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PATROLS

Advanced Tools for NanoSafety Testing

Introduction: Exposure to engineered nanomaterials (ENM) poses a potential risk to human and environmental health. Current ENM hazard assessment tools are based on short term, high-dose exposures using simple 2D *in vitro* test systems, which lack environmental realism in terms of dose delivery, exposure duration and biological complexity. Thus, there is an urgent need for more realistic and predictive methods for ENM safety assessment.

PATROLS Project Aim: Establish and standardise a battery of innovative, next generation **hazard assessment** tools that **more accurately predict** adverse effects caused by **long-term (chronic), low dose** ENM exposure in human and environmental systems to **support regulatory risk decision making** and help **reduce** the need for **animal testing**.

Work Package 1

ENM acquisition, identification & exposure assessment

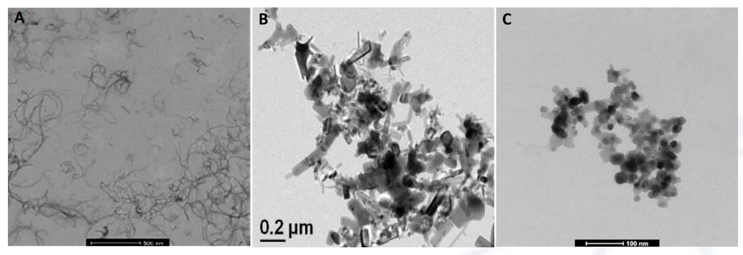


Figure 1. *TEM images: (A) Multi-Walled Carbon Nanotubes, (B) ZnO, (C) TiO_2 ENMs from the European Commission's Joint Research Centre (https://ec.europa.eu/jrc/en)*

- Generate ENM physico-chemical characterisation data.
- Model dispersion, transport & realistic dose exposure characteristics in advanced mammalian & ecological models.
- Establish ENM fate, uptake and translocation in biological systems.

Work Package 2

Biodistribution, biokinetics and *in vivo* anchoring

- Collect existing animal data from both acute & long-term/repeated inhalation and oral exposure studies.
- Define the biokinetics and key target tissues for ENM bio-accumulation.
- Identify key initiator events (KIEs) associated adverse outcome pathways (AOPs).

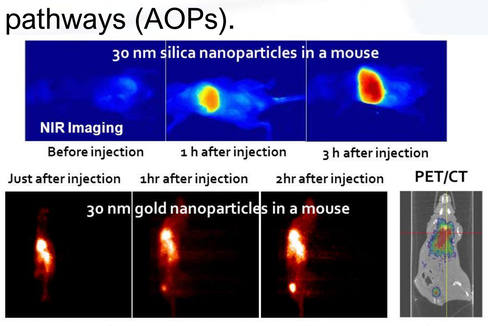


Figure 2. *Biodistribution of Nanoparticles in vivo. Department of Nuclear Medicine, Seoul National University (Kang, 2016)*

Work Package 7

Dissemination, exploitation and knowledge transfer

- Develop & implement plans for communication, exploitation & dissemination.
- Deliver guidance for new tools relevant to hazard identification and/or risk assessment.
- Ensure data is accessible to the various PATROLS stakeholders.

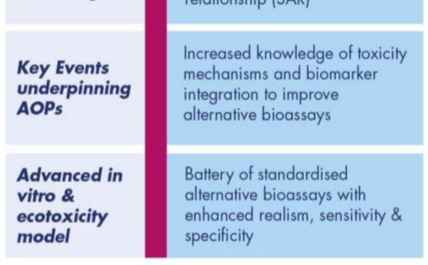
24 Partnering Institutions
3 Continents
1 Project (€12.7m)

Physiologically Anchored Tools for Realistic nanOmateriaL hazard aSsessment

Work Package 6

In silico modelling strategies for hazard assessment

- Establish a PATROLS database to support *in silico* modelling.
- *In vitro* dosimetry, modelling & experimental design to support *In Vitro* to *In Vivo* Extrapolation (IVIVE) & Quantitative Structure Activity Relationship (QSAR) model development.



