Deliverable Report for Grant Agreement Number 760813

Deliverable 6.7

PATROLS MODA

Due date of deliverable: 31/03/2018
Actual submission date: 26/032018

Lead beneficiary for this deliverable: *QSAR*

Dissemination Level:		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

TABLE OF CONTENTS

1. Description of task

Task 6.2 In vitro dosimetry modelling and experimental design; (IOM, Harvard, QSAR Lab, UNIPI, UNamur, RIVM); M1-33

1. QSAR modelling will be carried out, post-processing, (QSAR Lab, UNamur) to construct a relationship between ENM physico-chemical characteristics with the biological responses and design criteria, using the existing data from earlier projects (e.g. MARINA, SUN, NANOSOLUTIONS) – now, part of the PATROLS database. Later, when PATROLS data become available, they will be used to validate the QSAR model predictions.
2. The multiple path particle dosimetry (MPPD) modelcalculates the deposition fraction of inhaled particles in the different region of the experimental animals (including rat) and human (age 3 month up to adult) lung using the particle physico-chemical characteristics, the respiratory tract architecture, the physiological breathing pattern. The MPPD model has already been developed, user-friendly MPPD software that is available free to the public and used in many EU nanosafety projects. MPPD calculates deposition and clearance simultaneously for up to 4 lognormal distributions In PATROLS, the model will be used to calculate the deposited dose in different regions of the lung for the chosen ENM. Partners in this task have close connections with the developers of the model should adjustments be needed.
3. The fluidic model is a mathematical representation of the fluidic bioreactor prototypes of WP3 and 4 and will be used to inform their design and construction. The model will be parameterised for different bioreactor heights (for identification of optimum basal compartment height which ensures adequate oxygen and optimum apical compartment height for uniform particle deposition), pneumatic pressures (for determining membrane deformation according to its elastic properties and the amount of media to displace) and media flow rates (for shear stress calculations, which are necessary to minimize cell damage). The model will help in determining the optimal size for the lung model device to ensure it is easy to manage under a hood and in an incubator and still has a sufficiently small media height to ensure a physiological lung oxygen supply but with a sufficient height to allow uniform ENM aerosol deposition. To implement model simulations CFD (computational fluid dynamics) will be coupled with mass and energy transport to determine the oxygen concentration and average temperature on the apical and basal side of the bioreactor. For the WP3 bioreactor, we will simulate the formation and deposition of a ENM cloud (i.e aerosol) on a membrane using multiphase modelling. Moreover, we will use FSI (fluid-structure interaction) to evaluate the motion of the flexing membrane as a function of applied pressure. Furthermore, to aid experimentalists in designing more realistic biomimetic in-vitro systems, UNIPI will also develop allometry-scaling based design criteria such that in vitro experiments recapitulate quarter power “metabolically-supported functional scaling” using the methods outlined in Ahluwalia (Scientific Reports, 2017,7). These criteria, specifically cell density and the size of 3D constructs developed in WP3 and 4, will be used as a baseline by experimentalists to design cell culture systems.
4. In FP7 SUN, a kinetics model was developed by IOM to describe the dose-response in simple in vitro models. The model describes the distribution of the deposited dose into the in vitro cell population. IOM will further adapt this model for the more sophisticated in vitro models developed in PATROLS with several interacting cell populations. Harvard will simulate the deposition of ENM in these physiologically relevant in vitro environments using their published model which will help in calculating the exact dose interacting with the cells. A graphical user interface (GUI) will be constructed by IOM as user-friendly front end to the Harvard model to facilitate its use by the experimental partners.
The benchmark dose approach [Slob; Crit Rev Toxicol 2016,2,1-10] will also be carried out, by RIVM, in parallel for comparison.
The MODA (MOdelling DAta) for the 4 models will be submitted as a deliverable by M3 of the project.

2. Description of work & main achievements

2.1 Introduction

Computational modelling methods provide useful tools that support the development of novel materials (including nanomaterials) (Mikolajczyk, et al. 2016; Sikorska, et al. 2016) as well as assist in their risk assessment (Gajewicz, et al. 2012). Wide opportunities offered by these techniques attracted the interest of scientific communities and industry. Benefits from the application of modelling techniques in the risk assessment of nanomaterials and directions for further development were recently highlighted in publications summarizing discussions at the level of the EU NanoSafety Cluster (Puzyn et al., 2018) as well as in the "EU-US Nanoinformatics 2030 Roadmap" worked out within the joined EU-US initiative (https://www.nanosafetycluster.eu/Nanoinformatics2030.html). In parallel, the European Materials Modelling Council (EMMC) declared that, due to significantly reducing R&D time and costs, the modelling would have great impact on innovation and improvement of competitiveness and sustainability of industry (Baas 2017; Gerhard and Christa 2016).

In order to make the modelling methods more useful for industry, in 2017 the EMMC proposed, the standard scheme for collecting the information across the computational models (Baas 2017) named the MOdelling DAta fiche (so called MODA) (Baas 2017). The general objective of the proposed scheme is to introduce a uniform and informative description of the models. In principle, the provided information should be as instructional as possible to make it usable for the industry. It should also allow for linking particular models together and, consequently, using outputs from one model as input data for another one.

Proposed MODA templates were developed separately for: (i) physics-based models, and (ii) data-based models. According to the EMMC ontology, "a physics-based model" refers mainly to models and simulations based on physics/chemistry equations describing different levels of materials composition: (a) electronic models describe the behaviour of electrons as quantum mechanical waves, (b) atomistic models describe the behaviour of atoms, (c) mesoscopic models describe parts of molecules, and (d) continuum models describe the behaviour of a continuum in a finite volume (Baas 2017). "A data-based model" term refers to the approaches that describe relationships between data from the experiment or databases and, so-called, descriptors or predictor variables (Baas 2017).

The main goal of the activity described in Deliverable 6.7 (D6.7) was to verify the applicability of the MODA tools (templates) and ontology proposed by EMMC modelling for models that are under development within the PATROLS project.

2.2 Methodology

The MODA templates provided by the EMMC (Table 1-2) were applied to describe models planned to be developed within PATROLS. In the first step, a model has to be classified a physics-based or data-based one. In the second step, the model has to be described in detail with use of the appropriate MODA template (physics-based MODA template or data-based MODA template). Physics-based models should be documented in four chapters (Table 1), whereas the description of data-based models should include three chapters (Table 2).

Table 1. MODA template for physics-based models (https://emmc.info/moda/)

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*Describe the aspects of the user case textually.* *No modelling information should appear in this box. This case could also be simulated by other models in a benchmarking operation!* *The information in this chapter can be end-user information, measured data, library data etc.* *Simulated input which would have been calculated by another model should not be included (but in chapter 2.4)* *Also, the result of pre-processing necessary to translate the user case specifications to values for the physics variables of the entities can be documented here.*
1.2	MATERIAL	*Describe the chemical composition, and the values used for properties and from which database these are taken. If pre-processing was needed please specify the methodology.*
1.3	GEOMETRY	*Size, form, picture of the system (if applicable)* *Note that computational choices like simulation boxes are to be documented in chapter 3.*
1.4	TIME LAPSE	*Duration of the case to be simulated.* *This is the duration of the situation to be simulated. This is not the same as the computational times to be given in chapter 3.*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*If relevant, please list the conditions to be simulated (if applicable).* *These can be boundary, initial and global conditions.* *E.g. heated walls, external pressures and bending forces.* *Please note that these might appear as terms in the Physics Equations (PE) or as boundary conditions, and this will be documented in the relevant chapters.* *Please specify the values used for parameters and from which database these are taken. If pre-processing was needed please specify the methodology.*
1.6	PUBLICATION ON THIS DATA	*Publication documenting the simulation with this single model (if available and if not already included in the overall publication).*

2	GENERIC PHYSICS OF THE MODEL EQUATION		
2.0	MODEL TYPE AND NAME	*Model type and name **chosen from RoMM content list** (the PE).* *Please do not insert any other text although an indication of the Materials Relation (MR) is allowed.*	
2.1	MODEL ENTITY	*The entity in this materials model is <finite volumes, grains, atoms, or electrons>*	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE	**Equation**	*Name, description and mathematical form of the PE* *In case of tightly coupled PEs set up as one matrix, which is solved in one go, more than one PE can appear.*
		Physical quantities	*Please name the physics quantities in PE, these are parameters (constants, matrices) and variables that appear in the PE, like wave function, Hamiltonian, spin, velocity, and external force.* *Please specify the values used for parameters and from which database these are taken. If pre-processing was needed please specify the methodology.*
2.3	MATERIALS RELATIONS	**Relation**	*Please give the name of the material relation and which PE it completes.*
		Physical quantities/ descriptors for each MR	*Please give the name of the physics quantities, parameters (constants, matrices) and variables that appear in the MR(s)* *Please specify the values used for parameters and from which database these are taken. If pre-processing was needed please specify the methodology.*
2.4	PHYSICS FORMULATION OF THE CONDITIONS	*Please give the physics equations used to express the conditions (e.g. thermostats in MD)*	
2.5	SIMULATED INPUT	*Please document the simulated input and with which model it is calculated.* *This box documents the interoperability of the models in case of sequential or iterative model workflows. Simulated output of the one model is input for the next model. Thus, what you enter here in 2.4 will also appear in 4.1 of the model that calculated this input.* *If you do simulations in isolation, then this box will remain empty.*	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*Please give name and type of the solver* *e.g. Monte Carlo, SPH, FE, …iterative, multi-grid, adaptive,…*	
3.2	SOFTWARE TOOL	*Please give the name and if this is your own code, please specify if it can be shared with a link to website/publication.*	
3.3	TIME STEP	*If applicable, please give the time step used in the solving operations.* *This is the numerical time step, and this is not the same as the time lapse of the case to be simulated (see 1.4)*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*Computational representation of the physics equation, materials relation and material.* *There is no need to repeat user case info.* *"Computational" means that this only needs to be filled in when your computational solver represents the material, properties, equation variables, in a specific way.*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*If applicable.* *Please note that these can be translations of the physical boundary conditions set in the user case or they can be pure computational.*	
3.6	ADDITIONAL SOLVER PARAMETERS	*Please specify pure internal numerical solver details (if applicable), like* • *Specific tolerances* • *Cut-offs, convergence criteria* • *Integrator options*	

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*Please specify the post processed output.* *If applicable then specify the entity in the next model in the chain for which this is calculated: electrons, atoms, grains, larger/smaller finite volumes. If systematic coarse graining is used, please specify.* *In case of homogenisation, please specify the averaging volumes.* *Output can be calculated values for parameters, new MR and descriptor rules (data-based models)*
4.2	METHODOLOGIES	*Please describe the mathematics and/or physics used in this post-processing calculation.* *In homogenisation this is volume averaging. But also physics equations can be used to derive e.g. thermodynamics quantities or optical quantities from Quantum Mechanic raw output.*
4.3	MARGIN OF ERROR	*Please specify the margin of error (accuracy in percentages) of the property calculated and explain the reasons to an industrial end-user.*

Table 2. MODA template for data-based models (https://emmc.info/moda/)

