NIEHS and NTP Activities Evaluating the Safety of Nanoscale Materials

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NIEHS and NTP

• National Institute of Environmental Health Sciences (NIEHS)
  – One of 27 research institutes and centers that comprise the National Institutes of Health (NIH)
  – Located in Research Triangle Park, North Carolina
  – Mission: to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

• National Toxicology Program (NTP) (ntp.niehs.nih.gov)
  – Interagency program headquarterd at NIEHS, established in 1978 to coordinate toxicology testing programs within the federal government
  – Mission: to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology.
Nanotechnology Environmental Health and Safety

- NIEHS identifies nanotechnology as a high priority
- Global demand for nanomaterials and devices will reach $3.1 trillion by 2015
- Unanticipated exposure
- Unknown health consequences
- Biological interactions at nano-scale (physical and chemical properties) are not known
Overview of NIEHS and NTP nano activities

• Funded by NIEHS
  – Division of Extramural Research and Training (DERT)
    • Grants
    • Training
    • Superfund

• NIEHS research
  – Division of Intramural Research (DIR)
    • Investigator Initiated research
    • Application of nanotechnology in EHS
  – National Toxicology Program (NTP)
    • Contract based research and testing
Nanotechnology-Environmental Health and Safety

• Nano Grand Opportunity (GO) program
  – Established a consortium to address critical research need: develop reliable and reproducible methods for toxicity evaluation of engineered nanomaterials (ENMs)

• NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR)
  – To gain fundamental understanding of nanomaterials interactions with biological systems
  – How diverse physical and chemical properties (PCPs) dictate these interactions
  – Translate observations from in vitro to in vivo
  – Aid development of risk assessment models to predict safety of ENMs based on PCPs
NIEHS Nano Grand Opportunity (GO) Program

• $13 Million from ARRA
  – Consortium-based research model to develop reliable and reproducible methods to test engineered nano material (ENM) toxicity
    • 10 NanoGO Grants
    • 3 Challenge Grants

• Ongoing studies to predict toxicity of 3 different well characterized ENMs
  – Human and rodent cell lines (4 assays)
  – Preliminary results from 8 labs doing round robin testing show high reproducibility of data
NIEHS Centers for Nanotechnology Health Implications research (NCNHIR)

• Gain fundamental understanding of nanomaterial biological interactions as dictated by their physical and chemical properties
  – Five U19 Grants
  – Three U01 Grants

• Contract Support:
  – National Characterization Laboratory (NCL)
  – NIBIB: Nano Registry
Nanotechnology Applications

• Nanotechnology-based sensors
  – Characterization of exposures to multiple analytes with high sensitivity and temporal resolution in small inexpensive devices.

• Bioremediation Using Nanomaterials
  – Nano-towel to capture mercury vapor
  – Nano-scaled iron particles for water cleanup
  – Nanoparticles applied to reduce PCBs,
    – PAHs, PBDEs
Nano at NIEHS

- Funded by NIEHS
  - Division of Extramural Research and Training (DERT)
    - Grants
    - Training
    - Superfund
- Research at NIEHS
  - National Toxicology Program (NTP)
    - Contract based research and testing
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    - Investigator Initiated research
    - Application of nanotechnology in EHS
National Toxicology Program?

• Interagency program
  – Established in 1978 to coordinate toxicology research in DHHS
  – Headquartered at NIEHS, part of NIH

• Research on submitted “nominations”
  – Thousands of agents evaluated in comprehensive toxicology studies
  – GLP compliant “testing” through government contracts

• Analysis activities
  – Report on Carcinogens
  – Center for the Evaluation of Risks to Human Reproduction (CERHR)
  – NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
NTP Research and Testing Programs

- AIDS therapeutics
- Air/Food/Water contaminants
- Cardiovascular disease/toxicity
- Dietary supplements
- DNA-based therapeutics
- Endocrine disruptors
- Flame retardants
- Green chemistry
- Herbal medicines
- Mold
- **Nanoscale materials**
- Occupational exposures
- Phototoxicology
- Radiofrequency radiation
- Risk assessment issues/mixtures
NTP Activities on nanomaterial classes

