Exercise 10: Built-in Models in DME: Population PK/PD Model with PK Fixed

Background

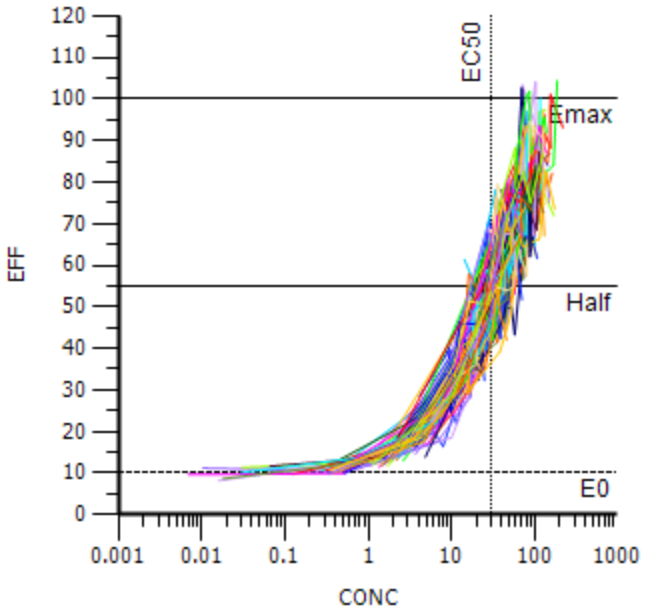
The dataset for this exercise contains simulated observations for 200 subjects.

Objectives:

- Obtain initial estimates using plotting and NCA
- Fit a Population PK model
- Fit a Population PKPD Model with PK parameters “fixed” or “frozen”
- Understand Results

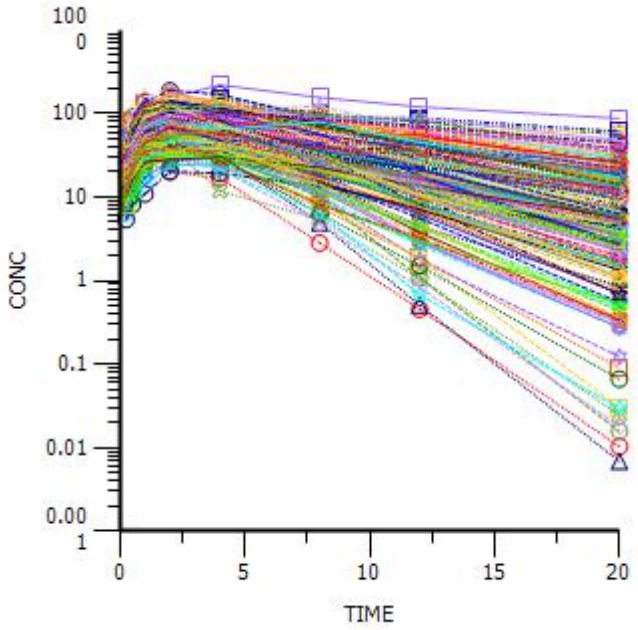
Part 1a – Exploratory Analysis: Plotting

1. Create a new Project and rename the project, **pkfix_pd.**
2. Import the dataset ‘**sim3102phx.xls**’.
3. Right-click on the worksheet and select Send To>Plotting>XY Plot. Plot CONC on the x-axis and EFF on the Y axis, grouping by ID. Execute. View the results.
4. Change the scale of the X-axis to logarithmic. From the plot, E0 appears to be 10, EC50 appears to be around 30, and Emax around 100.



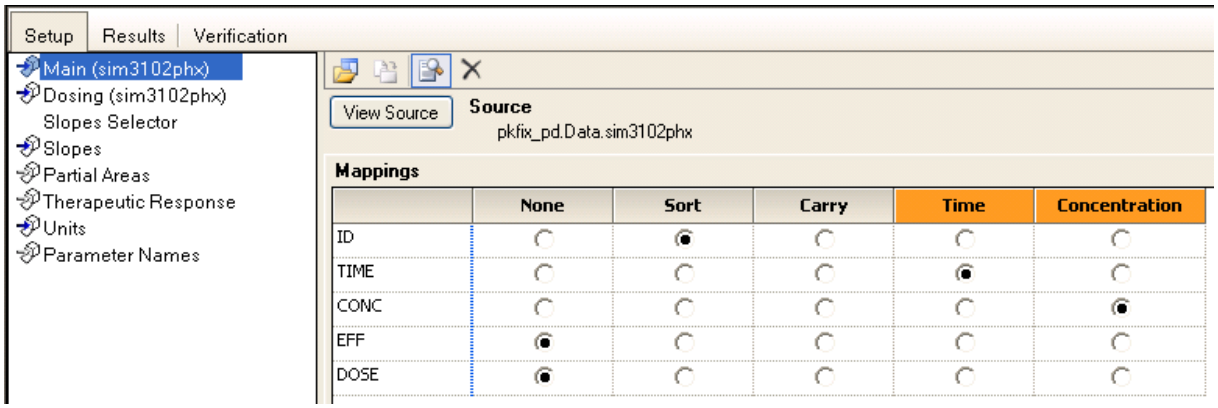
5. Right-click on the worksheet and select Send To>Plotting>XY Plot. Plot CONC on the y-axis and TIME on the X axis, grouping by ID. Execute. View the results.

6. Change the scale of the Y-axis to logarithmic. The PK data appear to follow a 1-compartment model with extravascular absorption. Also, the PK concentration data span several orders of magnitude. This suggests a multiplicative residual error model may be appropriate.

