Electronic Supplementary Material (ESI) for Environmental Science: Nano.

Supplemental Information

Towards an *in silico* Integrated Approach for Testing and Assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution

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1. PBPK Equations

The equations used in the PBPK model are presented in the following equations, with the descriptions of the parameters given in Table S1. Note that the deposition fractions are calculated using the empirical equations introduced by Hinds (1999). The values of the parameters are presented in Tables S2-S4.

Head airways:

$$\frac{dM_{ha}}{dt} = -k_{ha\_br} \cdot M_{ha} - CLE_{ha} \cdot M_{ha} + IVR \cdot EC \cdot D_{ha}$$

Tracheobronchial region:

$$\frac{dM_{tb}}{dt} = -k_{alpc\_tb} \cdot M_{al,pc} - CLE_{tb} \cdot M_t + IVR \cdot EC \cdot D_{tb}$$

Alveolar region:

$$\frac{dM_{al}}{dt} = k_{lu\_al} \cdot M_{lu,tis} - k_{al\_lu} \cdot M_{al} - (k_{ab,al} \cdot M_{al} - k_{de} \cdot M_{al}) + IVR \cdot EC \cdot D_{al}$$

$$\frac{dM_{al,pc}}{dt} = k_{ab,al} \cdot M_{al} - k_{de} \cdot M_{al} - k_{alpc_{tb}} \cdot M_{al,pc}$$

Lungs:

$$\frac{dM_{lu,cap}}{dt} = C_{ven} \cdot Q_{lu} - C_{lu,cap} \cdot Q_{lu} + \frac{x_{lu} \cdot Q_{lu} \cdot C_{lu,int}}{P_{lu}} - x_{lu} \cdot Q_{lu} \cdot C_{lu,cap}$$

$$\frac{dM_{lu,int}}{dt} = - \frac{x_{lu} \cdot Q_{lu} \cdot C_{lu,int}}{P_{lu}} + x_{lu} \cdot Q_{lu} \cdot C_{lu,cap} - (k_{ab,lu} \cdot V_{lu,int} \cdot C_{lu,int} - k_{de} \cdot M_{lu,pc})$$

$$\frac{dM_{lu,pc}}{dt} = k_{ab,al} \cdot V_{lu,int} \cdot C_{lu,int} - k_{de} \cdot M_{lu,pc}$$

Blood:

$$\frac{dM_{art}}{dt} = C_{lu,cap} \cdot Q_{lu} - C_{art} \cdot \sum_{j = li,spl, ki, ht, br, skel, skin, soft} Q_j - 0.19 \cdot k_{ab,blood} \cdot V_{blood} \cdot C_{art} + 0.19 \cdot k_{de} \cdot M_{blood,pc}$$

$$\frac{dM_{ven}}{dt} = C_{li,cap} \cdot (Q_{lu} + Q_{spl}) - \sum_{j = ki, ht, br, skel, skin, soft} C_{j,cap} \cdot Q_j - C_{ven} \cdot Q_{ven} - 0.81 \cdot k_{ab,blood} \cdot V_{blood} \cdot C_{ven} + 0.81 \cdot k_{de} \cdot M_{blood,pc}$$

$$\frac{dM_{blood,pc}}{dt} = k_{ab,blood} \cdot (0.81 \cdot V_{blood} \cdot C_{ven} + 0.19 \cdot V_{blood} \cdot C_{art}) - k_{de} \cdot M_{blood,pc}$$

Other organs:

$$\frac{dM_{i,cap}}{dt} = C_{art} \cdot Q_i - C_{i,cap} \cdot Q_i + \frac{x_i \cdot Q_i \cdot C_{i,int}}{P_i} - x_i \cdot Q_i \cdot C_{i,cap}$$

$$\frac{dM_{i,int}}{dt} = -\frac{x_i \cdot Q_i \cdot C_{i,int}}{P_i} + x_i \cdot Q_i \cdot C_{i,cap} - (k_{ab,i} \cdot V_{i,int} \cdot C_{i,int} - k_{de} \cdot M_{i,pc})$$

$$\frac{dM_{i,pc}}{dt} = k_{ab,al} \cdot V_{i,int} \cdot C_{i,int} - k_{de} \cdot M_{i,pc}$$

where $i =$ liver, spleen, kidneys, heart, brain, skeleton and soft tissues. The only exceptions to these generic organ equations are the following:

$$\frac{dM_{liver,cap}}{dt} = C_{art} \cdot Q_{liver} + C_{spleen,cap} \cdot Q_{spleen} - C_{liver,cap} \cdot Q_{liver} + \frac{x_{liver} \cdot Q_{liver} \cdot C_{liver,int}}{P_{liver}} - x_{liver} \cdot Q_{liver} \cdot C_{liver,cap}$$

$$\frac{dM_{liver,int}}{dt} = -\frac{x_{liver} \cdot Q_{liver} \cdot C_{liver,int}}{P_{liver}} + x_{liver} \cdot Q_{liver} \cdot C_{liver,cap} - (k_{ab,al} \cdot V_{liver,int} \cdot C_{liver,int} - k_{de} \cdot M_{liver,pc}) - CLE_{hep} \cdot M_{liver,int}$$

$$\frac{dM_{kidneys,cap}}{dt} = C_{art} \cdot Q_{kidneys} - C_{kidneys,cap} \cdot Q_{kidneys} + \frac{x_{kidneys} \cdot Q_{kidneys} \cdot C_{kidneys,int}}{P_{kidneys}} - x_{kidneys} \cdot Q_{kidneys} \cdot C_{kidneys,cap} - CLE_{ur} \cdot M_{kidneys,cap}$$

With:

$$C_{i,int} = \frac{M_{i,int}}{V_{i,int}}$$

$$C_{art} = \frac{M_{art}}{0.19 \cdot V_{blood}}$$

$$C_{ven} = \frac{M_{ven}}{0.81 \cdot V_{blood}}$$

$$C_{i,cap} = \frac{M_{i,cap}}{V_{i,cap}}$$

$$k_{ab,i} = k_{ab0} \cdot \left(1 - \frac{M_{i,pc}}{W_{i,pc} \cdot uptake_i}\right)$$

The subscripts $int, cap\ and\ pc$ stand for tissue interstitium, capillaries and phagocytizing cells, respectively.

