NanoSafety Cluster

Nanosafety Cluster Review

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Risk Prediction and Management Tools

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Projects involved in Risk Prediction

- ENPRA, ModNanoTox, NanoTransKinetics
- nanoPUZZLES, MembraneNanoPart, ModENPTox, PrenantoTox, MODERN
- eNanoMapper, nanoMILE

Shift from Risk Assessment to Risk Prediction via the computational modeling of nanomaterial properties, environmental behavior and biological responses

Challenges for model development

- Limited nanomaterial data
  - data quality
  - nanoparticle diversity
  - range of exposure conditions
- Need to integrate into de models heterogeneous data
  - structural, physicochemical and biological information
- Limited mechanistic knowledge

Relevant achievements

- Impact in different areas:
  - Collaboration / Community building
  - Nanosafety data management
  - NP modeling and nanodescriptors
  - NP behavior models
  - Identification of NP categories

Collaboration activities

- Harmonization of the NMP modeling projects
  - Coordinated activities via face-to-face meetings and joint mid-term review.
  - Organized in Working groups:
- Activities aligned with the objectives of the NSC WGs and US-EU CoRs.
- Collaboration with the NCI NanoWG to establish “data completeness” and “minimum information” standards

Nanosafety data management

- Adoption of ISA-TAB-Nano as standard format for data exchange
- Extraction of data from peer-reviewed literature (both manual and semi-automatic) and creation of a curated database on silica
- Generation of small datasets for model validation
- Completed a requirement analysis of existing NSC activities and identification of infrastructure needs for projects involved in RA/RP.
- Development of a prototype ontology to support nanosafety data assessment
- Development of an ISA-TAB-Nano compliant nanosafety data management system which is available for interested projects
- Development of a scoring system to quantify data quality and reliability

NP modeling

- Atomistic models describing size effects on particle stability and dissolution
- Computational protocol for the study of large interacting systems
- Models for physicochemical properties of NPs (e.g., thermal conductivity)
- Calculation of membrane wrapping energy cost and adhesion energy gain (NP shape, membrane curvature, bending rigidity, tension and adhesion strenght NP-membrane)

Nanodescriptors

- Constitutional (0D) for metal oxides (MeO)
- Topological, including optimal (CORAL) and Liquid Drop Model (LDM) descriptors
- Image-based (SEM/TEM/AFM)
- Library of size dependent nanodescriptors using Molecular Dynamic calculations
- Optimized method to compute Buckingham potentials for MeO systems
- Quantum chemistry descriptors using NP building blocks of different sizes

NP behavior models

- **Structure – activity relationships:**
  - PaCa2 cell uptake of a library of magnetofluorescent NPs modified with small organic molecules
  - Differential toxicity of MeO NPs to E. coli and Human keratocyte cell line
  - Cytotoxicity classification model for MeO based on an integrated endpoint generated from HTS data
  - Monte Carlo approach to develop quasi-QSPRs/QSARs from heterogeneous NP information
    - E.g., Mutagenicity of fullerenes in different conditions

NP behavior models

- **Mechanistic models**
  - Relevant pathways activated by NPs (mitochondrial function, p53 activation, NF-kB activation)
  - Size-dependent PBPK model for the dynamic interactions of ZnO in mice
- **Dose-response** (statistical) models from various *in vitro / in vivo* data
- **Quantitative criterion** for toxicity assessment that allows the integration of heterogeneous toxicity indicators

NP behavior models

- **Bioinformatics approaches**
  - Methods and tools for the analysis of NP molecular signatures including data preprocessing techniques for reliable hit-identification at low concentrations and web-based tools for pathway analysis
- **Protein-NP and NP-membrane interactions**
  - Multiscale model for protein adsorption on NPs
  - Multiscale model of protein corona formation
  - Cell membrane model for the interactions of NPs with lipid monolayers and bilayers

Category formation/identification

- Preliminary strategy for grouping nanomaterials based on key physicochemical descriptors
- Evaluation of a data mining framework for the automatic identification of nanoparticle categories
- Ongoing refinement of categories and development of nano-read-across

More to come in 2015 …