1	USER CASE		
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*Briefly describe context/purpose of the modelling.*	
1.2	MATERIAL	*Specify, what kind of material will be used for model development (provide references).*	
1.3	STRUCTURE	*Specify, what information about the material's structure is required.*	
1.4	TIME LAPSE	*If applicable, please give the time perspective used in the simulation.*	
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Please specify any relevant external conditions for manufacturing/using/studying the modelled nanomaterials (e.g. dispersion, properties of the system).*	
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*Refer to a publication documenting the simulation with this single model (if available and if not already included in the overall publication).*	

2	THE DATA-BASED MODEL		
2.1	MODEL NAME/TYPE	*Model name/type*	
2.2	DATABASE AND TYPE	INPUTS	• *Provide name, short description and type (continuous, nominal, ranks) of the parameters/variables/data used as model input(s).* • *Specify any data pre-processing procedures.* • *Specify the source of input data (e.g. database).*
		OUTPUTS	• *Provide name, short description and type (continuous, nominal, ranks) of the parameters/variables/data generated as the model output(s).* • *Specify any data post-processing procedures* • *Specify the source of output data (e.g. database) used for training/validation, if any.*
2.3	EQUATION(S)	HYPOTHESIS	*Specify the working hypotheses to be verified/described by the model.*
		PHYSICAL QUANTITIES	*Please name the quantities that are parameters (constants, matrices) and variables that appear in the model's equation(s)*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*Specify mathematical/statistical method of modelling (e.g. multiple linear regression, decision tree)*
3.2	SOFTWARE TOOL	*Provide name of the software to be used. If this is your own code, please specify, whether it can be shared (with a link to website/publication).*
3.6	MARGIN OF ERROR	*Please define the variables/parameters used for assessing model quality and briefly describe the validation procedure.*

2.3 Results and discussion

2.3.1. Descriptions of individual models

The PATROLS MODAs were prepared with using templates originally developed by the EMMC (Tables 1-2). There are twelve types of models that will be developed in the PATROLS project. Six models were classified as physics-based models, whereas the other six – as data-based models.

The physics-based models are:

- Computational Fluid Dynamics (CFD) transport models,
- Fluidynamics models,
- Physiologically-Based PharmacoKinetic models (PBPK),
- Multiple-Path Particle Dosimetry (MPPD) models,
- Molecular structure models,
- Allometric scaling models.

The data-based models are:

- Benchmark Dose Models (BDM),
- Structure-Activity Relationships (SAR) models,
- Predictive ToxiGenomics Space models (PTGS),
- *In vitro-in vivo* scaling (IVIVE) models,
- Quantitative Toxicity-Toxicity Relationships (QTTR) models,
- Quantitative trait-based models.

Models will be developed in order to include in their applicability domains, as far as possible, nanomaterials listed in the PATROLS project (TIER 1). Detailed description of each model type is provided in the Appendix_PATROLS MODA.

2.3.2. Connections between the models. MODAs development

The modelling techniques listed in Section 2.3.1. were applied to develop two MODAs: **MODA #1** referring to human toxicity models (Figure 1) and **MODA #2** referring to ecotoxicity models (Figure 2):

- The **MODA #1** consists of ten interconnected models, which can be clustered into three groups: (1) models based on *in vitro* in isolation data, (2) models based on *in vivo* data, and (3) models that scale the response from lower organisms/cell lines to humans. The output of these models will be applied to predict the adverse effect caused by realistic doses of nanomaterials for human.

- The **MODA #2** contains four models that predict environmental toxicity of nanomaterials based on their structures including information about the influence of the organism morphology on the measured effects.

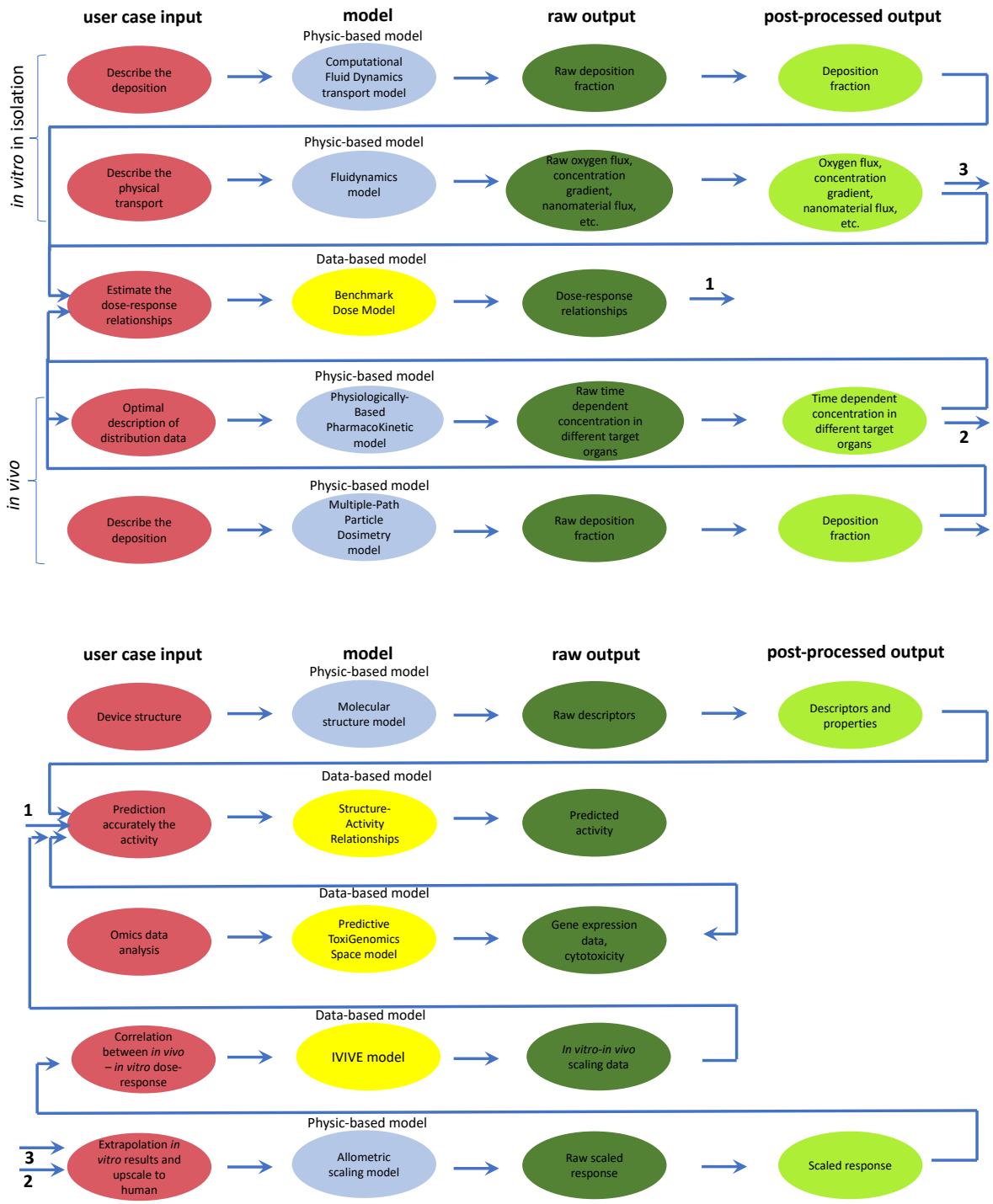


Figure 1. MODA #1 for human toxicity models. (1) Models based on *in vitro* in isolation data, (2) models based on *in vivo* data, and (3) models that scale the response from lower organisms/cell lines to human (red – user case input; blue – physic-based model; yellow – data-based model, dark green – raw output; green – post-processed output).

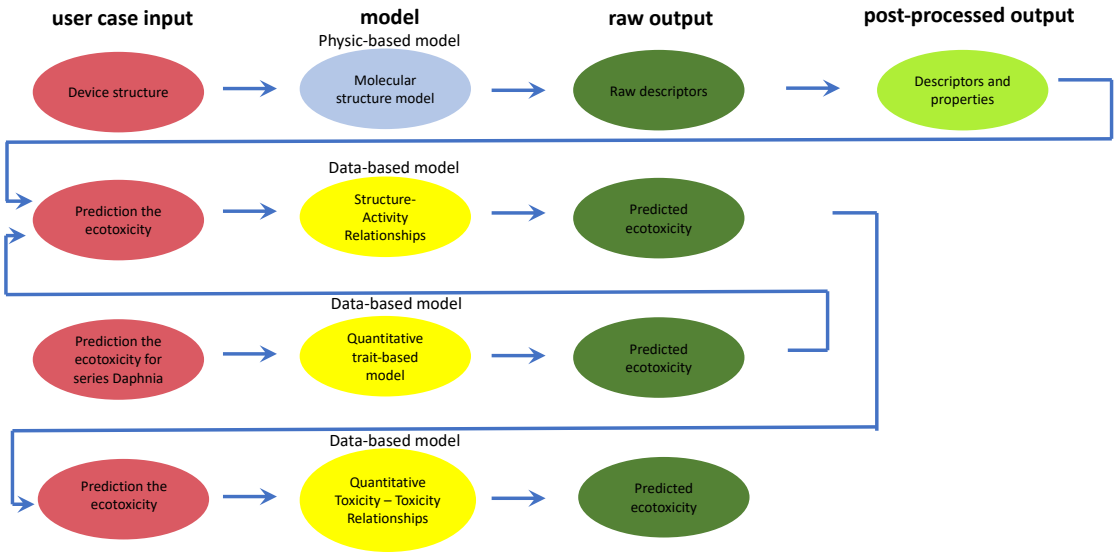


Figure 2. MODA #2 for ecotoxicity models (red – user case input; blue – physic-based model; yellow – data-based model, dark green – raw output; green – post-processed output).

2.3.3. Discussion

The idea of standardising the description of computational models, as it was proposed by EMMC, is highly appreciated. According to the proposed scheme, all models should be described with the same templates, which makes them more transparent and instructional for various users (stakeholders). In consequence, the modelling would be more frequently applied by the industry for developing new nanomaterials using a safe-by-design approach. Additionally, the MODA illustrates connections between particular models and ensures an exchange of data between computational approaches utilized in the project.

Since the main challenge of PATROLS is to deliver standardized tools to predict adverse effects caused by nanomaterial exposure to humans and the environment, the description of PATROLS models according to the standardized EMMC MODA scheme was feasible. Moreover, the input-output relations between the models allowed illustration of the data flow and helped harmonise the modelling work planned within the project.

All PATROLS models foreseen were attempted to be described using the templates provided by EMMC. However, according to the feedback provided by the participants of this exercise, both the ontology and the templates require further work and adjustments in order to be able to properly incorporate the specifics of the models developed in the PATROLS project.

Participants of this exercise raised several issues related to the filling of the templates and concluded that the original instructions provided in the templates require additional clarification. Another concern was related to the level of details that should be provided in the template. We decided to deliver the MODAs based on general model descriptions, because it obviously is not possible yet to describe, at this early stage of the project (the MODA is supposed to be delivered in month 3), individual models that will be developed in detail. When all models will be developed (more significant information related for individual models will be available), the PATROLS MODA should be updated.

