Open

Systems Pharmacology

Hands-On
Age-dependence
- Stepwise Solution -

Disclaimer:

Examples described herein have been designed to teach physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) modeling with PK-Sim® and MoBi®. Cases may have been simplified to focus on relevant didactic aspects and may not necessarily describe the best model variant.

Exercise - Age Dependence of Pharmacokinetics

Background

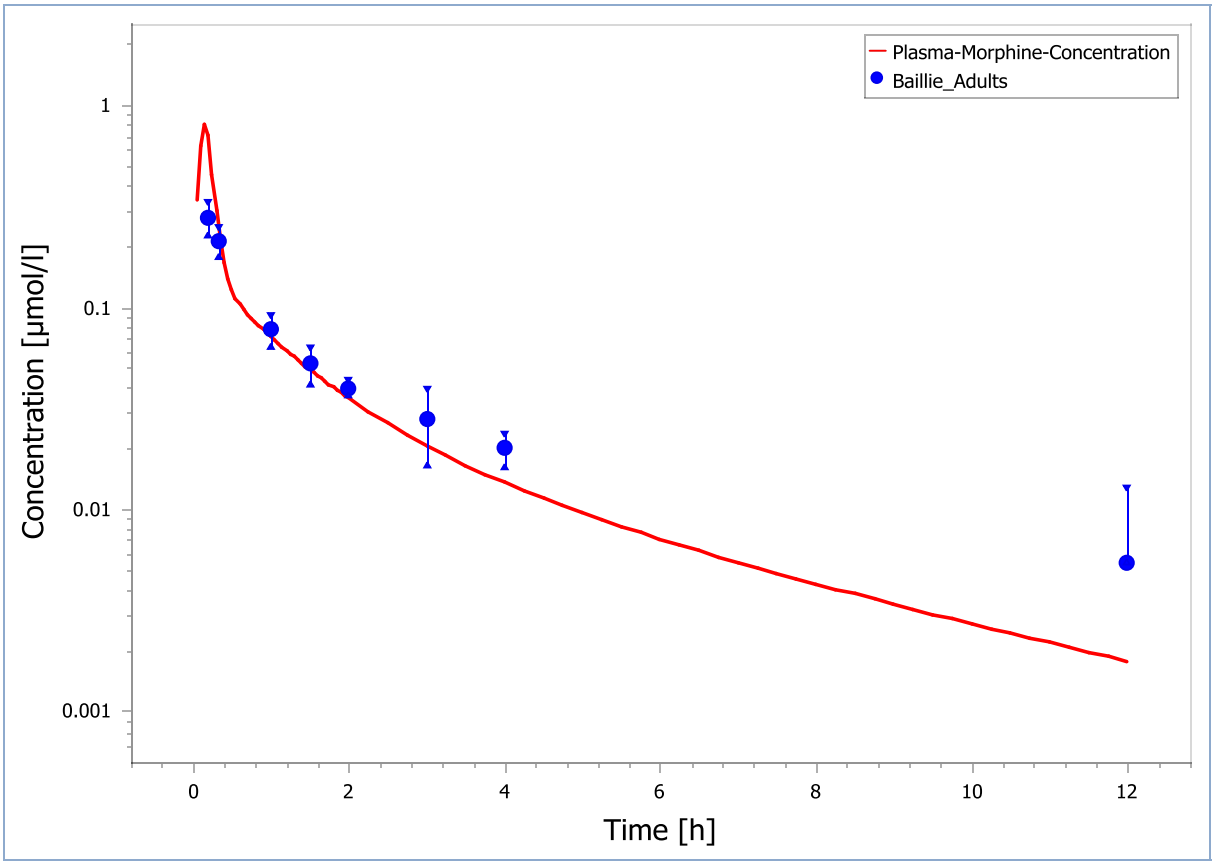
- Morphine is cleared in the liver via UGT2B7 and via the kidneys
- Thus, the ontogeny of UGT2B7 and the maturation of glomerular filtration determine the elimination of morphine in children
- Additionally, developmental changes in plasma protein concentrations and, of course, the organ growth and enzyme maturation have to be taken into account to appropriately predict morphine pharmacokinetics in children
- Physiological changes (i.e. blood flows, renal function and organ volumes) at a high age have to be taken into account for a proper prediction of morphine pkarmacokinetics in the elderly