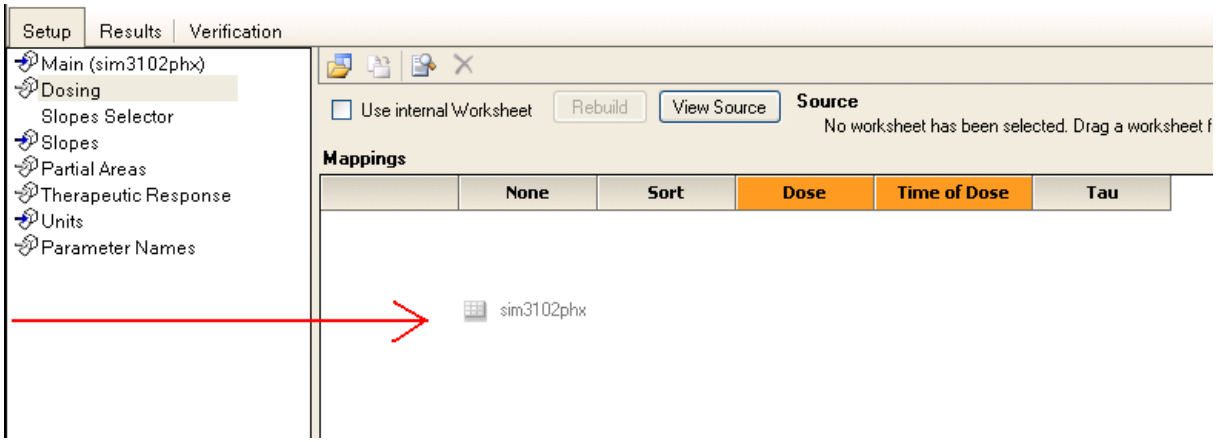


Part 1b – Exploratory Analysis: NCA to Obtain Initial Estimates

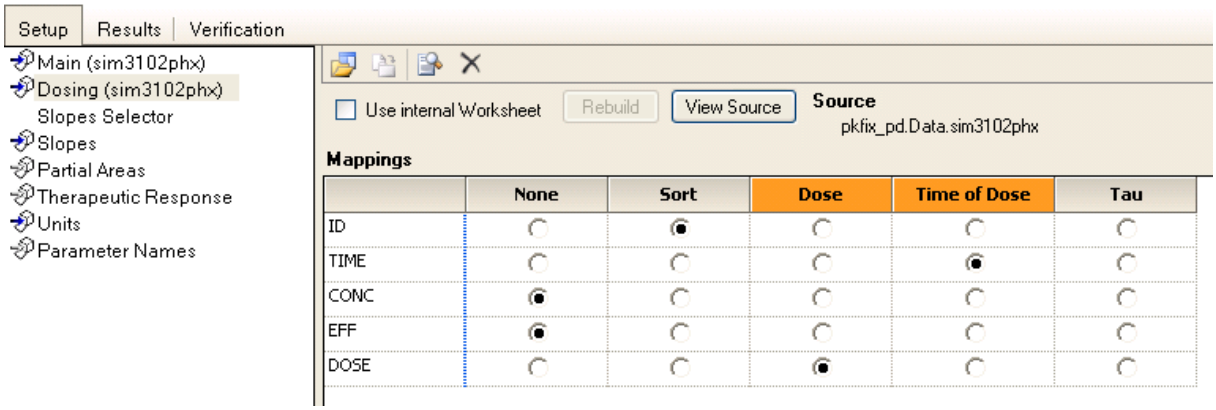
7. Right-click on the worksheet and Send to> NCA and Toolbox> NCA.
8. Make the following selections.



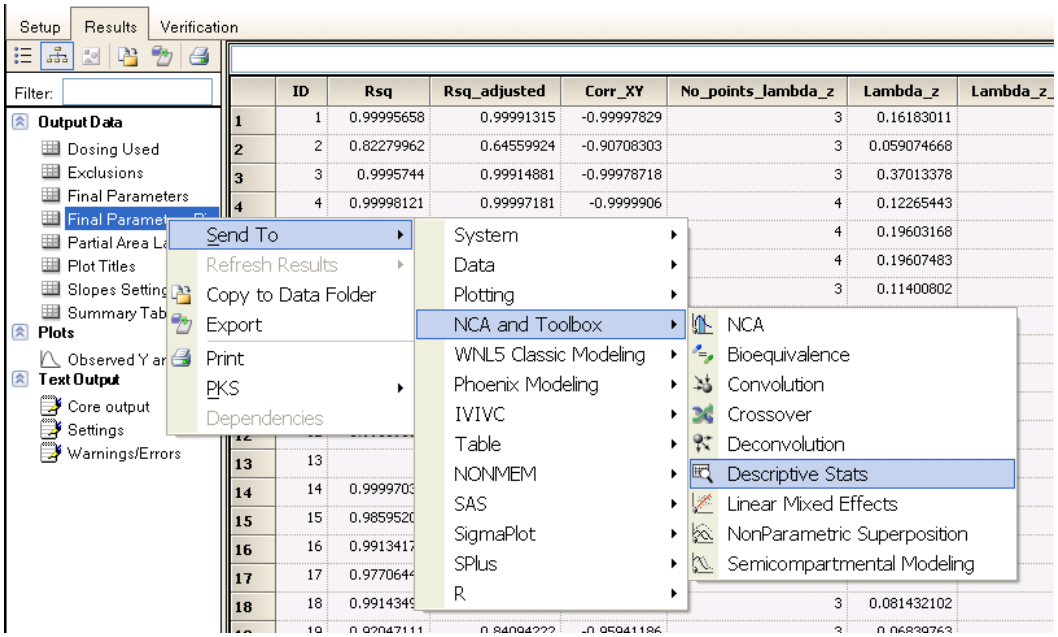
9. Select 'Dosing' in the Setup Tab. Drag the worksheet to the dosing section.



10. Make the following selections.

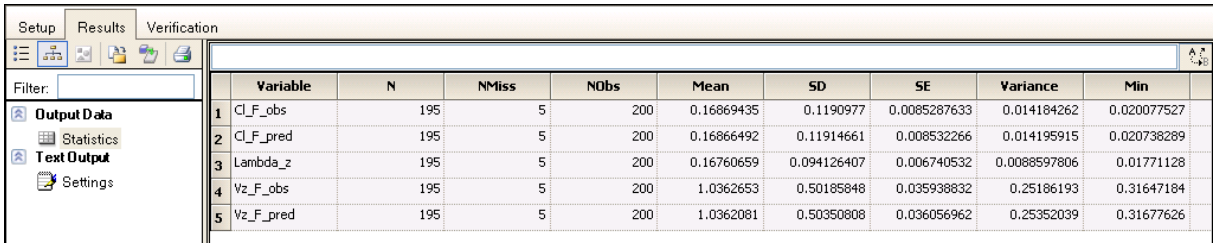


11. Execute the NCA object.
12. Right-click on the “Final Parameters Pivoted” worksheet and Send To> NCA and Toolbox> Descriptive Stats.