The “Review of Materials Modelling (RoMM)” (Baas 2017) published by EMMC provides a detailed description of “physics-based models”. However, the taxonomy proposed for this class of models (i.e.: electronic, atomic, mesoscopic, continuous) may be inadequate, when considering models developed in PATROLS. For example, it was not clear for us what we should describe as a ‘geometry’, since we are not focusing on the properties of materials. We noticed that the ontology developed by EMMC refers mainly to predicting properties of the materials based on the materials models at various scales (e.g. electronic, atomistic), whereas models developed in PATROLS predict properties of the materials based on models of various phenomena (e.g. metabolism, physiological transport). These are not only physical phenomena, but also biological and physiological ones. In our opinion, the performed exercise would open up the discussion on possible revisions of “physics-based models” definition and, possibly, on the extension of the classification of models for new types of models (e.g. “biology-based models” or “physiology-based models”).

Surprisingly, “data-based models” and the related ontology are discussed in RoMM at a general level with providing only few examples of such models. Since six types of “data-based models” are planned to be developed in PATROLS, our project would in the future contribute to the debate on possible extension of the templates applicability and to the further discussion on models’ ontology and classification.

3. Deviations from the Workplan

The MODA should deliver information about the linkage between models, the flow of data as well as knowledge on the models that will be exchanged within the project. Thus, MODA should be provided for each particular model to be developed in the project. However, since the models development is a vital contribution to and an important deliverable of PATROLS, it is not possible yet to describe the final models in sufficient detail in such an early stage. For example, to develop structure-activity models, detailed information about the experimental data availability is required to decide, which calibration method should be used. Therefore, at this stage (M3), we proposed only general MODAs, related to the main types of models to be developed in PATROLS. However, the work should be updated near the end of the project, when all necessary information is complete.

4. Performance of the partners

PATROLS MODA was prepared with collaboration of all PATROLS modelling groups, Table 3. Each group was asked to prepare a description of the model according to the EMMC templates.

Table 3. Partners delivering MODA

PARTNER	RESPONSIBILITIES
IOM	• Delivering MODA for MPPD model • Delivering MODA for IVIVE model • Delivering MODA for CFD transport model
UL	• Delivering MODA for Quantitative trait-based model
UNIPI	• Delivering MODA for Fluidynamics model • Delivering MODA for Allometric scaling model
RIVM	• Delivering MODA for PBPK model • Delivering MODA for BMD model
MISVIK	• Delivering MODA for PTGS model
QSAR LAB	• Developing templates for PATROLS MODA • Delivering MODA for Molecular structure model • Delivering MODA for Structure-activity model • Delivering MODA for QTTR model • Delivering the deliverable D6.7

All Partners fulfilled their tasks in satisfactory time and quality and the Steering Board deems this deliverable to be satisfactorily fulfilled.

5. Conclusions

The applicability of the MODA templates and ontology proposed by EMMC was verified and several issues were highlighted to be further discussed in order to make this tool more suitable for biology-based, physiology-based and data-based models.

During the exercises on MODAs, the following challenges have been faced:

- The original instructions provided in the templates require additional clarification.
- The taxonomy proposed by EMMC for physics-based models (i.e.: electronic, atomic, mesoscopic, continuous) may be inadequate, when considering models developed in PATROLS.
- The applicability of MODA templates for “data-based models” needs to be extended.
- It would be beneficial to update MODAs at the end of the project to include all individual models developed within the project and their mutual connections.

6. References

Baas, Anne F de, 2017, What makes a material function? Let me compute the ways... Luxemburg: EMMC.

Gajewicz, A., Rasulev, B., Dinadayalane, T. C., Urbaszek, P., Puzyn, T., Leszczynska, D., Leszczynski, J., 2012, Advancing risk assessment of engineered nanomaterials: Application of computational approaches. Advanced Drug Delivery Reviews 64(15):1663-1693.

Goldbeck, G., Court Ch., 2016, The econimic impact of materals modelling. Indicators, Metrics, and Industry Survey.: EMMC.

Mikolajczyk, A., Malankowska, A., Nowaczyk, G., Gajewicz, A., Hirano, S., Jurga, S., Zaleska-Medynska, A., Puzyn, T., 2016, Combined experimental and computational approach to developing efficient photocatalysts based on Au/Pd-TiO2 nanoparticles. Environmental Science-Nano 3(6):1425-1435.

Puzyn, T., Jeliazkova, N., Sarimveis, H., Marchese Robinson, R.L., Lobaskin, V., Rallo, R., Richarz, A.N. Gajewicz, A., Papadopulos, M.G. Hastings, J., Cronin, M.T.D. , Benfenati, E., Fernández A., 2018, Perspectives from the NanoSafety Modelling Cluster on the validation criteria for (Q)SAR models used in nanotechnology. Food and Chemical Toxicology 112:478-494.

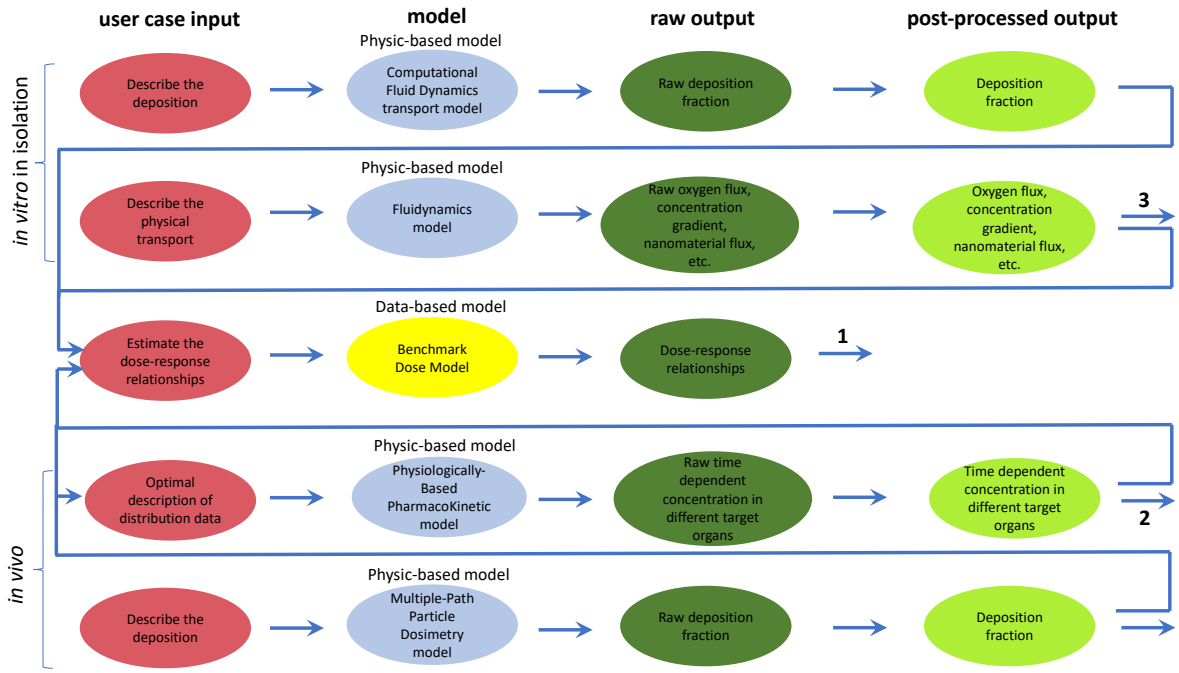
Sikorska, C., Gajewicz, A., Urbaszek, P., Lubinski, L., Puzyn, T., 2016, Efficient way of designing fullerene derivatives based on simplified DFT calculations and QSPR modeling. Chemometrics and Intelligent Laboratory Systems 152:125-133.

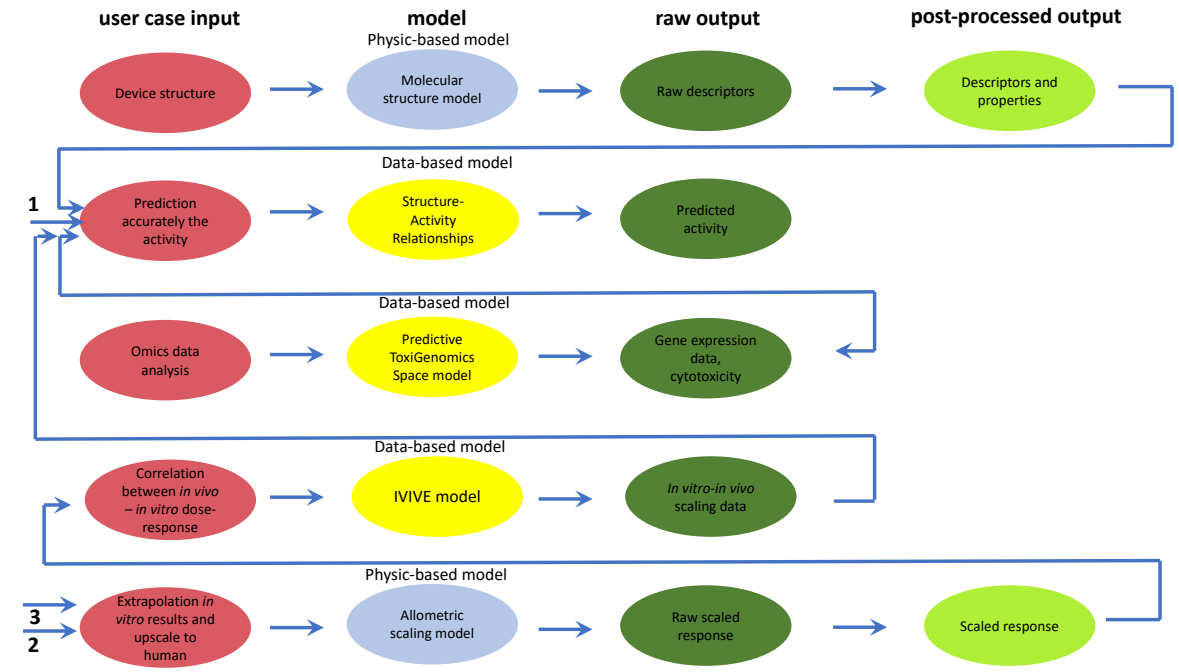
APPENDIX_PATROLS MODA (760813)

Summary of the project

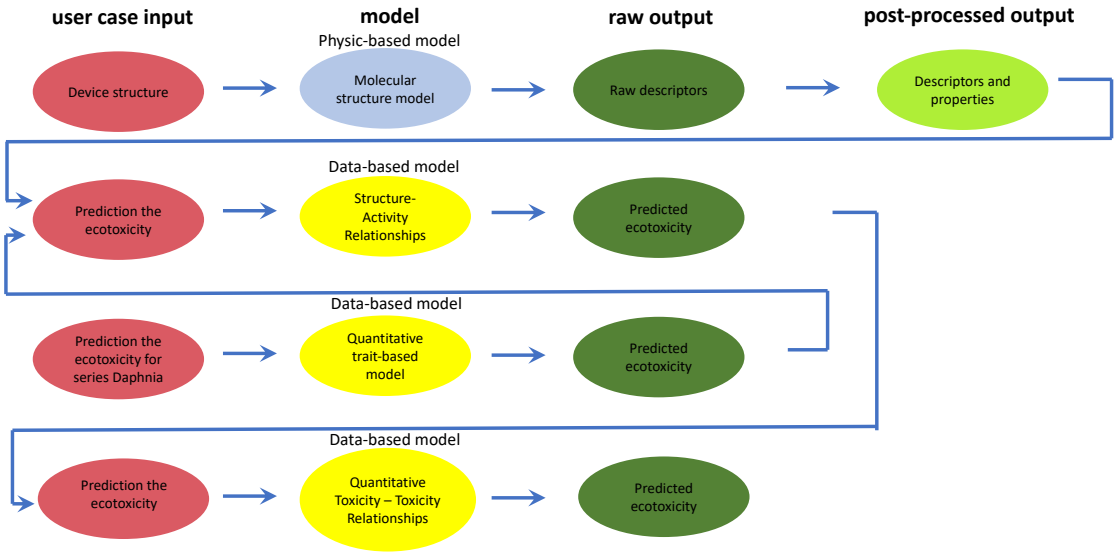
PATROLS main objective is to establish and standardize a battery of innovative, next generation physiologically anchored, hazard assessment tools that more accurately predict adverse effects caused by long-term, low dose ENM exposure in human and environmental systems to support regulatory risk decision making.

