UNIVERSITY OF CALIFORNIA
UC CEIN Center for Environmental Implications of Nanotechnology
NSF: DBI-0830117

Predictive Modeling for Health, with Material Characterization

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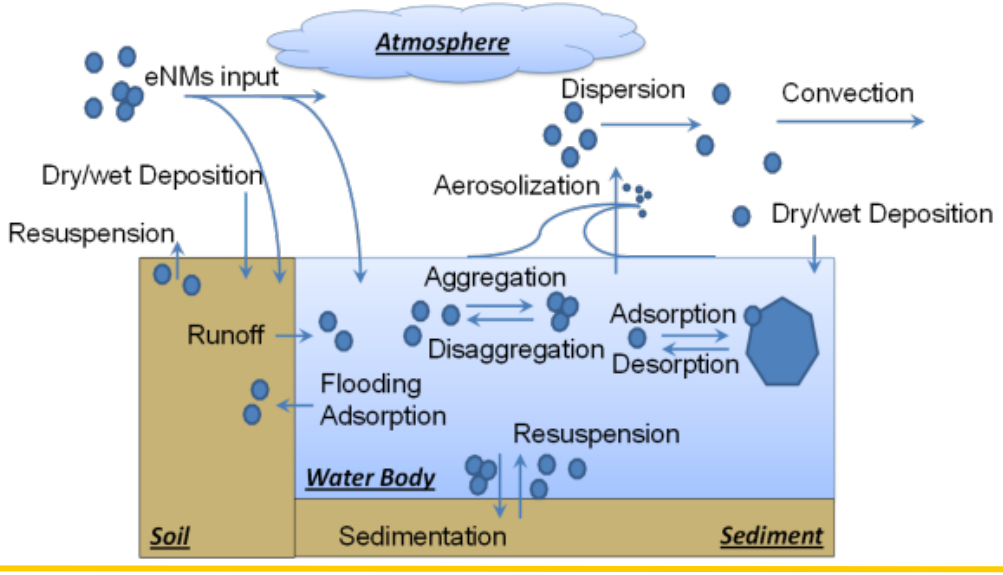


Is this Engineered Nanomaterial Environmentally Safe?

Information/Data Management

Experimental Studies / Models

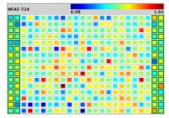
Hazard Identification

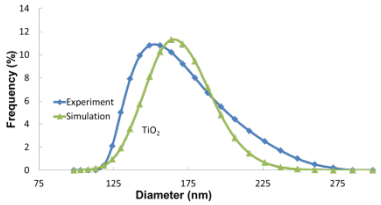
Physicochemical Characterization

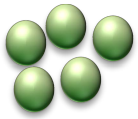
Exposure Assessment

In Vitro
In Vivo
Toxicity

In Silico Toxicity







Transport and Fate studies/ Modeling

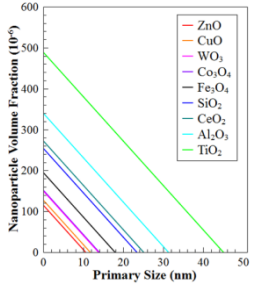
Monitoring

HT Exp.

LT Exp.

