us—eu
bridging nanoEHS research efforts

A Joint Workshop - March 10-11, 2011

Human Health Effects

(including effects and exposures….using Inhalation Toxicology as an example)

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NIEHS
National Institute of Environmental Health Sciences

Human Health Effects Discussion

1. Identify the Top Three Nearer Term Regulatory Challenges, and Data Needs to Address the Challenges

2. Identify Barriers to Implementation, and Areas of Near-term Cooperation for at least the No. 1 Regulatory Challenge

3. Provide suggestions for Longer Term Research (8-10 Year Timeframes)

Top Regulatory Challenges in the Field of Inhalation Toxicology

1. Validated and widely acceptable *in vitro* and *in vivo* screening platforms for regulatory decision making on inhalable ENMs

2. Dosimetry calculations that take into consideration hazardous material properties and also useful for setting exposure limits

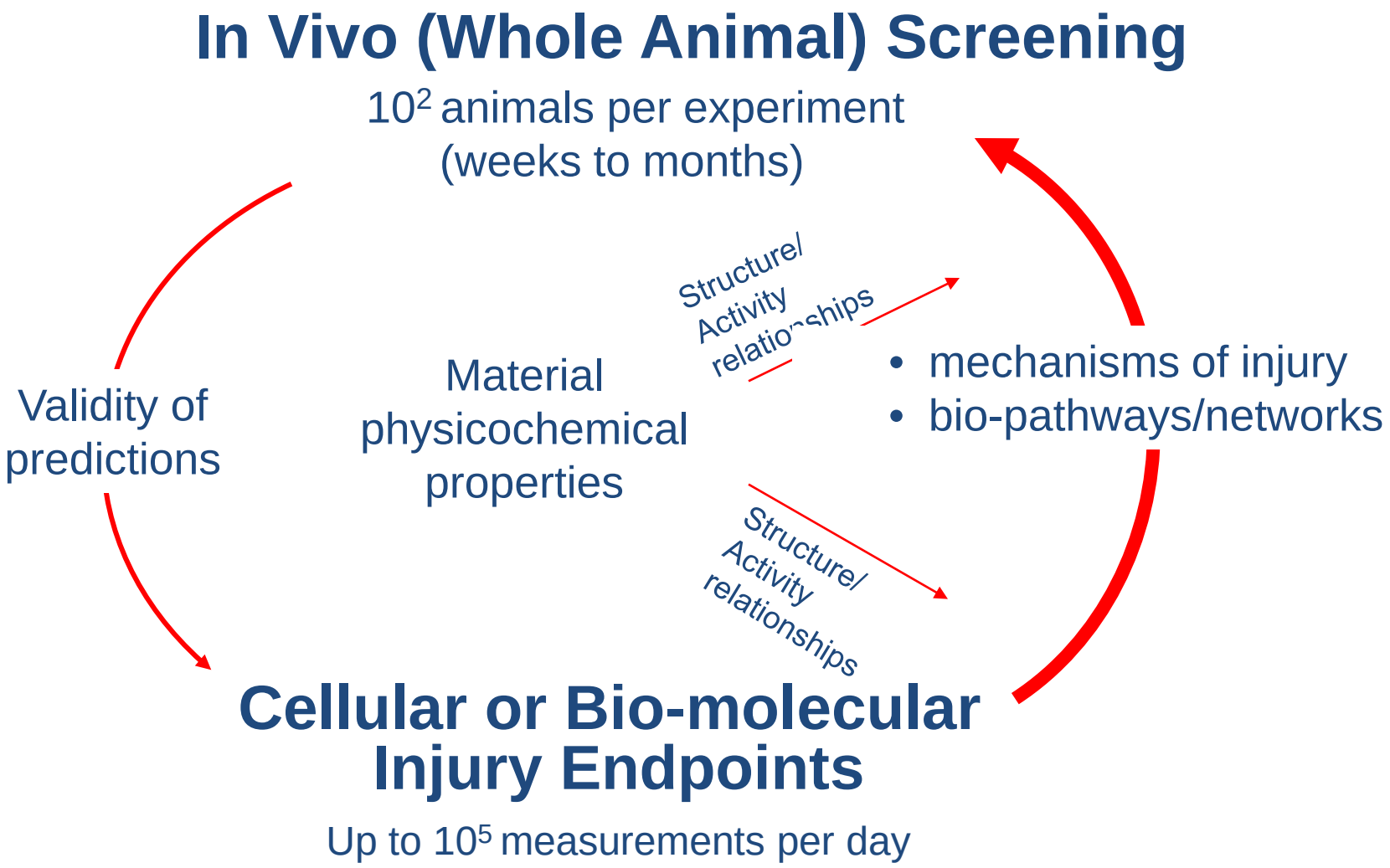
3. Personal exposure assessment

4. Implementation of risk reduction strategies while knowledge generation in points 1-3 is taking place

Barriers to accomplishing Validated and Harmonized *in vitro* and *in vivo* Screening Platforms for regulatory decision making

