NanoSolveIT Project: Innovative and integrated tools for in silico assessment and safe-by-design approaches of nanomaterials

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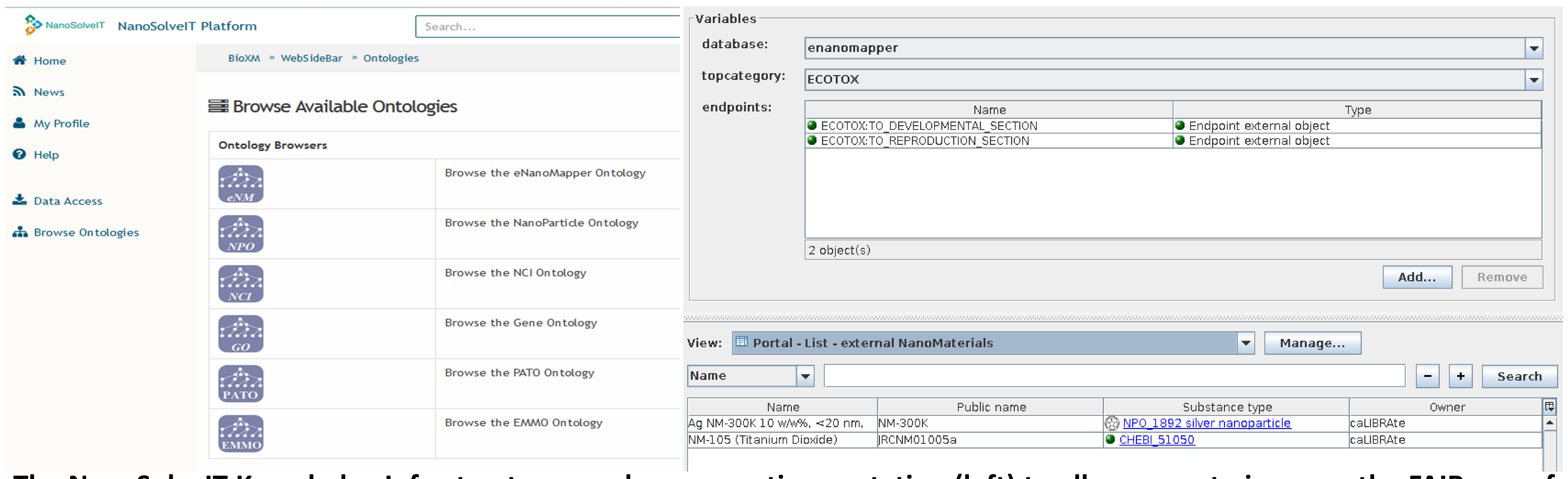
Background, motivation and objective

