

Setting up a simple PBPK model

Objectives

- Learn to set up an (adult model) simulation for morphine and compare simulation to observed data.
- Learn to create a second simulation for a Japanese adult.
- Learn to create population simulations for morphine PK in Japanese and Europeans.
- Learn to compare simulations.

Before start: Integrate the Gene database into PK-Sim

1. Open PK-Sim
2. Go to tab “**Utilities**” and click “**Options**”. Go to tab “**Application**”.
3. For “**human**”, click “...”. Select the **GENEDB_human** from the workshop material.
4. Click “**Ok**”

Open Setting up a simple PBPK Model/Ex 1 PBPK 1.pksim5.

Optional: Set up all relevant building blocks

If you want to create the building blocks for yourself, create a new project in PK-Sim instead of opening Ex_1_PBPK_1.pksim5

- Set up an individual building block “**European**” with the following properties:

age:	27.4 years
body weight:	67.6 kg

body height: 174.44 cm

Create Individual

Name:

Biometrics | Anatomy & Physiology | Expression

Population Properties

Species:

Population:

Gender:

Calculation methods:

Individual Parameters

Age:

Weight:

Height:

BMI:

- Set up an individual building block “**Japanese**” with the following properties:
age: 30 years
body weight: 61.87 kg
body height: 168.99 cm
- Add the metabolizing enzyme “**UGT2B7**” to both individuals. Use the “RT-PCR” expression profile
 - “**Right click**” on “**Metabolizing Enzymes**”, choose “**Add Metabolizing Enzyme... (Database Query)**”
 - Search for “**UGT2B7**”
 - “**Double click**” on “**UGT2B7**”
 - Go to tab “**Data transfer overview**”. Choose the “**RT-PCR**” profile and click “**Next**”
- Set up a compound “**Morphine**” with the following properties:
lipophilicity: 0.89 [-]
fraction unbound: 0.75 [-]
molecular weight: 285.3 g/mol

solubility: 9999 mg/l (unnecessary for intravenous administration)

Create Compound

Name:

☒ Basic Physico-chemistry ☒ ADME ☐ Advanced Parameters

☒ Is small molecule

Lipophilicity:

Experiment	Lipophilicity
Measurement	0.890 Log Units

Fraction unbound (plasma, reference value):

Binds to: ☒ Albumin ☐ α 1-acid glycoprotein ☐ Unknown

Experiment	Fraction Unbound	Species
Measurement	0.750	Human

Molweight:

Molecular weight	285.300 g/mol
Has halogens	No
Effective molecular weight	285.300 g/mol

Compound type / pka:

Neutral	<None>
Neutral	<None>
Neutral	<None>

Solubility:

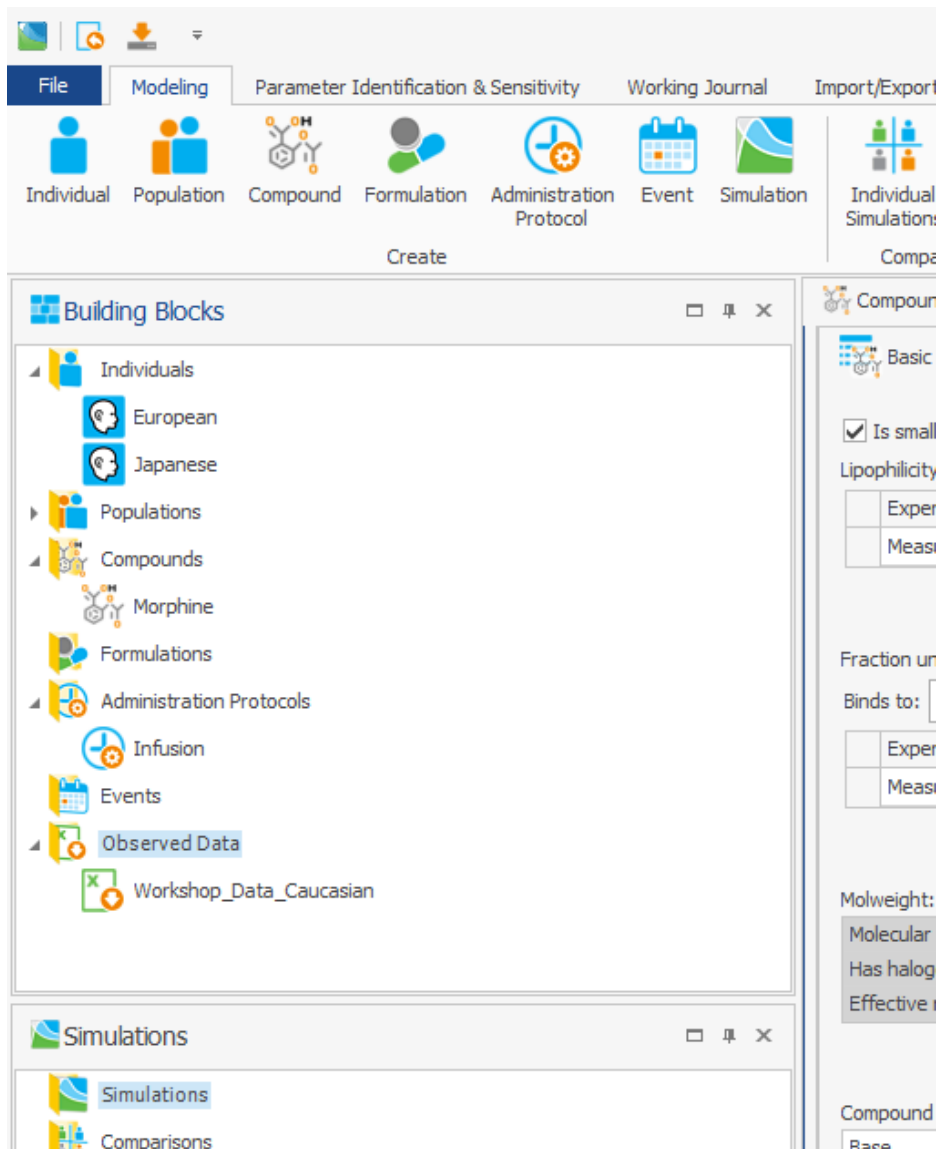
Experiment	Solubility at Ref-pH	Ref-pH	Solubility gain per c...	pH-dependent Solubi...
I Measurement	9999.000 mg/l	7.000	1000.000	Show Graph