13. Summarize the following variables.
    - Lambda_z
    - Vz_F_obs
    - Cl_F_obs
    - Vz_F_pred
    - Cl_F_pred

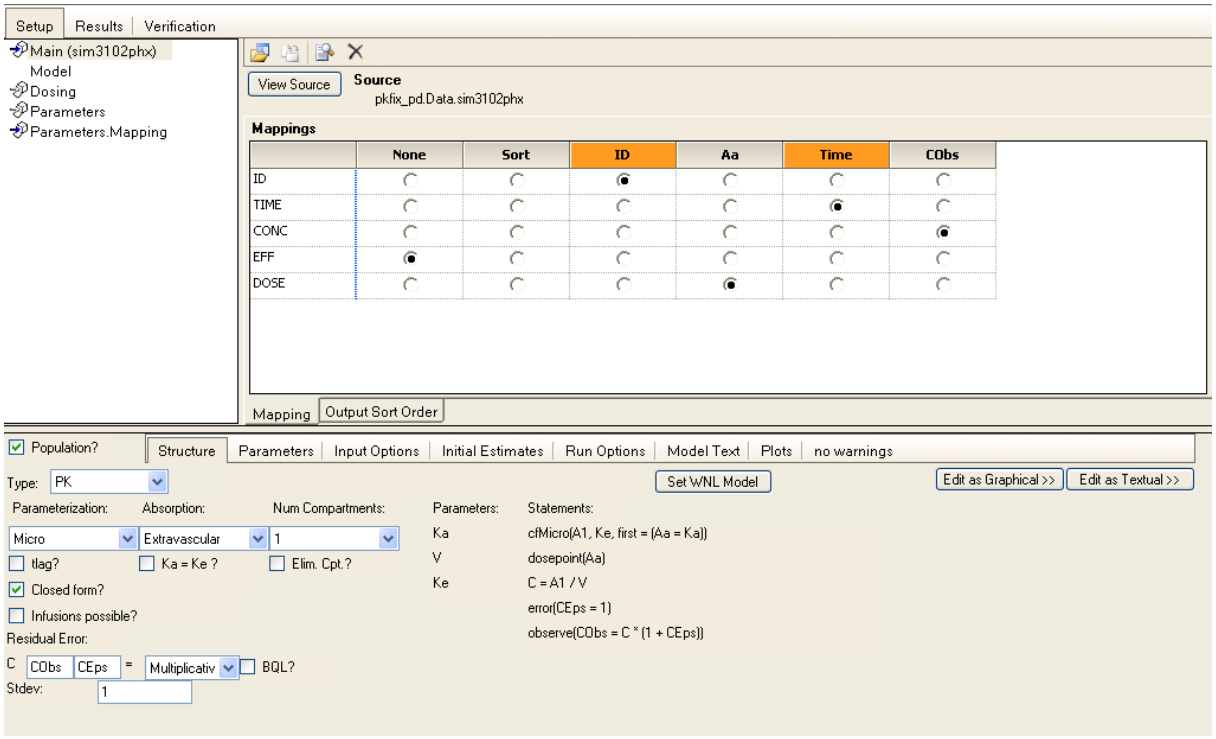
14. Execute the Descriptive Stats object. Initial estimates for V and Ke are 1 and 0.17, respectively.



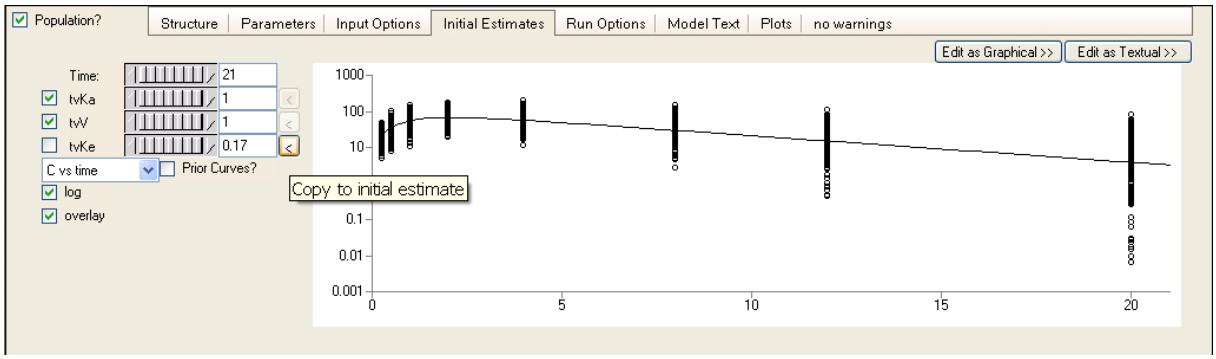
	Variable	N	NMiss	NObs	Mean	SD	SE	Variance	Min
1	Cl_F_obs	195	5	200	0.16869435	0.1190977	0.0085287633	0.014184262	0.020077527
2	Cl_F_pred	195	5	200	0.16866492	0.11914661	0.008532266	0.014195915	0.020738289
3	Lambda_z	195	5	200	0.16760659	0.094126407	0.006740532	0.0088597806	0.01771128
4	Vz_F_obs	195	5	200	1.0362653	0.50185848	0.035938832	0.25186193	0.31647184
5	Vz_F_pred	195	5	200	1.0362081	0.50350808	0.036056962	0.25352039	0.31677626

Part 2 – Population PK Base Model

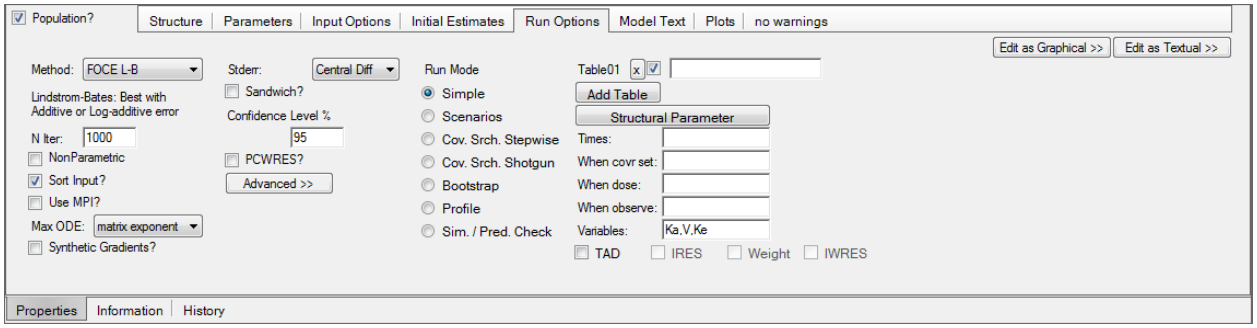
15. Right-click on the worksheet and Send To>Phoenix Modeling>Phoenix Model.
16. Set up the model mappings and Built-in options as shown below. The options are: PK model, Micro, Parameterization, Extravascular, 1 compartment, Multiplicative Residual Error. DOSE is mapped to Aa, and CONC is mapped to CObs.