MODA #1 for human toxicity models





MODA #2 for ecotoxicity models



Project Acronym and Number: PATROLS 760813

Project title: Physiologically anchored tools for realistic nanomaterial hazard assessment.

Start and End Dates: from 1/1/2018 till 30/6/2021

EU Contribution: 12 714 180 €

Coordinator: Shareen Doak, s.h.doak@swansea.ac.uk

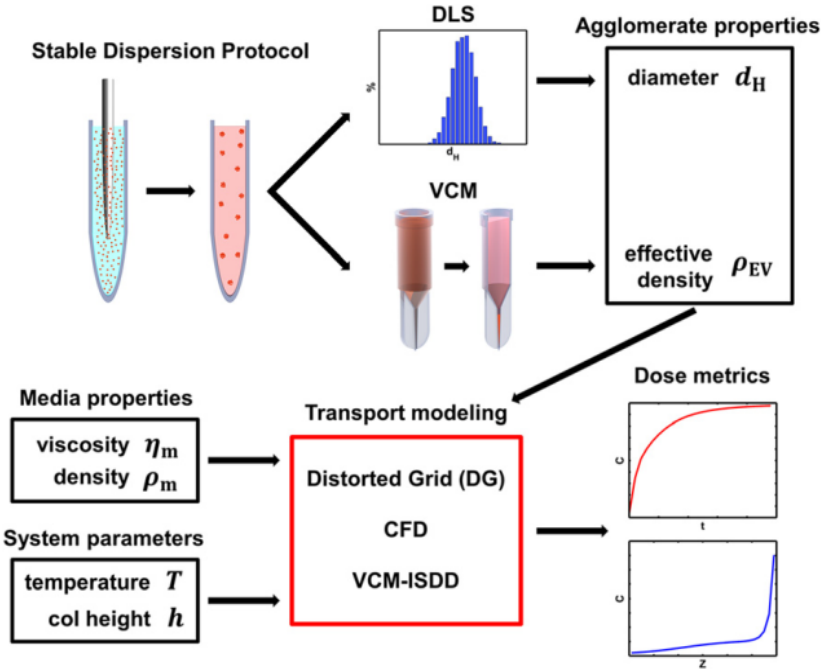
Modeller(s): Lang Tran, lang.tran@iom-world.org
Willie Peijnenburg, willie.peijnenburg@rivm.nl
Tomasz Puzyn, t.puzyn@qsarlab.com
Arti Ahluwalia, arti.ahluwalia@unipi.it
Keld A. Jensen, kaj@nfa.dk
Christiaan Dalmaar, Christiaan.delmaar@rivm.nl
Roland Grafström, grafstromrc@gmail.com

MODA

PATROLS: Advanced Tools for NanoSafety Testing

OVERVIEW of the simulation				
1	**USER CASE**	*Standardize battery of innovative, next generation physiologically anchored, hazard assessment tools that more accurately predict adverse effects caused by long-term, low dose ENM exposure in human and environmental systems to support regulatory risk decision making.*		
2	**CHAIN OF MODELS**	**MODA #1** for human toxicity models	**MODEL 1**	*Computational fluid dynamics transport model*
			MODEL 2	*Fluidynamics model*
			MODEL 3	*Benchmark dose model*
			MODEL 4	*Physiologically-based pharmacokinetic model*
			MODEL 5	*Multiple-Path Particle Dosimetry Model*
			MODEL 6	*Molecular structure model*
			MODEL 7	*Structure-Activity Model*
			MODEL 8	*Predictive Toxigenomics Space model*
			MODEL 9	*In vitro – in vivo model*
			MODEL 10	*Allometric scaling model*
		MODA #2 for ecotoxicity models	**MODEL 6**	*Molecular structure model*
			MODEL 7	*Structure-Activity Model*
			MODEL 11	*Quantitative trait-based model*
			MODEL 12	*Quantitative toxicity-toxicity model*
3	**PUBLICATION PEER-REVIEWING THE DATA**			
4	**ACCESS CONDITIONS**			
5	**WORKFLOW AND ITS RATIONALE**	*There are two MODAs developed.* *MODA 1 refers to human dose-response models and contains ten models. There are: (i) models based on in vitro in isolation data, (ii) models based on in vivo data, and (iii) models that scaling dose-responses for human. The output of these models will be, then applied to predict adverse effect cause by realistic doses of ENM for human.* *MODA 2 contains four models that predict environmental toxicity of nanomaterials based on their structures including information about the influence of the organism morphology on the measured effects.*		

MODEL 1: Computational fluid dynamics transport model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*Here we present the use of the three-dimensional computational fluid dynamics (CFD) transport model to estimate delivered dose metrics for industry-relevant Engineered Nanomaterials Materials (ENM) suspended in culture media. The model allows simultaneous modelling of full size distributions for polydisperse ENM suspensions and provides deposition metrics as well as concentration metrics over the extent of the well. The model also emulates the biokinetics at the particle-cell interface and allows modelling of ENM dissolution over time.*
1.2	MATERIAL	*Not applicable*
1.3	GEOMETRY	*The model provides practical and robust tools for obtaining accurate dose metrics and concentration profiles across the well, for high-throughput screening of ENMs. Accurate nano-dosimetry simulation requires: 1) standardized dispersion preparation protocols, 2) detailed colloidal suspension characterization including size and effective density of formed agglomerates, and 3) computational modelling of transport based on agglomerate, media and system properties. Standardized dispersion protocol to maximize stability of agglomeration state includes sonication of nanomaterial in deionized water to particle-specific critical dispersion sonication energy (DSEcr), followed by dilution into final application media. Dispersions are analysed by DLS to determine agglomerate hydrodynamic diameters, and by VCM to determine agglomerate effective density. Transport modelling to determine dose metrics requires dH from DLS and ρEV from VCM, as well as media properties (viscosity, ηm and density, ρm) and system parameters (temperature, T and media column height, h). Available computational transport models include VCM-ISDD, computational fluid dynamics (CFD).* *Possible output dose metrics include exposure concentrations in the cell microenvironment at the bottom of the well (including mass, surface area and particle number), fractional or absolute deposition (in terms of mass, surface area and particle number), as well as concentration as a function of vertical position within the well (concentration profile).*  *Taken from DeLoid et al (2015). Advanced computational modelling for in vitro nanomaterial dosimetry. Particle and Fibre Toxicology. 12:32*

1.4	**TIME LAPSE**	*Duration of simulation is the same as in vitro experiments (e.g. 24hr or 48hr).*
1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	*The model will simulate the time course of the transport of the ENM in an in vitro well. It will estimate the ENM dose reaching the cells (at the bottom of the well).*
1.6	**PUBLICATION ON THIS DATA**	*Thomas et al (2018). ISD3: a particokinetic model for predicting the combined effects of particle sedimentation, diffusion and dissolution on cellular dosimetry for in vitro systems. Particle and Fibre Toxicology 15:6*

GENERIC PHYSICS OF THE MODEL EQUATION

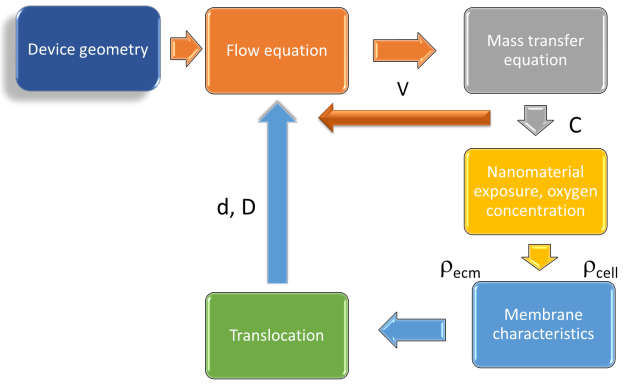
2.0	**MODEL TYPE AND NAME**	*Differential Equations and Partial Differential Equations*	
2.1	**MODEL ENTITY**	*The entity in this materials model is finite volumes*	
2.2	**MODEL PHYSICS/ CHEMISTRY EQUATION** **PE**	**Equation**	*The model is described by:* $$\frac{\partial N(D_p;x,t)}{\partial t} = D_{dif}(D_p)\frac{\partial^2 N(D_p;x,t)}{\partial x^2} - V_t(D_p)\frac{\partial N(D_p;x,t)}{\partial x} - \frac{\partial}{\partial D_p}\left(N(D_p;x,t)\frac{\partial D_p}{\partial t}\right)$$ *Where the 2 first terms on the right-hand side represents diffusion and sedimentation processes while the last 2 terms describe dissolution.* *N is the number of particles per unit area;* *D_p is the particle diameter;* *x is the position of the particles in the liquid column* *t is the time since the particles are first introduced to the in vitro system.* *D_{diff} is the diffusion term* $$D_{dif} = \frac{RT}{3N_A\pi\mu D_p};$$ *V_t is the sedimentation term* $$V_t = \frac{g\left(\rho_p - \rho_f\right)D_p^2}{18\mu}$$ *g is the gravitational constant*

		Physical quantities	R is the universal gas constant (in units: J mol^{-1} K^{-1}), N_A is the Avogadro's number, μ is the dynamic viscosity (in units, N s m^{-2}), and T is the temperature of the liquid medium (units of K). *ρ_p and ρ_f are the density of the particles and the liquid media respectively.* *Other physical quantities required to solve the model are:* Liquid media characteristics Media height, L (m) Media volume, V (mL) Media temperature, T (K) Media viscosity, μ(N s/m^2) Media density, ρ_f (g/mL) Surface area, A (m^2) Primary particle size / diameter, d_p (nm) Primary particle density, ρ_p(g/cm^3) Thickness of protein layer, ΔR_c(nm) Effective diameter, $d_{pc} = d_p + 2\Delta R_c$(nm) Effective density, ρ_{pc}(g/cm^3)
2.3	**MATERIALS RELATIONS**	**Relation**	*Not applicable*
		Physical quantities/ descriptors for each MR	*Not applicable.*
2.4	**PHYSICS FORMULATION OF THE CONDITIONS**	*Not applicable*	
2.5	**SIMULATED INPUT**	*Not applicable*	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*PDE numerical solver*	
3.2	SOFTWARE TOOL	*MATLAB*	
3.3	TIME STEP	*Most solvers will feature an adaptive step algorithm in which the time step is automatically optimized based on the scenario.*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*Not applicable*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*Surface area of the in vitro system* *Height of in vitro system*	
3.6	ADDITIONAL SOLVER PARAMETERS	*More equations will be included to describe the dissolution process in more details.*	