Objectives

Learn to set up an (adult model) simulation for morphine and compare simulation to observed data

1. Make yourself familiar with the given Individual, Compound and Administration Protocol (simulate for 12h).
2. Import observed data ("Workshop_Data.xlsx", sheet "Ex_ADP_Baillie_Adults") and drag&drop it to the figure panel.

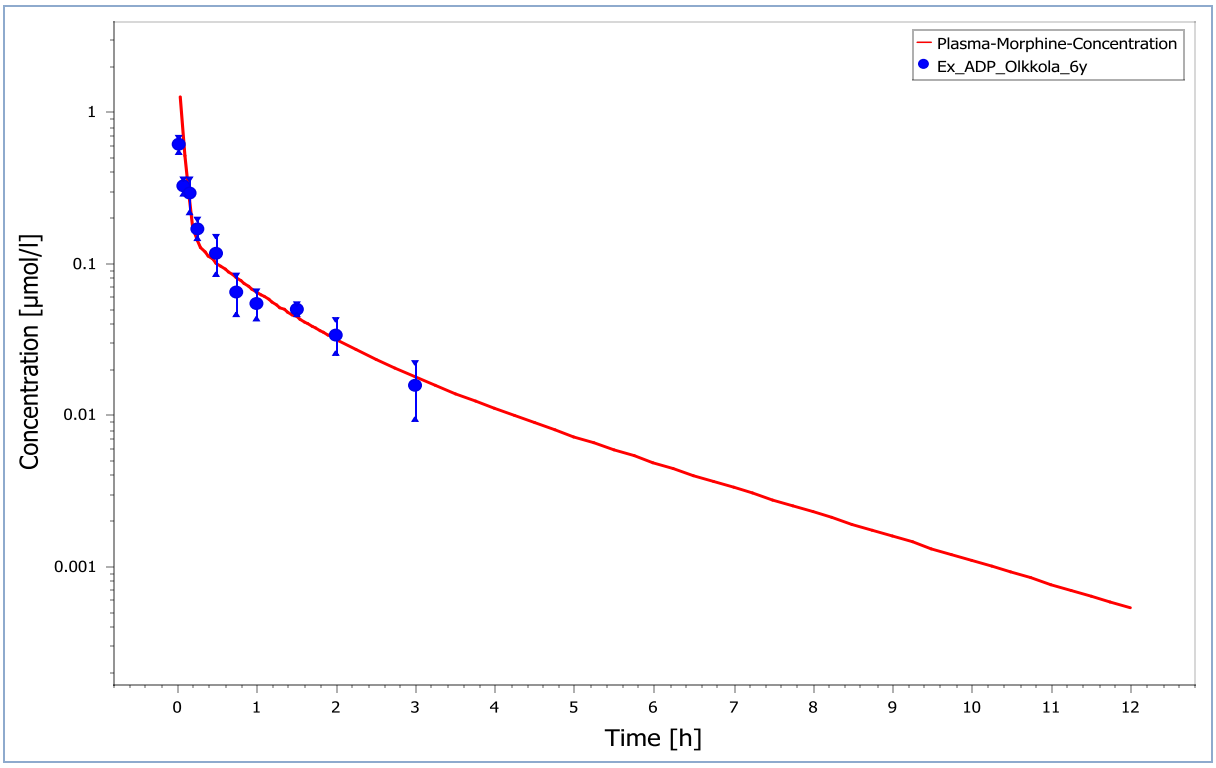
Compare the **Observed Data** with your **Simulation Results!**

