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# NanoInhale: a PBPK model for describing the biodistribution of TiO<sub>2</sub> in humans after inhalation exposure

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*A brief tutorial*

NanoSolveIT H2020 Nanoinformatics Project

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## Overview

This web application was developed in the context of the NanoSolveIT project for simulating the biodistribution of TiO<sub>2</sub> nanoparticles in humans after inhalation exposure. The PBPK model has been developed initially on the rat using the biokinetic data of Kreyling et al. (2019) that concern TiO<sub>2</sub> nanoparticles of 22 nm diameter and was subsequently extrapolated to humans. The application takes as input the concentration of TiO<sub>2</sub> (in µg/m<sup>3</sup>) over time and transforms it into internal biodistribution. The tissue compartments that are reported are the liver, spleen, kidneys, heart, brain, blood, Rob (Rest of the body; it includes the skeleton and the remaining soft tissues), alveolar region, tracheobronchial region, lung interstitium and capillaries, upper respiratory system and, finally, lower respiratory system (the sum of the mass found in the alveolar, tracheobronchial and lungs interstitium regions).

The tool can be easily accessed through the link:

<https://nanoinhale.cloud.nanosolveit.eu/>

## Instructions

The User Interface (UI) of the web service is presented in Figure 1. The application consists of two modules, the exposure scenario and the simulation information module. The user is requested to provide some input to both modules in order to simulate a complete biodistribution scenario stemming out of an occupational exposure event.

The screenshot shows the Nanolnhale web service interface. At the top is a teal header bar with the text "Nanolnhale" on the left and a download icon and "Logout" text on the right. Below the header, there is a disclaimer text block on the left and a funding information block on the right. The main content area contains two primary input modules: "Upload an Exposure Scenario" and "Set the Simulation Parameters". The "Upload an Exposure Scenario" module includes a text prompt "Please upload a csv file containing the exposure scenario" and two arrows (a green downward arrow and a red upward arrow) for file selection. The "Set the Simulation Parameters" module includes a text prompt "Please provide the necessary simulation information" and a label "Simulation start (hours)" with a text input field containing the value "0".

Nanolnhale

This web application was developed in the context of the NanoSolveIT project for **simulating the biodistribution of TiO<sub>2</sub> nanoparticles in humans** after inhalation exposure. The PBPK model was initially developed on rats using the biokinetic data of [Kreyling et al. \(2019\)](#) that concern **TiO<sub>2</sub> nanoparticles of 22 nm diameter** and was subsequently extrapolated to humans. Therefore, additional uncertainty should be considered in the case of distant nanoparticle sizes.

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Upload an Exposure Scenario

Please upload a csv file containing the exposure scenario

↓ ↑

Set the Simulation Parameters

Please provide the necessary simulation information

Simulation start (hours)

0

**Figure 1:** The UI of the Nanolnhale web service.

### Step 1: Defining an occupational exposure scenario

The exposure module offers the user the ability to upload an exposure scenario in the form of a csv file. The user can first download a template containing the necessary columns to be filled (Figure 2). Specifically, the user is asked to provide 2 time series, including time and TiO<sub>2</sub> concentration. After constructing the desired csv containing the exposure scenario, it can be uploaded on the web service by pressing the upward red arrow and selecting the desired csv file from the local user machine (Figure 3).

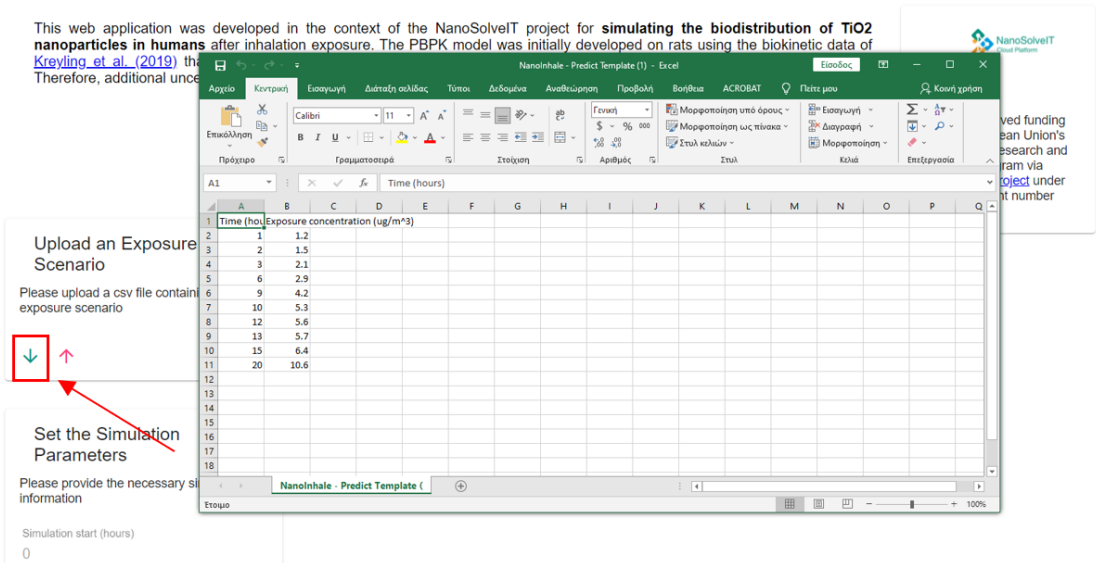


Figure 2: Downloading the csv template.