Previous Next OK Cancel

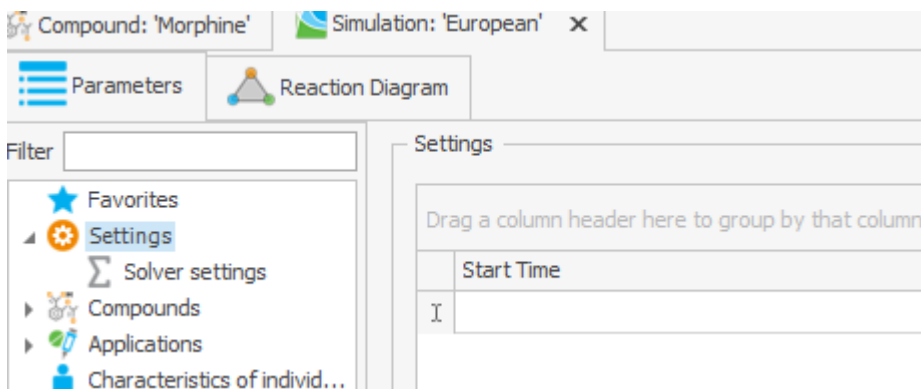
- In the tab “ADME”, add an intrinsic clearance process via metabolizing enzyme “UGT2B7” with an intrinsic clearance of 3 l/min
- Add “Glomerular filtration” as a renal clearance process. Set **GFR fraction** to 1
- Set up an administration protocol „Infusion“, with the following properties:
Administration type: intravenous infusion
Dose: 7.4 mg
Dosing interval: single
Infusion time: 10 min

Set up a simulation

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



- Click **“Simulation”** in the **“Create” Group** of the **“Modeling”** ribbon tab.
- Create the **Simulation “European”** using the predefined building blocks. Leave everything else on default. Please choose **“Infusion”** as **Administration Protocol** for the simulation. 10 mg morphine sulphate was given in the study(,) and morphine base was measured in plasma. Correction for the free base yields a dose of 7.4 mg which is used for simulation.
- In the **“Simulation Parameters” / “Settings”** set the **“End Time”** to **“12 h”**.