1. The complexity of the large # of ENM's and their novel properties
2. Determining which biological effects are truly predictive of real-life hazard and risk potential
3. Finding the correct systems biology approach for choosing the most appropriate *in vitro* and *in vivo* endpoints to study
4. The logistics, affordability and validation of testing
5. Who should fund and implement this testing: ? Academia, government or industry
6. Methods for dosimetry calculation that reflect the mechanism of injury

Correct Combination of *In Vitro* versus *In Vivo* knowledge generation required to meet the challenge



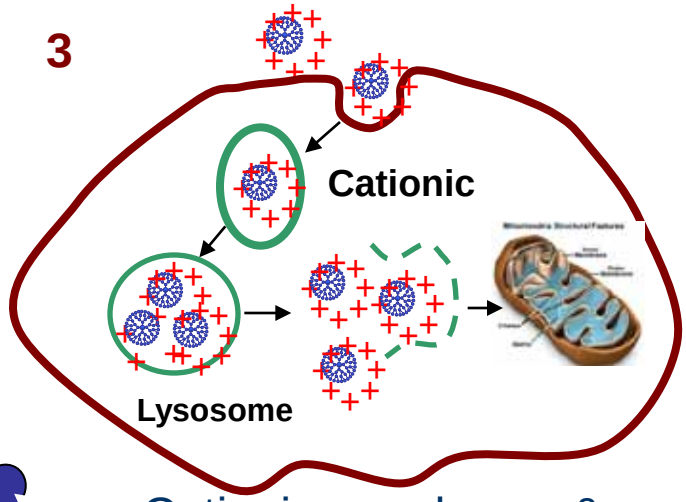
Nel et al Science, 2006.

Huan Meng et al ACS Nano,2009

Potentially useful Injury Paradigms for Pulmonary Toxicity Screening and Property-activity Relationships

1

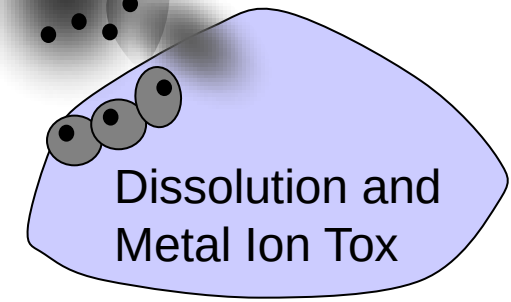
3



Cationic membrane & Organellar damage

5

Metal, MeO, QDs



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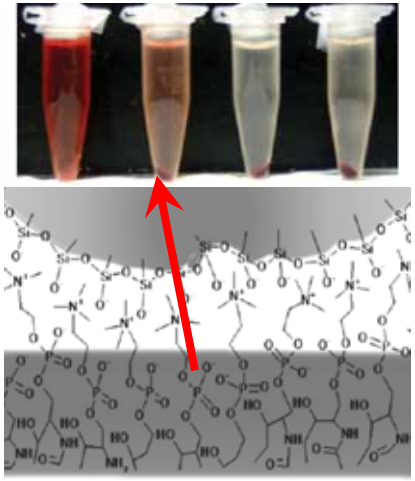
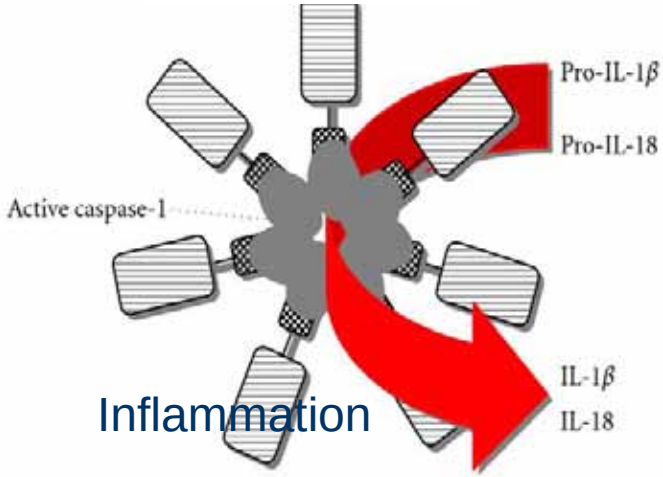