17. Click on the Initial Estimates Tab. Select the “log” and “overlay” checkboxes. Move the sliders to obtain initial estimates and/or use the initial estimates obtained from NCA. Click on the left arrow button (‘<’) when finished to use the number displayed in the field as the initial estimate. The button should turn grey after clicking on it.



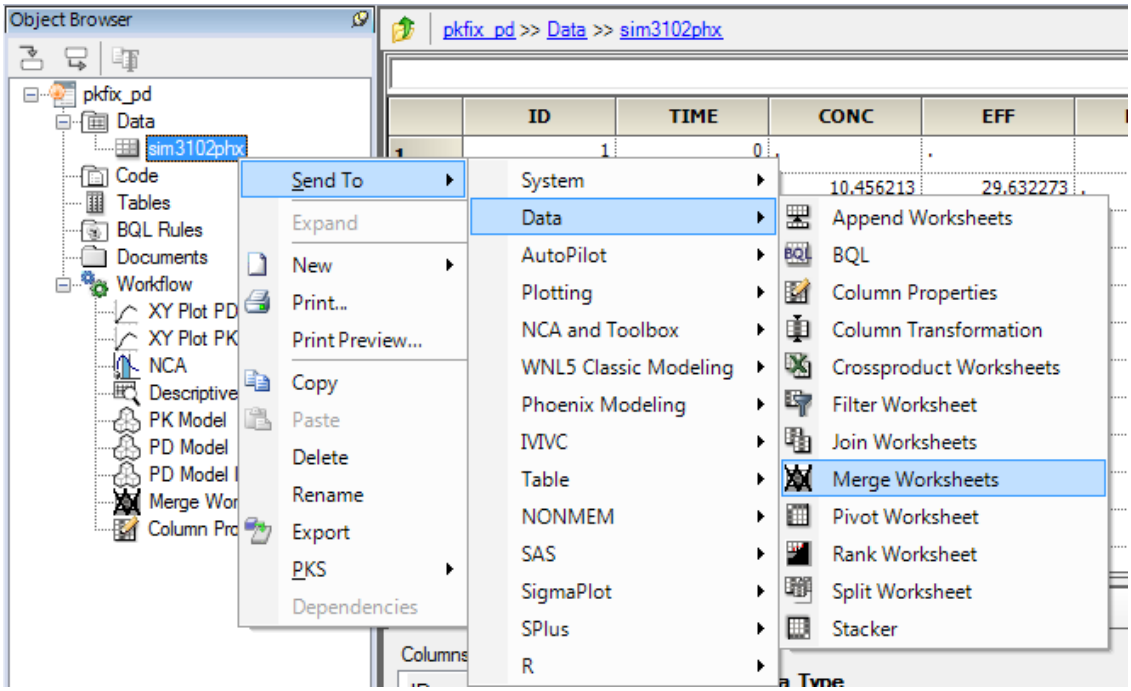
18. Go to the Run Options tab. Click “Add Table”. Click “Structural Parameter”. A table of the individual PK parameters will be outputted in a table called Table01 in the results tab after the model is executed.



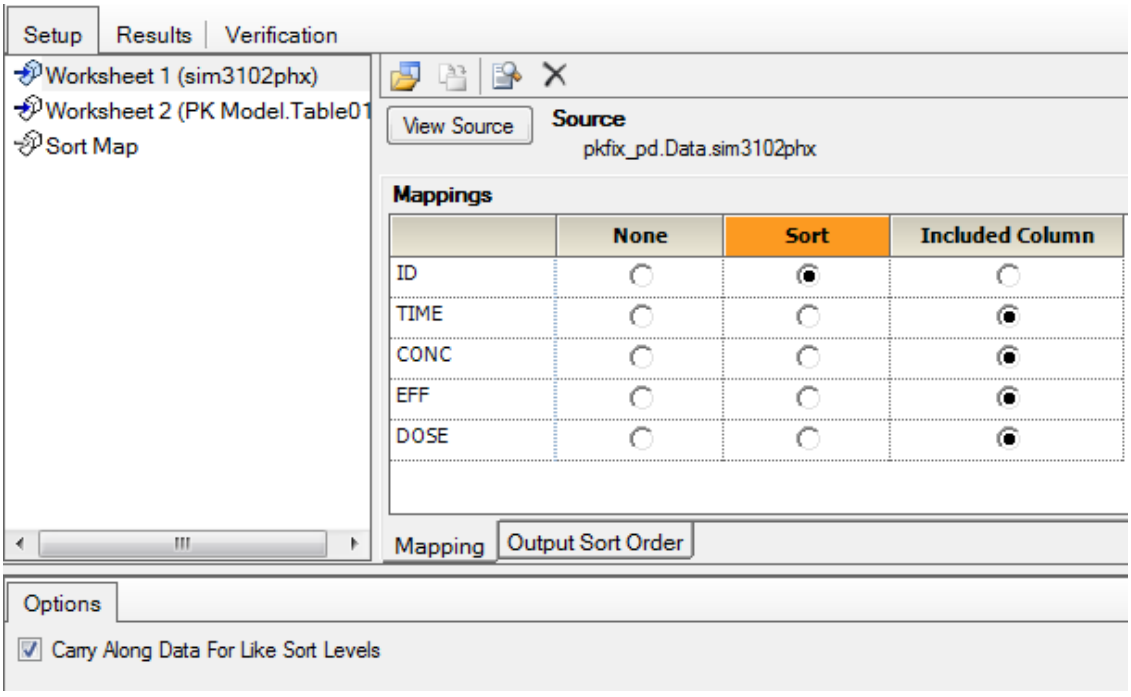
19. Execute the PK model.

