multiplied by the media intake rate.

In the user interface, each of these tabs had three sections:

- “discrete”: the media concentration section on the left
- “pulse train”: the media concentration section in the middle
- “Intake rates”: the media-specific intake rates on the right. Please aware that different names have been used across exposure tabs. For instance, this variable is called “Ventilation” in air tab, “Dust/soil/water ingestion” in dust/soil/water tab, and not used in “food” and “other” tabs.

In each case, the inputs allow the exposure parameters to vary in time and with age. In “discrete”, the user specifies the ages where the media concentrations change and the associated media concentrations for up to three different sources. The user can also specify the fraction of exposure attributed to each source (to account for different microenvironments for dust or for different drinking water sources for water, etc.).

In “pulse train”, the user can instead set up one-time or periodic pulses of exposure. These are suitable for acute exposures or periodic exposures. The user specifies the time period over which these pulses should be applied as well as the magnitude and length of the pulse. Again, the fraction of exposure from the pulse (versus discrete sources) can be specified.

Finally, the intake rate section allows entry of age-varying intake rates for each media. These can come from the EPA Exposure Factors Handbook or other sources.

The user entry is similar for “food” and “other”. However, similar to the IEUBK lead model, these two sources are entered as intakes ($\mu\text{g}/\text{day}$) directly rather than specifying age-varying media concentrations and media intake rates. For each, both discrete and pulse exposure profiles can be created.

The Excel user interface then creates the complete “ingestion” and “inhalation” time-varying exposure profiles by adding the ingestion pathways and using the “air” pathway for inhalation. The user interface has to translate these profiles into the format used by the Leggett model. Again, this process is seamless in AALM.CSL but is fairly intricate in AALM.FOR. Briefly, the

tool has to determine each age at which either the ingestion or inhalation intake varies and give the input file both these ages and the vector of intakes corresponding to these ages.

The tool also uses the RBA tab to estimate relative bioavailabilities for the different pathways. The user specifies a generic bioavailability (e.g., for food) and then specifies the relative bioavailability for the other media compared with food. The tool applies these relative bioavailabilities to the intakes and also supplies the input file with the absolute bioavailability that is applied to all ingestion pathways.

Consider two illustrative examples based on the air pathway only, although a similar approach can be applied to each pathway. The equation used to estimate intake dose from each exposure pathway is:

$$\begin{aligned}
 Intake_{Water} &= Intake_{Discrete\ exposure_{Water}} + Intake_{Pulse\ exposure_{Water}} \\
 &= [Discrete\ Conc_{Water} \times (1 - f_{pulse})] \times Ingest_{Water} \\
 &\quad + [Total\ Pulse\ Conc_{Water} \times f_{pulse}] \times Ingest_{Water} \\
 &= \left[\sum_{i=1}^3 Water_i \times f_{Water_i} \times (1 - f_{pulse}) \right] \times Ingest_{Water} \\
 &\quad + [(Baseline\ Pb_{Water} + Pulse\ Pb_{Water}) \times f_{pulse}] \times Ingest_{Water}
 \end{aligned}$$