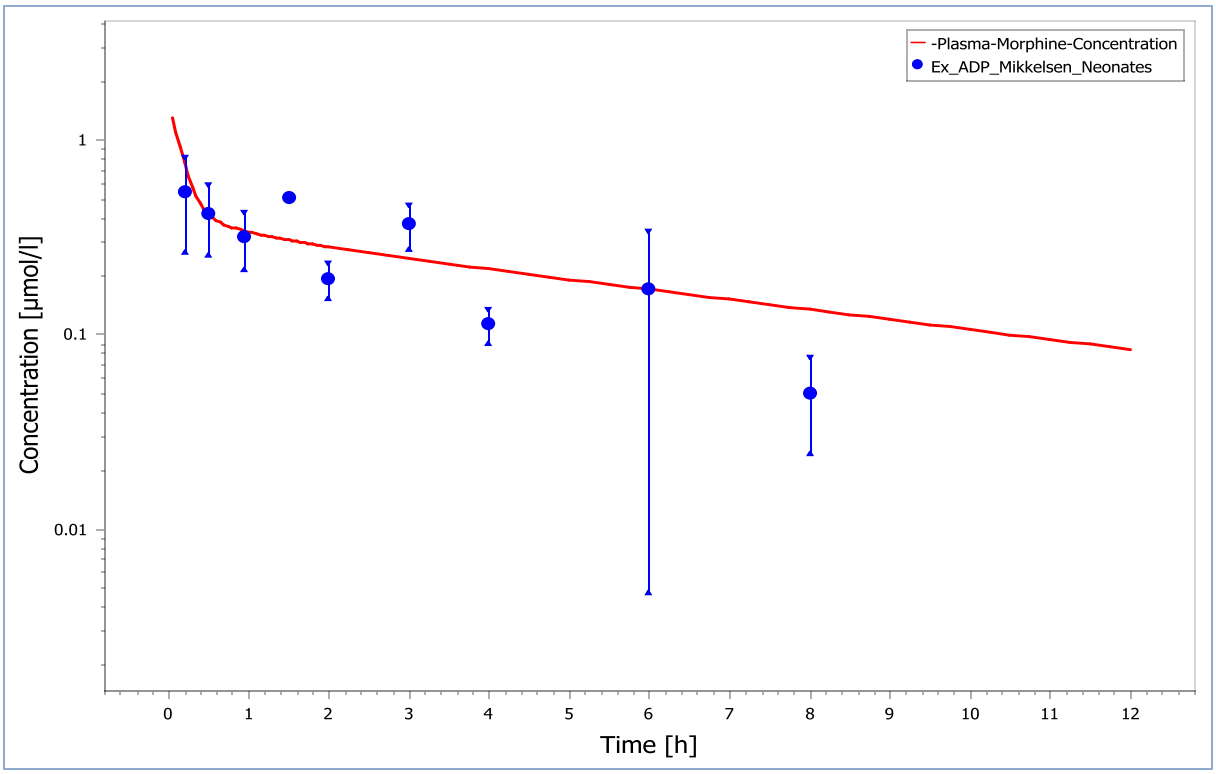


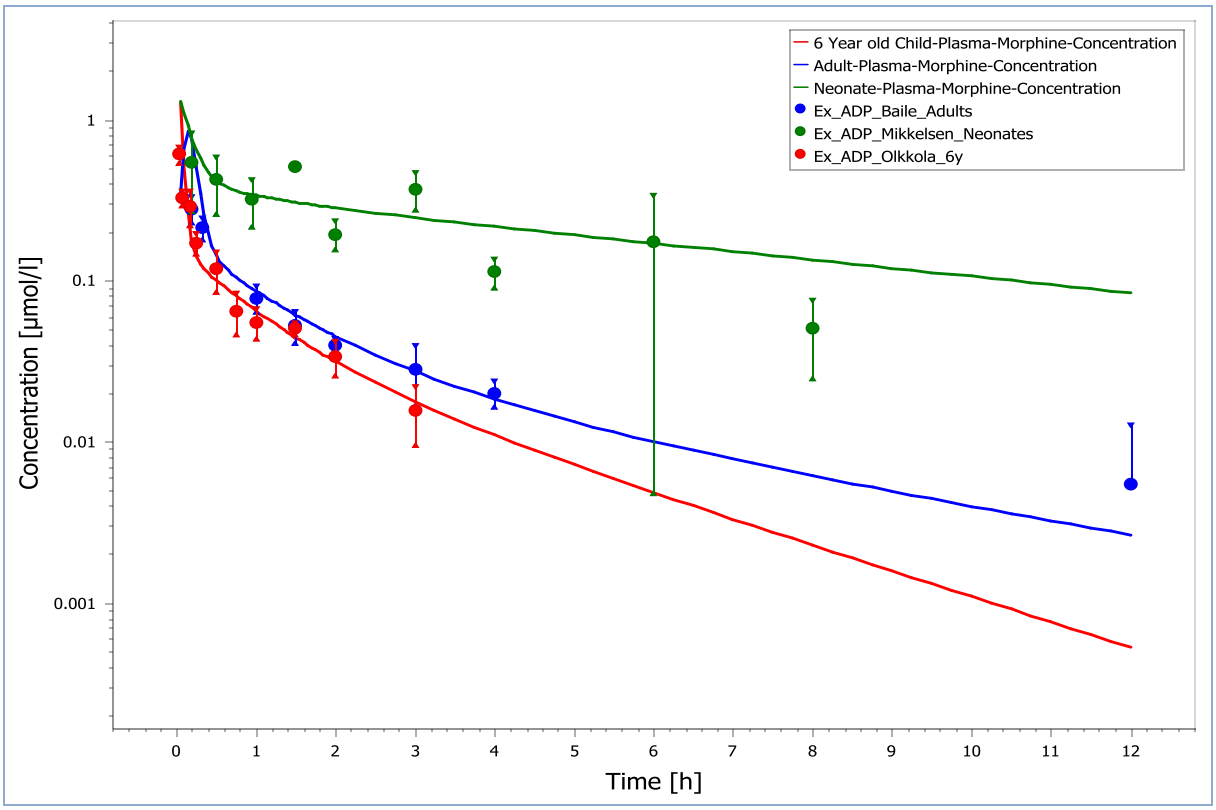
Objectives

Scale an adult model simulating morphine PK to a pediatric model using built clearance processes and development of physiology.

1. Prepare simulation by adding a metabolizing enzyme ("UGT2B7") and GFR for both, compound and individual (use RT-PCR expression database query for "UGT2B7" in individual; Process Type: Intrinsic Clearance – First Order" = 3 l/min; fraction GFR = 1)
2. Create individuals: „Child" and „Neonate", European, Male, 6 and 0 years (mean) and add metabolism and GFR as in adults
3. Create simulations for the Neonate and Child and compare to observed data ("Workshop_Data.xls", data Sheets "Ex_ADP_Mikkelsen_Neonates", and "Ex_ADP_Olkkola_6y").
4. Compare all 3 simulations results in one plot.


Plasma-Morphine-Concentration
Ex_ADP_Olkkola_6y
Concentration [µmol/l]
1
0.1
0.01
0.001
0
1
2
3
4
5
6
7
8
9
10
11
12
Time [h]