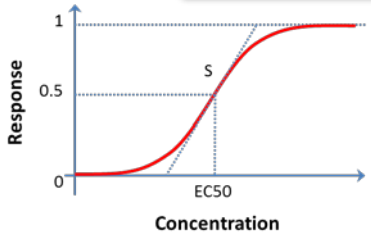
Mechanistic Conceptual

Quantitative Nano-SAR



Environmental Concentrations

- Dose- Response
- Hazard Thresholds



Environmental Impact Assessment

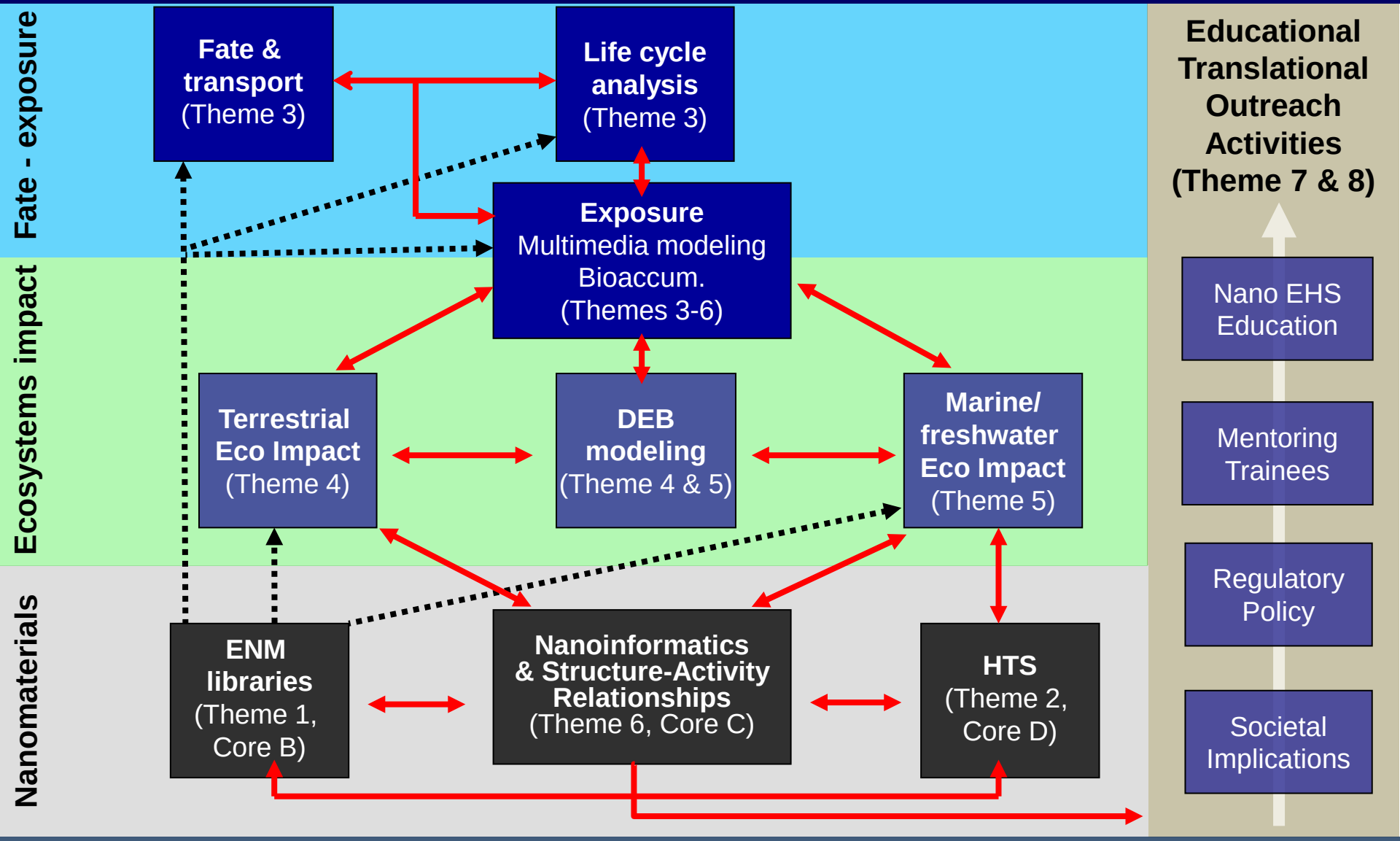
Decision Analysis

Product manufacturing & use approval

Product/process redesign

Exposure control

Process Flow for Integration of CEIN Activities



Center Outputs:

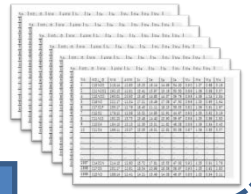
Predictive Toxicology; Hazard Ranking;
Environmental Decision Analysis; Risk Reduction and Safe Design Strategies