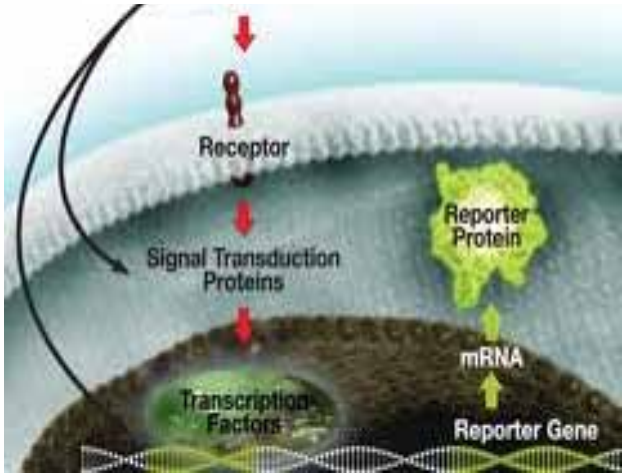
Membrane Injury and Perturbation

4 Inflammazone



Inflammation

6 Signaling pathway & Toxicogenomic responses

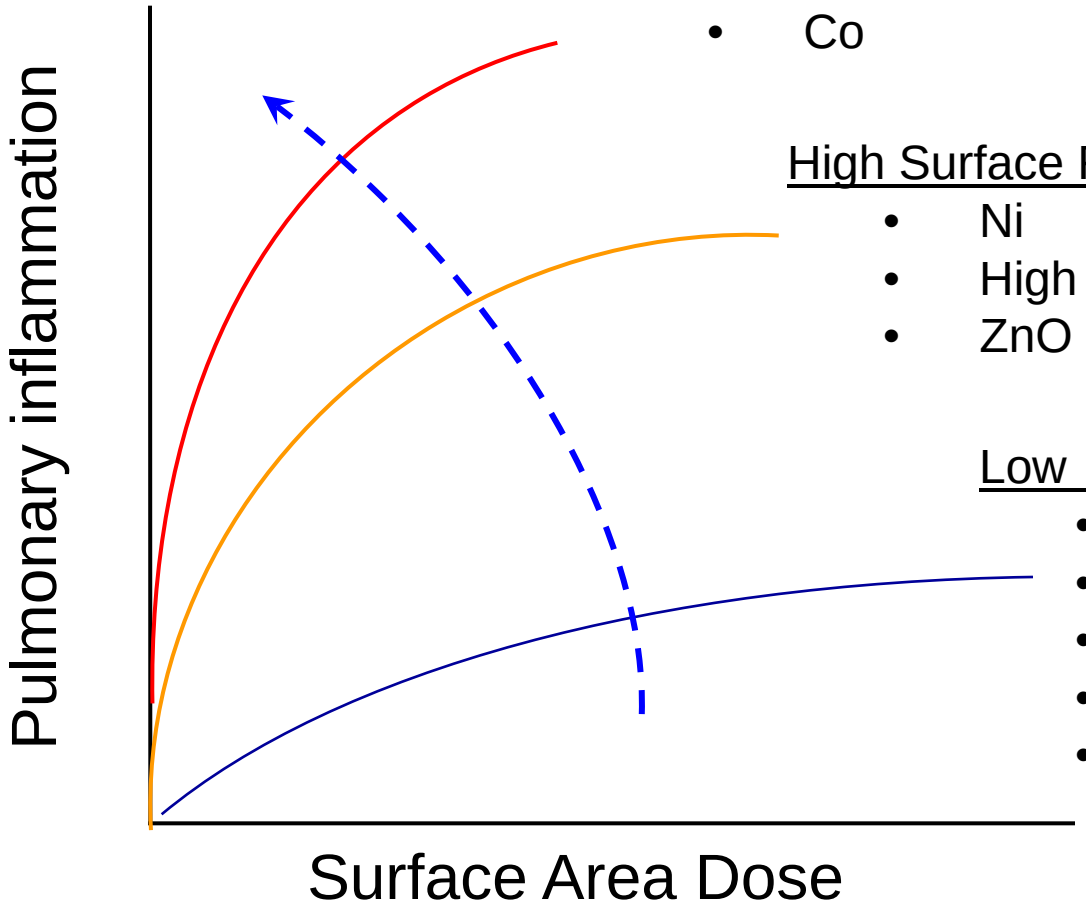


Nel et al. Science,2006; Nel et al. Nature Materials,2009

Particle and Fiber Hazards in the lung as a guide to ENM Toxicology Considerations

