Periklis Tsiros - Harry Sarimveis

Showcasing the NanoCommons exposure/risk assessment tool

http://enaloscloud.novamechanics.com/nanocommons/exposure

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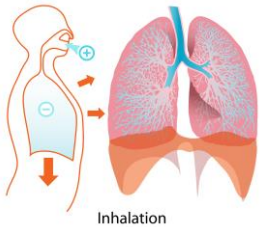
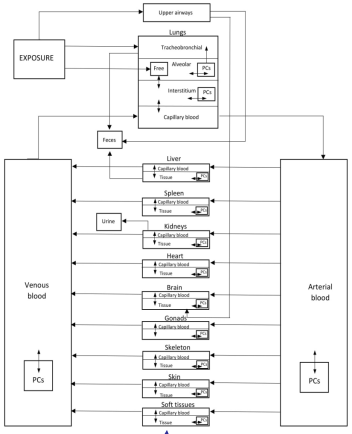
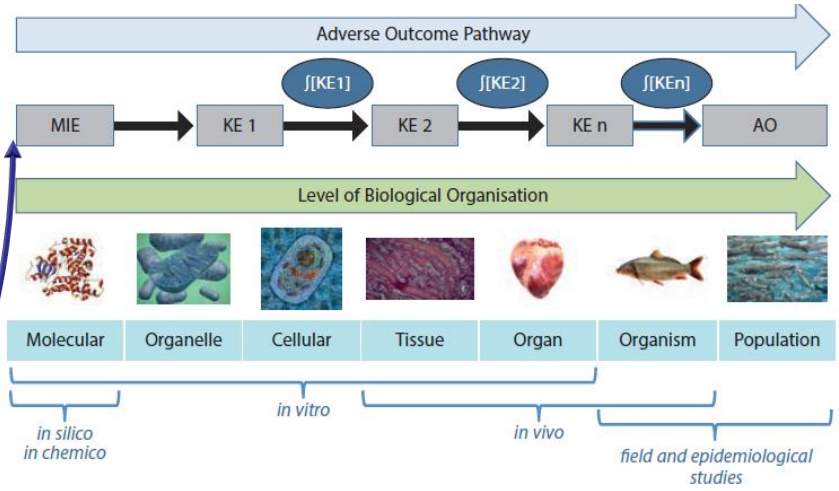
Risk Assessment through the AOP concept