Table S1: Extrapulmonary parameters of the rat model.

Parameter	Units	Description
$M_{i,cap}$	ug	Mass in capillaries of organ i
$M_{i,int}$	ug	Mass in tissue interstitium of organ i
k_{ha_br}	h^{-1}	Transfer rate from head airways to brain
k_{alpc_tb}	h^{-1}	Transfer rate from alveolar region to tracheobronchial
k_{lu_al}	h^{-1}	Transfer rate from lungs interstitium to alveolar region
k_{al_lu}	h^{-1}	Transfer rate from alveolar region to lungs interstitium
IVR	m^3/h	Inhalation volume rate
EC	ug/m^3	External concentration
D_{ha}	unitless	Deposition fraction in head airways
D_{tb}	unitless	Deposition fraction in tracheobronchial region

D_{al}	unitless	Deposition fraction in alveolar region
$M_{i,pc}$	ug	Mass in Phagocytizing Cells (PCs) of organ i
x_i	unitless	Permeability coefficient between blood and tissue
P_i	unitless	Partition coefficient between tissue and blood
CLE_i	h^{-1}	Clearance rate (hepatobiliary, urinary, tracheobronchial or from head airways)
Q_i	mL/h	Regional blood flow of organ i
$C_{i,int}$	ug/mL	Concentration in tissue interstitium of organ i
$V_{i,int}$	mL	Interstitial volume of organ i
$C_{i,cap}$	ug/mL	Concentration in the capillaries of organ i
$V_{i,cap}$	mL	Volume of capillaries of organ i
k_{de}	h^{-1}	NM release rater from PCs
k_{pc}	h^{-1}	Maximum uptake rate by PCs
$W_{i,pc}$	ug	Number of PCs in organ i
$uptake$	ug of NPs/cell	Maximum cell uptake capacity

2. Parameter Values

Table S2: Extrapulmonary parameters of the rat model.

Parameter	Units	Lungs	Liver	Spleen	Kidneys	Heart	Brain	Uterus	Skin	RoB	Blood
fV_{tis}[a]	-	0.0050	0.0366	0.0020	0.0073	0.0073	0.0057	0.0023	0.1903	0.7476	-
fQ[b]	-	1.000	0.160	0.014	0.141	0.049	0.020	0.0025	0.058	0.556	1.000
fV_{vas}[c]	-	0.262	0.115	0.282	0.105	0.262	0.05	0.217	0.019	0.026	-
fV_{int}[d]	-	0.188	0.163	0.150	0.200	0.100	0.120	0.120	0.302	0.118	-
N_{pc}[e]	#cells/g tissue	5.8e+06	2.7e+07	1.0e+08	3.2e+07	5.0e+06	5.0e+06	2.2e+07	2.0e+07	3.0e+07	5.0e+06
P[f]	-	1600.0	2.3	3.3	6.4	1.2	0.7	3	0.5	1.5	-
x[g]	-	6.9e-02	6.9e-02	6.9e-02	6.9e-02	6.9e-02	1e-05	6.9e-02	6.9e-02	6.9e-02	-
k_{pc}[h]	mL/h/cell	4e-12	4e-12	4e-12	4e-12	4e-12	4e-12	4e-12	4e-12	4e-12	4e-12
k_{de}[i]	1/h	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19	6.7e-19
CLE[i]	1/h	-	0.21	-	1.18	-	-	-	-	-	-

a: Tissue fraction of body weight. Values from Brown *et al*. (1997) and Bruce (1976). Total blood volume was calculated using the equation of Lee and Blaufox (1985).
b: Tissue fraction of total cardiac output. Values from Brown *et al*. (1997), Malik *et al*. (1976) and Bruce (1976). Total cardiac output was considered as a function of the body weight and was calculated using the respective equation of Brown *et al*. (1997).
c: Fraction of vascular volume. Values from Kawai *et al*. (1998), Watanabe *et al*. (2013) and Brody *et al*. (1974).
d: Fraction of interstitial volume. Values from Kawai *et al*. (1998).
e: Number of PCs per gram of tissue. Liver value from Alpini *et al.* (1994), Lung value from Lehnert *et al*. (1985) and the rest estimated.
f: Tissue:blood partition coefficient. Estimated.
g: Permeability coefficient. Estimated.
h: Maximum uptake rate by PCs. Estimated.
i: Release rate of NMs from PCs. Value from Li *et al*. (2016).
j: Clearance rate (hepatobiliary and renal). Estimated.

Table S3: Extrapulmonary parameters of the human model.