Example 1: Discrete exposure only

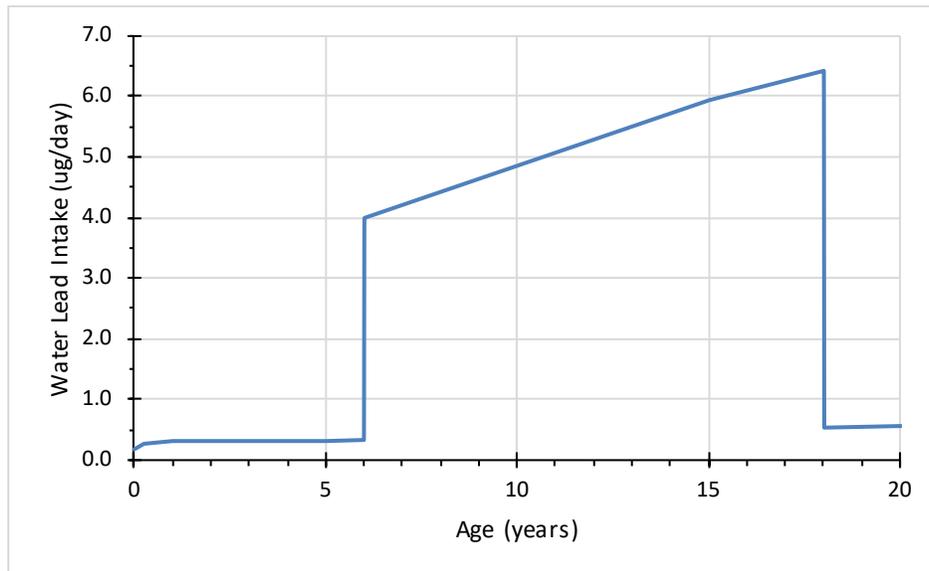
In this case, the user wants to specify exposure at discrete ages, and the exposure is not cyclical (no “pulse”). The way to implement this is to set f_Pulse_Pb to 0 (a screenshot is provided below), which indicates that exposures occur only from the discrete exposures; if f_Pulse_Pb is set to 1, it means that exposures only occur from the pulse train; and a setting of 0.5 means that half of the exposure is contributed by the pulse train and half by the discrete exposures. Variables used to implement this scenario are presented in the screenshot below, where in this example the exposure are “stepwise” and not interpolated. Results of this scenario including a plot of daily intake dose and a table with daily exposure time series are listed below.

A screenshot of variables used in Example 1 (run discrete only, f_Pulse Pb = 0)

Water Pb discrete: Assigns values to an age array of discrete water Pb concentrations (ug/L) from three sources and fraction (f_Water) from each source. The resulting concentrations are combined with age-dependent water ingestion rates to simulate daily water Pb intakes (ug/day). Ages (days) selected must be a monotonic series. Parameter values must be assigned to all ages. Values are interpolated between ages.

ROWN	Age year	Age day	Water_1 ug/L	f_Water_1 f	Water_2 ug/L	f_Water_2 f	Water_3 ug/L	f_Water_3 f	Water_TWA ug/L
1	2	3	4	5	6	7	8	9	10
2	0.0	0	0.9	1.00	0	0.00	0	0.00	0.90
3	0.2	90	0.9	1.00	0	0.00	0	0.00	0.90
4	1	365	0.9	1.00	0	0.00	0	0.00	0.90
5	2	730	0.9	1.00	0	0.00	0	0.00	0.90
6	5.99	2186.35	0.9	1.00	0	0.00	0	0.00	0.90
7	6	2190	0.9	0.30	15	0.70	0	0.00	10.77
8	5	1825	0.9	0.30	15	0.70	0	0.00	10.77
9	6	2190	0.9	0.30	15	0.70	0	0.00	10.77
10	7	2555	0.9	0.30	15	0.70	0	0.00	10.77
11	8	2920	0.9	0.30	15	0.70	0	0.00	10.77
12	9	3285	0.9	0.30	15	0.70	0	0.00	10.77
13	10	3650	0.9	0.30	15	0.70	0	0.00	10.77
14	15	5475	0.9	0.30	15	0.70	0	0.00	10.77
15	17.99	6566.35	0.9	0.30	15	0.70	0	0.00	10.77
16	18	6570	0.9	1.00	0	0.00	0	0.00	0.90
17	30	10950	0.9	1.00	0	0.00	0	0.00	0.90
18	40	14600	0.9	1.00	0	0.00	0	0.00	0.90
19	50	18250	0.9	1.00	0	0.00	0	0.00	0.90
20	60	21900	0.9	1.00	0	0.00	0	0.00	0.90