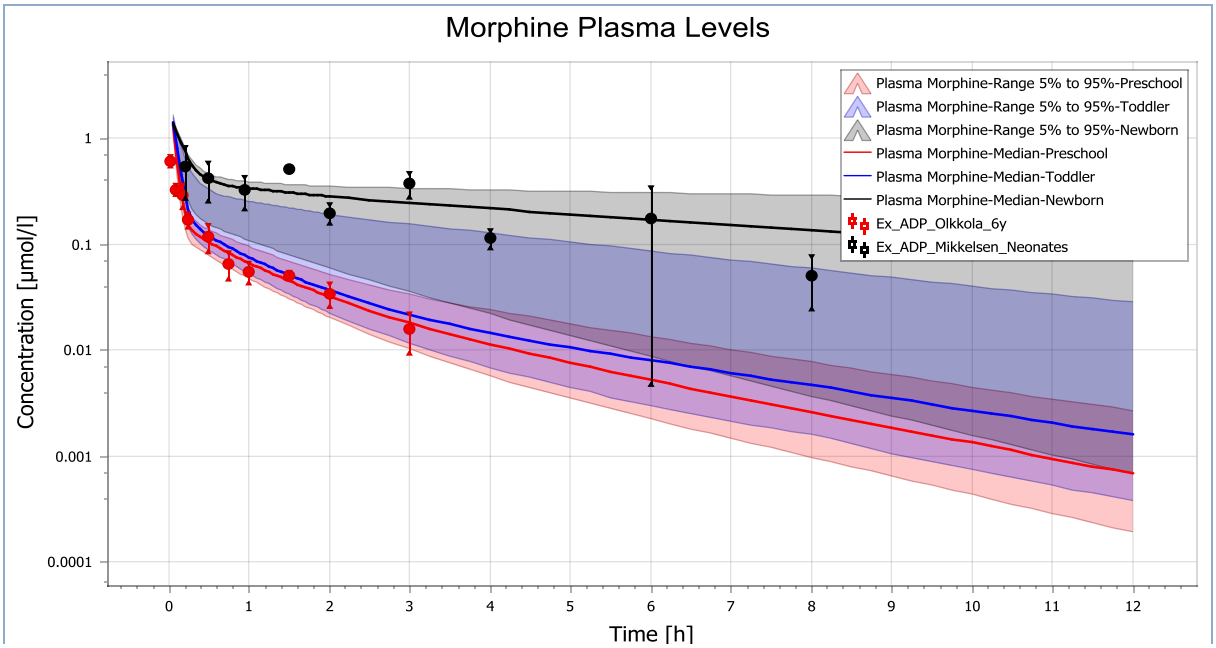

-Plasma-Morphine-Concentration
Ex_ADP_Mikkelsen_Neonates
Concentration [µmol/l]
1
0.1
0.01
0
1
2
3
4
5
6
7
8
9
10
11
12
Time [h]

