Case studies assessing suitability of *in silico* modelling tools and read-across approaches for nanomaterial hazard assessment

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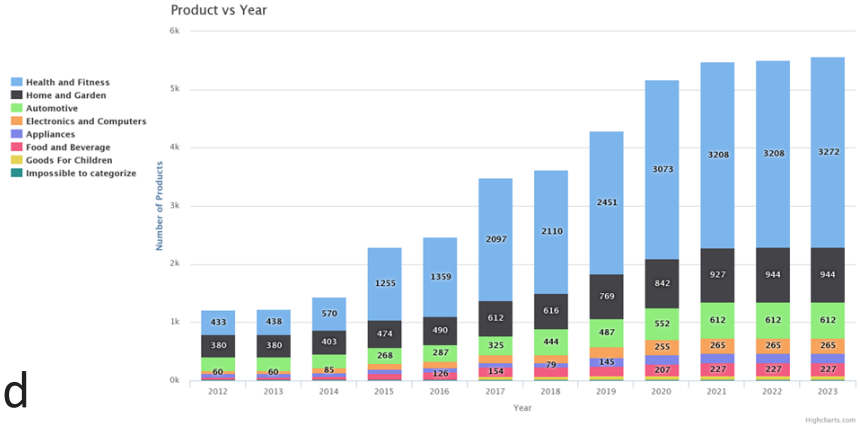
Background

- Numerous novel nanomaterials (NMs) are used in a wide spectrum of commercial products.
- Many NMs are not yet thoroughly evaluated for potential harmful biological effects.
- Development and application of reliable, accurate computational models and tools.
- Contribution to the speeding up of the hazard & risk assessment and safety-by-design (SbD) of existing and novel NMs.



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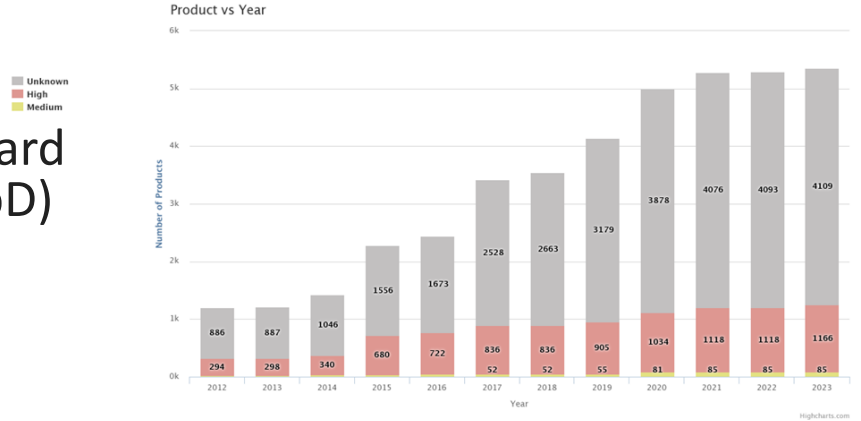

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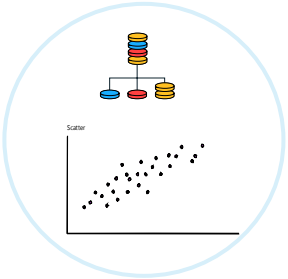
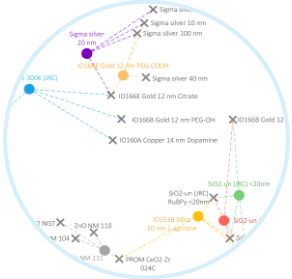
Objective

- Conduct a study compiling **reliably and transparently** the information on the **existing computational approaches** for the **hazard/risk assessment and SbD of novel Nanomaterials and their (regulatory) relevance** (project supported by European Union Observatory for Nanomaterials)