Approaches, Models and Nanoinformatics Tools Developed for ENMs Environmental Impact Analysis

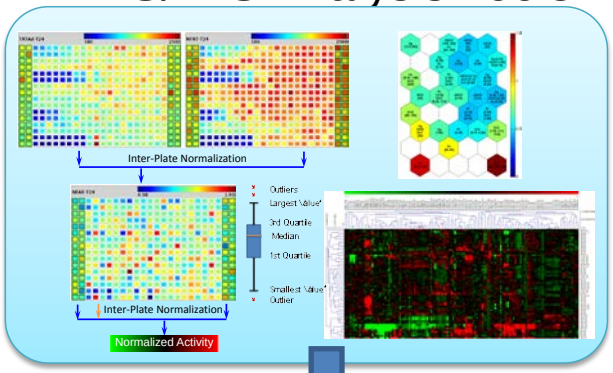
HTS/LTS

Studies

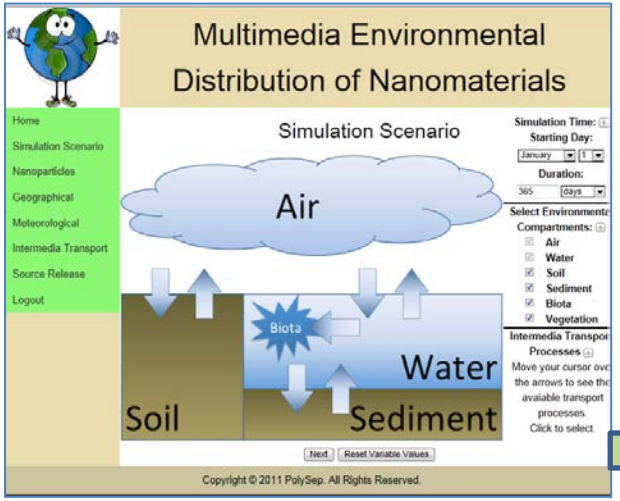
Data



HTS/LTS Analysis Tools



Mend-Nano

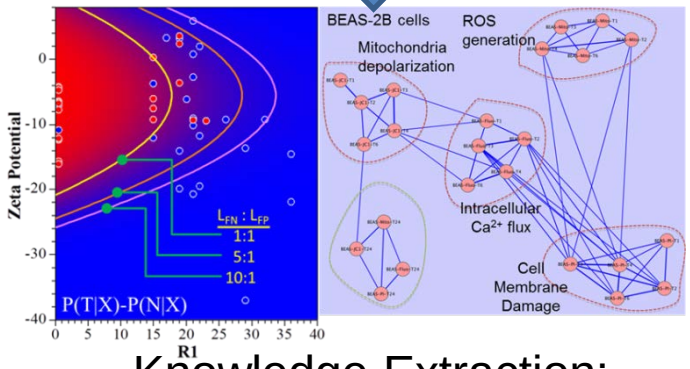


- ENMs F&T prop.