Part 3 – Population PD Base Model with PK Frozen

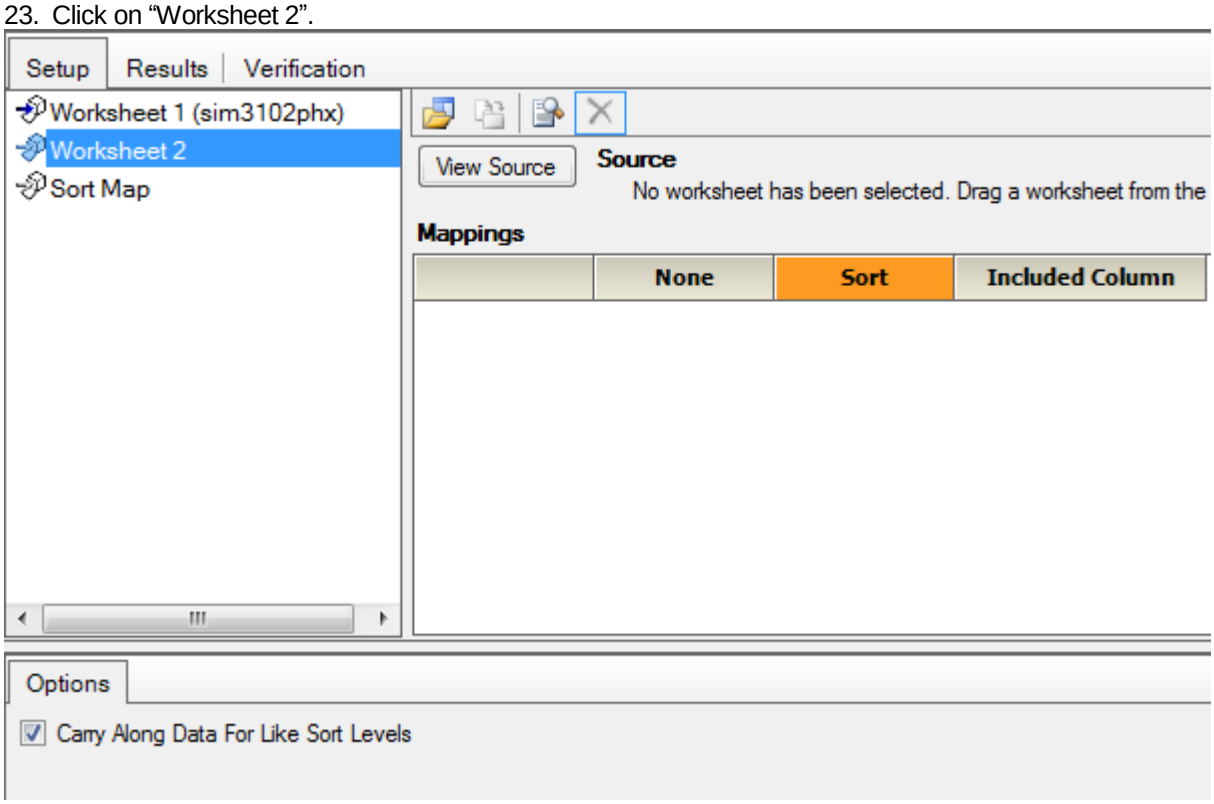
20. In the Results tab of the PK model, verify that the results look reasonable (thetas have low CV%, estimates are plausible, etc). If not, check the model settings and initial estimates and re-execute.
21. In the Object Browser, right-click on the dataset "sim3102phx" and Send To>Data>Merge Worksheets.



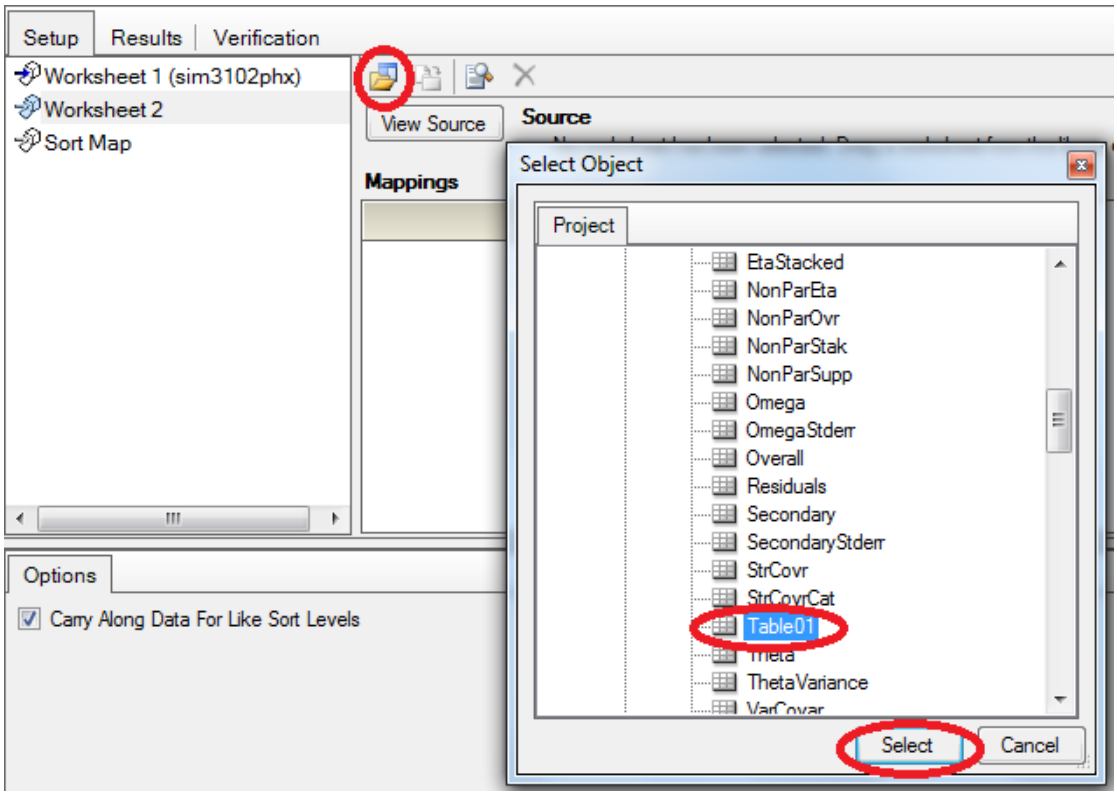
22. For Worksheet 1, Sort by ID and Include everything else.