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*The dose of particles reaching the bottom of the in vitro system can be converted into different units (such as mass, surface area, etc…)*
4.2	METHODOLOGIES	Dose conversions may be based on geometrical calculations (e.g. converting the mass of a sphere into its surface area based on information on its density and diameter) or using measured material information (e.g. surface area per unit mass).
4.3	MARGIN OF ERROR	*This will depend on the nature of the nanoparticles and will be assessed when the theoretical prediction is compared to experimental results.*

MODEL 2: Fluidynamics model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*The models are used to describe the physical transport of momentum, biomolecules and nanomaterials in a micro-fluidic or milli-fluidic in-vitro system used for culturing cells.* *The results are in the form of wall shear stress values, oxygen concentrations and fluxes, glucose concentrations and fluxes and nanomaterial exposure (nanoparticle flux). It may also be possible to quantify nanomaterial exposure per cell in 3D spheroids.*
1.2	MATERIAL	*The domain material is water at 37°. Its viscosity and density are tabulated. Oxygen concentration is obtained from Henry's law. Cell parameters such as oxygen consumption rate (OCR) and Michaeles Menten constants are from the literature. Nanomaterial physical constants will be from producers. Should the material used to fabricate in-vitro devices be oxygen permeable (e.g. PDMS), this factor will also be considered.*
1.3	GEOMETRY	*This box shows the logical workflow, starting from the geometry of the device to calculation of nanomaterial exposure, shear stress, molecular fluxes. C is concentration of the species in question, V is fluid velocity, ρ_{cell} is cell density, ρ_{ecm} is the density of extracellular matrix or mucus. D is the species diffusion constant in water and d is the thickness of the membrane.* 
1.4	TIME LAPSE	*The studies will be conducted in stationary conditions.*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Conditions to be simulated are: atmospheric dissolved oxygen, media glucose concentration, oxygen and glucose diffusion constants, cell oxygen and glucose consumption rates*

Initial media glucose, mM	C_{Gin}	5 mM
Glucose diffusion constant in water, 37°C	D_G	6.7×10^{-12} m^2/s
Initial oxygen concentration in culture medium mM	$c_{O2,in}$	0.21 mM
Oxygen diffusion in aqueous media	D_{O2}	3×10^{-9} m^2/s
Cellular maximum oxygen, glucose consumption rate	OCR, GCR	4.8×10^{-17} , 8×10^{-18} moles/(cell.s)
Michaelis-Menten constant for oxygen, glucose consumption, mM	K_{mo} , K_{mG}	7.39×10^{-3} , 6×10^{-2} mM

Other conditions to be obtained from experimenters are: inlet flow rate as initial input, cell density, membrane thickness, permeability and porosity. Spheroid

		diameter and cell density in spheroid, nanomaterial uptake rate, nanomaterial hydrodynamic radius. Device material characteristics (oxygen permeability and wall thickness).
1.6	**PUBLICATION ON THIS DATA**	*[1] Mattei G, Giusti S, Ahluwalia A. Design Criteria for Generating Physiologically Relevant In Vitro Models in Bioreactors. Processes; 2014;2: 548–569.* *[2] Ferroni M, Giusti S, Nascimento D, Silva A, Boschetti F, Ahluwalia A. Modeling the fluid-dynamics and oxygen consumption in a porous scaffold stimulated by cyclic squeeze pressure. Med Eng Phys. 2016;38.* *[3] Giusti S, Sbrana T, La Marca M, Di Patria V, Martinucci V, Tirella A, et al. A novel dual-flow bioreactor simulates increased fluorescein permeability in epithelial tissue barriers. Biotechnol J. 2014;9: 1175–84.*

2 GENERIC PHYSICS OF THE MODEL EQUATION

2.0	**MODEL TYPE AND NAME**	*Continuum model*	
2.1	**MODEL ENTITY**	*Finite volumes*	
2.2	**MODEL PHYSICS/ CHEMISTRY EQUATION** **PE**	**Equation**	*Navier stokes (1), continuity (2), dilute species transport (3), Michaeles Menten consumption (4), and their coupling.* $-\eta\nabla^2\boldsymbol{u}+\rho(\boldsymbol{u}\cdot\nabla)\boldsymbol{u}+\nabla p=\mathbf{F}$ (1) $\nabla\cdot\boldsymbol{u}=0$ (2) $\nabla\cdot(-D\nabla c)=R-\boldsymbol{u}\cdot\nabla c$ (3) $R=\mathrm{OCR}\cdot c/(K_m+c)$ (4)
		Physical quantities	*η is fluid viscosity, u is the velocity vector, ρ is fluid density, p is pressure and F is body force. D is the diffusion constant of the species of interest, c is its concentration and R its cellular volumetric consumption rate, which depends on maximal consumption rate (OCR) and Michaeles Menten constant (K_m).* *Fluid constants are tabulated as a function of temperature (37°C) and available in the software. Input velocity is from experimenters and the other data are from reference [1].*
2.3	**MATERIALS RELATIONS**	**Relation**	*If used, the following relation will be considered to determine the inward oxygen flux through the walls of in-vitro devices.* $J_{O2}=\frac{P_m}{L}\left(p_{O2}-\frac{c_{O2}}{H}\right)$
		Physical quantities/ descriptors for each MR	*J_{O2} is the inward flux, P_m is material permeability which is tabulated for PDMS. L is the wall thickness, p_{O2} is oxygen partial pressure in ai, c_{o2} is the oxygen concentration in the device close to the wall (calculated from 2.2) and H is Henry's constant for oxygen in water at 37°C.*
2.4	**PHYSICS FORMULATION OF THE**	*Not applicable*	

	CONDITIONS	
2.5	**SIMULATED INPUT**	*Run in isolation*

3	**SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS**		
3.1	**NUMERICAL SOLVER**	*Euler-Lagrange for particle tracking. COMSOL's UMFPACK direct solver for momentum and mass transport.*	
3.2	**SOFTWARE TOOL**	*COMOSL Multiphysics and ANSYS Fluent*	
3.3	**TIME STEP**	*Most solvers will feature an adaptive step algorithm in which the time step is automatically optimized based on the scenario.*	
3.4	**COMPUTATIONAL REPRESENTATION**	**PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL**	*Not applicable.*
3.5	**COMPUTATIONAL BOUNDARY CONDITIONS**		

Model	*Surface*	*Boundary Condition*
Oxygen convection and diffusion	*System side walls*	*Insulation/symmetry*
	Interface between the hydrogel construct and the fluid sub-domain	*Continuity*
	Fluid domain inlet	*Constant oxygen concentration*
	Fluid domain outlet	*Convective flux*
Navier-Stokes	*Solid-liquid interfaces*	*No slip (μ = 0)*
	Fluid domain inlet	*Normal inflow velocity (vin)*
	Fluid domain outlet	*Pressure, no viscous stress (p0 = 0)*

3.6	**ADDITIONAL SOLVER PARAMETERS**	*Cannot be specified in this stage as the model is yet to be implemented*

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*The output will be generated as oxygen and glucose flux and concentration gradient, surface shear stress, velocity vectors, Reynolds number, nanomaterial flux.*
4.2	METHODOLOGIES	*Post processing will involve surface or volume integration over surfaces or domains of interest.*
4.3	MARGIN OF ERROR	*In the models the accuracy depends on the accuracy of input parameters and physical data. Besides these, errors are usually of the order of 10%. This is much lower than the stochastic variability in cell cultures.*

MODEL 3: Benchmark dose model

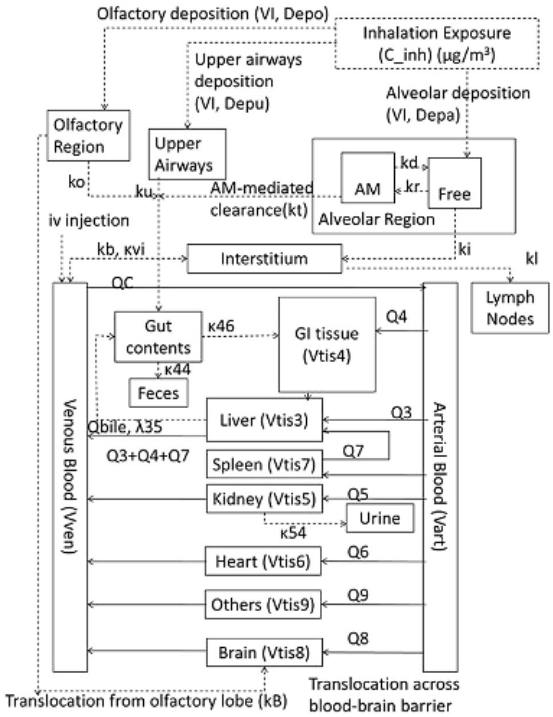
1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*PROAST is a benchmark dose (BMD) estimation model. It uses statistical methods to analyse toxicological dose-response data and to estimate the dose (the benchmark dose) that induces a certain, predefined response (the benchmark response, BMR). Typically, a benchmark dose will be used as a 'reference point' or 'point of departure' for a risk assessment. In PATROLS, PROAST will be used to derive dose-response relationships for nano material exposure in different in vitro systems. These dose-response relations will be used to predict responses in vivo (in experimental models such as rat). Subsequent whole animal BMD analysis in PROAST will be used to evaluate the predicted dose-response in vivo.*
1.2	MATERIAL	*PROAST will be used to estimate dose response relationships for nano materials in the experimental animal model. It is expected that this will be mostly rat, but if dose-response data become available for other species (e.g. mouse), these may be analyzed as well. PROAST is a statistical model and does not consider any physiological aspects of the experimental species or physical properties of the nano material used.*
1.3	STRUCTURE	*PROAST is a statistical model and does not consider any physiological aspects of the experimental species or physical properties of the nano material used.*
1.4	TIME LAPSE	*Time is usually not considered explicitly in dose-response modelling. If suitable, information on the time duration of the exposure experiment can be included in the analysis as a covariate.*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Not applicable.*
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*EFSA Scientific Committee, 2017. Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658*

<table>
<tr><td colspan="4">2 THE DATA-BASED MODEL</td></tr>
<tr><td>2.1</td><td>MODEL NAME/TYPE</td><td colspan="2">Model name/type</td></tr>
<tr><td rowspan="2">2.2</td><td rowspan="2">DATABASE AND TYPE</td><td>INPUTS</td><td>PROAST takes dose-response data as input. Data are presented as sets of (dose, response) tuples. Typically data are provided as text files, and are manually generated. Response data may be continuous or quantal, depending on the toxicological end point studied.</td></tr>
<tr><td>OUTPUTS</td><td>For the purpose of PATROLS, output of PROAST will be a dose-response relationship that provides an optimal description of the experimental dose-response data. This may be a in the form of a single parameterized model or in a non-parametric, table format generated by model averaging over a set of optimized dose-response models.</td></tr>
<tr><td rowspan="2">2.3</td><td rowspan="2">EQUATION(S)</td><td>HYPOTHESIS</td><td>PROAST is used for finding an optimal dose-response model, not for hypothesis testing.</td></tr>
<tr><td>PHYSICAL QUANTITIES</td><td>PROAST uses a set of parametric statistical models. These models are non-mechanistic, however the model parameters for continuous responses can be given a physiological interpretation.
<table>
<tr><th>Parameter</th><th>Interpretation</th></tr>
<tr><td>a</td><td>Response at zero dose</td></tr>
<tr><td>b</td><td>Measure of the potency of the nano material</td></tr>
<tr><td>c</td><td>Maximum fold change in the response relative to the background</td></tr>
<tr><td>d</td><td>Steepness of the dose-response on log scale</td></tr>
</table></td></tr>
</table>