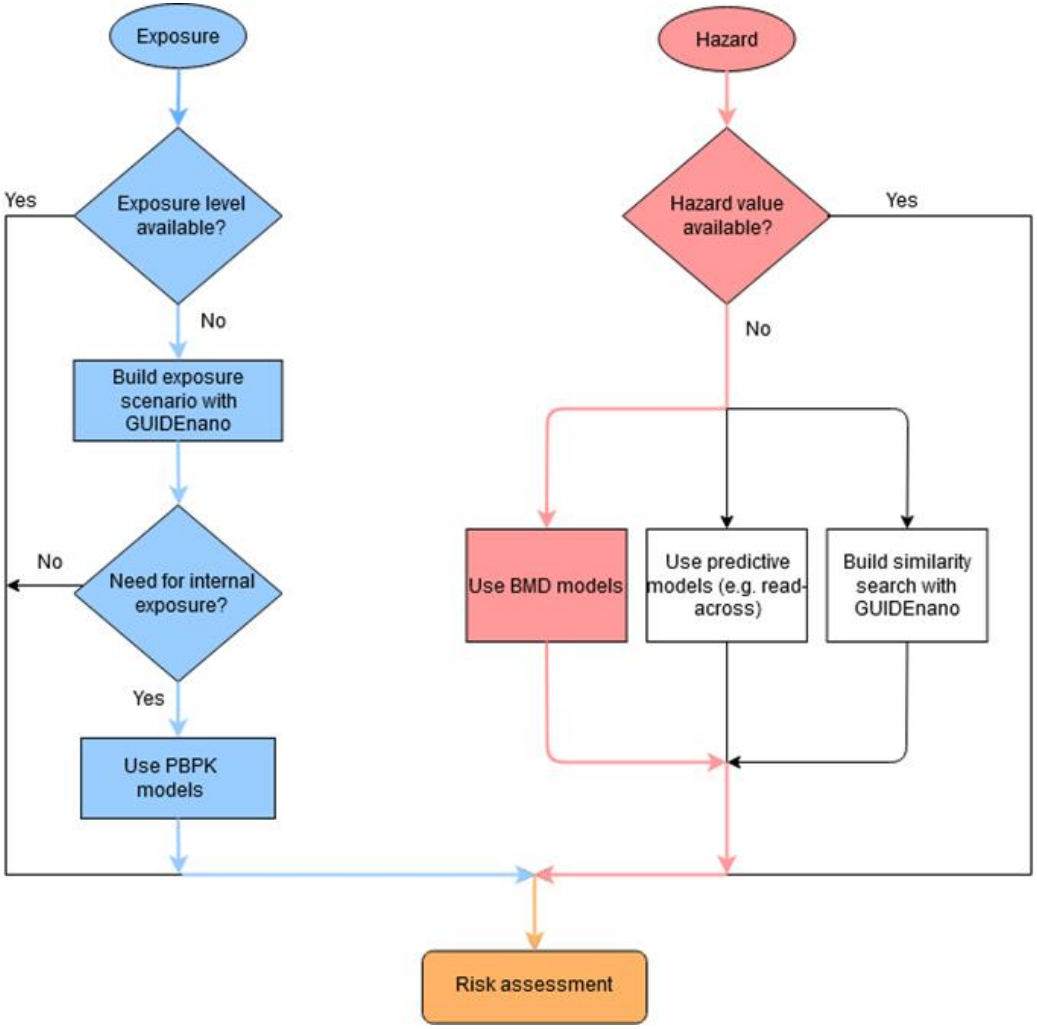
Exposure Models

Toxicokinetic Models

In-silico models predicting AOPs

OECD GUIDANCE DOCUMENT FOR THE USE OF ADVERSE OUTCOME PATHWAYS IN DEVELOPING INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA), ENV/JM/MONO(2016)67

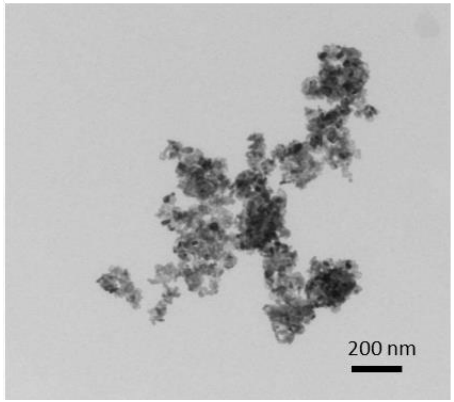
Risk Assessment Workflow

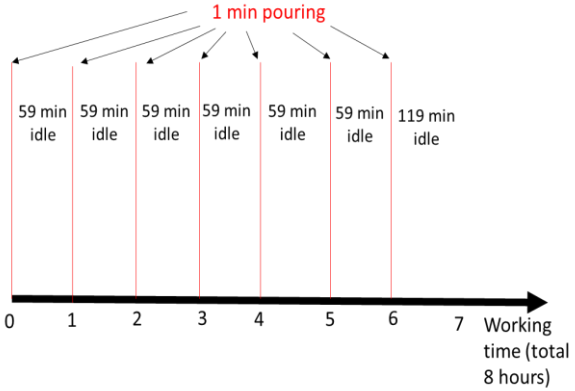


External exposure simulation using GUIDEnano

Nanomaterials property

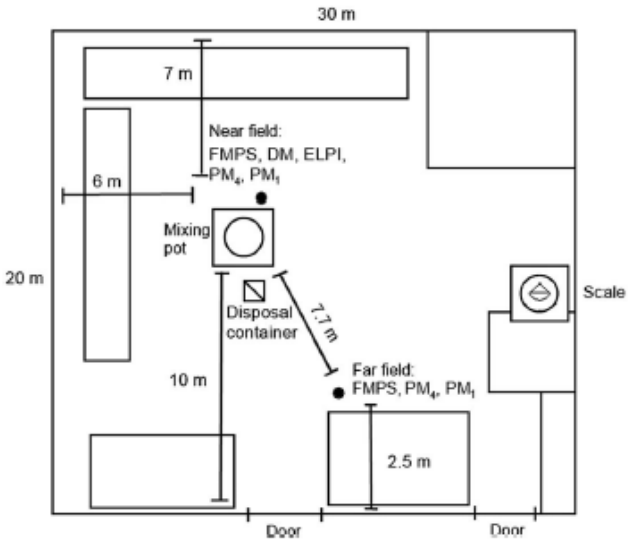
- TiO2 NM102
- CAS: 13463-67-7
- Anatase
- 21 +/- 2; 100% in 10 to 30 nm range
- Spherical
- Dustiness: 15 mg/kg
- Photocatalyst
- Pure
- Density: 4,3
- …