- Geographical & meteorological info.
- Emissions

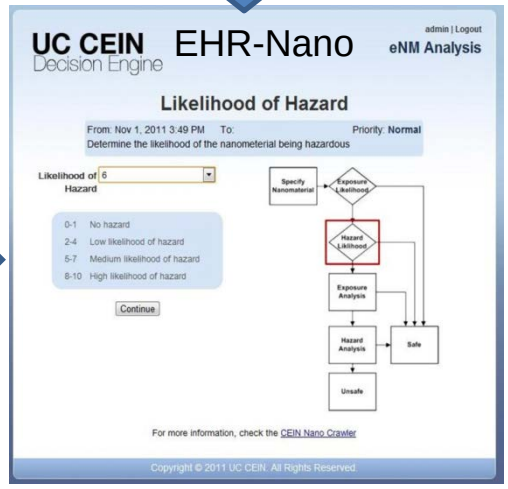
ENMs biota uptake parameters

Multimedia Analysis

ENM Concentrations & Mass Distribution



Knowledge Extraction: Toxicity Metrics & QSARs

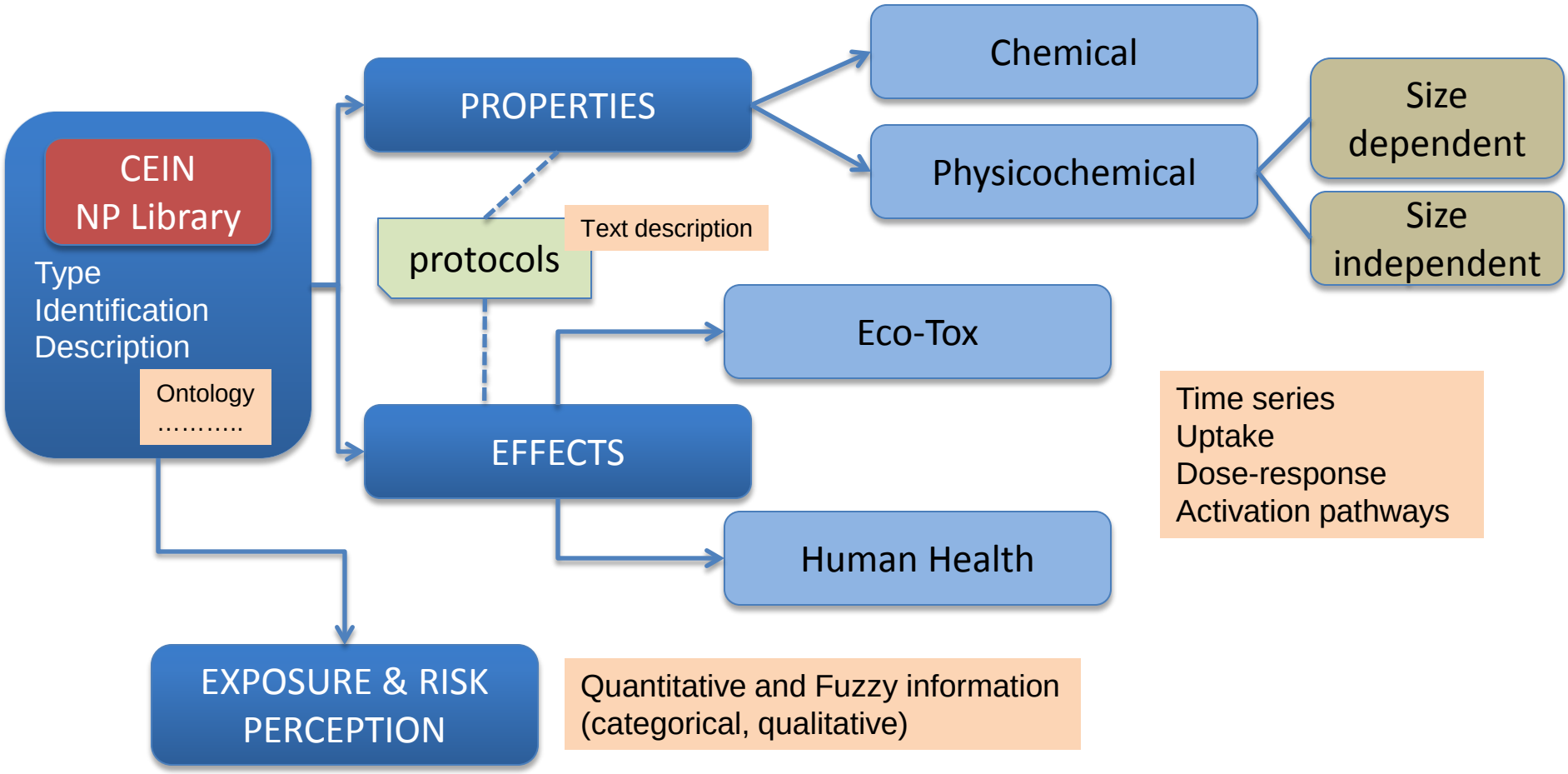


Environmental Impact Evaluation