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*PROAST uses numerical methods to optimize the log-likelihood of the model given the data.*
3.2	SOFTWARE TOOL	*PROAST is available as a web tool at proastweb.rivm.nl or as an R package.*
3.6	MARGIN OF ERROR	*PROAST determines the optimal model fit for a set of parametric models. When estimating a benchmark dose, the confidence interval in the BMD is determined, preferably using model averaging. Although this method accounts for model uncertainty, a separate validation is generally not conducted. In principle, model validation could be conducted by dividing the data set in training and validation sets and verifying the model fit against the validation data.*

MODEL 4: Physiologically-based pharmacokinetic model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*The pbpk model is used to simulate distribution in and elimination from the body of the rat of inhaled or ingested nano materials. As input the model requires an external exposure pattern, specifying the dosing amount and time pattern of nano material deposited in the alveolar lung region or ingested after oral administration.* *The result is the (time dependent) concentration of nano material in different organs, in particular the liver.* *The pbpk model will be calibrated for different nano materials (characterized by both physical chemical composition and particle geometry) by optimization its description of experimental distribution data. The physiology parameters for rat will be set to reference values from literature and will depend on the animal strain for which distribution information is available.*
1.2	MATERIAL	*Not applicable*

1.3	**GEOMETRY**	*In the pbpk model the rat is represented by a multi-compartment system, each compartment representing different organs or tissues into which the material may transfer. The size and complexity of the model (i.e. number of compartments) may vary with the detail of available distribution data and material properties.*  **Fig. 1.** Structure of rat nanoparticle PBPK model. *Taken from (Sweeney, L. M., L. MacCalman, L. T. Haber, E. D. Kuempel and C. L. Tran (2015). "Bayesian evaluation of a physiologically-based pharmacokinetic (PBPK) model of long-term kinetics of metal nanoparticles in rats." Regulatory Toxicology and Pharmacology **73**(1): 151-163.)*
1.4	**TIME LAPSE**	*The simulation will target long-term internal exposures, i.e. exposures on the timescale of several weeks to years.*
1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	*The model will simulate long-term internal organ concentrations (lung and liver) of the nano material after daily repeated exposure, or exposure during a limited period (e.g. single dose or a limited number of days of exposure).*
1.6	**PUBLICATION ON THIS DATA**	*The model is to be implemented and calibrated for nano materials selected in PATROLS. The model will be based on (adapted from) descriptions published in (among others) :* *Li, D., M. Morishita, J. G. Wagner, M. Fatouraie, M. Wooldridge, W. E. Eagle, J. Barres, U. Carlander, C. Emond and O. Jolliet (2016). "In vivo biodistribution and physiologically based pharmacokinetic modeling of inhaled fresh and aged cerium oxide nanoparticles in rats." Particle and Fibre Toxicology **13**(1): 45.* *Sweeney, L. M., L. MacCalman, L. T. Haber, E. D. Kuempel and C. L. Tran (2015). "Bayesian evaluation of a physiologically-based pharmacokinetic (PBPK) model of long-term kinetics of metal nanoparticles in rats." Regulatory Toxicology and Pharmacology **73**(1): 151-163.*

2 GENERIC PHYSICS OF THE MODEL EQUATION

2.0	MODEL TYPE AND NAME	*Continuum Model, Physiologically-based pharmaco-Kinetic (pbpk) model*	
2.1	MODEL ENTITY	*finite volumes*	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE	**Equation**	*The model solves the matrix differential equation* $$\frac{d\overline{C}}{dt} = A\overline{C}$$ *for the vector of compartment concentrations* $\overline{C}$ *and the system matrix A.*
		Physical quantities	$\overline{C}$ is the concentrations vector. It represents the concentrations (mg/cm^3) of nano material C_i {i ϵ (1, N)} in each of the N different physiological compartments. **A** *is the system matrix and consists of a representation of the mass balance equations between the N compartments of the system.* *The mass balance will in general depend on physiological parameters that describe the system (rat) and physical chemical parameters that describe the material. The general form of the mass balance equations for compartment i is:* $$V_i \frac{dC_i}{dt} = \theta_i Q_i \left(C_b - \frac{C_i}{P}\right) - \left(k_{i,ab} C_i - M_{i,seq} k_{i,de}\right) - V_i k_{i,el} C_i$$ Where

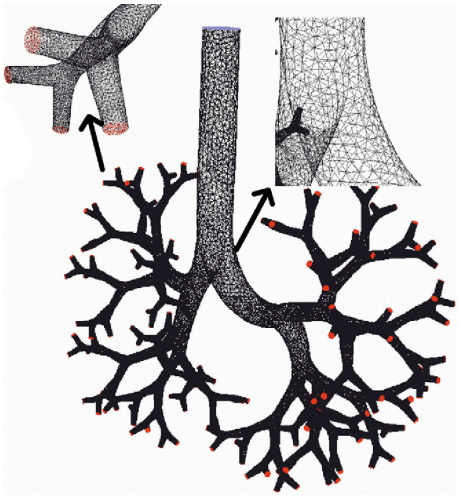
V_i	(distributional) volume of tissue (compartment) i
θ_i	measure of the transfer between capillary blood and tissue I (accounting for e.g. permeability)
Q_i	blood flow in tissue i
C_b	concentration in (arterial) blood
P	partition coefficient nano material between blood and tissue
$k_{i,ab}$	rate at which nano material is sequestered (e.g. taken up by phagocytizing cells)
$M_{i,seq}$	amount of nano material sequestered in tissue i
$k_{i,de}$	rate at which sequestered material is desorbed in tissue i

			$k_{i,el}$ elimination rate of nano material from tissue i
2.3	MATERIALS RELATIONS	**Relation**	Not applicable
		Physical quantities/ descriptors for each MR	Not applicable
2.4	PHYSICS FORMULATION OF THE CONDITIONS	Not applicable	
2.5	SIMULATED INPUT	Run in isolation	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*The model has not been implemented and a choice for the solver is yet to be made. The system is a linear system of ordinary differential equations. A likely choice for a solver might be a member of the 'Runge Kutta' familly of solvers. But the use of implicit numerical methods such as the implicit Adams method or the Rosenbrock method may be considered.*	
3.2	SOFTWARE TOOL	*A decision on the software tool to implement the model is yet to be made. Options are Matlab and R. Possibly the model itself may be implemented in C or C++ to enhance performance.*	
3.3	TIME STEP	*Most ode solvers will feature an adaptive step algorithm in which the time step is automatically optimized based on the scenario.*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*Not applicable*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*Not applicable*	
3.6	ADDITIONAL SOLVER PARAMETERS	*Cannot be specified in this stage as the model is yet to be implemented*	

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*Output will be generated as time dependent concentrations in different target organs (lung and liver in particular). Doses on mass base may be converted to other dose measures such as total surface area, total volume of material, number of particles in post-processing.*
4.2	METHODOLOGIES	*Dose conversions may be based on geometrical calculations (e.g. converting the mass of a sphere into its surface area based on information on its density and diameter) or using measured material information (e.g. surface area per unit mass).*
4.3	MARGIN OF ERROR	*Uncertainty in model parameters will be assessed in the model optimization procedure. The uncertainty in model parameters may then be extrapolated to a probability distribution of the estimated dose levels at the target organ or may be used to establish confidence intervals.*

MODEL 5: MPPD model

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*The Multiple-Path Particle Dosimetry Model (MPPD v 3.04) model is a computational model, used for estimating human and rat airway particle dosimetry.* *The MPPD model calculates the deposition and clearance of monodisperse and polydisperse aerosols in the respiratory tracts of rats and human adults and children (deposition only) for particles ranging in size from ultrafine (0.01 µm) to coarse (20 µm). The models are based on single-path and multiple-path methods for tracking air flow and calculating aerosol deposition in the lung. The single-path method calculates deposition in a typical path per airway generation, while the multiple-path method calculates particle deposition in all airways of the lung and provides lobar-specific and airway-specific information. Within each airway, deposition is calculated using theoretically derived efficiencies for deposition by diffusion, sedimentation, and impaction within the airway or airway bifurcation. Filtration of aerosols by the nose and mouth is determined using empirical efficiency functions. The MPPD model includes calculations of particle clearance in the lung following deposition.*
1.2	MATERIAL	*Monodisperse and polydisperse aerosols of (nano)-particles ranging in diameter from 0.01 to 20 µm. Descriptors for the particulate include, size, size distribution, density, mass median aerodynamics diameter, etc.*
1.3	GEOMETRY	• *Human (single-path symmetric, 5-lobe symmetric, and asymmetric stochastic) and rat (asymmetric) lung geometries included* • *Human adult and children lung geometries representing 10 distinct ages from 3 months old to 21 years old* • *Models upper respiratory tract deposition (nasal, oral, oronasal, or endotracheal breathing)* • *Models lobar, tracheobronchial, and alveolar lung airway deposition and clearance* • *Accounts for individual breathing parameters such as breath frequency, tidal volume, inspiratory and expiratory fractions, functional residual capacity, and upper respiratory tract volume*  *Theoretical model of the human airway up until the seventh generation used to calculate computational fluid dynamics (CFD).*
1.4	TIME LAPSE	*Variable exposure scenarios and activity patterns over any length of time (acute or chronic).*

1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	*The MDDP model calculates the deposition fraction for an inhaled dose of nanoparticles in the different regions of the rat/human lungs.*
1.6	**PUBLICATION ON THIS DATA**	*Anjilvel, S. and Asgharian, B. (1995). A multiple-path model of particle deposition in the rat lung. Fundam. Appl. Toxicol. 28, 41-50.* *National Institute for Public Health and the Environment (RIVM) (2002). Multiple Path Particle Dosimetry Model (MPPD v 1.0): A Model for Human and Rat Airway Particle Dosimetry. Bilthoven, The Netherlands. RIVA Report 650010030.*

2	**GENERIC PHYSICS OF THE MODEL EQUATION**		
2.0	**MODEL TYPE AND NAME**	*Computational Fluid Dynamics (CFD).*	
2.1	**MODEL ENTITY**	*Finite volumes*	
2.2	**MODEL PHYSICS/ CHEMISTRY EQUATION** **PE**	**Equation**	*Trajectories of aerosol particles under the simultaneous action of inertial impaction, gravitational settling, Brownian motion and interception are simulated by solving the particles' equations of motion - the three-dimensional Navier-Stokes equation - using Monte Carlo techniques.*
		Physical quantities	*Gravitational constant, g.* *Particle aerosol concentration, density, size, size distribution and mass median aerodynamics diameter*
2.3	**MATERIALS RELATIONS**	**Relation**	*N/A*
		Physical quantities/ descriptors for each MR	*N/A*
2.4	**PHYSICS FORMULATION OF THE CONDITIONS**	*N/A*	
2.5	**SIMULATED INPUT**	*N/A*	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*Finite difference, Monte Carlo techniques*	
3.2	SOFTWARE TOOL	*C++*	
3.3	TIME STEP	*Most solvers will feature an adaptive step algorithm in which the time step is automatically optimized based on the scenario.*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*N/A*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*Lung geometry for rats and humans*	
3.6	ADDITIONAL SOLVER PARAMETERS	*N/A*	