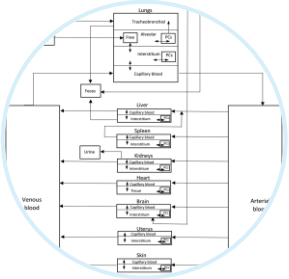


nanoQSAR

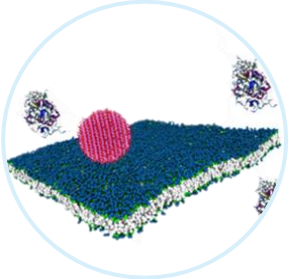


Grouping/read-across

AOPs



PBPK models



Simulations

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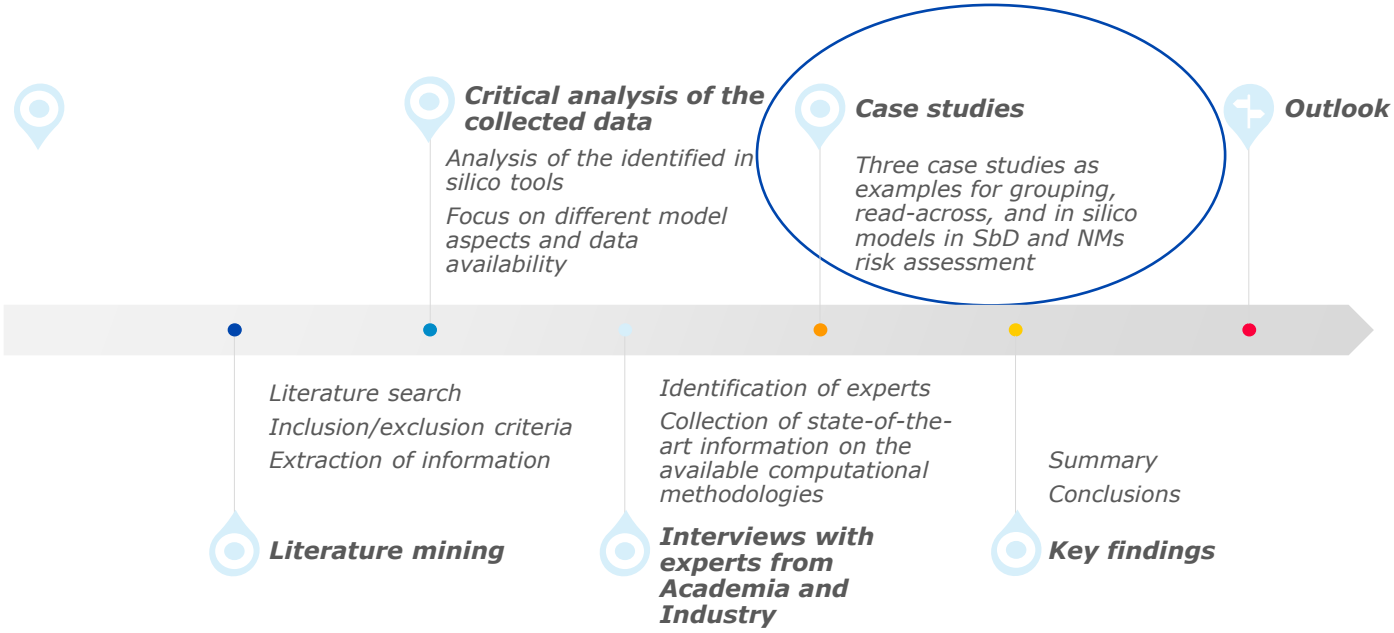
Project outline



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Case studies

Read-across models for the assessment of the anti-microbial activity of various carbon-based NPs