Parameter	Units	Lungs	Liver	Spleen	Kidneys	Heart	Brain	Skin	RoB	Blood
fV_{tis}[a]	-	0.0076	0.0257	0.0026	0.0044	0.0047	0.0200	0.0371	0.8979	-
fQ[b]	-	1.000	0.245	0.015	0.180	0.045	0.12	0.050	0.345	1.000
fV_{vas}[c]	-	0.262	0.115	0.282	0.105	0.262	0.05	0.019	0.026	-
fV_{int}[d]	-	0.188	0.163	0.150	0.200	0.100	0.120	0.302	0.118	-
N_{pc}[e]	#cells/g tissue	2.2e+07	10.4e+07	3.8e+08	1.2e+08	1.9e+07	1.9e+07	7.7e+07	1.2e+08	1.9e+07
P[f]	-	1600.0	2.3	3.3	6.4	1.2	0.7	0.5	1.5	-
x[g]	-	6.9e-02	6.9e-02	6.9e-02	6.9e-02	6.9e-02	1e-05	6.9e-02	6.9e-02	-
k_{pc}[h]	mL/h/cell	5e-12	5e-12	5e-12	5e-12	5e-12	5e-12	5e-12	5e-12	5e-12
k_{de}[i]	1/h	1e-19	1e-19	1e-19	1e-19	1e-19	1e-19	1e-19	1e-19	1e-19
CLE[j]	1/h	-	0.26	-	1.47	-	-	-	-	-

a: Tissue fraction of body weight. Values from Brown *et al*. (1997). Total blood volume was calculated using the equation of Nadler *et al*. (1962).
b: Tissue fraction of total cardiac output. Values from Brown *et al*. (1997) and Bernareggi and Rowland (1991). Total cardiac output was considered as a function of the body weight and was calculated using the respective equation of Nestorov (2001).
c: Fraction of vascular volume. Values from Kawai *et al*. (1998) and Lei *et al*. (2017).
d: Fraction of interstitial volume. Values from Kawai *et al*. (1998) and Lei *et al*. (2017).
e: Number of PCs per gram of tissue. Scaled from the rat animal by multiplying by the ratio of human to rat alveolar macrophages per gram of lung tissue.
f: Tissue:blood partition coefficient. Same as the rat model.
g: Permeability coefficient. Same as the rat model.
h: Maximum uptake rate by PCs. Scaled from the rat model.
i: Release rate of NMs from PCs. Scaled from rat model. j: Clearance rate (hepatobiliary and renal). Scale from rat model.

Table S4: Pulmonary parameters of the rat model. Human values were obtained by allometric scaling of these values, using b = -0.25 (Campbell *et al*., 2012).

Parameter	Units	Value
$\mathbf{CLE_{ua}}^{a}$	1/h	0.0
$\mathbf{CLE_{tb}}^{b}$	1/h	1.5e-01
$\mathbf{k_{alpc\_tb}}^{c}$	1/h	8.0e-04
$\mathbf{k_{lu\_al}}^{d}$	1/h	2.0e-03
$\mathbf{k_{al\_lu}}^{e}$	1/h	2.0e-01
$\mathbf{K_{ha\_br}}^{f}$	1/h	0.0
$\mathbf{N_{pc\_al}}^{h}$	#cells/g tissue	1.0e+07
$\mathbf{k_{pc\_al}}^{i}$	mL/h/cell	7.0e-09

a: Clearance from head airways. Value from Li *et al*. (2016).
b: Clearance rate from tracheobronchial region. Estimated.
c: Transfer rate from alveolar macrophages to tracheobronchial region. Estimated.
d: Transfer rate from lung interstitium to alveolar region. Estimated.
e: Transfer rate from alveolar to lung interstitium. Estimated.
f: Transfer rate from head airways to brain. Value from Li *et al*. (2016).
g: Number of PCs per gram of lung tissue. Value from Semmler-Behnke *et al*. (2007). Human value from Crapo *et al.* (1982).
h: Maximum uptake rate by alveolar macrophages. Estimated.

3. MPPD Input

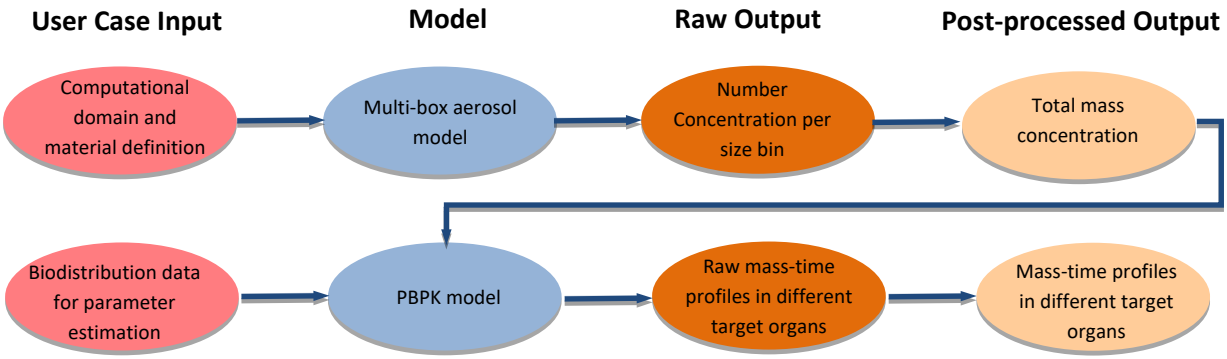
Table S5: Input data provided to MPPD (v.3.04)

Airway Morphometry	
Species	Human
Model	Yeh/Schum Symmetric
FRC (mL)	3300 (male) / 2680 (female)
URT volume (mL)	50 (male) / 3000 (female)
Inhalant Properties	
Density (g/cm^3)	4.26
Aspect Ratio	1 (sphere)
Diameter (μm)	0.022 (CMD)
GSD (diam.)	1
Exposure condition (Variable Exposure)	
Time Indication	Activity Pattern
Hour	8
Aerosol Concentration (mg/m^3)	5.85
Breathing Frequency (min^{-1})	20 (male) / 21 (female)
Tidal Volume (mL)	1250(male) / 990 (female)
Inspiratory Fraction	0.5
Pause Fraction	0
Breathing Scenario	Nasal