Activity

Compartment: factory

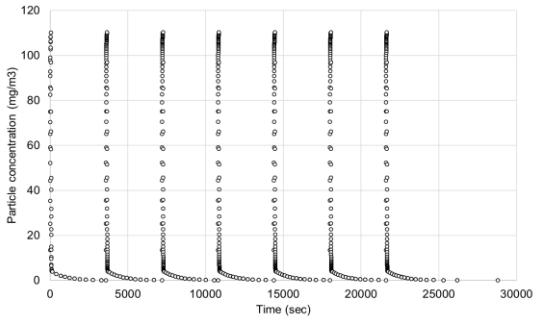


Release

Using the **Two-Box Nano-specific model** the time evolution of the particle size distribution (PSD) of NMs. In a two-box (or source-receptor) model the room is typically split into two boxes

- Far-Field (8 hours)
- Near-Field (8 hours)

External exposure data



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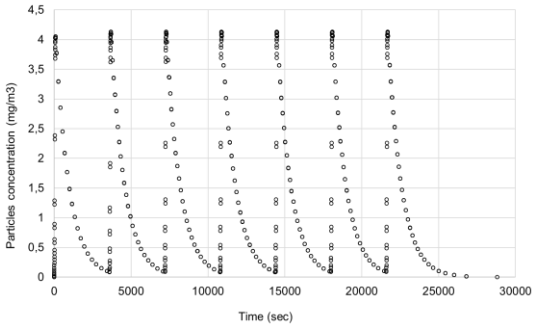