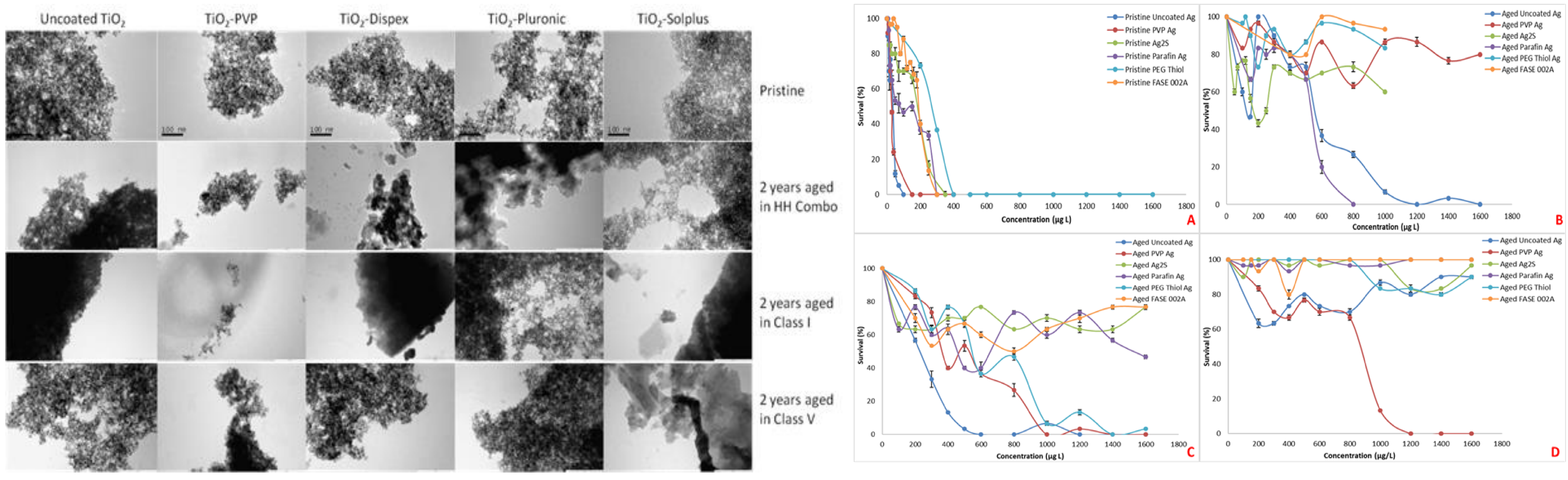
Technological advances have resulted not only in the development of a multitude of novel and complex nanomaterials (NMs), but also exponential growth of available data. While the unique properties of NMs have led to a large number of commercial applications, a paucity of comprehensive risk and hazard data may lead to adverse effects for humans and the environment. Full exploitation of the available data using *in silico* tools can assist with NMs assessment and the development of safe-by-design approaches, leading to specific Integrated Approaches to Testing and Assessment (IATA). The NanoSolveIT project (www.nanosolveit.eu) uses available NM databases and libraries, identifies and fills existing gaps and exploits these data to develop tools that address the needs of regulatory agencies and industry to understand and predict the exposure, hazard and risk from NMs and nano-enabled products, and facilitate computational 'safe-by-design' approaches to NMs. The developed tools and models can be used for the design of safer NMs or for the identification of NMs properties that drive hazardous phenomena. These tools are offered publicly via the NanoSolveIT cloud platform.