4. MODA DOCUMENTS

MODA #1 – An integrated multi-box aerosol and TiO_2 PBPK model

OVERVIEW of the simulation			
1	USER CASE	Coupling of external and internal exposure tools for predicting the deposited dose of TiO_2 nanoparticles in the human respiratory system and the subsequent biodistribution to other internal organs after occupational exposure.	
2	CHAIN OF MODELS	MODEL 1	Multi-box aerosol model for generating the spatiotemporal evolution of a selected nanoparticle concentration in interior spaces.
		MODEL 2	PBPK model for describing the distribution of TiO_2 nanoparticles in humans after inhalation exposure.
3	PUBLICATION ON THE SIMULATION	Tsiros, P., Cheimarios, N., Tsoumanis, A., Jensen, A.C.Ø., Jensen, K.A., Melagraki, G., Lynch, I., H. Sarimveis, H., Afantitis, A. Towards an in silico Integrated Approach for Testing and Assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution. *Environ Sci Nano*.2021 (In review)	
4	ACCESS CONDITIONS	The models have been developed in the NanoSolveIT research infrastructure project under grant agreement nº 814572 and can be freely accessed in https://exposurepbpk.cloud.nanosolveit.eu/	



MODEL 1: Multi-box aerosol model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED AND HOW IT FORMS A PART OF THE TOTAL USER CASE	A multi-box spatio-temporal model of nanomaterial (NM) exposure in a closed environment (room). The model represents a closed room divided into multiple areas (boxes) with each box having its own properties based on the type of the box. The model is driven by NM emissions data, and predicts spatio-temporal environmental concentrations in each box based on the size distribution of the NM particles.
1.2	MATERIAL	carbon black, TiO_2, TiO_2;AgX, user defined materials
1.3	GEOMETRY	Currently assumes spherical NMs.
1.4	TIME LAPSE	Varies from seconds to days depending on the time horizon that the user has specified.
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	Not applicable.
1.6	PUBLICATION ON THIS ONE SIMULATION	A. C. Ø. Jensen, M. Dal Maso, A. J. Koivisto, E. Belut, A. Meyer-Plath, M. Van Tongeren, A. Sánchez Jiménez, I. Tuinman, M. Domat, J. Toftum and I. K. Koponen, Comparison of Geometrical Layouts for a Multi-Box Aerosol Model from a Single-Chamber Dispersion Study, *Environments*, DOI:10.3390/environments5050052.

2	GENERIC PHYSICS OF THE MODEL EQUATION	
2.0	MODEL TYPE AND NAME	Continuum Model.
2.1	MODEL ENTITY	Mass population balances.

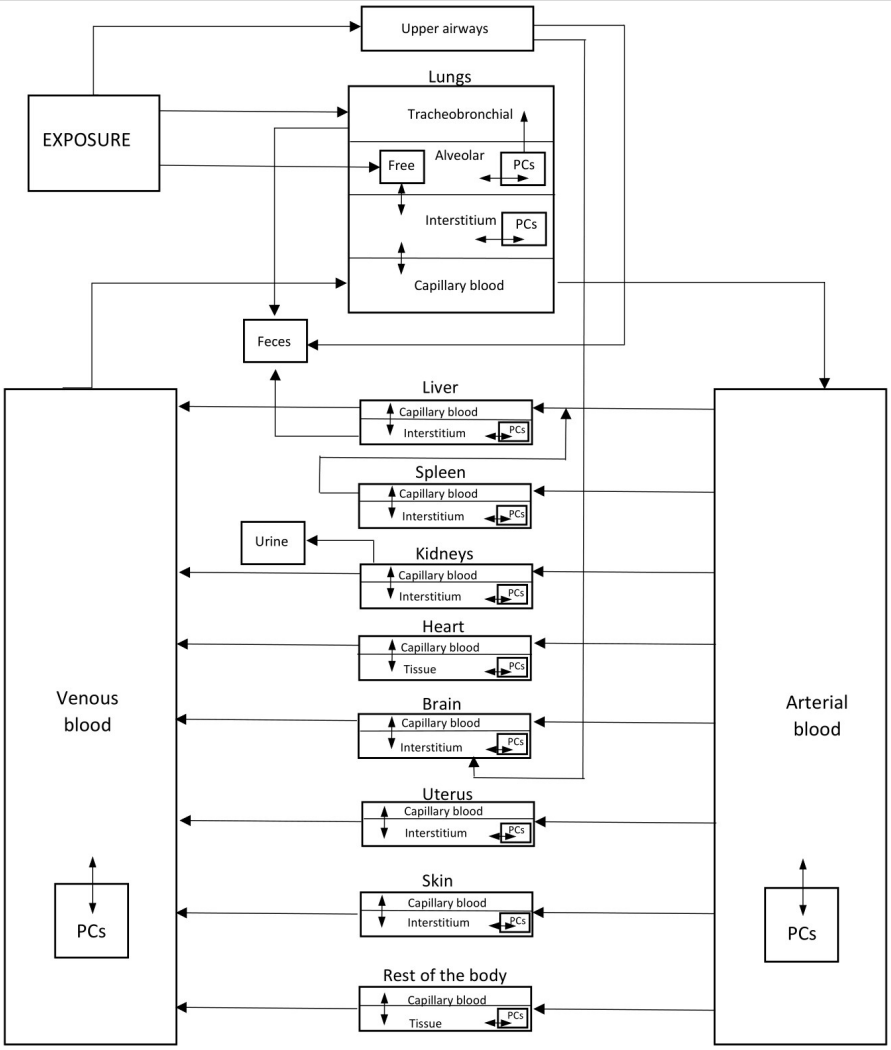
2.2	Model Physics/ Chemistry equation PE's	**Equations**	The model includes a number of physiological and substance-specific parameters which are reported in detail in Section 2.1 of the manuscript, Eq. 1-6.
		Physical quantities for each equation	The model includes a number of physiological and substance-specific parameters which are reported in detail in Section 2.1 of the manuscript.
Materials relations		**MR Equations**	The model includes a number of MR which are reported in detail in Section 2.1, Eq. 1-6.
		Physical quantities/ descriptors for each MR	The model includes a number of MR which are reported in detail in Section 2.1, Eq. 1-6.
2.4	Simulated input	Not applicable.	