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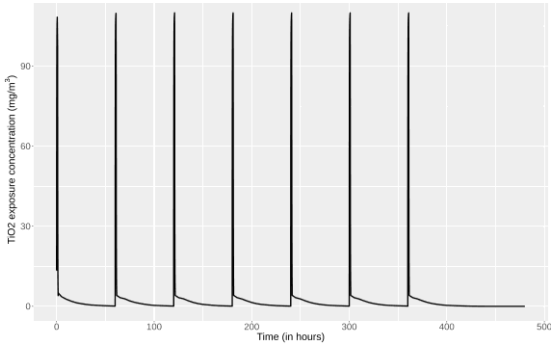
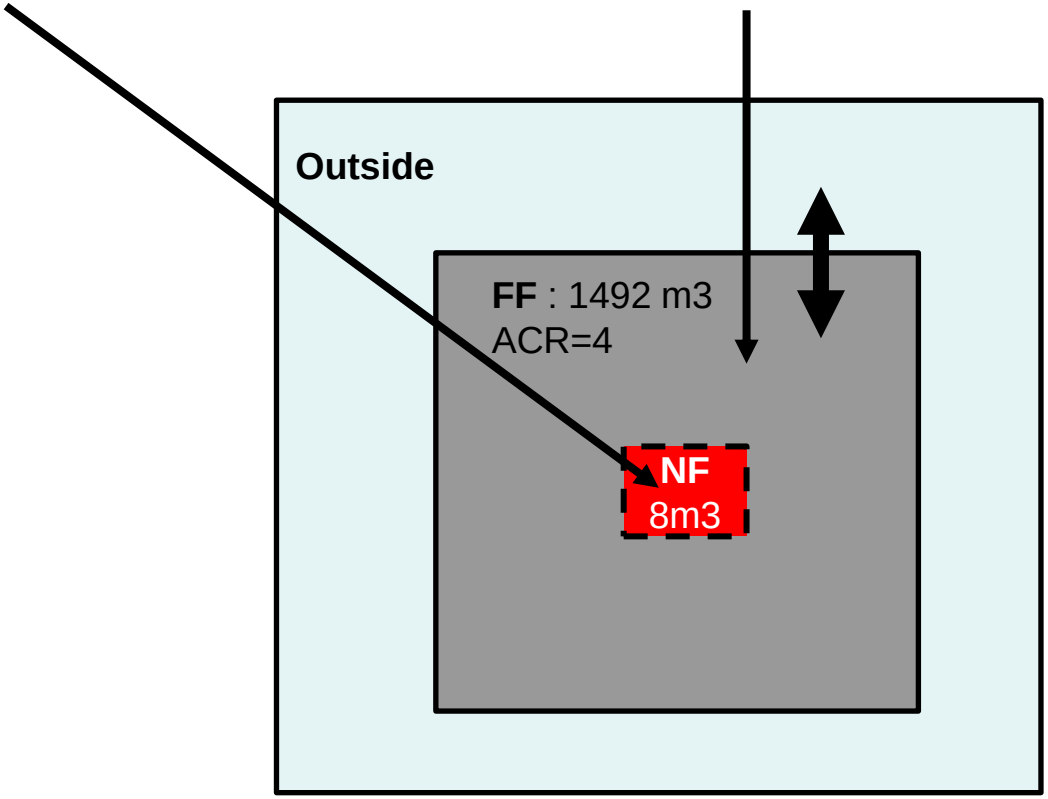
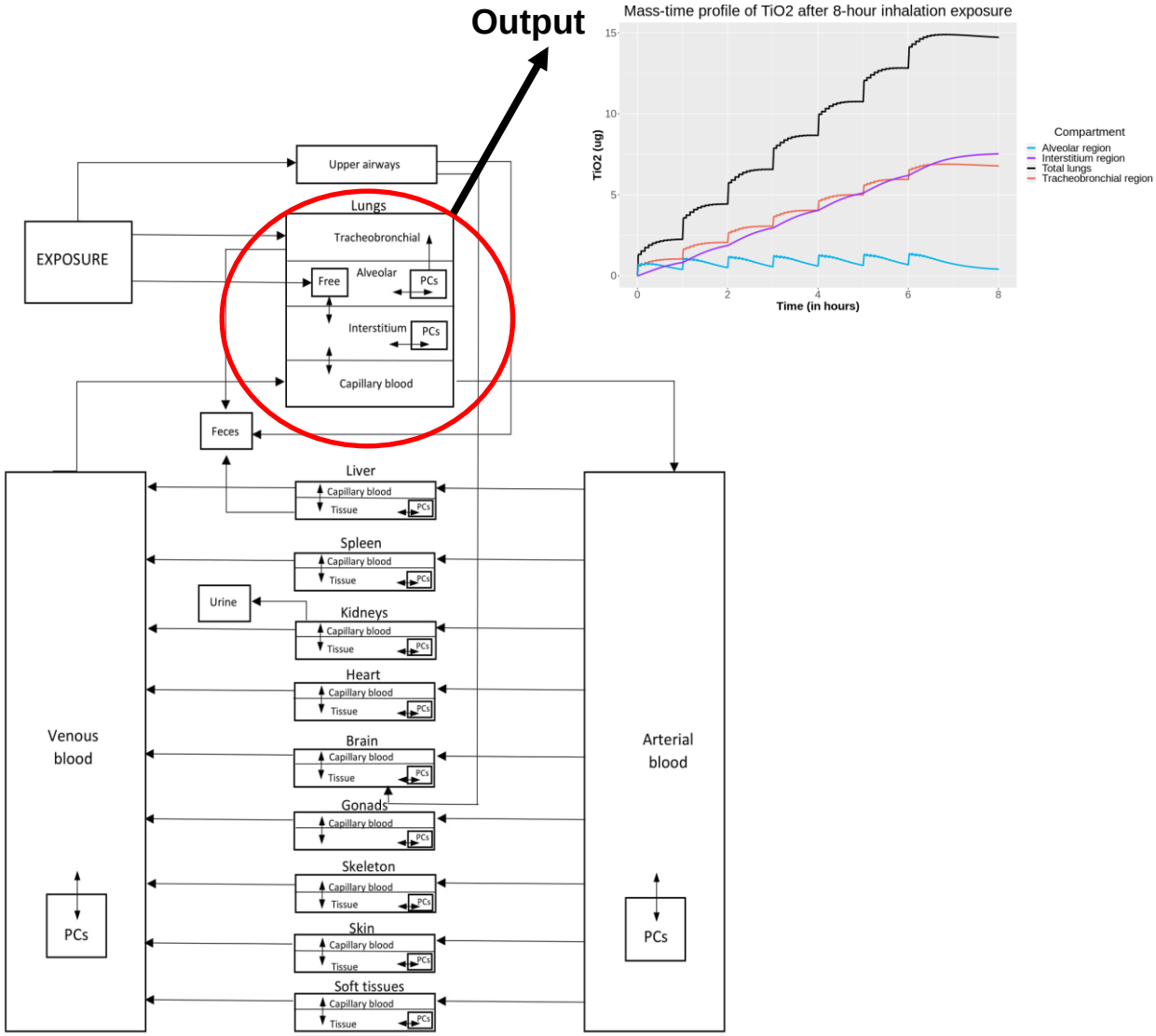