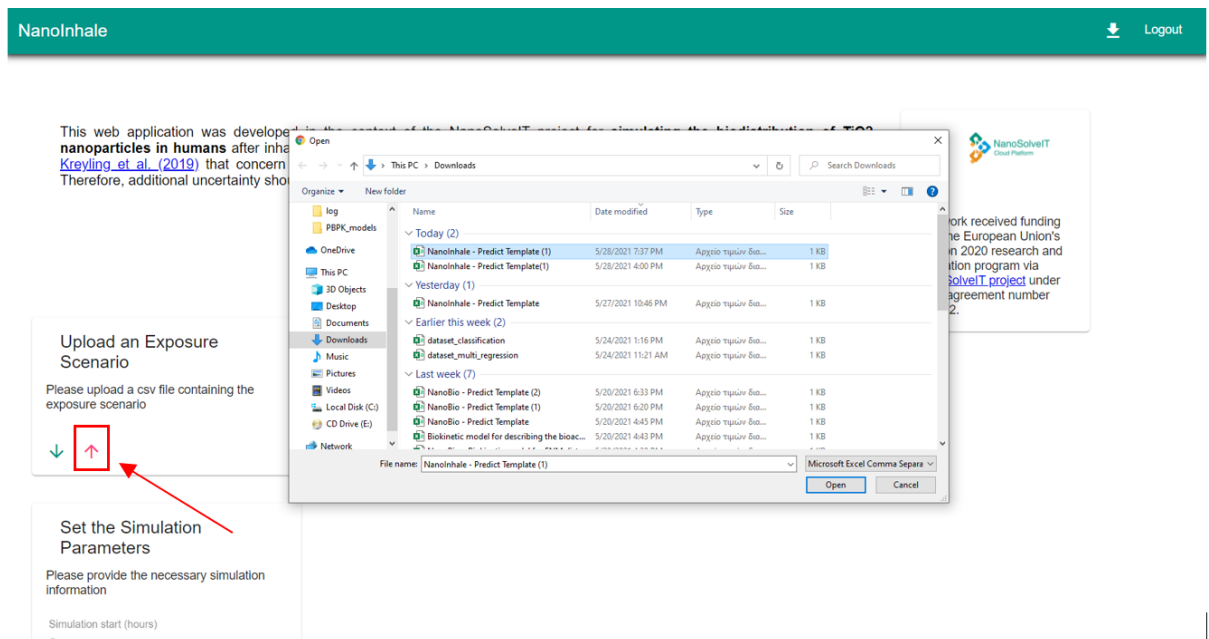
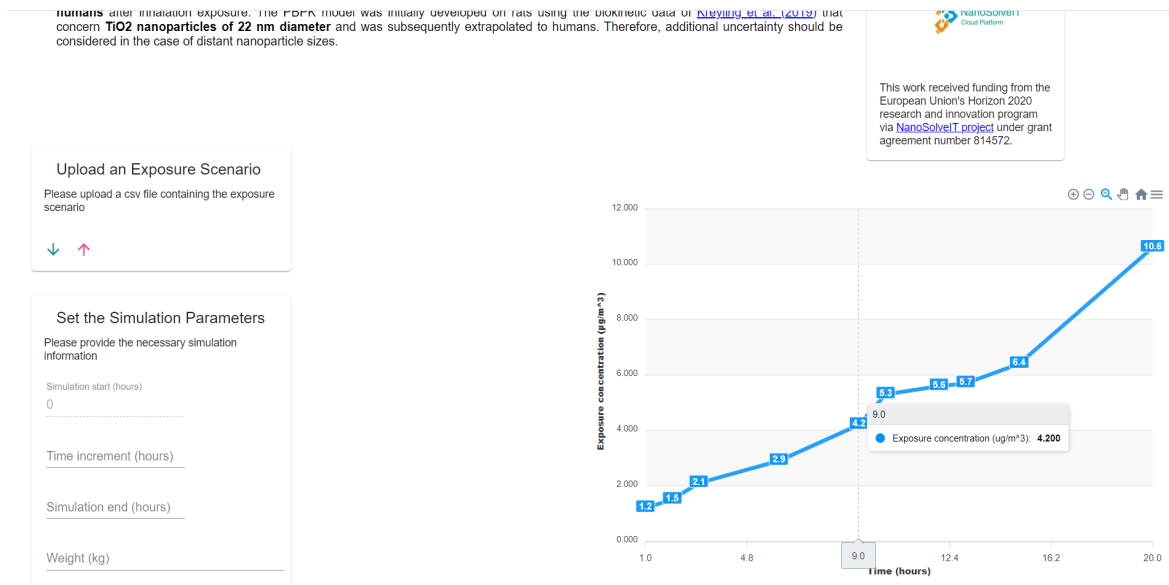


Figure 3: Uploading a csv file.