Daily water intake for Example 1



Time Series of Water Exposure Pathway for Example 1

Year	Water_TWA (ug/L)	Ingestion (L/day)	Discrete water intake dose (ug/day)
0	0.9	0.20	0.18
1	0.9	0.35	0.32
5	0.9	0.35	0.32
5.99	0.9	0.37	0.33
6	10.8	0.37	3.98
10	10.8	0.45	4.85
17.99	10.8	0.60	6.41
18	10.8	0.60	0.54
20	0.9	0.63	0.56

Example 2: Pulse exposures only:

In this case, the exposure is an event with a known start day and length, and the exposure pattern may repeat (cyclical). As an example, consider a baseline Pb concentration of 0.9 µg/L with pulse increase in water Pb concentration to 15 µg/L exposures:

- The pulse is set to start at 2190 days (6 years) and end at 6569 days (end of 17 year)
- Pulse_1: width or duration is 5 days out of 7 days (the period)
- Pulse_2: sets the period over which PULSE_1 occurs, in this example 270 (9 months) out of 365 days (12 months).

Variables used to implement this scenario are presented in the screenshot below, in which f_pulse Pb is set to 1 since discrete exposure is not considered. Results of this scenarios including a plot of daily intake dose and a table with daily exposure time series are listed below.

Screenshots of variables used in Example 2

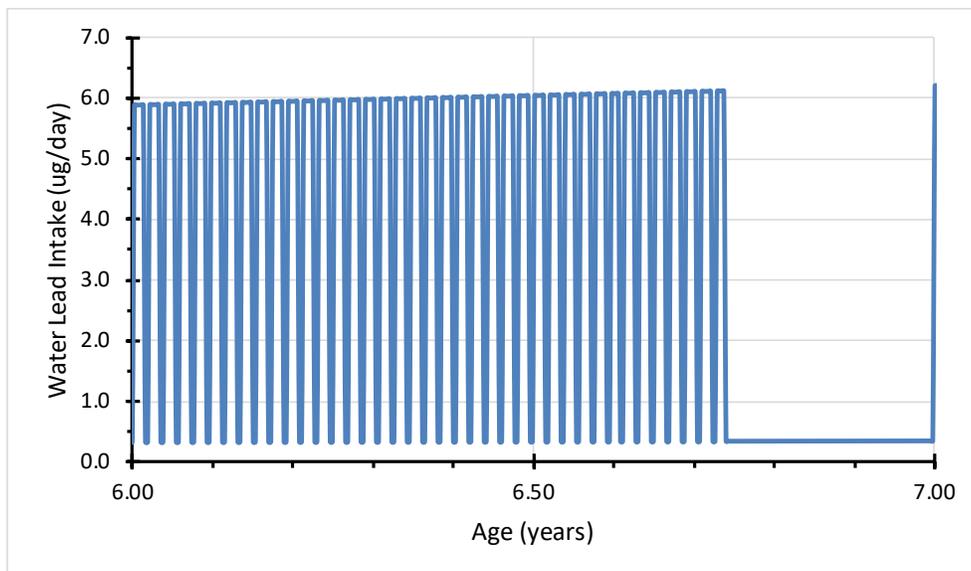
Water Pb pulse train: Assigns values for simulating episodic water Pb concentrations (ug/L) that occur at a fixed frequency and duration schedule (e.g., 2 days per 7 days, 3 mo per year). Baseline is used between episodes. If used in combination with discrete exposures, the pulsed and discrete Pb intakes are apportioned according to the fraction assigned to the pulse (f_Pulse Pb) to simulate daily Pb intakes (ug/day).