Toxicological Paradigm	Possible pathology/disease
Metal and metal oxide toxicity based on bandgap and oxidative stress parameters (wide range materials)	Oxidant injury, lung inflammation, fibrosis (concept of low and high surface reactive materials)
Dissolution chemistry with shedding toxic metal ions (Zn, Cu, Ag) or leaching metal contaminants (CNTs)	Acute neutrophil inflammation (e.g., metal fume fever syndrome, ZnO) or CNT contribution to granulomatous inflammation/fibrosis
Crystallinity, surface reconstruction and surface display of dangling hydroxyls oxygens (crystalline Si polymorphs)	Chronic inflammation/fibrosis (silicosis equivalent) (includes oxidative stress)
Cationic injury to the lysosome or surface membrane (cationic functionalized NPs)	Acute pulmonary edema and bronchiolitis obliterans (Ardystil syndrome)
Inflammazone activation, chronic granulomatous inflammation or pro-fibrinogenic responses (CNTs)	Pulmonary fibrosis, granulomas and Mesothelial inflammation (CNT)

A proposed paradigm for ENM pulmonary toxicity evaluation: Concept of NP Surface Reactivity



Very High Surface Reactivity:

- Crystalline Si (quartz)
- Cu
- Co

High Surface Reactivity:

- Ni
- High cationic charge
- ZnO

Low Surface Reactivity:

- TiO_2
- Au, Ag
- Carbon black
- Amorphous Si
- Polystyrene

Suggestions for Longer Term Collaborative Research

- Develop predictive toxicological approaches that utilize the correct balance between *in vitro* and *in vivo* testing
- Develop validated screening methods, harmonized protocols and risk reduction strategies
- Develop appropriate dosimetry metrics and improved technology to track and calculate personal exposures
- Develop high throughput and high content screening as a universal tool for studying ENM toxicity, hazard ranking, and *in vivo* prioritization
- Develop computational analysis and *in silico* decision-making tools (computational biology, nano informatics, modeling)
- Develop a stepwise approach to nano EHS governance that takes into consideration incremental knowledge generation
- More robust, and more meaningful, decision-analysis tools that accommodate broad perspectives on risks and benefits

Example: Streamlined Risk Reduction Approach for setting Exposure Limits and Effective Exposure Control by NIOSH

Prioritize CNT

- Widespread use
- High volume of production

Animal hazard studies

- Acute exposures
- Multiple study review
- No single study yields sufficient risk assessment
- Coherence of data revealing lung fibrosis and granulomas

Achieves risk prevention without:

Complete risk characterization
Chronic inhalation data
Complete exposure data

New Technology

Facilitates airborne CNT detection

Calculated

Assess occupational exposure potential

- Workplace surveys/measurement
- Significant airborne levels
- Limits of detection
- Exposure events: weighing, mixing, vortexing, transfer, etc.

Potential human exposure levels & dose based on

- Animal lung burden assessment
- Animal to human comparisons based on alveolar epithelium surface area ratios

Establish Exposure Limit

Effective control measures (HEPA filters, ventilation, respirators) ↓ human exposure below LOD

Example: Stepwise approach to the formulation of Nano-regulatory Policy

Stage 1: Short-term Approach

Changes we could implement with existing information and statutes through coordination:

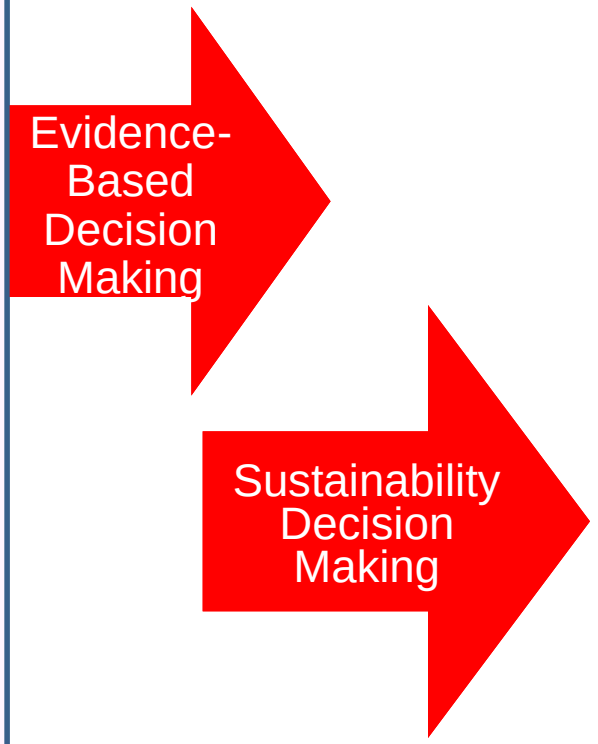
- Data collection (e.g., Tox Testing approaches)
- Safe and best practices (e.g., occupational exposures)
- Hazard ranking
- Exposure assessment
- Harmonization
- International cooperation
- Streamlined risk reduction