Following successful upload of the exposure csv, a visualisation module plots the exposure concentration-time profile to the right side of the application (Figure 5). The plot is interactive and the user can hover over each point to obtain the exact value and zoom in or out of the plot (Figure 4).



**Figure 4:** Interactive visualisation of the exposure time series.

## Step 2: Providing the simulation details

The additional information needed for the simulation to run is the simulation subject weight, the time increment, the last time point of the simulation time vector and the size of the TiO<sub>2</sub> nanoparticles. By default, the starting point is set to zero. Figure 5 illustrates the provided information for a scenario concerning TiO<sub>2</sub> and witnesses the progression of the biodistribution over a time period of 1000 hours. At this point, the user is advised to simulate scenarios for TiO<sub>2</sub> nanoparticles of diameter close to 22 nm (diameter of nanoparticles of the biodistribution study used to build the PBPK model), to reduce additional prediction uncertainty. At last, the user can hit the “Run the Simulation” button to obtain the simulation results.

Upload an Exposure Scenario

Please upload a csv file containing the exposure scenario

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Set the Simulation Parameters

Please provide the necessary simulation information

Simulation start (hours)

0

Time increment (hours)

1

Simulation end (hours)

1000

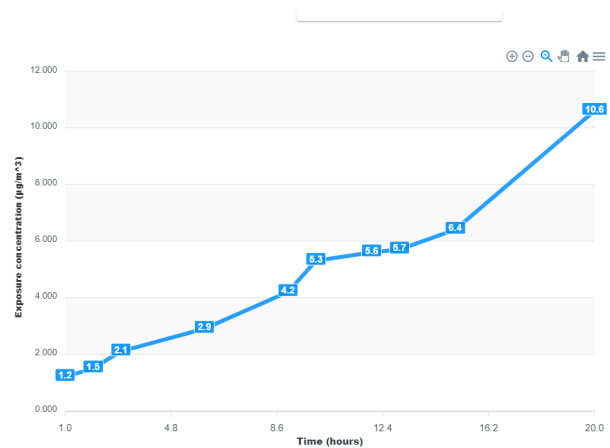
Weight (kg)

70

Size (nm)

1000

Run the Simulation



**Figure 5:** Setting the simulation information.

After the simulation results become available, the user can select which organs/tissues to plot in the corresponding visualisation box. The user can again hover over the time series to obtain exact values, zoom in and out and download the csv containing the simulation results (Figure 6). Finally, in order to change any simulation parameters or upload a new exposure scenario, the page must be refreshed.

70

Size (nm)

1000

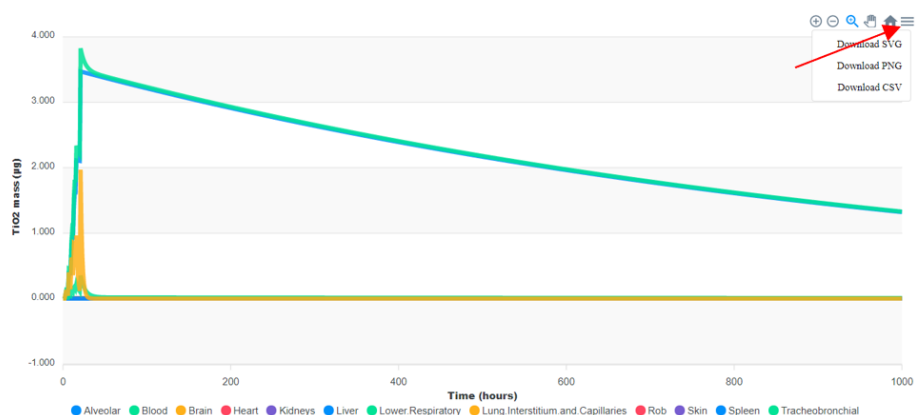
Run the Simulation

Biodistribution Plots

Please select the organs/tissues you want to plot

☒ Plot all organs/tissues
 

- ☒ Skin
- ☒ Blood
- ☒ Liver
- ☒ Alveolar
- ☒ Brain
- ☒ Upper.Respiratory
- ☒ Spleen
- ☒ Lower.Respiratory
- ☒ Kidneys
- ☒ Rob
- ☒ Tracheobronchial
- ☒ Heart
- ☒ Lung.Interstitium.and.Capillaries



**Figure 6:** Biodistribution plots module and download capabilities.

Support