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*Output will be generated as deposition fraction of the inhaled dose in different parts of the human/rat lungs*
4.2	METHODOLOGIES	*N/A*
4.3	MARGIN OF ERROR	*N/A*

MODEL 6: Molecular models of the structure

1	ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*Molecular models of the structure of nanoparticles are simulated. Nano-descriptors expressing the complexity of nano-structures as well as their physicochemical properties are obtained.*
1.2	MATERIAL	*Molecular models of the nanoparticles are based on crystallographic data, as well as information about morphology, size, volume, and surface.*
1.3	GEOMETRY	*the complete crystal structure or representative cluster built from the bulk crystal structure*
1.4	TIME LAPSE	
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	
1.6	PUBLICATION ON THIS DATA	*T. Puzyn, N. Jeliazkova, H. Sarimveis, et al., Perspectives from the NanoSafety Modelling Cluster on the validation criteria for (Q)SAR models used in nanotechnology, Food and Chemical Toxicology, 2018, 112, 478-494.*

2	GENERIC PHYSICS OF THE MODEL EQUATION		
2.0	MODEL TYPE AND NAME	*Structural model*	
2.1	MODEL ENTITY	*N.A.*	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE	**Equation**	*N.A.*
		Physical quantities	*N.A.*
2.3	MATERIALS RELATIONS	**Relation**	*N.A.*
		Physical quantities/ descriptors for each MR	*N.A.*
2.4	PHYSICS FORMULATION OF THE CONDITIONS	*N.A.*	
2.5	SIMULATED INPUT	*Molecular model of the nanoparticles*	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*N.A.*	
3.2	SOFTWARE TOOL	*Gaussian, VASP*	
3.3	TIME STEP	*N.A.*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*N.A.*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*N.A.*	
3.6	ADDITIONAL SOLVER PARAMETERS	*N.A.*	

4	POST PROCESSING	
4.1	THE PROCESSED OUTPUT	*Nano-descriptors expressing the complexity of nano-structures as well as their physicochemical properties will be developed. This will include for example: surface chemistry, surface charge, particle size and shape.*
4.2	METHODOLOGIES	*N.A.*
4.3	MARGIN OF ERROR	*N.A.*

MODEL 7: Structure-Activity model

1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*To define the qualitative (SAR) or quantitative (QSAR) relations between high-quality experimental data related to biological activity and the structural and/or physicochemical characteristics of nanomaterials.* *Model will be utilized: i) to predict accurately the activity (dose), and ii) to assist in the identification of possible mechanisms of toxicity induced by nanomaterials at different levels of biological organisation.*
1.2	MATERIAL	*Nanomaterials studies within finished and/or on-going projects (e.g. NanoREG2, SUN, NANOIMUNE, etc.) related to nanosafety.*
1.3	STRUCTURE	*Appropriate types of nano-descriptors expressing the complexity of nano-structures as well as their physicochemical properties will be developed. This will include for example: surface chemistry, surface charge, particle size and shape.*
1.4	TIME LAPSE	*Not applicable*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*The changes of the structures and, in consequence the properties of nanomaterials in the external conditions will be investigated. The appropriate system-depended descriptors will be provided.*
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*All developed models will be published.* *The application of existing formats and repositories (e.g. QMRF, QsarDB) for documenting QSAR models will be analysed in order to ensure reproducibility of the developed models (including easy transfer and exchange across different platform).*

2	THE DATA-BASED MODEL		
2.1	MODEL NAME/TYPE	Nano - (Quantitative) Structure – Activity Relationships (Nano(Q)SAR, n(Q)SAR) – developed by applying the statistical or machine learning algorithm to a training set containing a matrix of descriptors with associated endpoint values. Alternatively, the terms (Quantitative) Nanostructure – Activity Relationships ((Q)NAR) and (Quantitative) Nanostructure – Toxicity Relationships ((Q)NTR) are also used in the literature.	
2.2	DATABASE AND TYPE	INPUTS	*Endpoint (y) experimentally measured values of cytotoxicity, genotoxicity and ecotoxicity gathered from available databases, if necessary logarithmically transformed. Quantitative as well as qualitative data will be investigated.* *Matrix of descriptors (X) calculated (e.g. electron affinity, surface charge) and/or experimentally measured (e.g. zeta potential), if necessary, logarithmically transformed and/or normalized*
		OUTPUTS	*Predicted values of cytotoxicity, genotoxicity and ecotoxicicty and novel knowledge related to mechanism of toxicity of nanomaterials*
2.3	EQUATION(S)	HYPOTHESIS	*Nano(Q)SARs are based on the assumption that when the descriptors are known for a group of nanomaterials, and the experimental activity data are available only for a few of them, it is possible to predict the unknown activity directly from the descriptors and a suitable mathematical model. Model is derived from algorithm analysing the available data.*
		PHYSICAL QUANTITIES	y = *f(X)*, *where:* y – *endpoint*, **X –** *descriptors*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*TO develop the models linear and non-linear chemometric techniques will be investigated, for example: multiple linear regressions, partial least squares regression and support vector machine.*
3.2	SOFTWARE TOOL	*Software developed in the frame of NanoBRIDGES project (EU FP7) (http://nanobridges.eu/software/) as well as other tools available for QSAR models development and validation (e.g. QSARINS, http://www.qsar.it/ , Double – Cross Validation, https://sites.google.com/site/dtclabdcv/) will be employed.*
3.6	MARGIN OF ERROR	*To assess the predictive ability and quality of Nano(Q)SAR models the parameters recommended by OECD will be applied. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2007)2)*

MODEL 8: Predictive Toxicogenomics Space model

1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*Will be assessed during project*
1.2	MATERIAL	*Any (None specified by the model)*
1.3	STRUCTURE	*Any (None specified by the model)*
1.4	TIME LAPSE	*Biological samples treated with nanomaterial*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Any (None specified by the model)*
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*Bioinformatics analysis according to: Kohonen P, Parkkinen JA, Willighagen EL, Ceder R, Wennerberg K, Kaski S,Grafström RC. A transcriptomics data-driven gene space accurately predicts liver cytopathology and drug-induced liver injury. Nat Commun. 2017 Jul 3;8:15932. doi:10.1038/ncomms15932.*

2	THE DATA-BASED MODEL		
2.1	MODEL NAME/TYPE	*Model name/type: PTGS tool*	
2.2	DATABASE AND TYPE	INPUTS	• *Gene expression data on 1331 Predictive Toxicogenomics Space (PTGS) genes. Continuous or microarray, counts for RNA-seq or tempO-seq data (high-throughput RNA-seq).* • *Measurements are done preferably on cellular in vitro models, or in whole model organisms* • *Pre-processing according to measurement technology* • *Microarray or RNA-seq measurement + PTGS gene sets (see article doi:10.1038/ncomms15932 for details) + reference values for cytotoxicity and organ injury.*
		OUTPUTS	• *Cytotoxicity probability estimate (continuous), exceeds virtual GI50 dosage (binary), organ (liver) injury probability estimate (continuous), exceeds 50% threshold (binary), PTGS component activities for mode-of-action (continuous)* • *For details on interpretation see article doi:10.1038/ncomms15932.*
2.3	EQUATION(S)	HYPOTHESIS	*Gene expression data analysed with the PTGS tool (patent pending) predicts nanomaterial toxicity and cytotoxicity, including mode-of-action, and serves potentially for grouping*
		PHYSICAL QUANTITIES	*None, completely based on measurement data, external reference values are used as decision criteria (see above and the reference article for details)*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*Gene Set Enrichment Analysis (GSEA), Bayesian linear modelling, R and Bioconductor*
3.2	SOFTWARE TOOL	*R and Bioconductor packages according to technology for pre-processing, limma (linear models for microarray analysis) for downstream analysis (limma and voom for RNA-seq or count data in general), R and tidyverse for data manipulations, R and ggplot2 for data visualization*
3.6	MARGIN OF ERROR	*Model quality is assessed using positive and negative controls. Assessed against cytotoxicity or organ toxicity data if available.*

MODEL 9: IVIVE model

1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*In vitro/in vivo extrapolation (IVIVE) is a method to establish the correlation between the corresponding in vitro dose-response results with the in vivo counterpart.*
1.2	MATERIAL	*In vitro and in vivo dose-response data from FP7 projects (ENPRA, MARINA, SUN), H2020 project (NanoREG2, CaliBRATE) and data generated from PATROLS.*
1.3	STRUCTURE	*The dose-response in vitro will be described using the descriptors identified by QSAR modelling plus the estimation of the real dose (available to cells) from HARVARD model.* *The dose-response in vivo will be described using the MDDP model for inhalation exposure. For other routes of exposure (e.g. ingestion), the dose-response will have to assessed by statistical data analysis (non-linear regression).*
1.4	TIME LAPSE	*Time is not considered explicitly in dose-response modelling. If suitable, information on the time duration of the exposure experiment can be included in the analysis as a covariate.*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Not Applicable*
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*No publications so far.*

2	THE DATA-BASED MODEL		
2.1	MODEL NAME/TYPE	*Model name/type*	
2.2	DATABASE AND TYPE	INPUTS	• *Nanoparticle physico-chemical characteristics.* • *Cell density (number of cell per cm2 of affected region in vitro and in vivo).* • *Dose-Response data (corresponding in vitro and in vivo data)*
		OUTPUTS	• *Correlation between in vitro and in vivo dose response data.*
2.3	EQUATION(S)	HYPOTHESIS	*The hypothesis is that for equivalent dose (described with the relevant receptors) the vitro and in vivo systems yield equivalent results.* *The assumption is that if the in vitro system is realistic enough then the hypothesis above will hold.*
		PHYSICAL QUANTITIES	• *Nanoparticle physico-chemical characteristics.* • *Cell density (number of cell per cm2 of affected region in vitro and in vivo).* • *Dose-Response data (corresponding in vitro and in vivo data)*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	Multiple and non-linear regression
3.2	SOFTWARE TOOL	MATLAB
3.6	MARGIN OF ERROR	The margin of error is dependent on the variation of the data. This method accounts for data uncertainty. In principle, the validation could be conducted by dividing the data set into one for training and one for validation to assess the accuracy of the in vitro to in vivo extrapolation.

