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

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Laurence Deydier Stephan1, Marianne Matzke1, Andrea Richarz1, Dimitra-Danai Varsou2, Maria Antoniou² & Antreas Afantitis

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.
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
Project outline

Critical analysis of the collected data
- Analysis of the identified in silico tools
- Focus on different model aspects and data availability

Case studies
- Three case studies as examples for grouping, read-across, and in silico models in SbD and NMs risk assessment

Literature search
- Inclusion/exclusion criteria
- Extraction of information

Identification of experts
- Collection of state-of-the-art information on the available computational methodologies

Interviews with experts from Academia and Industry

Literature mining

Summary

Conclusions

Key findings

Outlook
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
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 ($E_{\text{int}}$)
- Modelling: Three read-across methods from the literature
- Consensus Model: Averages predictions of 2 individual models to avoid biases
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.

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NovaMechanics
Cheminformatics & Nanoinformatics Excellence

EUON
European University of the Ocean

ECHA
European Chemicals Agency
Case study 2

Assessment of different tools for the prediction of TiO₂-based NMs’ endpoints

**QSAR for nano-mixtures**
- Toxicological endpoints (EC₅₀, immobilisation) of TiO₂-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 TiO₂ 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
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.
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\textsuperscript{3}bD model by Papadiamantis et al., a fully validated kNN predictive model for zeta potential in water (pH=7).

Model B: MLR model by Wyrzykowska et al. that predicts zeta potential in KC\textsubscript{l} solution. 

\[ \zeta_{\text{KC}l} = 3.98 + 21.68 \cdot \zeta_{\text{H}2\text{O}} + 7.88 \cdot \text{PN} \]
Case study 3

• Solely ζH₂O 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.


Results & Outcome

190 models & methodologies  
Surveys with 36 field experts  
3 case studies

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  
Existing nano-oriented databases

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

Standardised model reporting  
User-friendly tools  
Real-case validation  
Interdisciplinary communication

QMRF MODA etc.  
Make use of existing deployment platforms  
Comparison of predictions with existing conventional experimental results  
Feedback to enhance models’ usefulness & applicability

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

Store and digitalise data and metadata while they are produced  
eNanoMapper NanoPharos NanoCommons KB caNanoLab etc.  

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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)