NanoSolveIT Knowledge Infrastructure



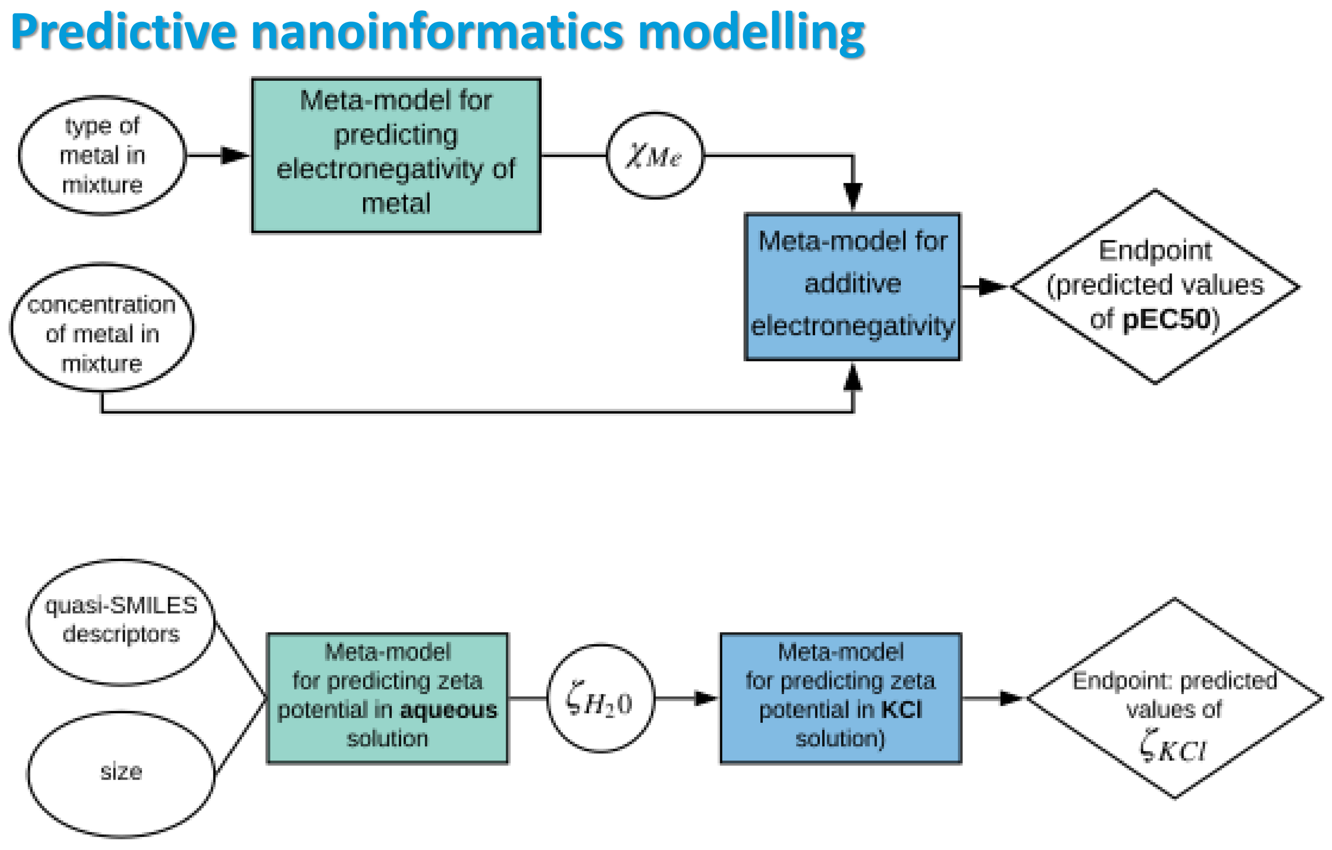
The NanoSolveIT Knowledge Infrastructure employs semantic annotation (left) to allow users to increase the FAIRness of their data and to retrieve interoperable data from linked databases. The administration client of the NanoSolveIT Knowledge Base (right) uses APIs to link and integrate with other databases (e.g. eNanoMapper) for the retrieval of NMs for which specific endpoint measurements are available.

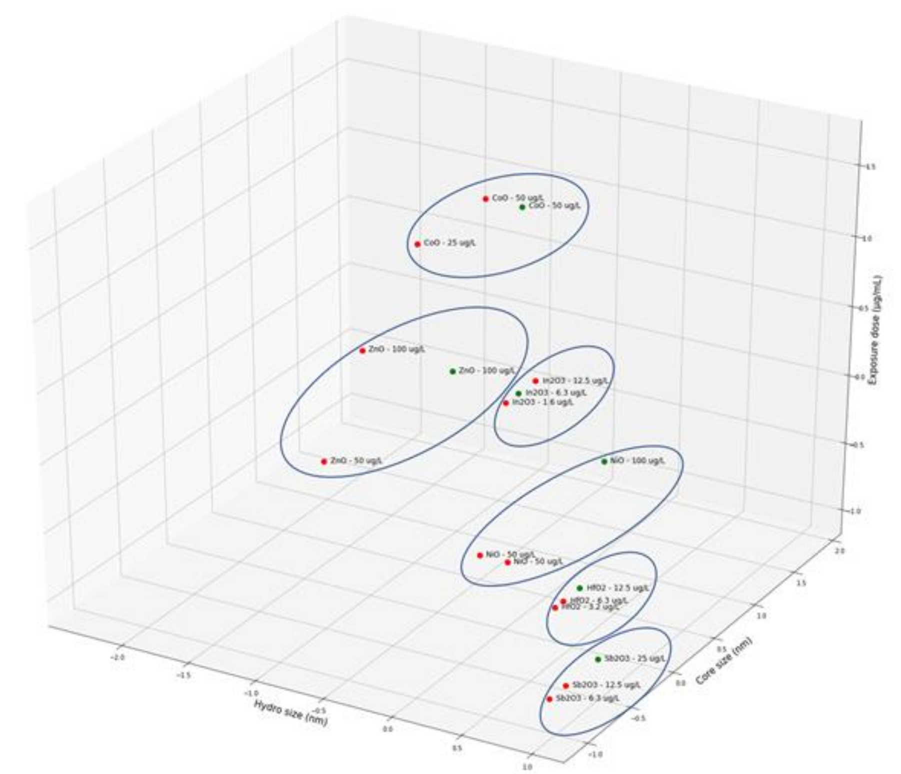
Design of experiments for data gap filling



