Nanotoxicology Program

Jenny R. Roberts, Ph.D.
HELD/ACIB
NTRC Toxicology and Internal Dose Critical Area Coordinator
National Institute for Occupational Safety and Health
Morgantown, WV

DEPARTMENT OF HEALTH AND HUMAN SERVICES · USA

CDC Workplace Safety and Health

National Institute for Occupational Safety and Health NIOSH®

Definitions

- Nanoparticle:
  - A particle having one dimension less than 100 nm.

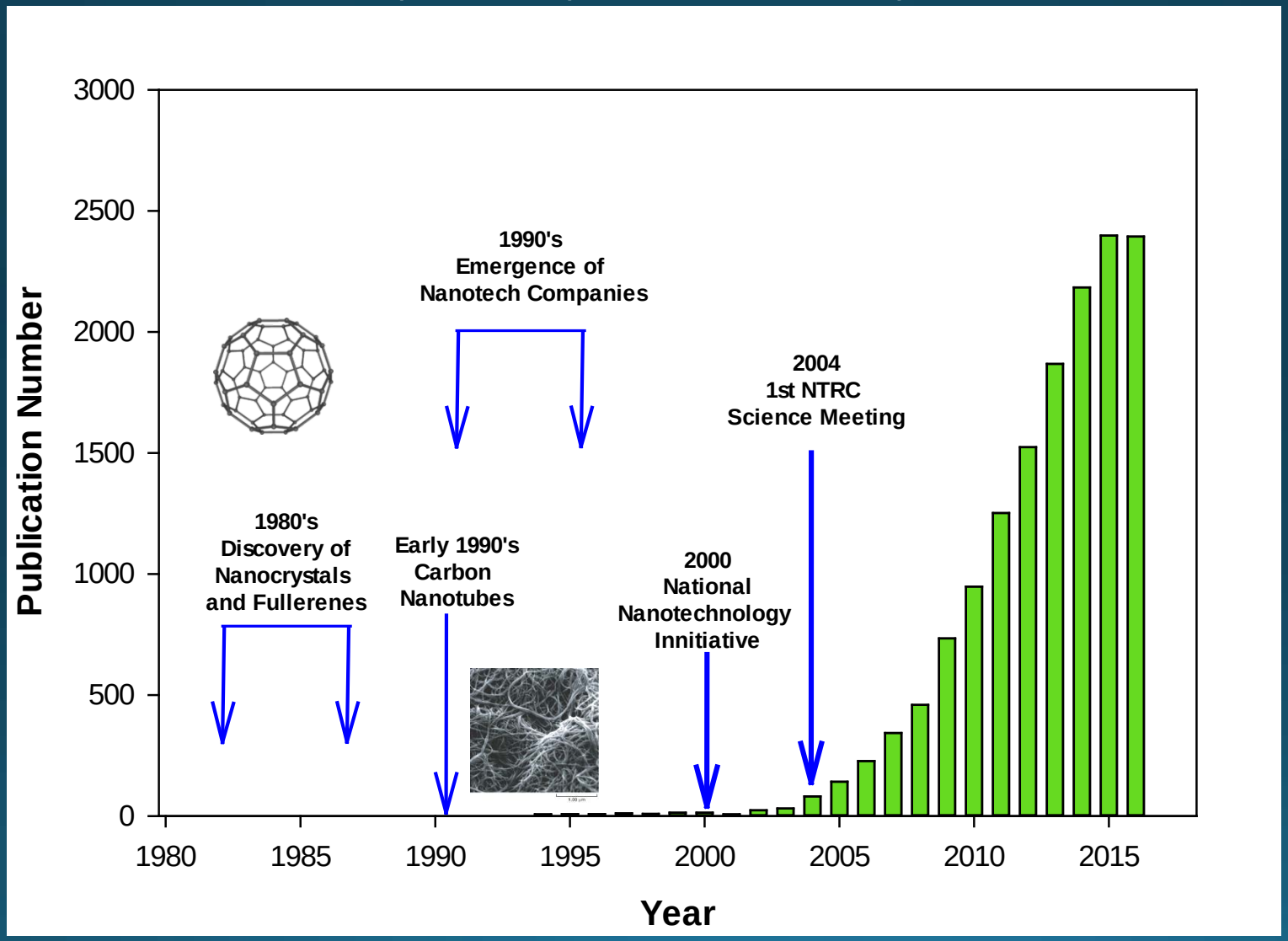
  Carbon Nanotube (1 nanometer) x 100,000 = Strand of Hair (100 microns)

- Engineered Nanoparticle:
  - Created for a purpose with tightly controlled size, shape, surface features and chemistry.

- Incidental Nanoparticle:
  - Created as an inadvertent side product of a process.