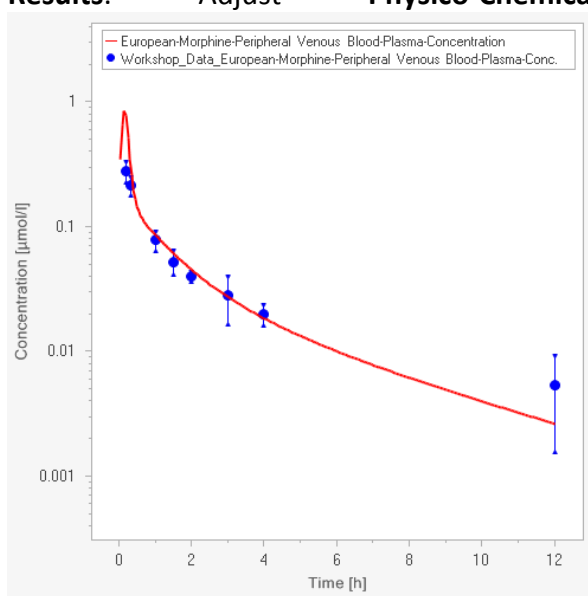


- Click **“Run”** in the **“Simulation”** group of the **“Run & Analyze”** ribbon tab.
- Select the predefined **“Peripheral Venous Blood Plasma Morphine Concentration”** and click **“OK”**.
- The simulation is processed.

*In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Setting up a simple PBPK Model/Ex 1 PBPK 2.pksim5**.*

Compare to observed data

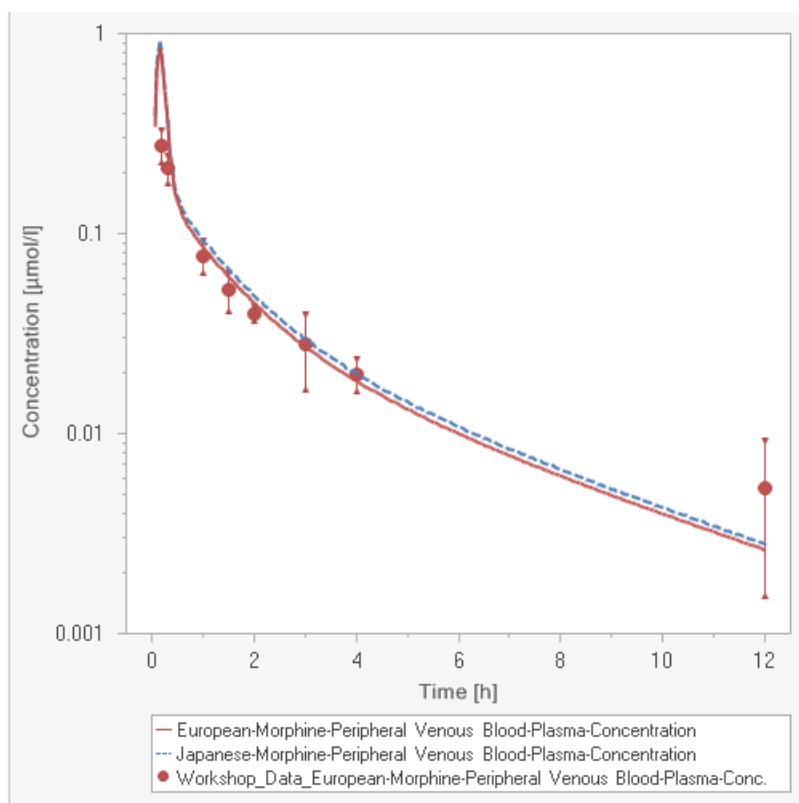
- Expand the node of the **“Observed Data”** in the **“Building Blocks Explorer”**.
- Drag and drop the imported **Observed Data “Workshop_Data_European”** into the **Results Window**.
- Compare the **Observed Data “Workshop_Data_European”** with your **Simulation Results**. Adjust **Physico-Chemical 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 Setting up a simple PBPK Model/Ex 1 PBPK 3.pksim5.

Clone and configure a second simulation

- **Clone Simulation** for the pharmacokinetics of morphine in Europeans and replace the individual “**European**” in your cloned simulation with “**Japanese**”. Re-name the simulation from “European” to “Japanese”. Delete the observed data for Europeans from the simulation for Japanese.
- In the “**Simulation Parameters**” / “**Settings**” set the “**End Time**” to “**12 h**”.
- Click “**Run**” in the “**Simulation**” group of the “**Run & Analyze**” tab.
- Select the predefined “**Peripheral Venous Blood Plasma Concentration**” and click “**OK**”.
- The simulation is processed.
- Make a **Comparison Chart** to compare all the **Observed Data** and **Simulation Results**. To do so click on “**Individual Simulation**” in the “**Compare Results**” **Group** of the “**Modeling**” ribbon. 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.



In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file Setting up a simple PBPK Model/Ex 1 PBPK 4.pksim5.