Exposure Likelihood

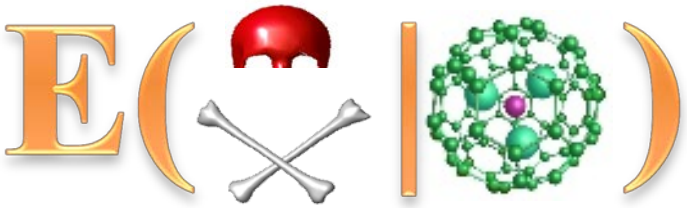
Environmental Hazard Ranking

Data Integration – Structured and Unstructured Datasets



(Q)SARs and Nano-SARs

QSAR
(Regression)



Continuous

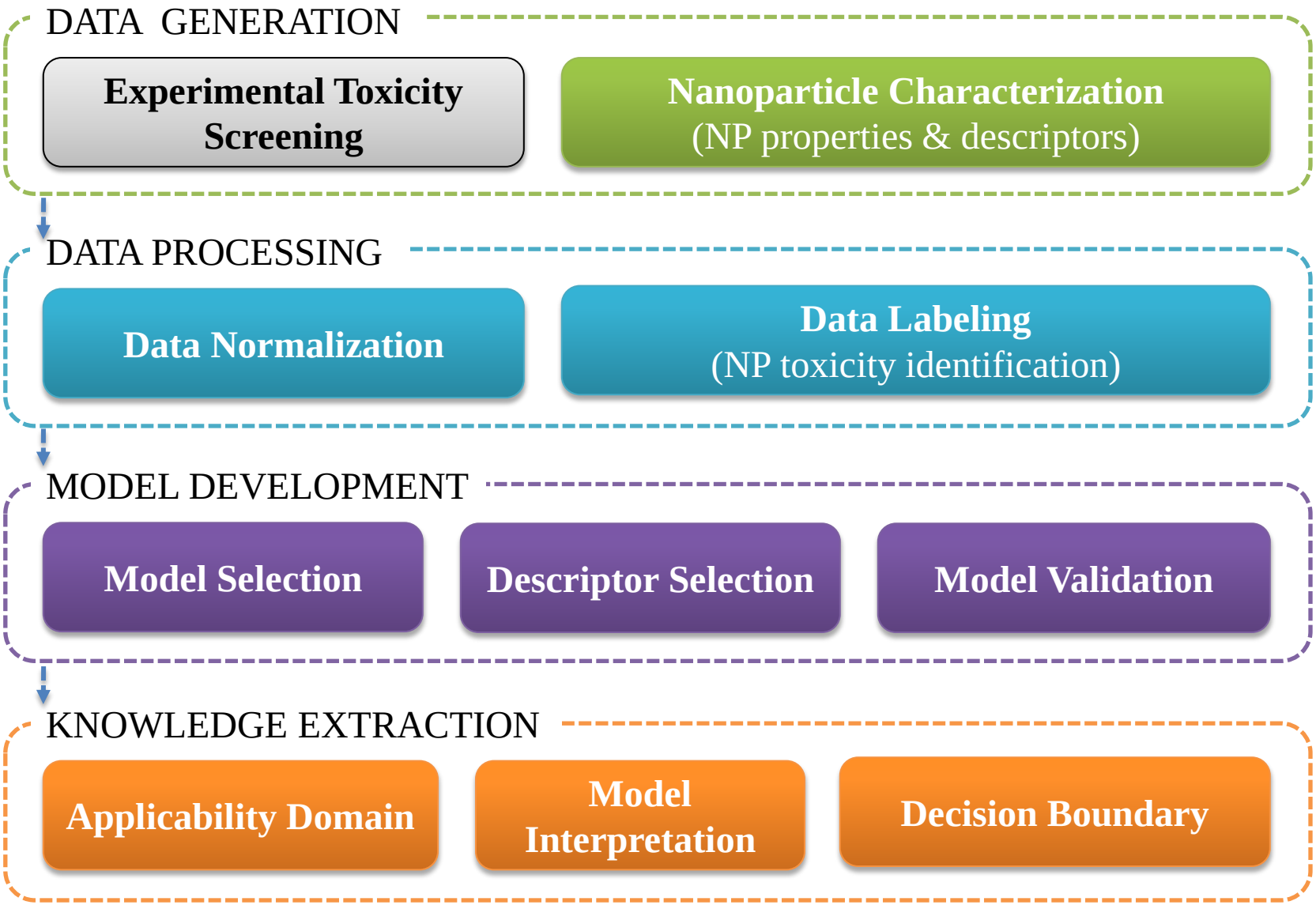
Activity ← Physicochemical NP descriptors and Env. conditions