Assessment of different tools for the prediction of TiO_2-based NMs' endpoints

Combination of nanoinformatics models into SAPNets

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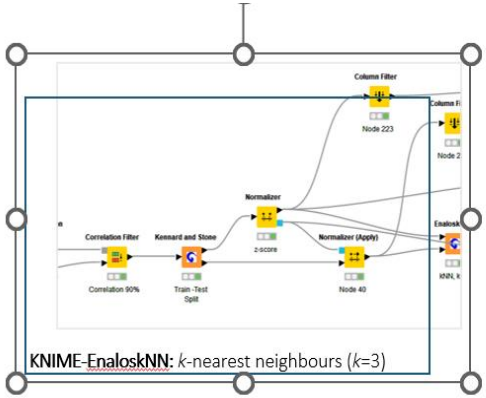
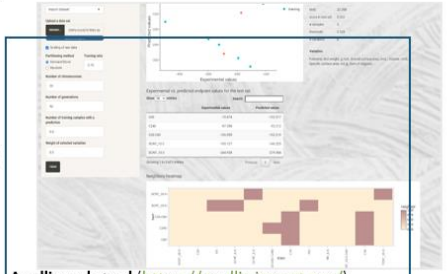
Case study 1

Development of read-across models for the assessment of the anti-microbial activity of various carbon-based NPs

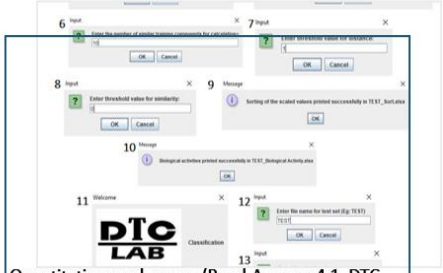
- Dataset derived from Zhang *et al*., 2021 (https://doi.org/10.1016/j.ecoenv.2021.112357) physicochemical descriptors of 17 CNPs
- Interactions between carbon-based NPs and a SARS-CoV-2 RNA fragment (potential of fragment stabilisation and application in anti-microbial coatings)
- Endpoint: Total Potential Energy (E_{int})
- Modelling: Three read-across methods from the literature
- Consensus Model: Averages predictions of 2 individual models to avoid biases



KNIME-EnaloskNN: *k*-nearest neighbours (*k*=3)



Apellis web-tool (https://apellis.jaqpot.org/): Automated read-across model development



Quantitative read-across (Read-Across-v4.1, DTC Lab): Similarity-based toxicity prediction.

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Case study 1

Comparisons between models

- EnaloskNN: user-friendly environment, data visualisation and flexibility, Enalos+ nodes require a license scheme.
- Apellis: user-friendly interface, automatic training (menus and buttons), convergence delays cause server timeouts.
- DTC-Lab: complex software and training material, program terminates easily, results are not explained.

CNP	Actual values [kJ/mol]	EnaloskNN [kJ/mol]	DTC-Lab: Euclidean kernel [kJ/mol]	DTC-Lab: Gaussian kernel [kJ/mol]	DTC-Lab: Laplacian kernel [kJ/mol]	Consensus [kJ/mol]
C36	-109	-110	-109	-109	-113	-110
C60	-80	-101	-107	-100	-102	-102
C70	-96	-92	-87	-91	-101	-93
SCNT(6,6)	-153	-192	-158	-159	-163	-168
DCNT(6,6)	-262	-274	-249	-253	-286	-266
	MAE	15.4	10.8	8.2	12.9	9.1
	RMSE	20.4	14.0	10.5	15.6	12.2
	Q^2_{ext}	0.96	0.98	0.99	0.97	0.98

CNP	Actual values [kJ/mol]	Apellis predictions [kJ/mol]
C60	-80	-102
C240	-87	-92
C20@C60	-100	-102
SCNT(10,0)	-185	-146
DCNT(10,0)	-245	-280
	MAE [kJ/mol]	20.6
	RMSE [kJ/mol]	25.5
	Q^2_{ext}	0.93

Case study 2

Assessment of different tools for the prediction of TiO_2-based NMs' endpoints

QSAR for nano-mixtures

- Toxicological endpoints (EC_{50}, immobilisation) of TiO_2-based nano-mixtures.
- Input data through menus and sliders.
- Ecotoxicity risk level indication after results are generated
- Complex manual, lacks explanation for "positive" and "negative" interactions.
- Missing Domain of Applicability (DoA)

-> Connections between phenotypic entities based on their effects on genes.