Growth of Nanotoxicology as a Field of Study

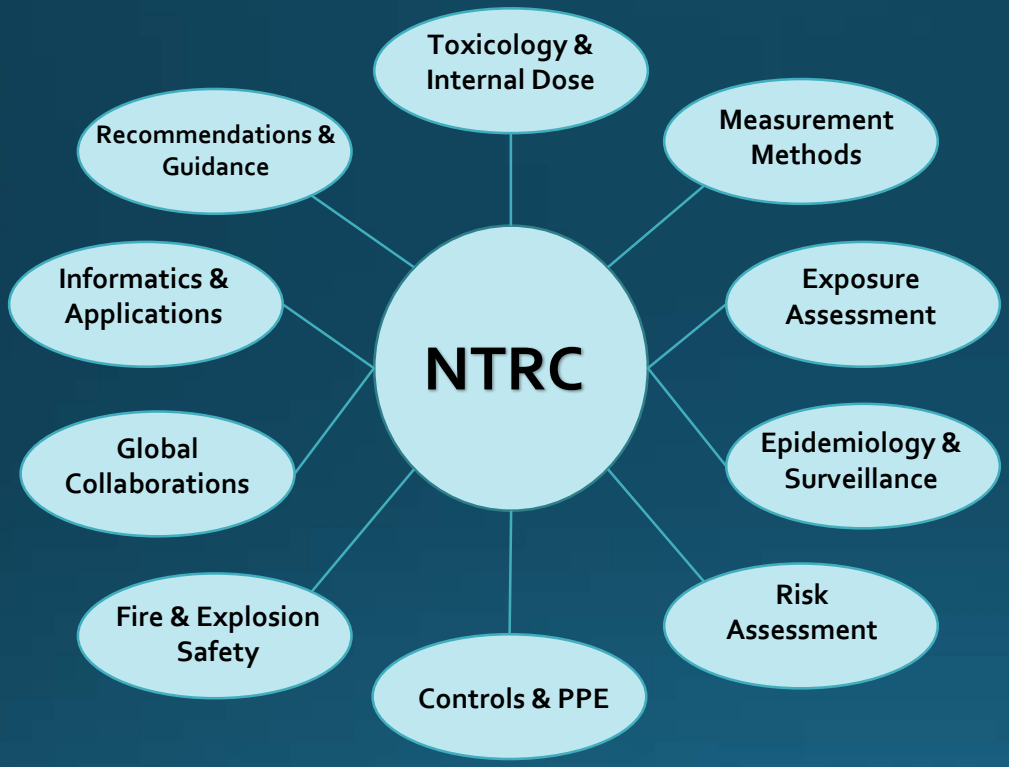
Scopus: Nanoparticles and Toxicity



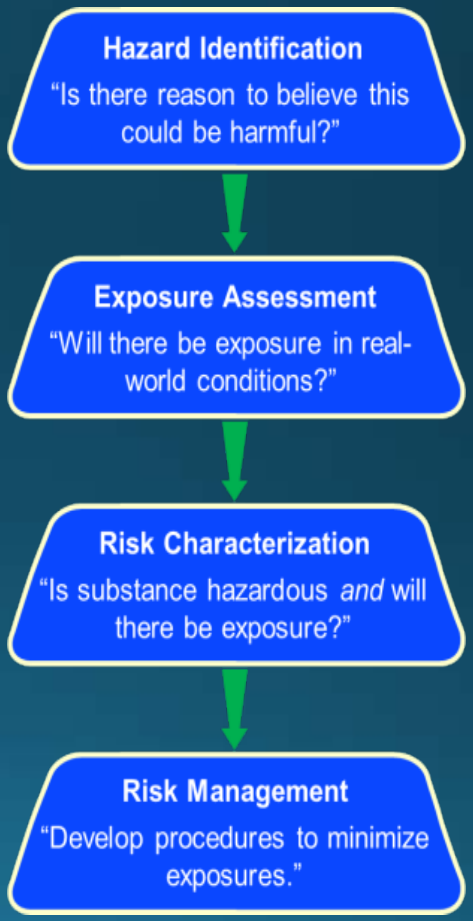
Timeline and Images: www.nano.gov

Nanotechnology Research Center (NTRC)

NTRC: 10 Critical Areas



NIOSH Program



2016
Nanotoxicology Projects: 11 HELD, 13 NTRC
> 40 Extramural Collaborations – Academia, Government, **Industrial**

- **Strategic Plan Goals Pertaining to Toxicology**

1. Increase understanding of new hazards and related health risks to nanomaterial workers.

Conduct research to contribute to the understanding of the toxicology and internal dose of emerging ENMs.

Determine whether nanomaterial toxicity can be categorized on the basis of physicochemical properties and mode of action.

2. Expand understanding of the initial hazard findings of engineered nanomaterials.

Determine whether human biomarkers of nanomaterial exposure and/or response can be identified.