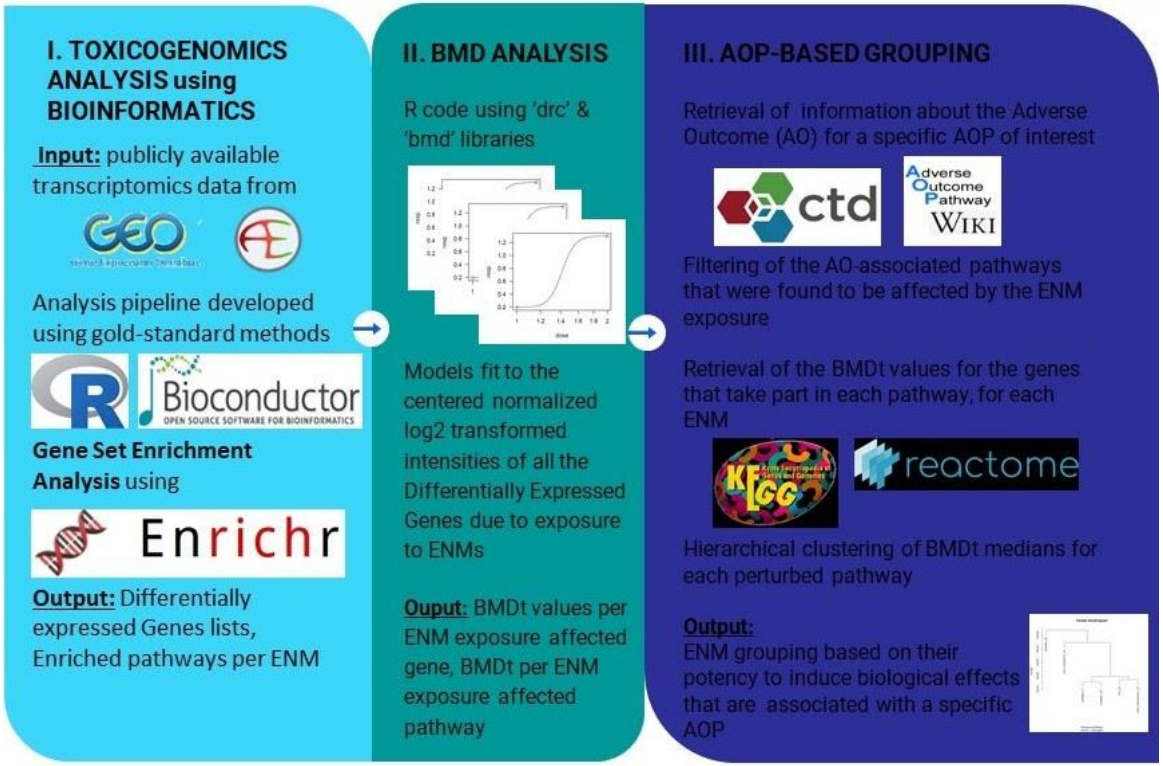


Internal exposure simulation – Development of a PBPK model

- Rat inhalation biokinetic data from Kreyling *et al*. (2019).
- Samples from 13 compartments over 5 time points, from 2 to 28 days post exposure.
- Structural model similar to Li *et al*. (2016).
- Extrapolation from rat to mice by scaling physiological parameters using literature information and deposition and clearance rates using MPPD (Multiple-Path Particle Dosimetry Model).