NanoSolveIT undertakes a very focused set of experiments, (e.g. ecotoxicology, see above) designed purposefully to fill gaps identified in the existing large datasets that would prevent the *in silico* models from performing at optimum levels, and thus reduce the predictive power of the overall IATA. Based on the gap analysis, and the information needs identified, a design of experiments has been and is being implemented to minimize the number of experiments needed.

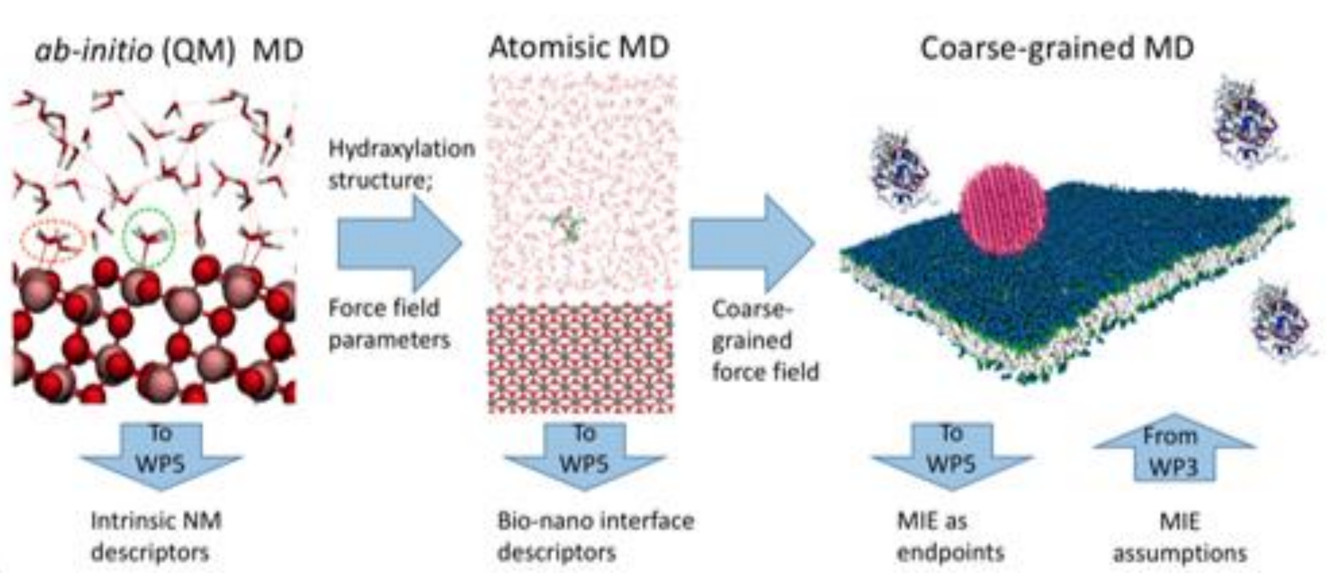
Predictive nanoinformatics modelling





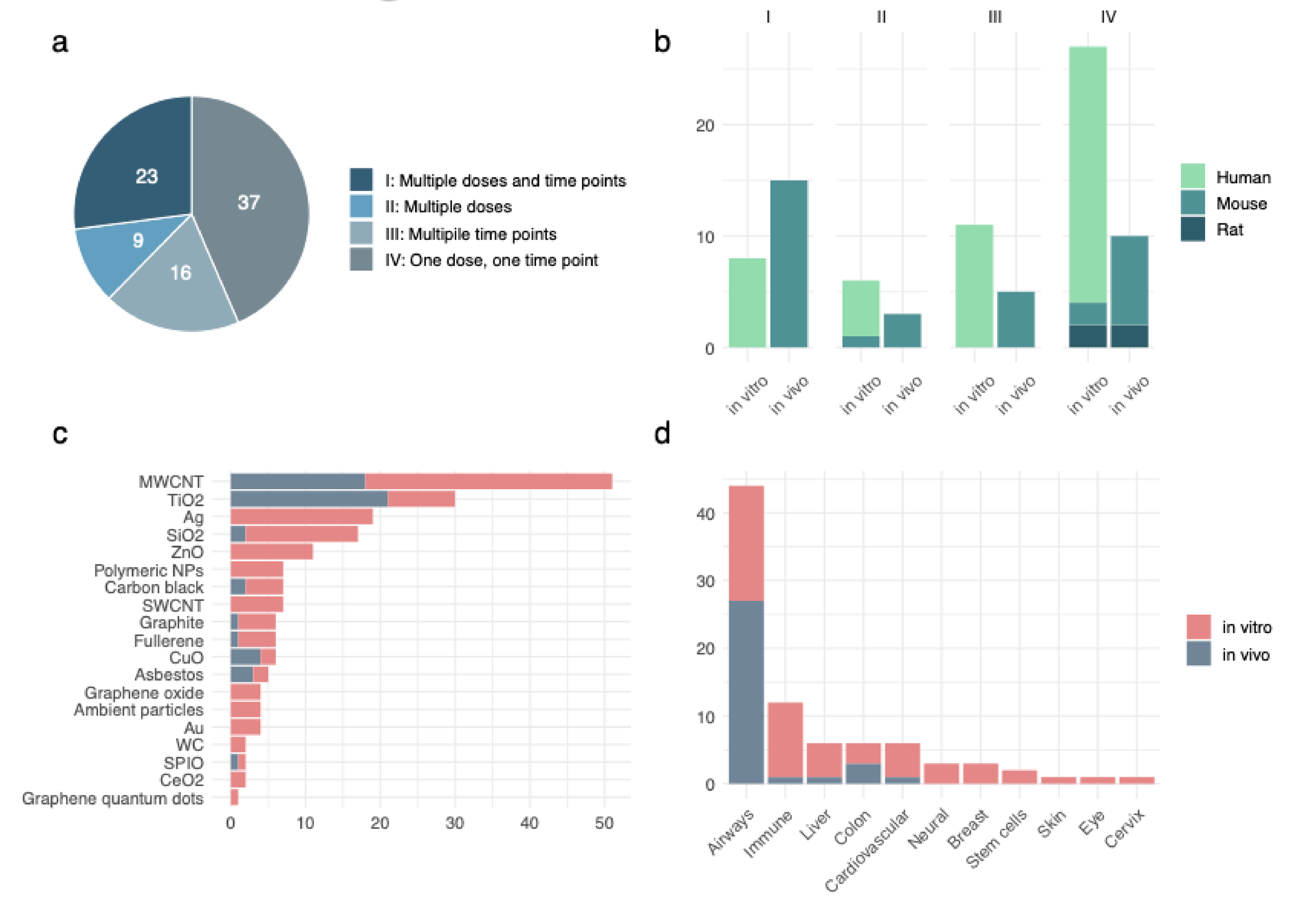
The development of cost effective nanoinformatics tools and models based on Artificial Intelligence (AI) for the prediction of crucial NMs functionalities and adverse effects is at the core of NanoSolveIT. The objective is the development of data-driven metamodels and predictive models that find complex relationships between descriptors and physical characteristics of NMs with functionalities and adverse biological effects, with particular focus on MIEs, KEs and AOs in AOPs (left). Based on this methodologies read across approaches can be developed, identifying relationships in the identified descriptors space. For example, the cytotoxicity of metal oxide NMs can be predicted using the normalised *k*NN space of a predictive model employing a combination of physicochemical and molecular descriptors (Papadiamantis et al. 2020). The NPs are placed based on their Euclidean distances. Red and green spheres correspond to NPs from the training and test sets respectively.