Simulate a European Population

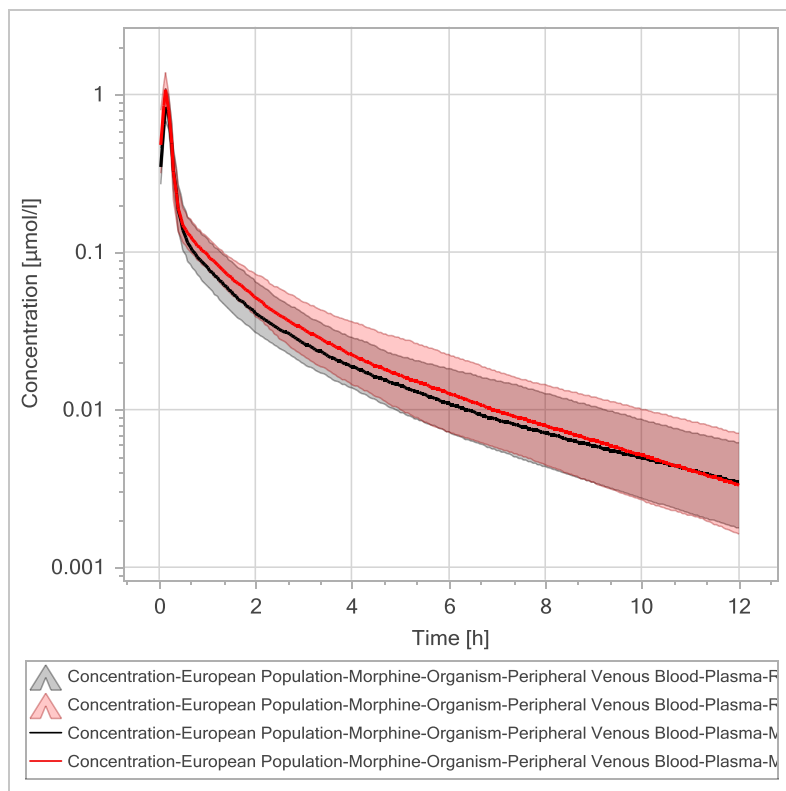
- Set up a new simulation named “European Population”, now choose the population “**Europeans**” instead of an individual.
- Have a look at the distribution (e.g. Weight, Age, GFR).
- In the “**Simulation Parameters**” / “**Settings**” set the “**End Time**” to “**12 h**”.
- Click “**Run**” in the “**Simulation**” group of the “**Run & Analyze**” tab.
- Select the predefined “**Peripheral Venous Blood Plasma Concentration**” and click “**OK**”.
- The simulation is processed.
- In the popup menu, choose “**Organ: Peripheral Venous Blood|Plasma Morphine Concentration**” if not already selected.
- Choose “**Median**”, and “**Range 5 -95 %**” as graphs to be shown in the output
- Choose Log Scaling for the concentration axis. Click “**Next**” three times and then “**OK**”.
- Drag and drop the imported **Observed Data** “**Workshop_Data_European**” into the **Results Window**.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Setting up a simple PBPK Model/Ex 1 PBPK 5.pksim5](#).

Simulate a Japanese Population

- Set up a new simulation named “Japanese Population”, now choose the population “**Japaneses**” instead of an individual.
- Have a look at the distribution (e.g. Weight, Age, GFR).
- In the “**Simulation Parameters**” / “**Settings**” set the “**End Time**” to “**12 h**”.
- Click “**Run**” in the “**Simulation**” group of the “**Run & Analyze**” tab.
- Select the predefined “**Peripheral Venous Blood Plasma Concentration**” and click “**OK**”.
- The simulation is processed.
- In the Pop up Menu, choose “**Organ: Peripheral Venous Blood|Plasma Morphine Concentration**” if not already selected.
- Choose “**Median**”, and “**Range 5 -95 %**” as graphs to be shown in the output
- Choose Log Scaling for the concentration axis. Click “**Next**” three times and then “**OK**”.
- Make a **Comparison Chart** to compare all the **Observed Data** and **Simulation Results**. To do so, click on “**Compare Results**” **Group** of the “**Run & Analyze**” ribbon. Alternatively, you can click on “**Population Simulations**” in the “**Compare Results**” **Group** of the “**Modeling**” ribbon. Choose all population simulations you want to compare (here: Japanese and Europeans) and click “**OK**”. Choose in the **Output** Tab “**Median**” and “**Range 5 -95 %**” as graphs to be shown. Chose log scaling for the concentration axis. Click “**Next**”. Choose in the **Population Parameters** Tab under “**Characteristics of the**

Individual “**Population Name**” and click “**Add**”. Click “**Next**” twice. Now drag and drop “**Population Name**” under “**Available Parameters**” to “**Colors**”. Click “**OK**”.



In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Setting up a simple PBPK Model/Ex 1 PBPK End.pksim5](#).