Workflow of the AOP-based BMD method on toxicogenomics data



AOP-based BMD for TiO2

	ENM_1	ENM_2	...	ENM_n
DEG_1	↓	↑	...	↓
DEG_2	↑	↓	...	↑
DEG_3	↓	↓	...	↓
...	...	...	...	
DEG_m	↓	↑	...	↑

→

	ENM_1	ENM_2	...	ENM_n
DEG_1	$BMDt_{1,1}$	$BMDt_{2,1}$	...	$BMDt_{n,1}$
DEG_2	$BMDt_{1,2}$	$BMDt_{2,2}$	...	$BMDt_{n,2}$
DEG_3	$BMDt_{1,3}$	$BMDt_{2,3}$	...	$BMDt_{n,3}$
...	...	...	...	...
DEG_m	$BMDt_{1,m}$	$BMDt_{2,m}$	...	$BMDt_{n,m}$

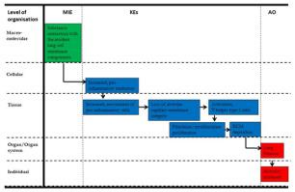
→

Enrichr

ENM exposure associated pathways

- Enriched pathway$_1$
- Enriched pathway$_2$
- ...
- ...
- ...
- Enriched pathway$_k$

AOP of interest (AOP 173)



ctd →

AO = Lung fibrosis associated pathways

- Lung fibrosis-associated pathway$_1$
- Lung fibrosis-associated pathway$_2$
- ...
- ...
- ...
- Lung fibrosis-associated pathway$_k$

↓

	1d p.e.	28d p.e.
AOP pathway$_1$	median$BMDt_{ENMn,\ 1,\ 1d}$	median$BMDt_{ENMn,\ 1,\ 28d}$
AOP pathway$_2$	median$BMDt_{ENMn,\ 2,\ 1d}$	median$BMDt_{ENMn,\ 2,\ 28d}$
...	...	...
AOP pathway$_m$	median$BMDt_{ENMn,\ m,\ 1d}$	median$BMDt_{ENMn,\ m,\ 28d}$
AOP(10 most sensitive pathways)	median(min(median$BMDt_{ENMn,\ m,\ 1d}$))	median(min(median$BMDt_{ENMn,\ m,\ 28d}$))

Thank you

Tool showcasing supporting material

Risk assessment tool

NanoCommons Risk Assessment Tool

Short description

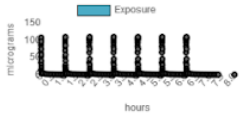
The workflow is a combination of nanoinformatics tools available through the NanoCommons computational infrastructure. This web application, hosted and implemented within Enalos Cloud Platform, estimates the risk of triggering AOP 173 (Lung Fibrosis) in mice due to exposure to 20nm TiO2 engineered nanoparticles.

External exposure: Four different exposure scenarios have been simulated using the GUIDENano tool. The user can alternatively enter a custom-made scenario.

Case 1

45 g (initial mass 3000 kg) of TiO2 (22nm) poured over 7 hours in the NF, with 1 min activity duration every hour. For every hour the mouse stays 90 s in the NF and spends the rest of the time in the FF.

Download timeseries



Internal exposure: Concentration-time profiles for mice are simulated using a PBPK model which has been developed and implemented in the Jaqpot platform. A plot depicting the mass-time profile in the lung is automatically generated.

Weight (5 - 50 grams)

Compute

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration i with Points of Departure (POD) that have been computed using a gene expression analysis worl user can select the POD of interest among different pathways involved in AOP173 or the mediar defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: IL-17 signaling pathway

Time: Median pathway BMDt (1d p.e)

logarithmic scale

*This work project has received funding from European Union Horizon 2020 Programme (H2020) via NanoCommons research infrastructure project under grant agreement n° 731032

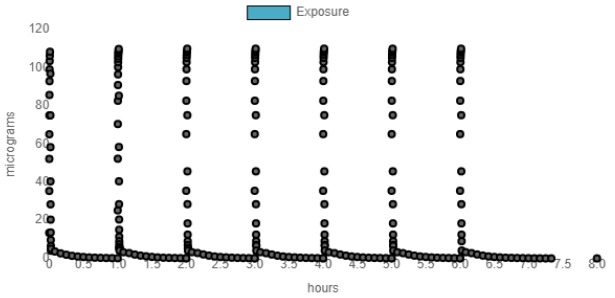
First component: external exposure

External exposure: Four different exposure scenarios have been simulated using the GUIDENano tool. The user can alternatively enter a custom-made scenario.

Case 1

45 g (initial mass 3000 kg) of TiO2 (22nm) poured over 7 hours in the NF, with 1 min activity duration every hour. For every hour the mouse stays 90 s in the NF and spends the rest of the time in the FF.