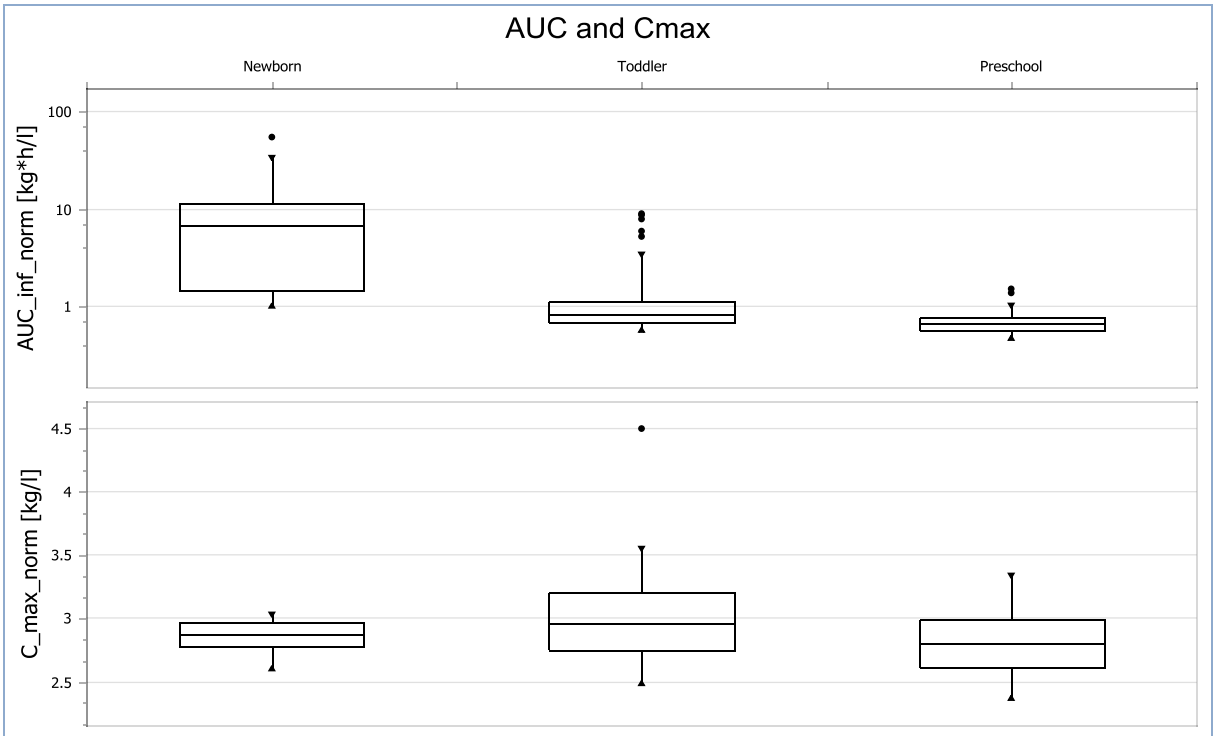


Objectives

Create population simulation for morphine PK in children. Define relevant age groups and compare relevant PK Parameters (AUC and Cmax) for each age group. Decide which dose would be needed for neonates to reach similar Cmax and AUC levels as in preschool children or Adults. Would simple adjustment of the dose by bodyweight or by allometric scaling lead to the same results?

1. Create a Population "Children" based on the Individual (500 Individuals "Age 0-6 years") and simulate "**median**", and "**5 -95 % Range**" of peripheral venous blood.
2. Create age based subgroups in the population simulation file for plotting, name it "Age Groups" with 0-0.1 (Newborn), 0.1 to 2 (Toddlers) and 2-6 Years (Preschool).
3. Compare to observed data.
4. Make a Box Whisker Analysis and compare dose-normalized AUC_inf and Cmax.





AUC and Cmax Comparison in Different age Groups (Newborn, Toddler and preschool childreen)

Solution - Age-Dependence of Pharmacokinetics

Objectives

Learn to set up an (adult model) simulation for morphine and compare simulation to observed data
Scaling from an Adult Simulation to 6 year old and newborn children.
Scale an adult model simulating morphine PK to a pediatric model using built-in ontogeny of clearance processes and development of physiology.
Create population simulation for morphine PK in children. Define relevant age groups and compare relevant PK Parameters (AUC and Cmax) for each age group. Decide which dose would be needed for neonates to reach similar Cmax and AUC levels as in preschool children or adults. Would simple adjustment of the dose by bodyweight or by allometric scaling lead to the same results?

Open **Exercise_ADP_1.pksim5**.

Set up a Simulation

- Make yourself familiar with the given **Individual**, **Compound** and **Administration Protocol**.

- Click "**Individual"** in the "**Create**" **Group** of the "**Modeling**" **Tab**.

- Create the **Simulation** "**Adult**" using the predefined building blocks. Leave everything else on default. Please choose "**Infusion Adult**" as **Administration Protocol** for the simulation. **N.B.** As a dose of 10 mg Morphine sulphate was given in this study and morphine base was measured in plasma input for PK-Sim is 7,4 mg after correction for free base.

- In the "**Simulation Parameters"** / "**Settings"** set the "**End Time**" to "**12 h**".

- Click "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" ribbon tab.
- Select the predefined "**Venous Blood Plasma Morphine Concentration**" and click "**OK**".