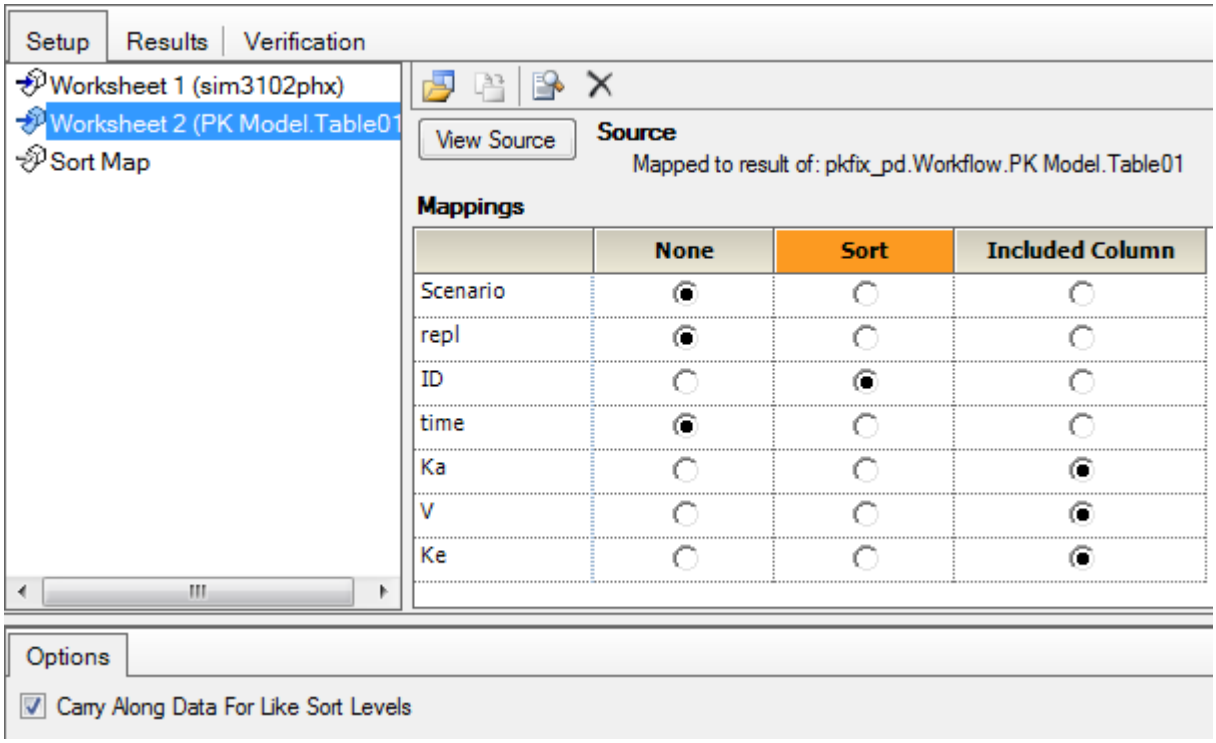
23. Click on “Worksheet 2”.



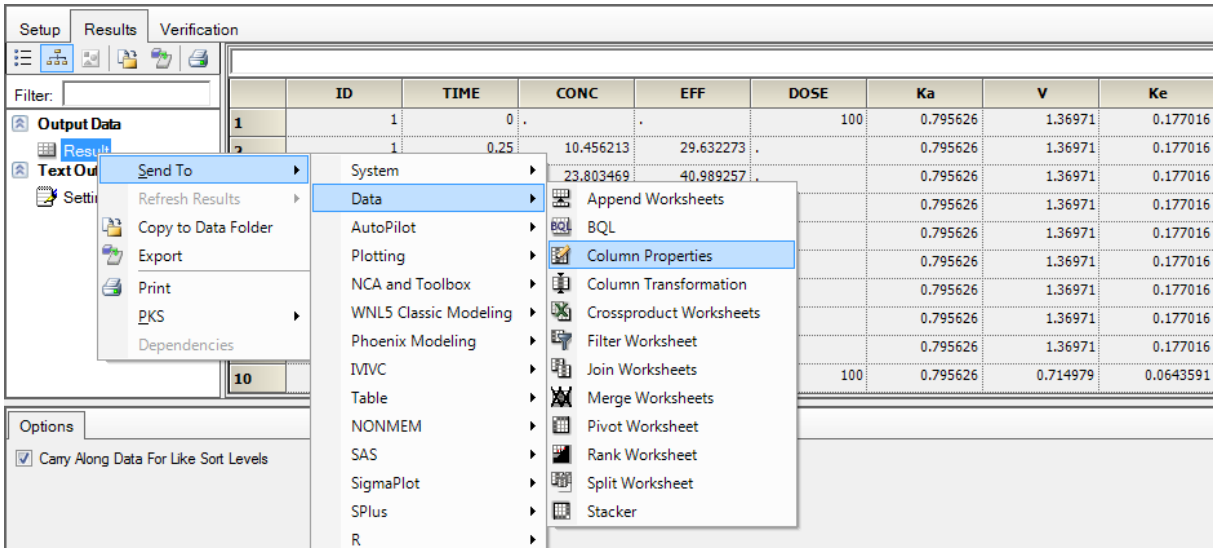
24. Click the “Select Source” button and select Table01 from the PK model.



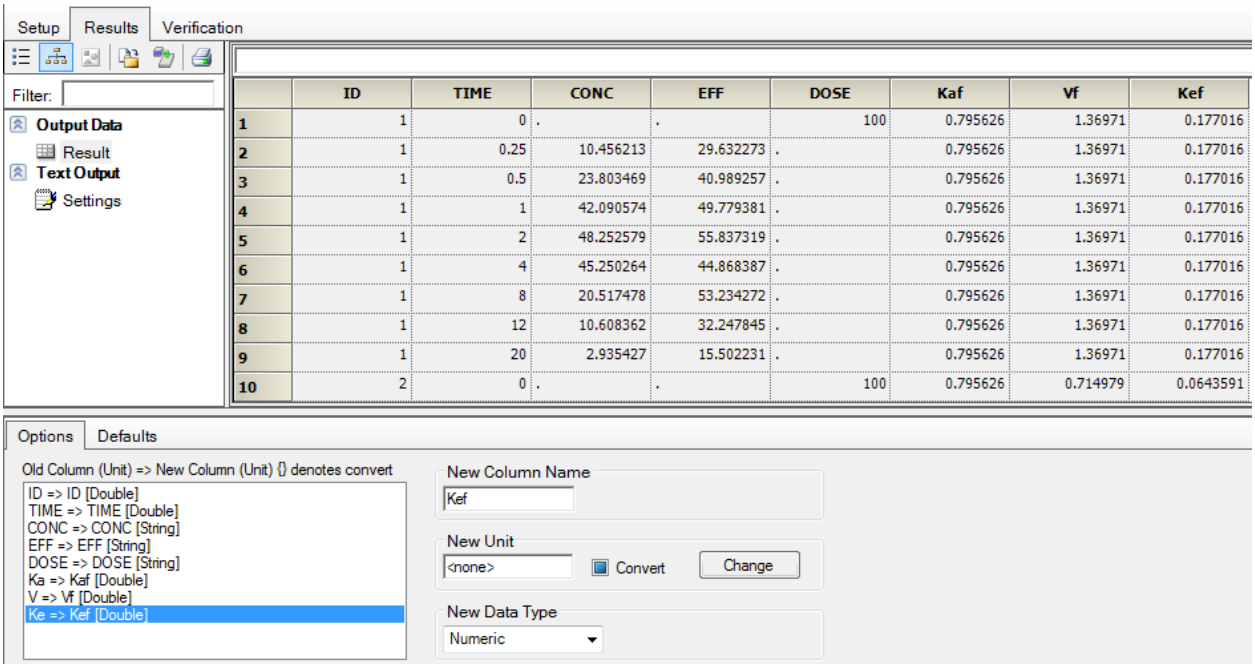
25. For Worksheet 2, Sort by ID and Include Ka, V, and Ke.