Categorical

SAR
(Classification)

ENMs of similar physicochemical /structural properties are likely to induce similar response in biological receptors exposed to ENMs

Outline of SAR Development



Knowledge Extraction and Nano-SARs

Plate Visualization

HTS Data

Preprocessing

- Normalization
- Outlier Removal

Exploration

- Hit-Identification
- Heatmaps/clustering
- Self-organizing maps

Modeling

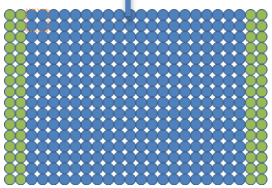
- Activity-Activity Relationships
- Structure-Activity Relationships

Application

- -Toxicity Metrics -Hazard Ranking
- Experiment Planning

Progressive Learning

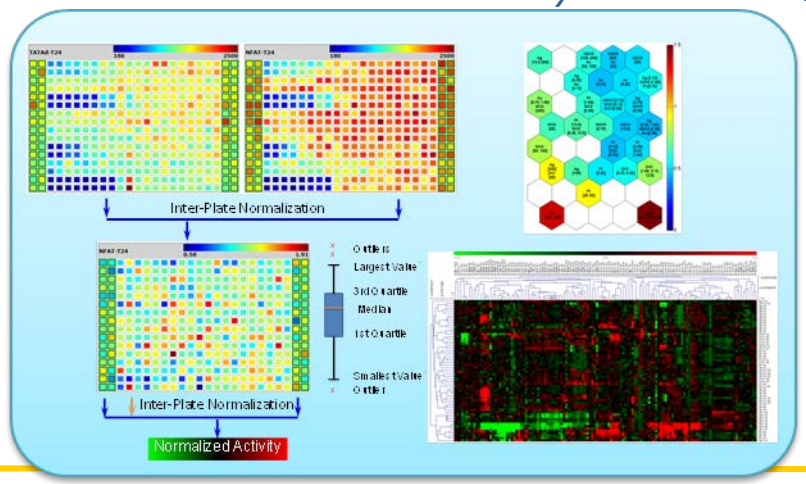
Image-based Phenotyping



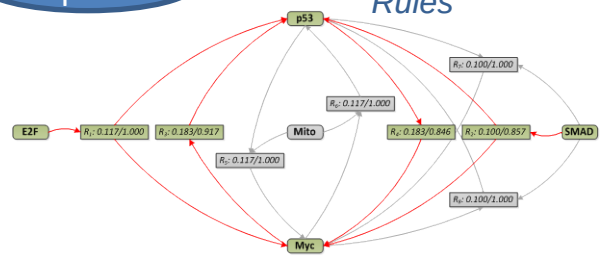
HTS – cytotoxicity/ signaling pathways

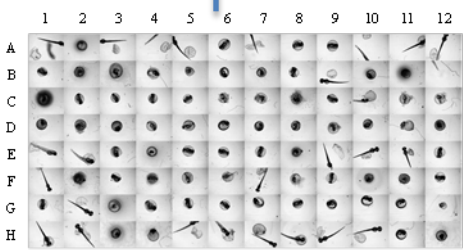
Physico-chemical Properties

Web-based HTS Data Analysis Tool



Association Rules





Zebrafish-based HTS

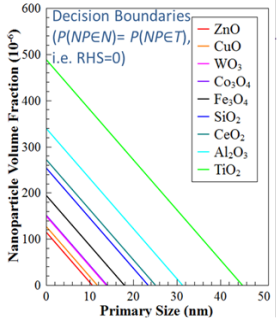
Nano-SARs

$$\ln\left(\frac{P(NP\in T)}{P(NP\in N)}\right) = 3600.6 + 103.5 \times d + 9.5 \times \theta_v + 97.6 \times P_{Me} - 58.5 \times E_{MeO}$$