3	Specific Computational Modelling Metadata		
3.1	Numerical Solver	Dormand Prince integrator	
3.2	Software tool	Java.	
3.3	Time step	The time step is automatically set by the solver.	
3.4	Computational Representation	Physics Equation, Material Relations, Material	Not applicable
3.5		Boundary Conditions	Not applicable
3.6		additional Solver Parameters	The relative and absolute tolerance are both set to 10^{-6}.

4	POST PROCESSING	
4.1	The processed output is calculated for	The raw output is the NM number concentration-time profile in each bin in cm^{-3}. The final output is the average NM concentration-time profile over all bins in $\mu g/m^3$.
4.2	Methodologies	Not applicable.
4.3	Margin Of Error	The model does not include uncertainty quantification.

MODEL 2: PBPK model

1	Aspect of the User Case/System to be Simulated	
1.1	Aspect of the User Case to be simulated and how it forms a part of the total user case	The model aims to simulate the deposition and biodistribution of TiO_2 nanoparticles in humans after inhalation exposure in an occupational setting. The PBPK model was developed initially for rats, and was calibrated using the biokinetic data of Kreyling et al. (2019) that concerns 20 nm TiO_2 nanoparticles, and was subsequently extrapolated to humans. The model takes as input the external NM concentration (in $\mu g/m^3$) from Model 1, the subject's body weight and a simulation time vector and the output of the model includes the NM mass in each of the model compartments representing the various organs.
1.2	Material	TiO_2
1.3	Geometry	The structural model is similar to that of Li *et al.* (2016). Each organ is represented by three sub-compartments, which are the capillary blood, tissue interstitium and Phagocytizing Cells (PCs) The respiratory system is represented in greater complexity to cover the mechanistic details of inhalation exposure. NMs are excreted via the liver, through the hepatobiliary system, the kidneys, where NMs are excreted to urine, and through tracheobronchial clearance. The tissue compartments that are included in the model are the liver, spleen, kidneys, heart, brain, blood, Rob (Rest of the body), alveolar region, tracheobronchial region, lung interstitium and capillaries and upper airways. The figure below visualises the structural model. PCs indicate PCs (macrophages) which take up and transport NMs.

		
1.4	**TIME LAPSE**	The simulation can span from a few hours (short-term exposure) to several weeks, months or even years (long-term exposure)
1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	The TiO_2 nanoparticles should preferably have a mean diameter close to that of the particles used in the biodistribution study of Kreyling *et al.* (2019) which was used to build the PBPK model, i.e., 20 nm.
1.6	**PUBLICATION ON THIS ONE SIMULATION**	Tsiros, P., Cheimarios, N., Tsoumanis, A., Jensen, A.C.Ø., Jensen, K.A., Melagraki, G., Lynch, I., H. Sarimveis, H., Afantitis, A. Towards an in silico Integrated Approach for Testing and Assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution. *Environ Sci Nano*.2021 (In review)

2	**GENERIC PHYSICS OF THE MODEL EQUATION**		
2.0	**MODEL TYPE AND NAME**	Continuum Model, Physiologically-based Pharmacokinetic (PBPK) model	
2.1	**MODEL ENTITY**	Finite volumes	
2.2	**MODEL PHYSICS/ CHEMISTRY EQUATION PE'S**	**Equations**	The model includes a number of physiological (organism-specific) and substance-specific parameters which are reported in detail in section 1 of the current document.
		Physical quantities for each equation	The model includes a number of physiological (organism-specific) and substance-specific parameters which are reported in detail in Table S1 of the current document.
MATERIALS RELATIONS		**MR Equations**	Not applicable
		Physical quantities/ descriptors for each MR	Not applicable

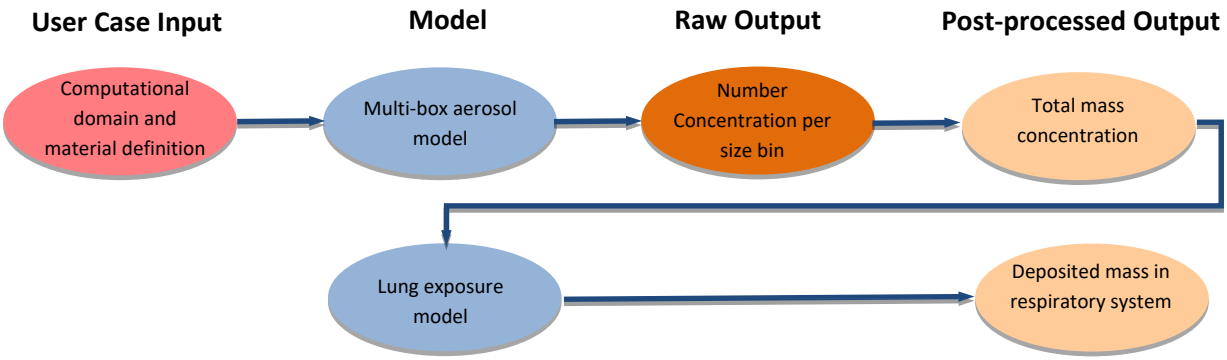
2.4	SIMULATED INPUT	The model receives a concentration-time profile in μg/m^3 which can either be directly provided by the user or simulated using the Multi-box aerosol model.

