

Human Toxicity COR



Predictive Modeling  
for Human Health

# Human Toxicity COR - Breakout Session

Briefing by COR Co-Chairs: Yoram Cohen and Robert Rallo

## Presentations:

- Tina Bahadori – National Program Director, Chemical Safety for Sustainability (ORD/EPA)  
“US EPA’s perspective regarding present R&D efforts pertaining to assessment of human exposure to and toxicity of ENMs”
- Dario Greco – Finnish Institute of Occupational Health  
“Challenges in systems Nanotoxicology”

Outline of selected issues

Group discussion

# Data Relevance to Toxicity Modeling

What are the limitations of currently available (public) data for modeling endpoints/metrics that are relevant to human health?

How do we quantify data uncertainties, variability and quality in a manner that is suitable for regulatory decision support?

Do we generate a sufficient number of replicas to ensure statistical consistency?

What are the limitations of toxicity data? What are the suitable approaches to evaluate/quantify variability of biological systems and diversity of technical approaches/models?



# Modeling ENM Toxicity

Data-driven models based on the integration of available data (i.e., body of evidence)

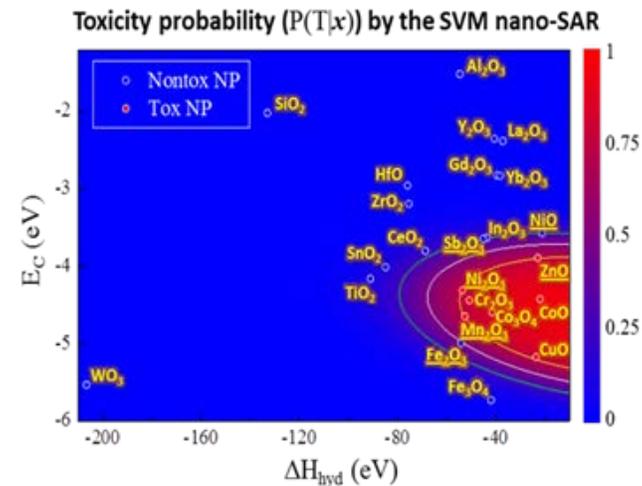
Need for systems biology models that focus on interactions due to exposure to ENMs

Develop understanding of modes of action (toxicity mechanisms)

Feature (descriptor) selection is critical for model development

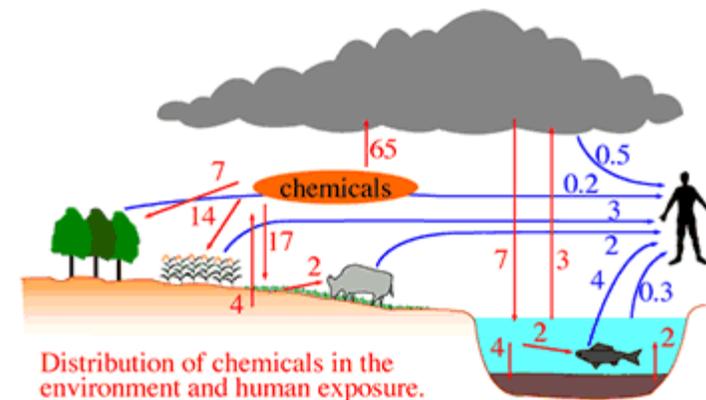
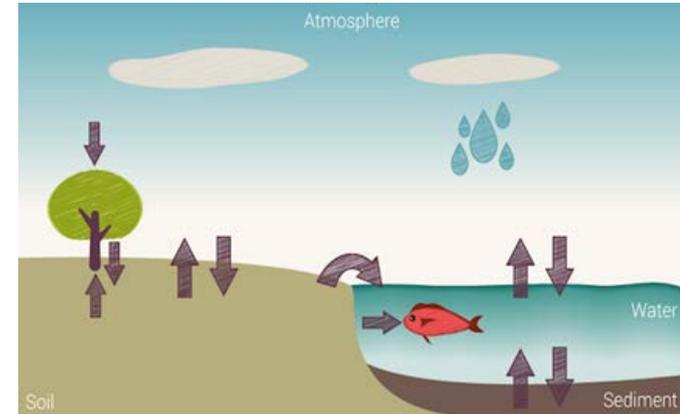
- Models based on specific bioactivity metrics (e.g., QSARs for  $EC_{50}$ )
- Classification based models (e.g., ranking of severity of impact; toxicity classes)

- Is computational systems biology at a sufficient stage of development to provide useful models for predictive toxicology?



# Relevance of Exposure to Toxicity Outcomes

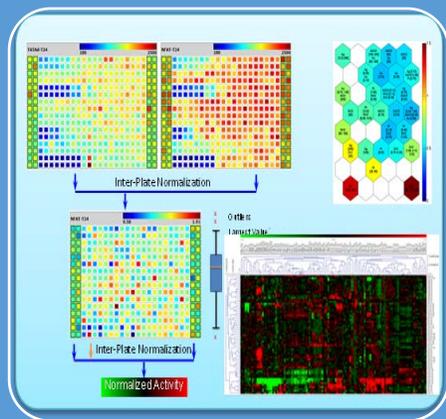
- Most toxicity evaluations are focused on pristine materials
  - There is a need to evaluate the relevance of mixtures (e.g., ENMs and chemicals)
  - Need standardized protocols for quantifying aging and degradation of ENMs
- For evaluated ENMs the regulatory concern appears to be well covered under regulations for the underlying chemicals constituting the bulk materials
- There is a need for clear and acceptable methodology of ascertaining the relevance of the material that is being evaluated (e.g., in its actual application) relative to the pristine material
- It is critical to evaluate toxicity at the expected critical routes and exposure levels throughout the lifecycle of the ENM (i.e., integrating lifecycle analysis with exposure assessment)



# Other Issues



What should be the role of modelers in the process of experiment planning & data generation?



Do the current OCDE guidelines for QSAR development need to be refined/updated to deal with the special characteristics of ENMs and available nanosafety data (e.g., limited size of nanoparticle datasets)?