Human Health Effects

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

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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.

**In Vivo (Whole Animal) Screening**
- 10^2 animals per experiment (weeks to months)
- Material physicochemical properties
- Structure/Activity relationships
-_validity of predictions
- Cellular or Bio-molecular Injury Endpoints
- Up to 10^5 measurements per day
-_mechanisms of injury
- bio-pathways/networks

_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. Redox activity
   Oxidant injury
   Bandgap status

2. Membrane Injury and Perturbation

3. Cationic membrane & Organellar damage
   Cationic
   Lysosome

4. Inflammasome
   Pro-IL-1β
   Pro-IL-18
   Active caspase-1
   IL-1β
   IL-18

5. Metal, MeO, QDs
   Dissolution and Metal Ion Tox

6. Signaling pathway & Toxicogenomic responses
   Receptor
   Signal Transduction Proteins
   mRNA
   Reporter Gene
   Transcription Factors

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

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

**New Technology**
Facilitates airborne CNT detection

**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**

**Achieves risk prevention without:**
- Complete risk characterization
- Chronic inhalation data
- Complete exposure data

**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

- Evidence-Based Decision Making
- Sustainability Decision Making