3	SPECIFIC COMPUTATIONAL MODELLING METADATA		
3.1	NUMERICAL SOLVER	LSODES	
3.2	SOFTWARE TOOL	*DeSolve* package of the *R* programming language.	
3.3	TIME STEP	The time step is automatically set by the solver.	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	Not applicable
3.5	BOUNDARY CONDITIONS		Not applicable
3.6	ADDITIONAL SOLVER PARAMETERS		The relative and absolute tolerance are both set to 10^{-6}.

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT IS CALCULATED FOR	The final output includes, apart from the individual tissue mass-time profiles, the mass-time profile of the lower respiratory system.
4.2	METHODOLOGIES	The mass in the lower respiratory system is equal to the sum of the mass found in the alveolar, tracheobronchial and lung interstitium regions.
4.3	MARGIN OF ERROR	The model does not include uncertainty quantification.

MODA #2 An Integrated multi-box aerosol and Lung exposure model

OVERVIEW of the simulation			
1	USER CASE	Coupling of external and internal exposure tools for predicting the deposited dose of TiO_2 nanoparticles in the human respiratory system and the subsequent biodistribution in other internal organs after occupational exposure.	
2	CHAIN OF MODELS	MODEL 1	Multi-box aerosol model for generating the spatiotemporal evolution of a selected NM concentration in interior spaces.
		MODEL 2	Lung exposure model for calculating the dose of deposited NMs in the respiratory system of human.
3	PUBLICATION ON THE SIMULATION	Tsiros, P., Cheimarios, N., Tsoumanis, A., Jensen, A.C.Ø., Jensen, K.A., Melagraki, G., Lynch, I., H. Sarimveis, H., Afantitis, A. Towards an in silico Integrated Approach for Testing and Assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution. *Environ Sci Nano*.2021 (In review)	
4	ACCESS CONDITIONS	The models have been developed in the NanoSolveIT research infrastructure project under grant agreement nº 814572 and can be freely accessed in https://lungexposure.cloud.nanosolveit.eu/	



MODEL 1: Multi-box aerosol model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED AND HOW IT FORMS A PART OF THE TOTAL USER CASE	A multi-box spatio-temporal model of NM exposure in a closed environment (room). The model represents a closed room divided into multiple areas (boxes) with each box having its own properties based on the type of the box. The model is driven by NM emissions data, and predicts spatio-temporal environmental concentrations in each box based on the size distribution of the NM particles.
1.2	MATERIAL	carbon black, TiO_2, TiO_2;AgX, user defined materials.
1.3	GEOMETRY	Currently assumes spherical NMs.
1.4	TIME LAPSE	Varies from sec to days depending on the time horizon that the user has specified.
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	Not applicable
1.6	PUBLICATION ON THIS ONE SIMULATION	A. C. Ø. Jensen, M. Dal Maso, A. J. Koivisto, E. Belut, A. Meyer-Plath, M. Van Tongeren, A. Sánchez Jiménez, I. Tuinman, M. Domat, J. Toftum and I. K. Koponen, Comparison of Geometrical Layouts for a Multi-Box Aerosol Model from a Single-Chamber Dispersion Study, *Environments*, DOI:10.3390/environments5050052.

2	GENERIC PHYSICS OF THE MODEL EQUATION		
2.0	MODEL TYPE AND NAME	Continuum Model	
2.1	MODEL ENTITY	Mass population balances	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE'S	**Equations**	The model includes a number of physiological and substance-specific parameters which are reported in detail in Section 2.1 of the manuscript.

		Physical quantities for each equation	The model includes a number of physiological and substance-specific parameters which are reported in detail in Section 2.1 of the manuscript.
MATERIALS RELATIONS		**MR Equations**	The model includes a number of MR which are reported in detail in Section 2.1 of the manuscript.
		Physical quantities/ descriptors for each MR	The model includes a number of MR which are reported in detail in Section 2.1, Eq. 1-6.
2.4	**SIMULATED INPUT**	Not applicable.	

3	**SPECIFIC COMPUTATIONAL MODELLING METADATA**		
3.1	**NUMERICAL SOLVER**	Dormand Prince integrator	
3.2	**SOFTWARE TOOL**	Java. Freeware. https://aerosol.cloud.nanosolveit.eu/	
3.3	**TIME STEP**	The time step is automatically set by the solver.	
3.4	**COMPUTATIONAL REPRESENTATION**	**PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL**	Not applicable
3.5		**BOUNDARY CONDITIONS**	Not applicable
3.6		**ADDITIONAL SOLVER PARAMETERS**	The relative and absolute tolerance are both set to 10^{-6}.

4	**POST PROCESSING**	
4.1	**THE PROCESSED OUTPUT IS CALCULATED FOR**	The raw output is the NM number concentration-time profile in each bin in cm^{-3}. The final output is the average NM concentration-time profile over all bins in $\mu g/m^3$.
4.2	**METHODOLOGIES**	Not applicable
4.3	**MARGIN OF ERROR**	The model does not include uncertainty quantification.