NanoMixHamster

- Cytotoxicity prediction of TiO_2 towards CHO-K1 cells using the SAPNet approach.
- Step 1: Input of metallic NM composition, its additive electronegativity value is acquired.
- Step 2: Toxicity prediction and graph visualisation of the DoA
- Simple web application, tool is described in original publication in detail.

-> **Lung Exposure dose calculator**

NanoToxRadar

- Cytotoxicity to A549 cell line and zeta potential predictions.
- Required input data: NM core composition, doping parameters and coating materials.
- Risk indication according to cytotoxicity prediction.
- Simulation of TiO2 internal biodistribution
- Missing manual, warning limits explanation and results interpretation.

-> **IATA**

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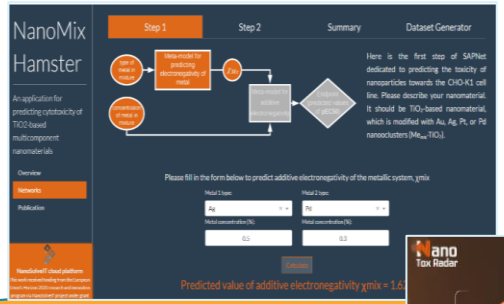
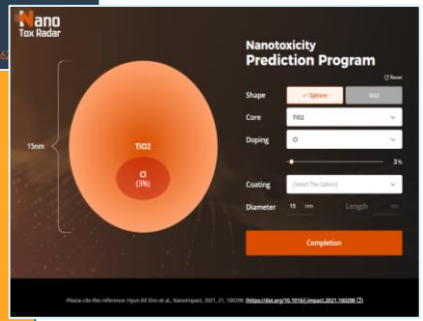
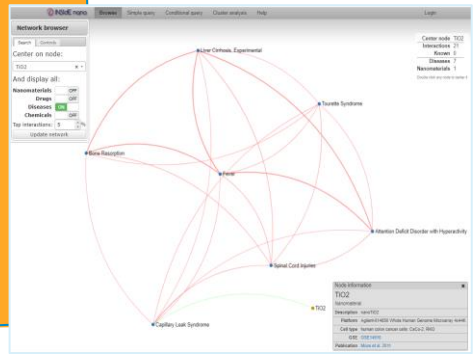
Case study 2

Assessment of different tools for the prediction of TiO_2-based NMs' endpoints

- Fast sensitivity analyses or virtually screen newly synthesised NMs.
- Suitable for use in an SbD framework → explore the correlations between different properties and the nanotoxicity → define the limits within which NMs are safe.







- Missing domain of applicability limits (even if it exists in the relevant publication).
- Missing tutorials (or too technical manuals, missing results interpretation).
- Inconsistencies with original publications.
- Slow execution.
- Need for frequent update.

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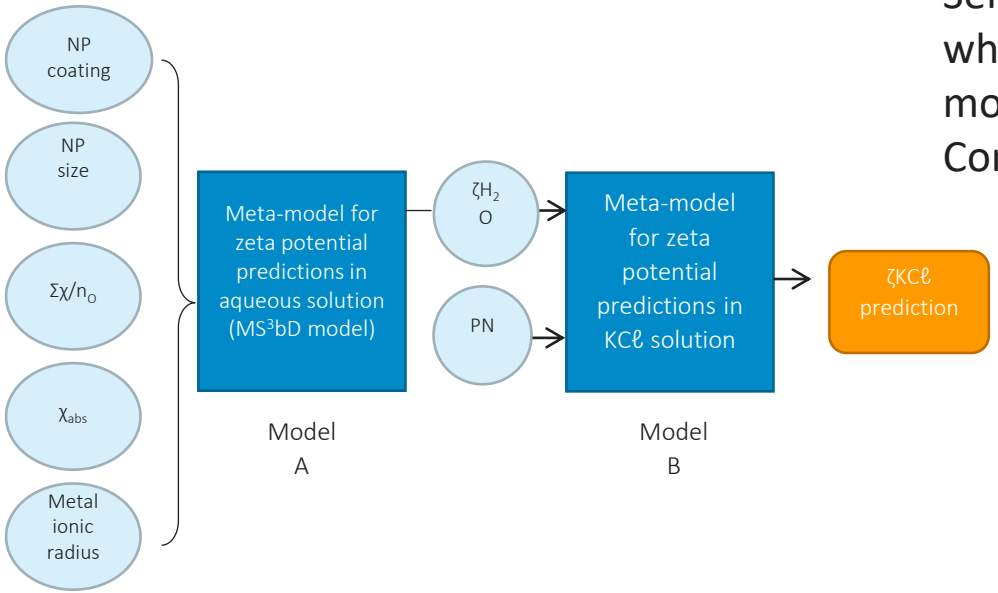
Case study 3