- Cadmium based “quantum dots”
  - Role of skin integrity on pharmacokinetic studies after dermal exposure
- Titanium dioxides
  - Dermal pharmacokinetics
- Carbon based fullerenes; Pulmonary and oral toxicity
  - Impact of size of C60 aggregates
- Multiwalled carbon nanotubes
  - Influence of length and diameter on pulmonary toxicity
- Exposure assessments
- Nanosilvers
  - Role of particle size and shape on PK and toxicity
Lack of dermal Penetration of skin by Quantum dots

- Supported by Interagency agreement between NIEHS and NCTR/FDA
- Gopee et al 2007, 2009
- Dermal exposure to SKH-1 mice
  - Intact and dermabraded
- Use of quantum dots as model system
  - ((CdSe)CdS)-PEG (Emax621nm)
  - Quantitation of Cd in tissues by ICP-MS and confocal fluorescence microscopy
- No consistent penetration through intact skin

- Gopee et al 2007, 2009
Lack of dermal penetration by metal oxides

• Gopee et al 2009
• Dermal exposure to SKH-1 mice
  – Intact and dermabraded
• Use of uncoated anatase P25 Ti02
  – 5% Ti02 in representative emulsion
  – Spatial evaluation by Cytoviva dual mode darkfield microscopy
  – Quantitation of Ti in sentinel tissues by ICP-MS
• No consistent penetration through intact or dermabraded skin
Carbon-based NSMs

- **Fullerenes**
  - eg C60 “Buckyballs”

- **Nanotubes**
  - Single walled (SWNT)
  - Multi walled (MWNT)

- **Nanofibres/nanofibrils**

Source: J Nucl Med 48: 1039
Pulmonary toxicity evaluation of Fullerene-C60

- NTP inhalation study conducted under GLP
  - 90 days-nose only exposure, 3hrs/day, 5d/wk
  - B6C3F1 mice and Wistar-Han rats
  - 50nm (0.5 and 2 mg/m³)
  - 1μm (2, 15 and 30 mg/m³)
- Preliminary findings
  - Shorter clearance in mouse vs rat
    - Not size effect
  - No biologically significant toxic responses
  - Expected response to particles
  - Comparable surface area-based doses between 50nm and 1μm study
Occupational exposures to Carbon nanomaterials

- Interagency agreement with NIOSH
  - Chuck Geraci and Mary Schubauer-Berigan, NIOSH
- Evaluate the feasibility of industry-wide exposure assessment and epidemiology studies of US manufacturers of engineered carbonaceous nanomaterials (ECN)
- Information includes
  - Nanomaterials produced, characterization of size and shape
  - Size of worker population by facility
  - Tonnage of materials used or produced
  - Workforce size
- Status
  - Approx 60 companies, >50% CNTs, fullerenes the next most common
  - Several hundred workers, workforce growing annually
A National Toxicology Program for the 21st Century

• Roadmap to Achieve the NTP Vision (2004)
  – “To support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target specific, mechanism-based, biological observations.”

• Key activities
  – Develop high-throughput capabilities
  – Further evaluate and refine the use of non-mammalian models
  – Improve the use of toxicokinetic information
NTP High Throughput Screening

• **Main goals**
  – Identify mechanisms of action
  – Prioritize substances for further in-depth toxicological evaluation
  – Develop predictive models for in vivo biological response

• **Tox21**
  – Collaboration with USEPA, NCGC
  – Focus on small molecules
  – EPA testing set includes nanomaterials
Nanotechnology at NIEHS

• NIEHS is actively involved in US federal research efforts coordinated by National Nanotechnology Initiative

• Took leadership roles in addressing environmental health and safety concerns of widespread use of nanotechnology.

• Supports research programs in:
  – Health implications of nanotechnology based materials and devices
  – Application of nanotechnology-based sensors/tools for environmental monitoring
  – Superfund remediation efforts
Key Personnel

• NIEHS; Grants Programs
  – EHS - Sri Nadadur, PhD
  – Superfund: Heather Henry, PhD
  – Applications-David Balshaw, PhD

• NIEHS; Toxicology Liaison (Bethesda office)
  – Chris Weis, PhD

• National Toxicology Program
  – NIEHS; Nigel Walker, PhD
  – FDA; Paul Howard, PhD
  – NIOSH; Mark Torasson PhD, Charles Geraci PhD, CIH