Sustainable multiscale modelling framework for NMs property prediction



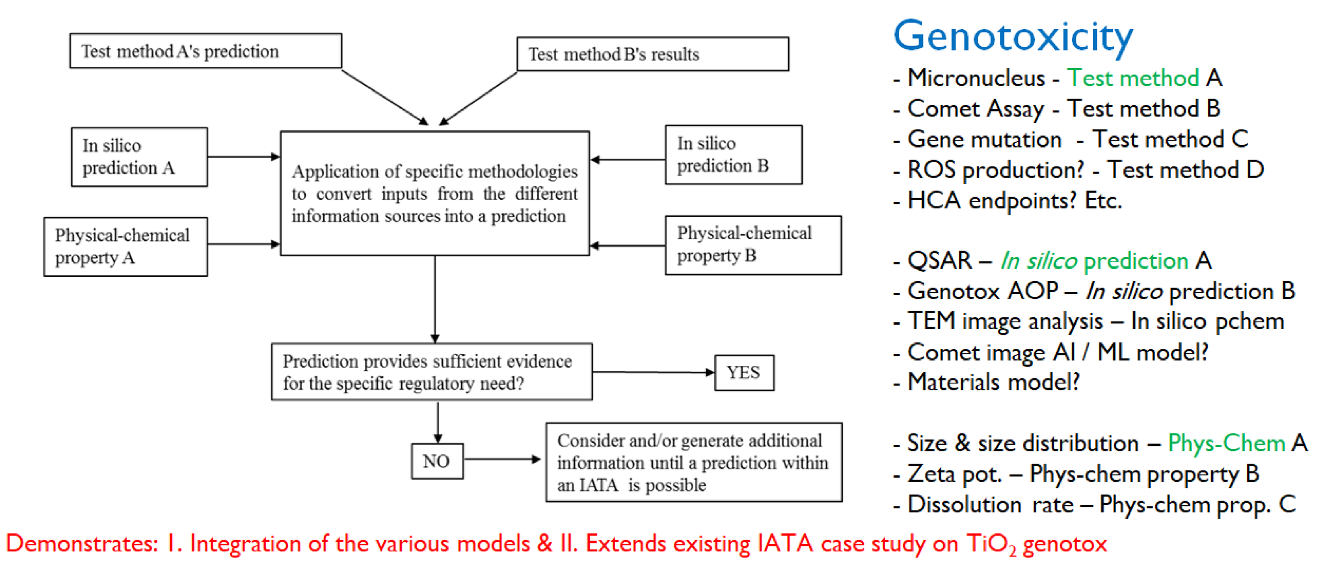
A multi-scale modelling framework for the quantitative characterization of NMs, interactions between NM and their transport in the application environment will enable an assessment of potential hazardous effect and a prediction of functionalities of the NMs based on their basic physicochemical properties and the delivery history. A hierarchical bottom up scheme involving materials models at different spatial resolutions is being employed to calculate NM descriptors relevant for each selected application or functionality.