26. Execute the Merge Worksheets object.
27. Right-click on the resulting worksheet and Send To> Data>Column Properties.

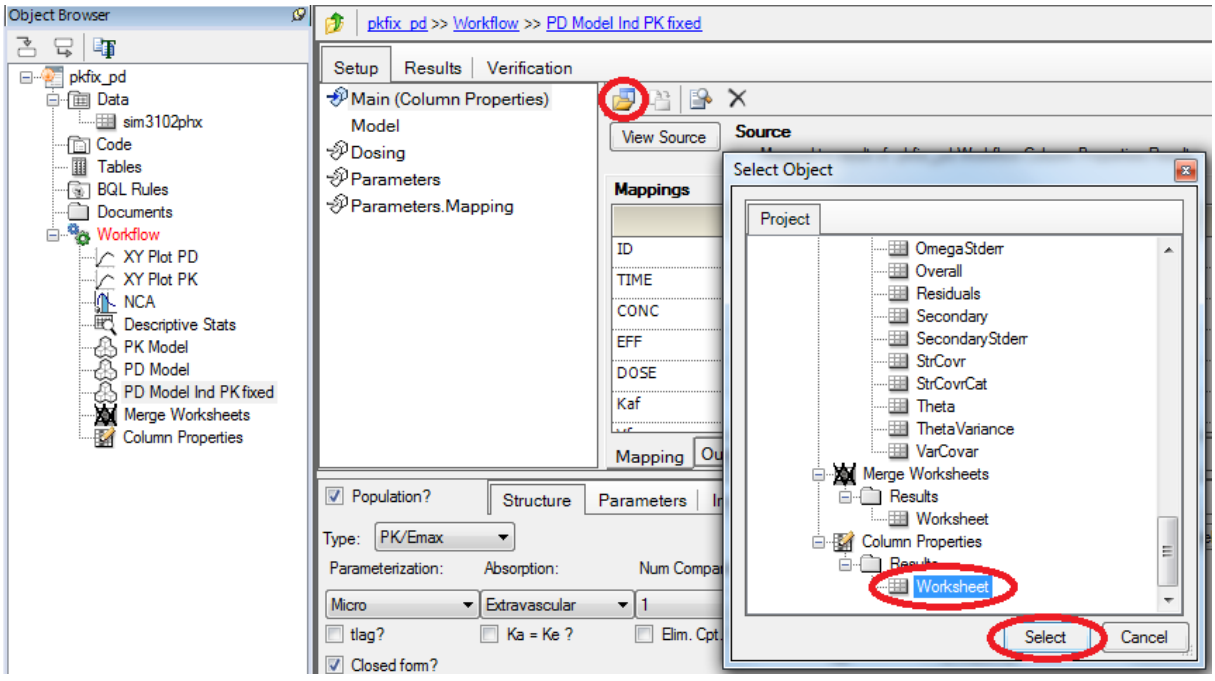


28. Rename the columns “Ka”, “V”, and “Ke” to “Kaf”, “Vf”, and “Kef” using the Options panel. (Hint: Use “Enter” to set the new names or else they might not register as entered.)

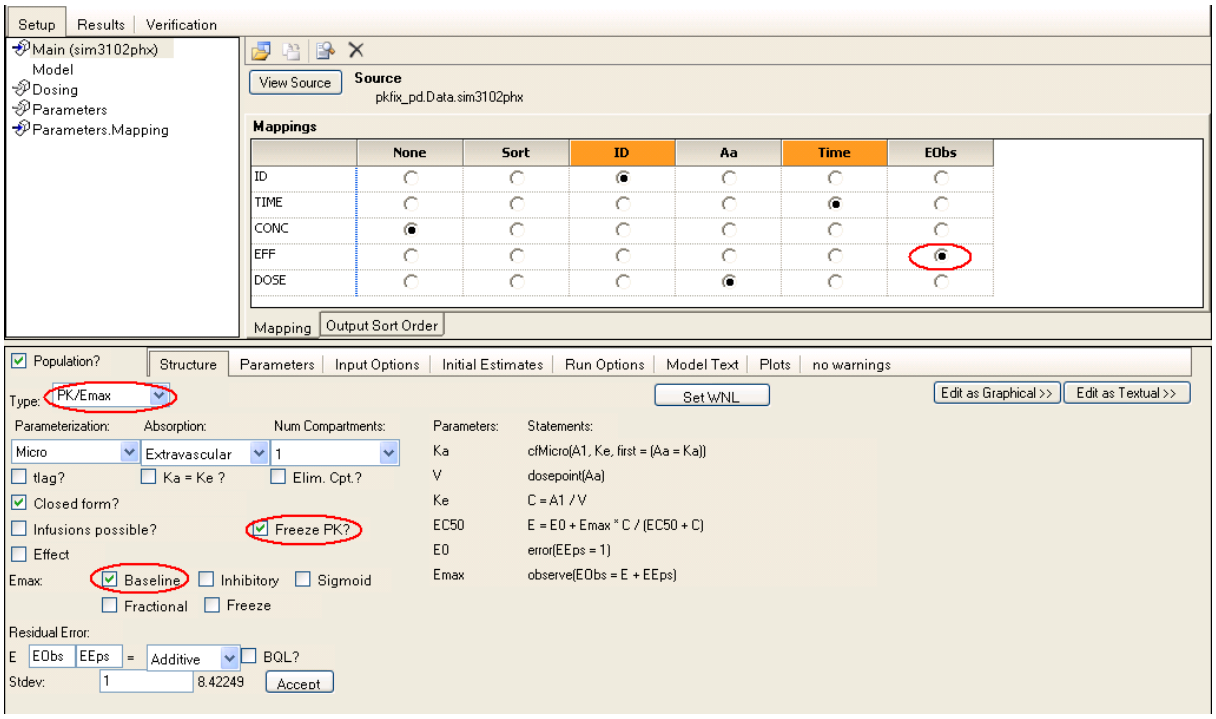


	ID	TIME	CONC	EFF	DOSE	Kaf	Vf	Kef
1	1	0	.	.	100	0.795626	1.36971	0.177016
2	1	0.25	10.456213	29.632273	.	0.795626	1.36971	0.177016
3	1	0.5	23.803469	40.989257	.	0.795626	1.36971	0.177016
4	1	1	42.090574	49.779381	.	0.795626	1.36971	0.177016
5	1	2	48.252579	55.837319	.	0.795626	1.36971	0.177016
6	1	4	45.250264	44.868387	.	0.795626	1.36971	0.177016
7	1	8	20.517478	53.234272	.	0.795626	1.36971	0.177016
8	1	12	10.608362	32.247845	.	0.795626	1.36971	0.177016
9	1	20	2.935427	15.502231	.	0.795626	1.36971	0.177016
10	2	0	.	.	100	0.795626	0.714979	0.0643591