Development of Nano-SARs based on HTS Toxicity Metrics

QSARs for toxicity of metal oxides ENMs

- Applicability domain
- Decision boundaries based on the acceptance ratio of false negatives to false positives
- Single end-point, multiple end-points, integrated end-points
- Quantification of uncertainties

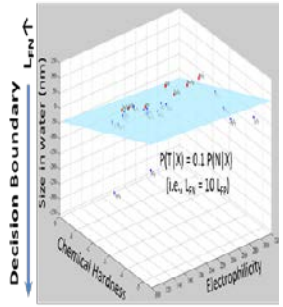


QSAR for metal oxides (9), based on cytotoxicity data for BEAS-2B cells, with 100% classification accuracy.

Liu et al., Small, 7(8): 1118-1126 (2011)

Predictive Classifier $h \geq 0$ → toxic; $h < 0$ → non-toxic

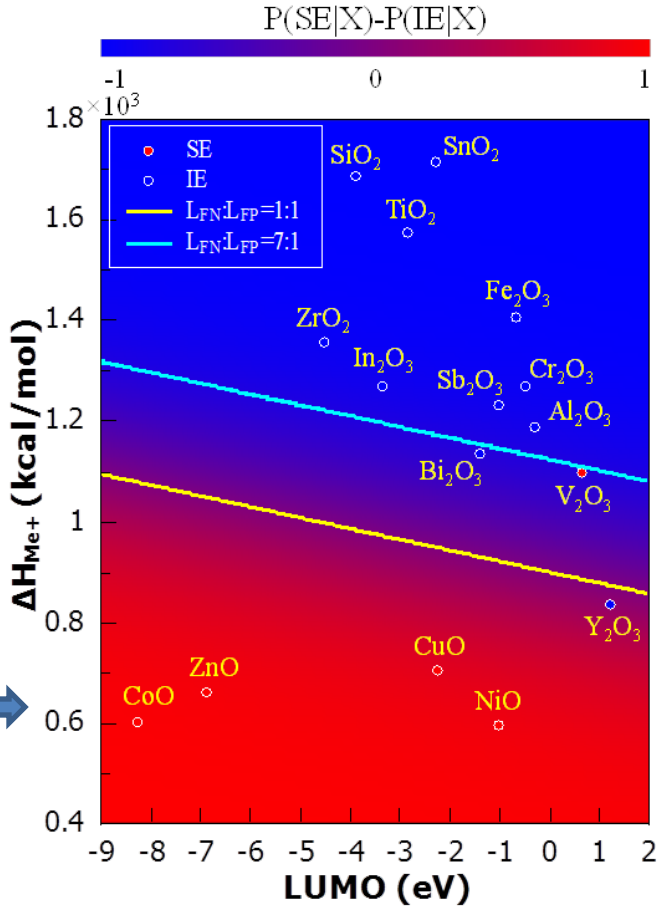
$$h = -58.5E_{AMZ} + 103.5d + 9.5\Theta_V + 97.6P_{Me} + 3600.6$$



Nano-SAR for metal oxides (24) (BEAS-2B and RAW cell lines; 3 assays)

Liu et al., ACR, in press

Based on Dose-Response Data



Issues for Discussion

- Considerations of nano-SAR intended use in the development process
- Documentation of nano-SAR development process
- Identification of statistically defensible and biologically meaningful toxicity metrics
- Basis for selection of nanomaterials and environmental descriptors
- Quantification of uncertainties
- Integration of nano-SAR development with experimental toxicity studies

QUESTIONS?