MODEL 2: Lung exposure model

1	**ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED**	
1.1	**ASPECT OF THE USER CASE TO BE SIMULATED AND HOW IT FORMS A PART OF THE TOTAL USER CASE**	The model aims at calculating the deposition of NMs in the respiratory system of humans, namely in the Alveolar, Head airways and Tracheobronchial regions. The model takes as input the external NM concentration (in $\mu g/m^3$) and a simulation time vector and the output of the model includes the NM mass in each of the aforementioned respiratory compartments.
1.2	**MATERIAL**	Any NM whose indoor air concentration is known or supported by the Multi-box aerosol model.
1.3	**GEOMETRY**	Currently assumes spherical NMs.
1.4	**TIME LAPSE**	Seconds.
1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	Not applicable
1.6	**PUBLICATION ON THIS ONE SIMULATION**	Tsiros, P., Cheimarios, N., Tsoumanis, A., Jensen, A.C.Ø., Jensen, K.A., Melagraki, G., Lynch, I., H. Sarimveis, H., Afantitis, A. Towards an in silico Integrated Approach for Testing and Assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution. *Environ Sci Nano.*2021 (In review)

2	**GENERIC PHYSICS OF THE MODEL EQUATION**	
2.0	**MODEL TYPE AND NAME**	Continuum Model
2.1	**MODEL**	Algebraic equations

	ENTITY		
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE'S	**Equations**	Algebraic equations reported in detail in section 2.2, Eq. 7-13.
		Physical quantities for each equation	Algebraic equations reported in detail in section 2.2, Eq. 7-13.
MATERIALS RELATIONS		**MR Equations**	Not applicable
		Physical quantities/ descriptors for each MR	Not applicable
2.4	SIMULATED INPUT	The model receives a concentration-time profile in μg/m^3 which can either be directly provided by the user or simulated using the Multi-box aerosol model.	

3	SPECIFIC COMPUTATIONAL MODELLING METADATA		
3.1	NUMERICAL SOLVER	Not applicable.	
3.2	SOFTWARE TOOL	Java. Freeware. https://lungexposure.cloud.nanosolveit.eu/	
3.3	TIME STEP	Steady state.	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	Not applicable
3.5	BOUNDARY CONDITIONS		Not applicable
3.6	ADDITIONAL SOLVER PARAMETERS		Not applicable

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT IS CALCULATED FOR	The final output is the deposition dose of NMs in μg in the Alveolar, Head airways and Tracheobronchial regions of the respiratory system.
4.2	METHODOLOGIES	Not applicable
4.3	MARGIN OF ERROR	The model does not include uncertainty quantification.

5. Figures

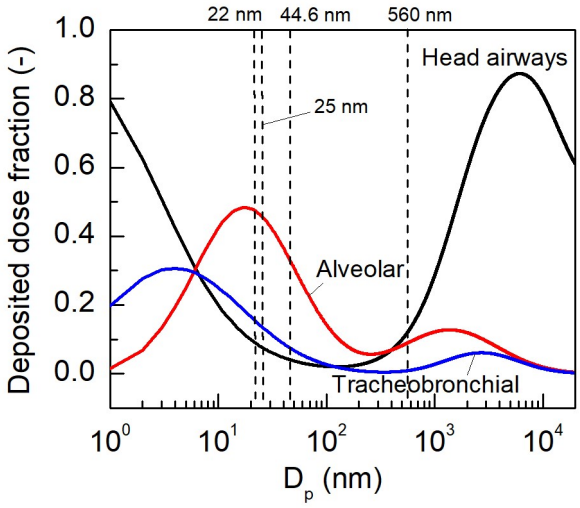


Figure S1. The deposited dose fraction versus D_p calculated previously using the multi-box model. The dashed lines depict the NMs sizes used in this work.

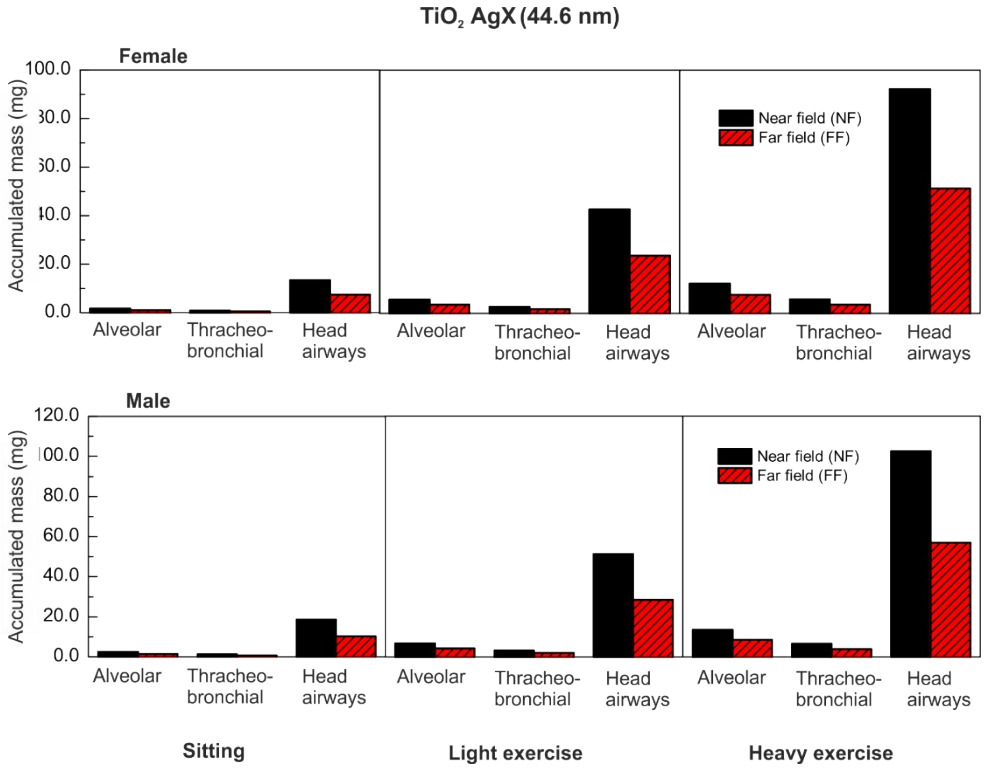


Figure S2. Accumulated mass of particles from the TiO_2:AgX NMs (44.6 nm) emission scenario during a working day when the NMs are being emitted into the NF for 15 out of every 30 minutes.