Download timeseries

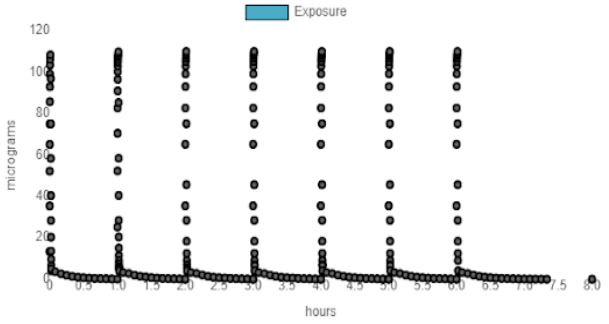


External exposure: Four different exposure scenarios have been simulated using the GUIDENano tool. The user can alternatively enter a custom-made scenario.

Case 1

Case 1
Case 2
Case 3
Case 4
Custom-made scenario

) poured over 7 hours in the NF, with 1
/ hour the mouse stays 90 s in the NF



Second component: internal exposure

Internal exposure: Concentration-time profiles for mice are simulated using a PBPK model which has been developed and implemented in the Jaqpot platform. A plot depicting the mass-time profile in the lung is automatically generated.

Weight (5 - 50 grams)

Compute

Third component: risk assessment

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: IL-17 signaling pathway

Time: Median pathway BMDt (1d p.e)

logarithmic scale

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: IL-17 signaling pathway

- IL-17 signaling pathway
- Cytokine-cytokine receptor interaction
- Chemokine signaling pathway
- NOD-like receptor signaling pathway
- PPAR signaling pathway
- Pathways in cancer
- AOPmedianBMDt

Time

logarithmic scale

Pathways: IL-17 signaling pathway

Time: Median pathway BMDt (1d p.e)

- Median pathway BMDt (1d p.e)
- Median pathway BMDt (28d p.e)

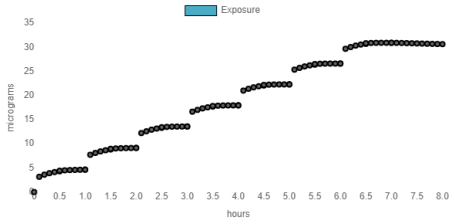
logarithmic scale

Scenario 1: 45g of TiO_2 for 40g mouse

Internal exposure: Concentration-time profiles for mice are simulated using a PBPK model which has been developed and implemented in the Jaqpot platform. A plot depicting the mass-time profile in the lung is automatically generated.

Weight (5 - 50 grams) 40

Compute



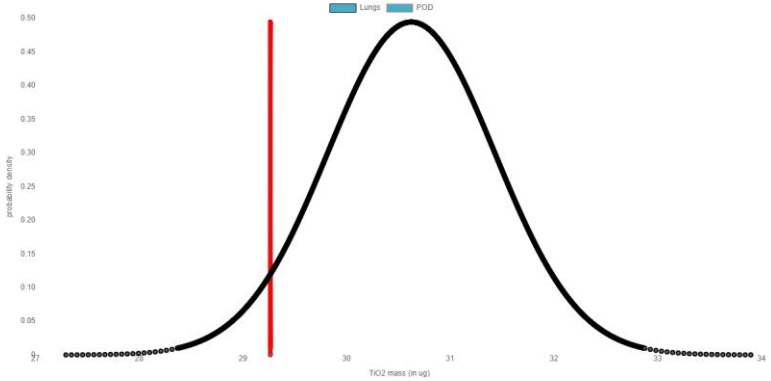
Resulting TiO2 mass – time profile for the simulated exposure setting

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: Chemokine signaling pathway

Time: Median pathway BMDt (1d p.e)

logarithmic scale



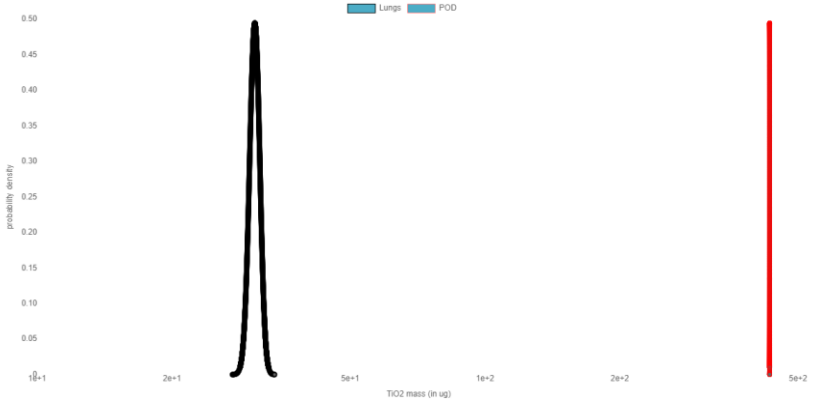
POD and TiO2 mass probability density function (PDF) intersect: risky scenario