MODEL 10: Allometric scaling model

<table>
<tr><th>1</th><th colspan="2">ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED</th></tr>
<tr><td>1.1</td><td>ASPECT OF THE USER CASE TO BE SIMULATED</td><td>Allometric scaling models are used to i) determine physiological parameters in downscaled in-vitro systems, ii) extrapolate and upscale in-vitro results to the mass of an adult human.</td></tr>
<tr><td>1.2</td><td>MATERIAL</td><td>The basic unit of allometry is body mass and the basic material is water. All physiological parameters (Y) are correlated with body mass (M) through the so-called allometric relationship. The constant a is a proportionality factor for the particular parameter, whereas b is the allometric exponent. b varies in magnitude and sign and has a specific value for each parameter according to how it scales with mass.
$Y = aM^b$
Perhaps the best-known relationship Kleiber's law, which correlates the metabolic rate (MR), the rate at which an organism burns energy, with organism mass.
$MR = aM^{3/4}$
It is reasonable to assume that in order for a down-scaled in-vitro system to manifest physiologically relevant behaviour, it should obey physiological allometric correlations. This is particularly relevant for metabolic rates, since Kleiber's law holds for 8 orders of magnitude of mass (from 1g shrew to 150 tonne blue whale) [1]</td></tr>
<tr><td>1.3</td><td>GEOMETRY</td><td>The mass of an in-vitro system is given by the overall volume of the cellular construct. In the case of a fluidic system the media volume is also relevant.</td></tr>
<tr><td>1.4</td><td>TIME LAPSE</td><td>Not applicable. However, time also scales with mass and this will be taken into consideration.</td></tr>
<tr><td>1.5</td><td>MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS</td><td>
<table>
<tr><th>b</th><th>Significance</th><th>Example (b value)</th></tr>
<tr><td>0</td><td>Parameter does not change with body mass</td><td>Bone density in mammals, cell radius</td></tr>
<tr><td>1</td><td>Parameter changes in direct proportion with body mass</td><td>Body volume, cell number</td></tr>
<tr><td>0<b<1</td><td>Parameter increases at a slower rate than body mass</td><td>Metabolic rate (3/4), blood flow rate (3/4), external surface area (2/3), life span (1/4)</td></tr>
<tr><td>>1</td><td>Parameter increases at a faster rate than body mass</td><td>Bone mass (4/3)</td></tr>
<tr><td><0</td><td>Parameter decreases with increasing body mass</td><td>Almost all frequencies or rates (cardiac frequency, respiratory frequency, -1/4)</td></tr>
</table>
The table shows the scaling exponents for some physiological parameters</td></tr>
<tr><td>1.6</td><td>PUBLICATION ON THIS DATA</td><td>[1] Ahluwalia A. Allometric scaling in-vitro. Sci Rep. 2017;7: 42113.
[2] Ucciferri N, Sbrana T, Ahluwalia A. Allometric Scaling and Cell Ratios in</td></tr>
</table>

		Multi-Organ in vitro Models of Human Metabolism. Front Bioeng Biotechnol. 2014;2: 74.

2	**GENERIC PHYSICS OF THE MODEL EQUATION**		
2.0	**MODEL TYPE AND NAME**	*Allometric scaling models*	
2.1	**MODEL ENTITY**	*Finite volumes*	
2.2	**MODEL PHYSICS/ CHEMISTRY EQUATION** **PE**	**Equation**	*General allometric equation (1). Kleiber's law (2) Michaeles Menten Oxygen consumption rate (3), oxygen diffusion and reaction (4).* $Y = aM^b$ $MR = aM^{3/4}$ $R=V_{max}\cdot c/(K_m+c)$ (2) $\nabla\cdot(-D\nabla c)=R-\boldsymbol{u}\cdot\nabla c$ (3)
		Physical quantities	*D is the diffusion constant of oxygen, c is its concentration and R its volumetric consumption rate, which depends on maximal volumetric consumption rate (V_{max} OCR, ρ) and Michaeles Menten constant (K_m). u is the velocity vector. Importantly V_{max} depends on the cell packing density (ρ), and this is the principal physical quantity that an experimenter can decide.* *All data are from reference [1] and will be updated after input from experimenters.*
2.3	**MATERIALS RELATIONS**	**Relation**	*Not applicable*
		Physical quantities/ descriptors for each MR	*Not applicable*
2.4	**PHYSICS FORMULATION OF THE CONDITIONS**	*Not applicable*	
2.5	**SIMULATED INPUT**	*Although the models will be run in isolation, there is scope for coupling with inputs from fluid dynamic and PBPK models.*	

3	SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS		
3.1	NUMERICAL SOLVER	*Most of the considerations will be analytical. However, oxygen reaction and diffusion evaluated in the computational regime can be equated with average cellular metabolic rates to determine the validity of Kleiber's law in in-vitro devices following the methods described in ref [1].*	
3.2	SOFTWARE TOOL	*Matlab and COMOSL Multiphysics*	
3.3	TIME STEP	*Not applicable*	
3.4	COMPUTATIONAL REPRESENTATION	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*In the analytical case we will use allometric scaling relationships to derive time of exposure and repeated dose frequency. Here, the equations to be employed are:* $T = aM^{1/4}$ *for time and* $f = aM^{-1/4}$ *for rates or frequencies.* *In the computational case, considering a symmetrical spherical coordinate system, the basic relationships for correlating metabolic rate (MR) and cellular oxygen consumption in an in-vitro construct of radius R, are:* $\frac{\partial c}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) - \frac{V_{\max} c}{k_m + c}$ $MR = D\left.\frac{dc}{dr}\right\|_R 4\pi R^2$ *These equations can be solved numerically in COMSOL.*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS	*Stationary conditions will be employed. For the computation, the boundary conditions are constant dissolved oxygen concentration in the media as given by Henry's law.*	
3.6	ADDITIONAL SOLVER PARAMETERS	*None*	

MODEL 11: Quantitative trait-based models

1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	***Quantitative trait-based models*** *In more detail an example is provided here on the case of acute aquatic toxicity of spherical and rod-shaped copper nanoparticles for a series of daphnid species. The endpoint of assessment is the predicted toxicity of a given copper nanoparticles to a series of Daphnid species*
1.2	MATERIAL	*The particles of interest in this example are spherical and rod-shaped copper nanoparticles with sizes in between 25 and 500 nm.*
1.3	STRUCTURE	*A set of phys.chem. properties of the particles is required, including as a minimum: chemical composition (in this case the models are applicable only to Cu particles), particle size, particle volume, morphology. For each particle tested a different model is obtained as the endpoint of assessment is toxicity of Daphnid*

		species to copper nanoparticles.
1.4	**TIME LAPSE**	*The time lapse of the simulation is irrelevant in this case.*
1.5	**MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS**	*The exposure conditions are restricted according to the OECD guideline that deals with toxicity testing of Daphnia species: OECD guideline 202. It is to be noted that the fate of the particles needs to be assessed in the test suspension as a function of exposure time, including assessment of particles aggregation, particle sedimentation, and rate of dissolution of the particles.* *The full reference of the OECD test guideline is: Organisation for Economic Co-operation and Development. 2004. Test No. 202: Daphnia sp., acute immobilisation test and reproduction test. OECD Guidelines for the Testing of Chemicals. Paris, France.*
1.6	**PUBLICATION ON THIS ONE DATAMINING OPERATION**	*L. Song, M. Vijver, G. de Snoo, W. Peijnenburg. Assessing toxicity of copper nanoparticles across five cladoceran species. Environ. Toxicol. Chem., 34, 1863-1869, 2015.*

2 THE DATA-BASED MODEL

2.1	**MODEL NAME/TYPE**	*Model name/type*	
2.2	**DATABASE AND TYPE**	**INPUTS**	• *Model input is information on the characteristics of daphnid species: volume, length and surface area of the animals. The type of information is continuous.* • *Pre-processing of information on volume, length and surface area of the animals is not needed.* • *No specific sources of input data are available. The original publication/data source contains experimental input data. These data may be supplemented with information from any source.*
		OUTPUTS	• *The endpoint of assessment is the LC50 (i.e. the concentration of copper particles that causes 50 % mortality of specific daphnid species after 48 h of exposure). It is to be noted that this endpoint is dissimilar from LC50 values obtained after testing of copper nanoparticle suspensions as these suspensions contain Cu-ions which induce additional toxicity. The generated LC50-values are continuous.* • *No post-processing procedures are needed.* • *The only source of output data suited for (internal) validation is the reference given under the heading "User case".*
2.3	**EQUATION(S)**	**HYPOTHESIS**	*Particle toxicity is proportional to either the surface area, volume, or length of the animals tested. These animal properties are the ecological traits upon which the model is based.*
		PHYSICAL QUANTITIES	*The model equation is of the general form:* *$LC50_{48h}$ = a + b * X, with X = either surface area, volume or body length of daphnias*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*Simple linear regression*
3.2	SOFTWARE TOOL	*Excel software*
3.6	MARGIN OF ERROR	*Statistics of the model are described in term of values of R^2_{adj}, p, F.*

MODEL 12: Quantitative toxicity-toxicity model

1	USER CASE	
1.1	ASPECT OF THE USER CASE TO BE CALCULATED	*Model will be utilized to predict the ectoxicity based on the measured toxic effect for different organism.*
1.2	MATERIAL	*Nanomaterials studies within finished and/or on-going projects (e.g. NanoREG2, SUN, NANOIMUNE, etc.) related to nanosafety.*
1.3	STRUCTURE	*Appropriate types of nano-descriptors expressing the complexity of nano-structures as well as their physicochemical properties will be developed. This will include for example: surface chemistry, surface charge, particle size and shape.*
1.4	TIME LAPSE	*Not applicable*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*The changes of the structures and, in consequence the properties of nanomaterials in the external conditions will be investigated. The appropriate system-depended descriptors will be provided.*
1.6	PUBLICATION ON THIS ONE DATAMINING OPERATION	*All developed models will be published.* *The application of existing formats and repositories (e.g. QMRF, QsarDB) for documenting QSAR models will be analysed in order to ensure reproducibility of the developed models (including easy transfer and exchange across different platform).*

2	THE DATA-BASED MODEL		
2.1	MODEL NAME/TYPE	Nano - (Quantitative) Toxicity – Toxicity Relationships (Nano(Q)TTR) – developed by applying the statistical or machine learning algorithm to a training set containing a matrix of descriptors and measured biological effects (toxicity) with associated endpoint values.	
2.2	DATABASE AND TYPE	INPUTS	*Endpoint (y) experimentally measured values of ecotoxicty gathered from available databases, if necessary logarithmically transformed. Quantitative as well as qualitative data will be investigated.* *Matrix of descriptors (X) calculated (e.g. electron affinity, surface charge) and/or experimentally measured biological effects.*
		OUTPUTS	*Predicted values of ecotoxicicty and novel knowledge related to mechanism of toxicity of nanomaterials*
2.3	EQUATION(S)	HYPOTHESIS	*Nano(Q)TTRs are based on the assumption that for structurally similar compounds the toxic effect should be comparable, and therefore, there is the possibility to predict one toxic effect based on another one.*
		PHYSICAL QUANTITIES	y = *f(X)*, *where:* y – *endpoint*, **X –** *descriptors and/or toxic effect*

3	COMPUTATIONAL DETAIL OF DATAMINING OPERATION	
3.1	NUMERICAL SOLVER	*To develop the models linear and non-linear chemometric techniques will be investigated, for example: multiple linear regressions, partial least squares regression and support vector machine.*
3.2	SOFTWARE TOOL	*Software developed in the frame of NanoBRIDGES project (EU FP7) (http://nanobridges.eu/software/) as well as other tools available for QSAR models development and validation (e.g. QSARINS, http://www.qsar.it/ , Double – Cross Validation, https://sites.google.com/site/dtclabdcv/) will be employed.*
3.6	MARGIN OF ERROR	*To assess the predictive ability and quality of Nano(Q)SAR models the parameters recommended by OECD will be applied. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2007)2)*