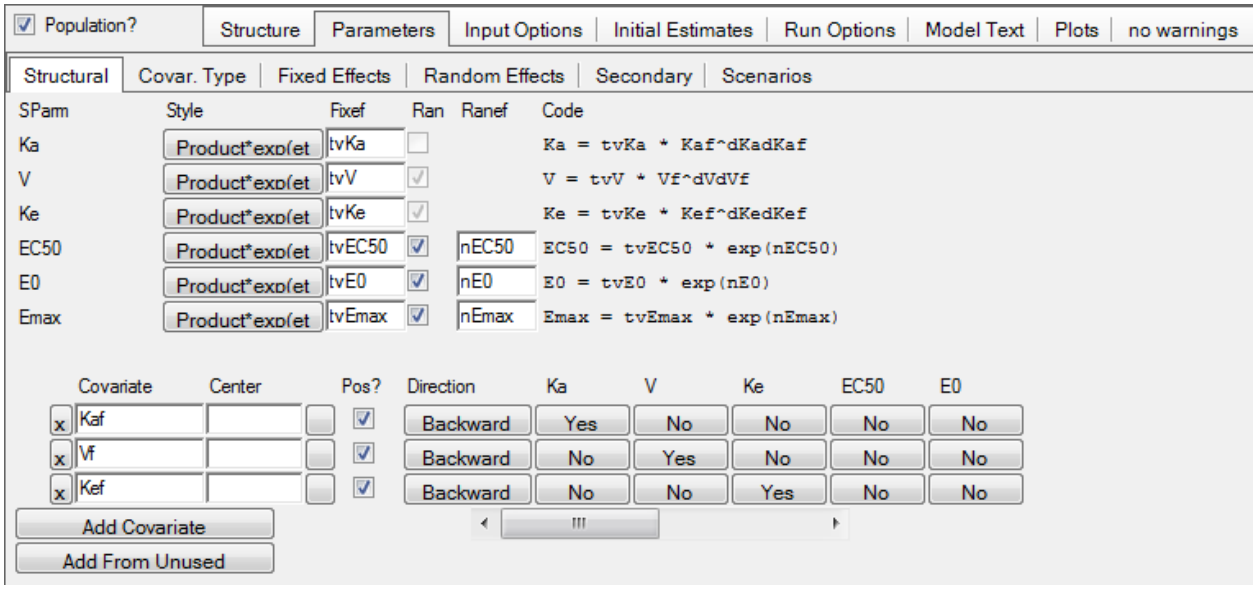
29. Execute the Column Properties object.
30. Copy/Paste the PK model. Renamed the copied model to “PD model Ind PK fixed”.
31. Click the “Select Source” button, and select the result from the Column Properties object as the data input for the PD model.



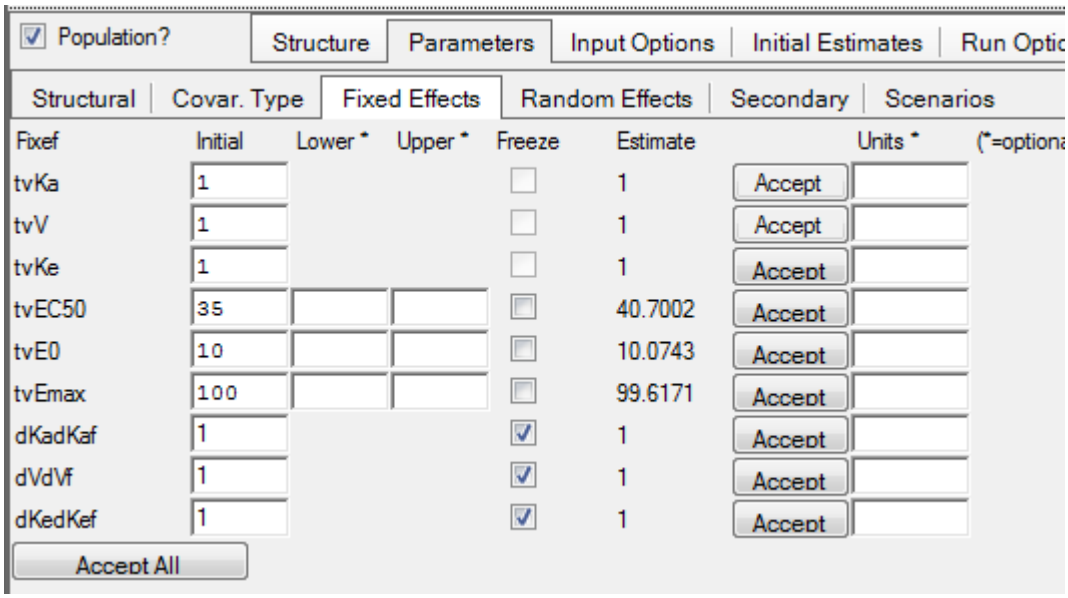
32. Click on the “Structure” Tab at the bottom, and click on the “Setup” Tab at the top. Change the model type to “PK/Emax” and select “Freeze PK” and “Baseline”. Map EFF to EObs.



33. In the Parameters Tab>Structural Tab, click “Add From Unused”. Select “Kaf”, “Vf”, and “Kef”. Click “Add”. Click “Yes” for a “Kaf” effect on “Ka”, etc, until effects are added for Ka, V, and Ke.



34. Select the Fixed Effects Tab. Enter initial estimates for the PD model as shown below. Freeze the PK parameters to 1 (Note: Parameters are frozen if the “freeze” check box is greyed out).



35. Execute the model object and view the results.

Part 4 – Covariance Model

36. Look at the Omega Worksheet and note the high shrinkage values for several of the parameters. Click on the Parameters Tab>Strucutral Tab. Remove the random effects for the parameters with the highest shrinkage values, one at a time (if time permits), executing the model and viewing the results until all random effects left in the model have fairly low shrinkage values (less than 0.3 or 0.4).
37. Save the project and continue on to the next exercise without closing.