Combination of nanoinformatics models into SAPNets



Series of interconnected predictive models, where descriptors are predicted by other "meta-models", as proposed by Rybińska-Fryca *et al*. Combination of two models:

Model A: MS^{3}bD model by Papadiamantis *et al*., a fully validated *k*NN predictive model for zeta potential in water (pH=7).

Model B: MLR model by Wyrzykowska *et al*. that predicts zeta potential in KCℓ solution.

$$\zeta KC\ell = 3.98 + 21.68 \cdot \zeta H_2O + 7.88 \cdot PN$$

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Case study 3

- Solely ζH_2O predictions characterised as “reliable” in model A were fed into model B.

  → Domain of Applicability definition and model requirements should be clearly stated.

- Unknown experimental conditions that regulate NM behaviour (pH, temperature etc.), impossible to determine the models’ compatibility.
- Large errors propagation.

→ Experimental and computational data and meta-data sharing is essential.

→ SAPNets-models integration can be applied to the filling of nano-data gap while no experimental data generation is needed.

Rybińska-Fryca, A., *et al*. Structure-activity prediction networks (SAPNets): A step beyond Nano-QSAR for effective implementation of the safe-by-design concept. Nanoscale **12**, 20669–20676 (2020).
Papadiamantis, A. G. *et al*. Computational enrichment of physicochemical data for the development of a ζ-potential read-across predictive model with Isalos Analytics Platform. NanoImpact **22**, 100308 (2021).
Wyrzykowska, E., *et al*. Development of a novel *in silico* model of zeta potential for metal oxide nanoparticles: A nano-QSPR approach. Nanotechnology **27**, 1–8 (2016).

Results & Outcome

190 models & methodologies

Surveys with 36 field experts

3 case studies

1. Read-across models for the assessment of the anti-microbial activity of various carbon-based NMs
2. Assessment of different tools for the prediction of TiO_2-based NMs' properties
3. Combination of nanoinformatics models into predictive workflows

High quality of algorithms and methodologies, automation and optimization, deep learning

The NMs unique characteristics are incorporated in many of the developed methods

Nano-data barriers

Lack of integration

FAIR & Open Data

Store and digitalise data and metadata while they are produced

Existing nano-oriented databases

eNanoMapper
NanoPharos
NanoCommons KB
caNanoLab etc.

Standardised model reporting — QMRF, MODA etc.

User-friendly tools — Make use of existing deployment platforms

Real-case validation — Comparison of predictions with existing conventional experimental results

Interdisciplinary communication — Feedback to enhance models' usefulness & applicability

Successful integration of the *in silico* methods in **NMs'** industrial and regulatory SbD, hazard and risk assessments

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Key findings

Is it sensible ?

- Reliable NMs models with satisfactory quality levels
- Including various unique NM characteristics
- Ongoing work to integrate optimisation functions and user-friendly tools

Is it accessible ?

Public repositories, platforms and databases applying FAIR principles increase their visibility and use

Can it be used/integrated in the research & regulatory context ?

- through fully available, consistent and standardised data and meta data
- through transparent & clear communication on models' development/validation/DoA/Manuals
- already used as NAMs and considered within NAMS for NM framework program (ECHA/EFSA)

https://euon.echa.europa.eu/documents/2435000/3268573/ECHA_2022_61_study_report.pdf/739900b3-bd9c-a4f0-d3bc-88f4aa801f68?t=1694691997584

Questions?

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