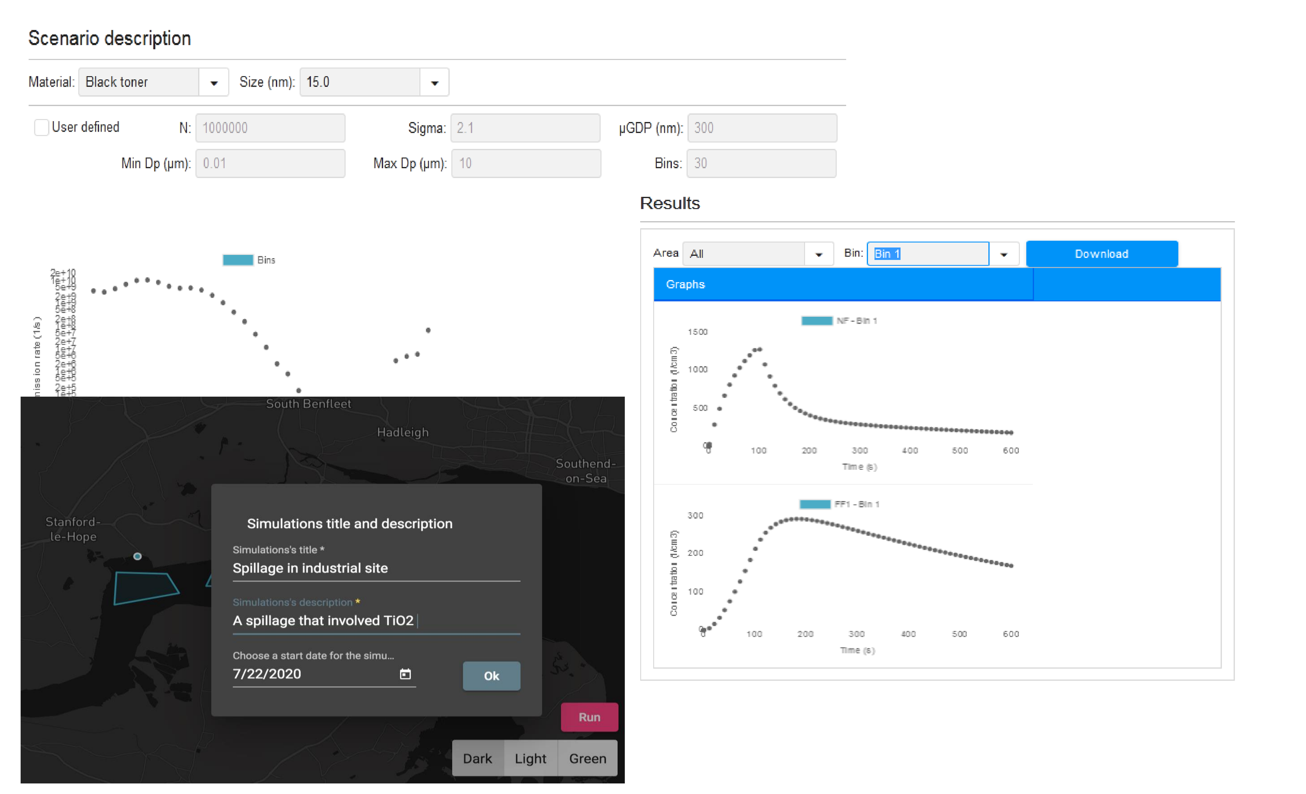
Predictive toxicogenomics



NanoSolveIT will provide a common and unified methodological framework to perform all the analytical steps needed to achieve several complementary goals using toxicogenomics data, such as preprocessing of the omics data, retrieval of biomarkers, read-across analysis and reconstruction of AOPs. We have created a unified collection of publicly available transcriptomics data on ENM exposures (Saarimäki, Serra, and Greco 2020. Federico et al. 2020). The resulting data collection comprises 85 data sets totalling to 506 unique ENM vs. control comparisons for differential expression divided into four classes based on the experimental set up.

NanoSolveIT IATA for human and environmental risk assessment





The NanoSolveIT IATA provides a systematic framework for integration of the data and models to generate meaningful hazard and risk assessment predictions. Key features include the optimization of the sequence in which tools are run, ensuring that the data input and output formats from the different tools are aligned. The NM fingerprint will be the core of the integration, linking laboratory characterization data, computational characteristics, biological signatures and effects. For example, the NanoSolveIT IATA approach for genotoxicity integrating relevant experimental and modelling approaches (top) can be used for the optimization of data curated/produced in the project and the adaptation of relevant models for further exploitation and prediction (bottom).

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