- The simulation is processed.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_2.pksim5**.

Load and Compare to Observed Data

- Click "**Observed Data**" in the "**Import**" **Group** of the "**Import/Export**" **Tab**.

- Choose the right path to your "**Observed Data**", select the **Excel File** "**WorkShop_Data.xlsx**" and click "**OK**".

- Choose the **Data Sheet** "**Ex_ADP_Baillie_Adults**", check for correct mapping of "**Time**" and "**Concentration**" and click "**Import(1)**".

- Name the Observed Data **"Baillie Adults"** under **Naming Pattern**

- Choose "**Molecule**", "**Species**", "**Organ**", and "**Compartment**" referring to the **Data Sheet** and click "**OK**".

- Drag and drop the imported **Observed Data** into the **Results Window**.

- Compare the **Observed Data** with your **Simulation Results**. Adjust **Physico-Chemical Parameters** if necessary.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_3.pksim5**.

Prepare for Scaling

- Edit **Individual** "**Adult**"

    - Add "**UGT2B7**" by right click on "**Metabolizing Enzyme**", **"Add Metabolizing Enzyme…(Database Query)"**. Be sure to have the Genexpression Database file (GENEDB_human.mdb) connected to the appropriate species. Within the Application Tab, you can specify the path to a species-specific Expression Database you would like to use. To do so go to "**Utilities**/**Options/ Application**" and click on the three dots in the Expression Database column in the row of the species you require. Then navigate to the Folder were you have saved the database file.
    - Search for **"UGT2B7"** and choose it by double clicking on the enzyme. Make yourself familiar with the Expression Data evaluated by different assays in the **"Expression Data Analysis"** Tab. Choose the **"RT-PCR"** Assay in the final **"Data Transfer Overview"** tab and finish the selection with **"Ok"**.

- Edit Compound "**Morphine**"**.**

- Add "**UGT2B7**" as "**Metabolizing Enzyme**", **Data Source** "**Paper**" as "**Intrinsic Clearance – First Order" = 3 l/min"**

- Add "**Renal Clearance Process**" "**Glomerular filtration**", **Data Source** "**default GFR**" (**fraction GFR** = **1.0**)

- Configure **Simulation** "**Adult**": Update **Individual** and **Compound** deactivate "**Total Hepatic Clearance**" and "**Renal Clearance**", activate "**UGT2B7**" and "**default GFR**".

- Re-run the **Simulation** "**Adult**" and compare to **Observed Data**. Adjust the name of the Simulation curve and the measured data in the **Chart Editor** if needed.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_4.pksim5**.

Scale an Individual

- Right click on the Individual "**Adult**" in the "**Individuals Building Blocks**" **Group** and select "**Scale**" in the context menu.

In the Scaling Wizard change the name (*e.g.:* "**6 year old Child**"), define the age of the individual in the Individual parameters field. The anthropometric data from the underlying PK-Sim® database should correspond to those in the following table:

Anthropometric data of 6-year old Child		
		Unit
Species	Human	
Population	European (ICRP, 2002)	
Gender	Male	
Age	6	years
Weight	21.6	kg
Height	114.8	cm

Click on next and leave everything else on default. Finish scaling the new **Individual** by clicking "**OK**".

- Repeat the process to create a "**Neonate**" with the following **Parameters**:

Anthropometric data of Neonate		
		Unit
Species	Human	
Population	European (ICRP, 2002)	

Gender	Male	
Age	0	years
Weight	3.5	kg
Height	51	cm

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_5.pksim5**.

Set up a Simulation / Load and Compare to Observed Data

- **Clone Simulation** for the pharmacokinetics of morphine in adults and replace the individual "Adult" in your cloned simulation with "**Neonate**" and "**6 year old Child**", respectively. Please choose "**Bolus Child**" as **Administration Protocol** for the simulations in both age groups. **N.B.** As a dose of 0,15 mg/kg mg Morphine chloride was given in this study and morphine base was measured in plasma input for PK-Sim is 0,134 mg/kg after correction for free base.
  Take care to appropriately match the elimination processes.