Water ingestion: Assigns values for water ingestion rates (L/day) used to simulate daily water Pb intakes (ug/day). Values are interpolated between ages. (based on US EPA 2011, Table 3-1, per capita)

Parameter	Unit	ROWN	Value
Baseline Pb	ug/L	1	0.9
Pulse Pb	ug/L	2	15
f_Pulse Pb	f	3	1
Pulse_start	day	4	2190
Pulse_stop	day	5	6569
Pulse_1 width	day	6	5
Pulse_1 period	day	7	7
Pulse_2 width	day	8	270
Pulse_2 period	day	9	365

ROWN	Age year	Age day	IRW L/day
1	0	0	0.200
2	0.2	90	0.300
3	1	365	0.350
4	5	1825	0.350
5	10	3650	0.450
6	15	5475	0.550
7	25	9125	0.700
8	50	18250	1.040
9	70	25550	1.040
10	90	32850	1.040

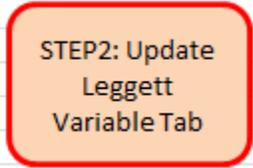
Daily water intake for Example 2 – the scatter plot appears of first year of pulsed exposure.



4. Make any Necessary Changes to the Biokinetic Parameter Input Tabs

The remaining tabs contain the different biokinetic parameters and growth parameters used by the model. These include variables like the transfer rates and fraction of lead distributed to the different compartments, the non-linear red blood cell parameters, the compartment weights, etc. Some parameters are configured in the original model to vary by age while others are not, so these are reflected in the right-hand and left-hand tables on the “Systemic” tab, respectively. For most users, these tabs will not need to be changed, unless the model is being recalibrated or used in a sensitivity analysis. However, each tab contains the different parameters with a brief description of how they are used in the model.

One notable departure from AALM.CSL is the treatment of the lung compartments. The AALM.CSL expanded the model to include additional compartments, and the AALM.CSL user interface has a corresponding set of input parameters. This user interface for AALM.FOR contains only the parameters needed for the original lung algorithms.



STEP2: Update
Leggett
Variable Tab

After configuring the biokinetic/growth parameters, click the “Step 2: Update Leggett Variable Tab” button to copy the changes to the Leggett_Variables reference sheet.

A Microsoft Visual Basic “Run-time error ‘53’ File not found” error will occur if cell D44 in the Simulation Control tab is set to “Yes” and the file “Intermediate Exposure Time Series.csv” is not located within the directory/folder where the Excel user interface file is located. To resolve error, press “End” in the error box, then in the “Simulation Control” tab set cell D44 in to “No.” Alternatively, press “End” in the error box and copy the “Intermediate Exposure Time Series.csv” file into the directory/folder with the Excel user interface file prior to running STEP2 again.

5. Run the Model and Import the Results



STEP3: Run
Leggett

Finally, click the STEP3: Run Leggett button. The Excel file will create the text version of the input file using the template (and a copy is also in the Pounds.Dat reference sheet as well), run the model, and import the results. If you have an error, ensure that the executable file is saved in the same folder as the Excel file.

On some systems, if the files are placed in the “Documents” folder or subfolder, a Microsoft Visual Basic “Run-time error ‘5’: Invalid procedure or call or argument” will occur when the STEP3 macro tries to determine the file path. Should this error occur, try placing the folder on a part of the C: drive where you have read/write permissions.

A Microsoft Visual Basic “Run-time error ‘-2147024894 (80070002)’: Method ‘Run’ of object ‘IWshShell3’ failed” or similar message occurs if the file “ICRPv008d_aalm_in_32bit.exe” is not located in the folder with the Excel user interface file. To resolve this error, make sure the executable is located in the folder with the Excel user interface and that its filename has not been altered.

The outputs provided by the user interface are summarized on the ReadMe tab. Generally speaking, they include the time in the simulation, the time-varying intake profiles, lead concentrations in compartments (begin with a “C”) and lead masses in compartments (begin with an “A”).

6. QA Step: Confirm the Intake Results Give the Correct Time Series

As a final QA step, the user is encouraged to inspect the output and verify that the intake time-varying profiles match what was intended. Remember that if exposure is varied over a very brief time period but the communication interval was longer than that time period, the actual intake change will not be recorded in the output (e.g., a pulse of exposure from age 1.25 to 1.75, but outputs only saved every year).