Stage 2: Longer term approaches

Risk prevention paradigm

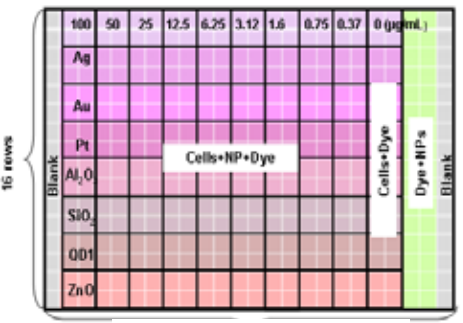
- Proof of hazard, exposure reduction
- Effective control measures
- Continuously improving best practices
- Restrict specific ENM if risk is compelling
- Safe-by-design materials
- Active role for industry

Future Stages



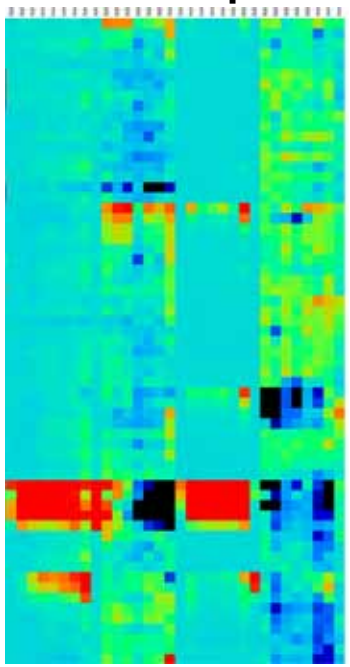
Me, MeO Libraries

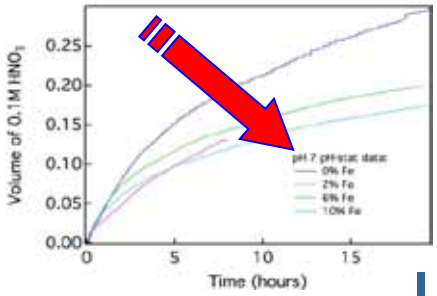
Metal Ions



HTS Plate Map

Heatmap



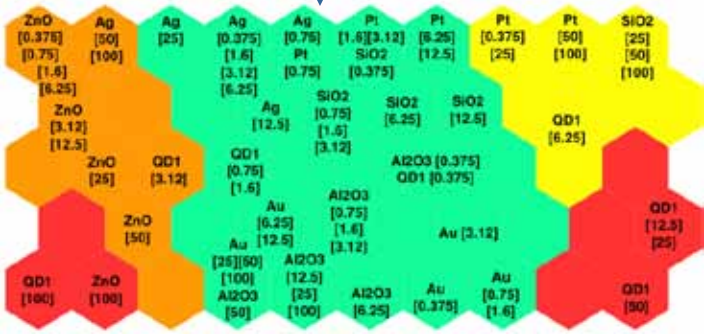


Zebrafish embryo

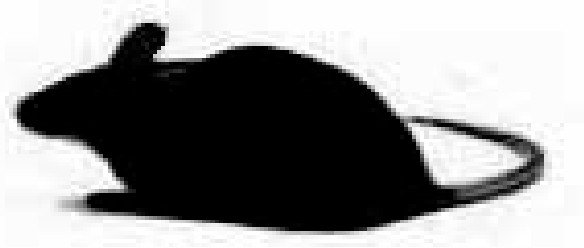
Fe-doped
↓ Dissolution

ZnO

George et al ACS Nano, 2010
George et al ACS Nano, 2011
Xia et al ACS Nano, 2011
Thomas et al ACS Nano, 2011



Material Cluster Map and QSARs



Mouse, Rat Lung