- Set the "**End Time**" to "**12 h**" before running the simulation.

- Compare the **Simulation Result** with **Observed Data** which can be found in the **Excel File** "**WorkShop_Data.xls**", **Data Sheets** "**Ex_ADP_Mikkelsen_Neonates**", and "**Ex_ADP_Olkkola_6y**". Adjust the name of the Simulation curve and the measured data in the **Chart Editor** if needed.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_6.pksim5**.

Task

Make a **Comparison Chart** to compare all the **Observed Data** and **Simulation Results**. To do so, click on "**Comparison Chart**" in the "**Simulation**" **Group** of the "**Modeling & Simulation**" **Tab** and choose **"For Individual Simulations"**. Drag and drop the **Simulations** and their corresponding **Observed Data** into the white field. In the **Chart Editor** select the curves you wish to be displayed.

How do the plasma concentrations change with age? Does curve shape change with age? What does this mean?

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_7.pksim5**.

Simulate a Child Population

- Add a Population **"Children**" based on **Individual** "**Neonate**" with 500 Individuals "**Age 0-6 years**". This may take some time…enjoy a coffee break ;-)

- Click "**Next**" and then "**OK**" after having a look at the distribution (e.g. Weight, Age, GFR).

- Clone a **Simulation** (Neonates or 6 Year olds) and chose "**Children**" as **Population**

- A **Simulation** is set up now. Click "**Run**".

- In the Pop up Menu, choose "**Organ: Peripheral Venous Blood|Plasma Morphine Concentration**" and click "**OK**".

- Choose "**Median**"**,** and "**Range 5 -95 %**" as graphs to be shown. Change Name to Plasma Morphine and click "**Next**".

- Chose the Population parameters you would like to investigate. Here the age is interesting. In **Population Parameters, Characteristics of the Individual** look for age and add it to the right side by clicking on the upper arrow. Create Grouping, name it "**Age Groups**" with 0-0.1 (Newborn), 0.1 to 2 (Toddlers) and 2-6 Years (Preschool). Click OK. Right click on "**Age Groups**" in the right table and "**Save Grouping**" for later Analyses.

- In "**Time Profile Analysis**" drag "**Age Groups"** from "**Available Parameters**" to "**Colors**"

- Drag and drop the **Observed Data** "**Ex_ADP_Mikkelsen_Neonates**" and "**Ex_ADP_Olkolla_6y**"into the **Results Window**.

User mouseover tooltips to investigate the plasma concentration time curves (upper and lower limit). In which age groups seems to be the most dramatic change in PK?
Is the variability of the newborns correctly described? Do we have to add additional variability?
In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_8.pksim5**.

Optional Box-Whisker Analysis

Go to button Analysis in the simulation ribbon and choose Box Whisker Analysis.
Chose the Population parameters you would like to investigate. Here the age is interesting. In **Population Parameters, Characteristics of the Individual** look for age and add it to the right side by clicking on the upper arrow. Right click on Age in the right table, chose load from Template and select Age Groups.

In **PK Parameters,** look for AUC_inf_norm (dose normalized AUC from time 0 to infinity) and C_max_norm (dose normalized Cmax) and add them to the right side by clicking on the upper arrow.
Change Units to kg*l/h for AUC_inf_norm and to kg/l for C_max_norm. Leave everything else on default.
In **Box Whisker Analysis** drag Age groups to X-Grouping. Activate AUC_inf_norm and C_max_norm in selected Outputs
And click OK.
Use mouseover tooltips to investigate the plasma concentration time curves (upper and lower limit). Think about why the dose normalized AUC differs between the age groups whereas the dose normalized Cmax seems to be similar.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_ADP_END.pksim5**.