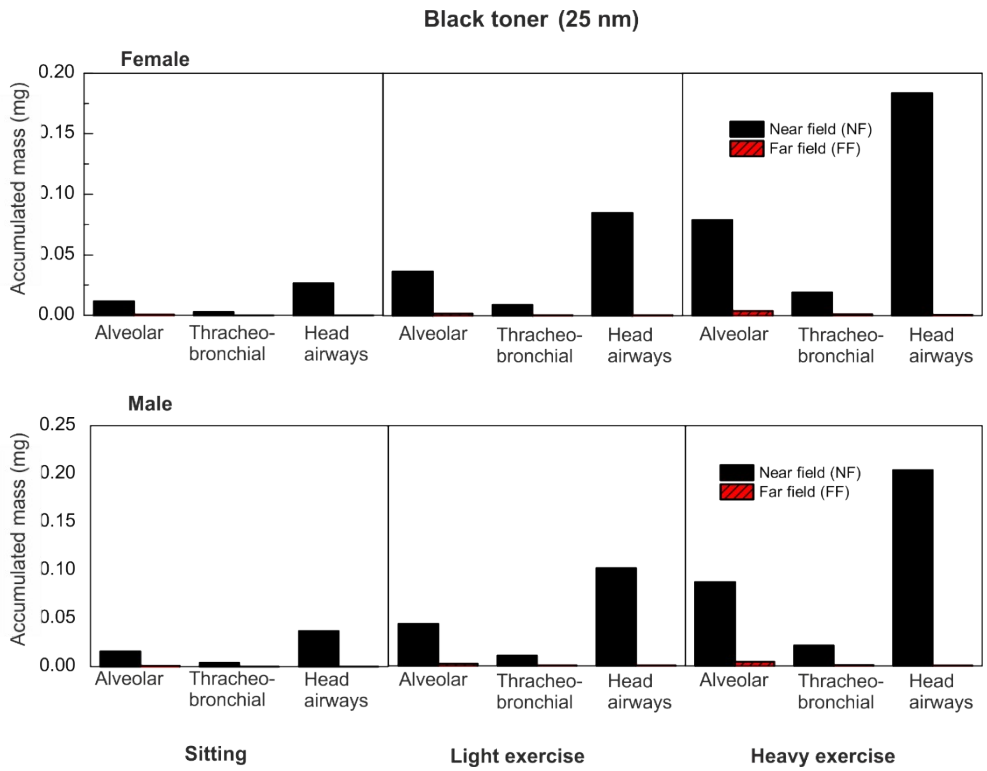


Figure S3 Accumulated mass of the particles from the Black toner (25 nm) emission scenario during a working day, with the NMs being emitted into the NF for 15 out of every 30 minutes.

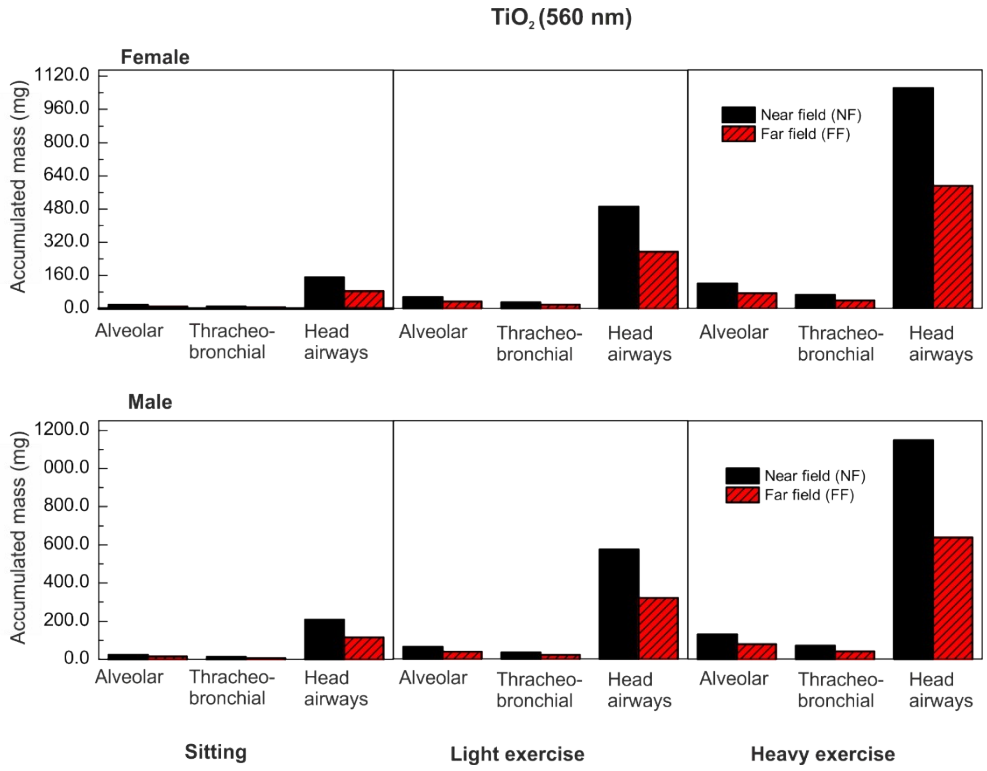


Figure S4. Accumulated mass of the particles from the TiO_2 particles (560 nm) emission scenario during an 8h working day with the NMs being emitted into the NF for 15 out of every 30 minutes.

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