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: Chemokine signaling pathway

Time: Median pathway BMDt (28d p.e)

logarithmic scale



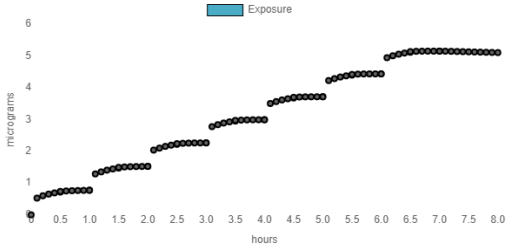
The same pathway for the same exposure is not activated 28 days p.e.

Scenario 2: 7.5g of TiO_2 for 40g mouse

Internal exposure: Concentration-time profiles for mice are simulated using a PBPK model which has been developed and implemented in the Jaqpot platform. A plot depicting the mass-time profile in the lung is automatically generated.

Weight (5 - 50 grams) 40

Compute

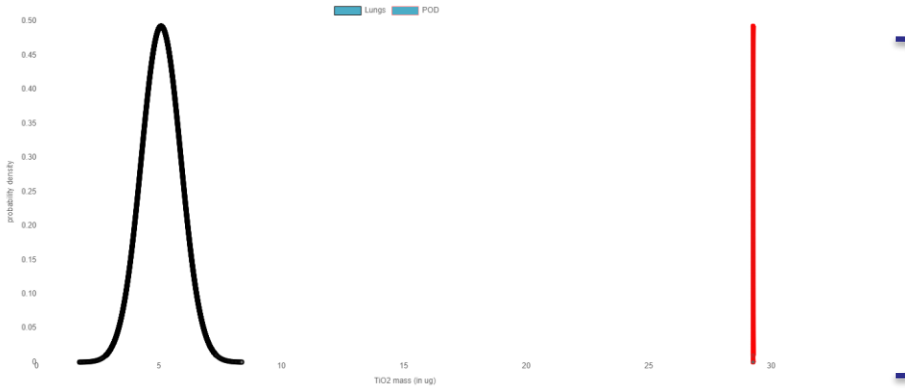


Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: Chemokine signaling pathway

Time: Median pathway BMDt (1d p.e)

logarithmic scale



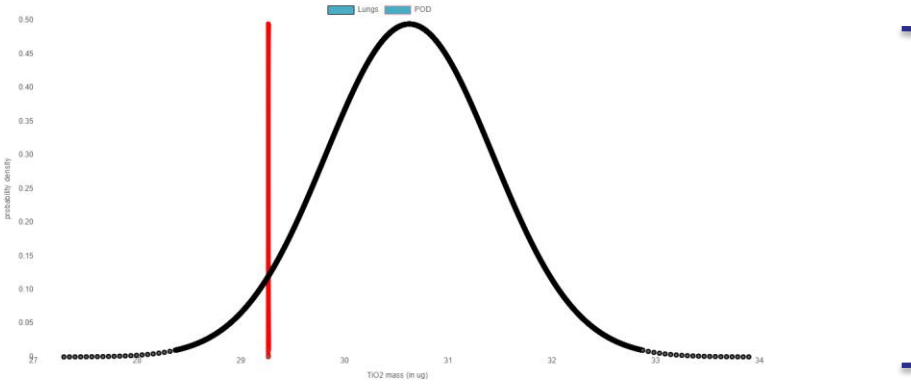
POD is greater than TiO2 mass PDF : no risk

Risk assessment: Is performed by comparing the predicted distribution of TiO2 concentration in the lungs with Points of Departure (POD) that have been computed using a gene expression analysis workflow. The user can select the POD of interest among different pathways involved in AOP173 or the median value that defines the POD of the AOP and short term (1 day) or long term (28 days) effects.

Pathways: Chemokine signaling pathway

Time: Median pathway BMDt (1d p.e)

logarithmic scale



Reminder: Risk Assessment plot for 40g of TiO2

Thank you