- Environmental dosimetry, modelling & experimental design.

Work Package 3

Advanced *in vitro* lung models for ENM hazard assessment

- Optimise lung models for long-term & repeated exposures.
- Adapt lung models to enhance their physiological relevance (mechanical flexing & fluid flow)
- Establish bioassays for long-term events based on KIEs as mechanistic indicators for AOPs.

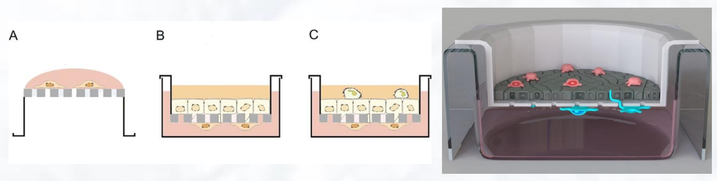


Figure 3. *Construction of a 3D pulmonary model using (A) endothelial cells on the basal side of the membrane, (B) epithelial cells on the apical side of the membrane and (C) the addition of macrophages on the membrane. (D) illustrates a 3D advanced pulmonary co-culture model on a transwell membrane insert. Adapted from (Rothen-Rutishauser et al., 2005).*

Work Package 5

Advanced ecotoxicity testing strategies and cross-species models

- Combining insights on ENM fate, uptake, bio-distribution and toxicological effects at increasing levels of bio- and ecological organisation (*e.g.* trophic transfer) in algae, daphnia and zebrafish to predict the risks of ENM in environmentally relevant context.

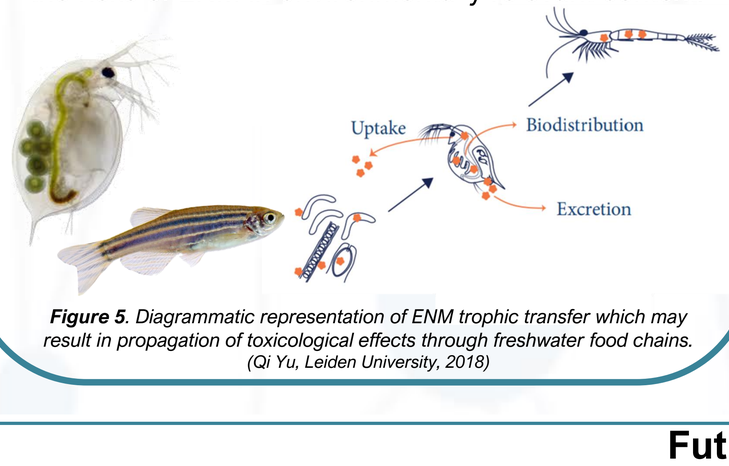


Figure 5*. Diagrammatic representation of ENM trophic transfer which may result in propagation of toxicological effects through freshwater food chains. (Qi Yu, Leiden University, 2018)*

Work Package 4

Advanced *in vitro* Gastro-Intestinal Tract (GIT) & liver models for ENM hazard assessment

Figure 4. *Optimisation of 3D GIT and liver models for long-term, repeated ENM exposures*

- Adapt GIT & liver models to enhance physiological relevance (inclusion of multiple cell types, fluid-flow & mechanical flexing).
- Establish bioassays for long-term events based on KIEs as mechanistic indicators for AOPs.

Future Impact:

1. Produce realistic and predictive *in vitro* 3D tissue models of the human lung, GIT & liver for ENM safety assessment, reducing the need for animal testing.
2. Provide innovative methods for safety assessment using advanced ecological test systems relevant to a range of species or organisms.
3. Create robust computational methods for predictive ENM exposure, dose & risk modelling.
4. Develop test method guidance to support hazard assessment frameworks & provide input into ongoing regulatory nanosafety policy development.
5. Characterise ENM under relevant experimental conditions dictated by the advanced human and environmental model development.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement No. 760813