Determine the relevance of in vitro and in vivo screening tests to worker response to inhalation of ENMs.

Identification of materials of interest for investigation

- through directives and/or partnerships with other agencies/organizations (military, CPSC, EPA, FDA, NIST, NTP, OECD, ISO, WHO)
- through partnership with Industry – availability of materials that address NIOSH research questions (life cycle, prevention through design, structure – function relationships, etc.), pairing of field studies and toxicological evaluation (occupationally relevant materials and exposures)
- highly produced/utilized materials – global concern or globally identified as high priority
- nanomaterials that allow us to answer a specific research question - identify physical chemical properties and related mechanisms of action, address prevention through design

Nanomaterials Investigated at NIOSH

MWCNT – Mitsui 7

DWCNT – double walled CNT

MWCNT – amine and carboxyl functionalized

MWCNT – Doped (Nitrogen, Aluminum)

MWCNT – Heat Treated

Vapor-grown Carbon nanofibers (CNF)

CNT and CNF – 10 US Facilities in Epidemiology Study

SWCNT – single-walled CNT

Carbon Nanodots

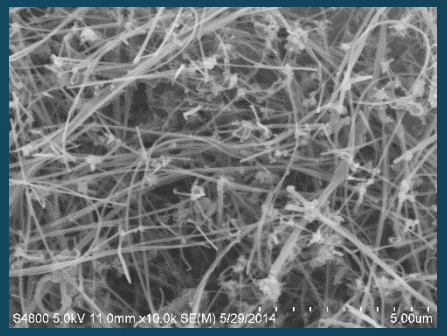
Graphite Nanoplatelets or Nanoplates

Graphene

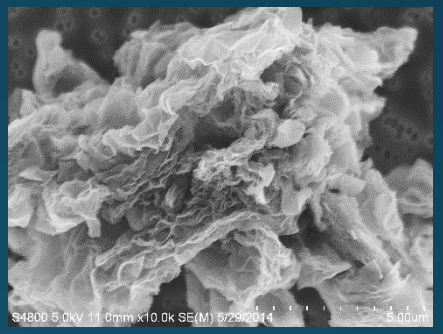
Graphene Oxide

Nanocellulose Nanomaterials

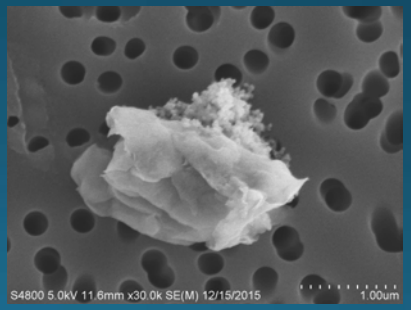
Natural and Organomodified Montmorillonite Nanoclay



MWCNT- Mitsui 7 – Courtesy of Bob Mercer



Layered Reduced Graphene Oxide

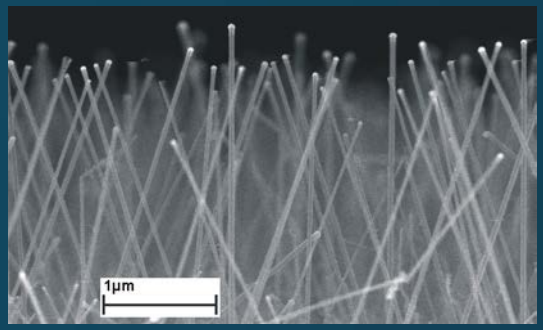


Stacked Plates of Nanoclay – courtesy of Todd Stueckle

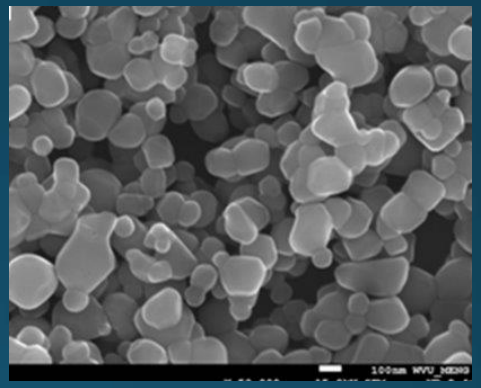
Nanomaterials Investigated at NIOSH

Boron Nitride Nanotubes
Boron Nitride Nanopowder
Silicon nanowires
Elemental nano-silver
Cerium Dioxide
Lanthium Oxide
Cobalt Oxides
Nickel Oxide
Iron Oxides – SiO2 coated and uncoated
Zinc Oxide Spheres and Nanowires
Elemental Zn
Titanium Dioxide Nanorods, nanowires, nanobelts
SiO_2 – amorphous and crystalline
Tungstate (particles and rods) CaWO4, SrWO4, BaWO4
Tungsten carbide-cobalt
Tungstate (particles and rods)
- $CaWO_4$
- $SrWO_4$
- $BaWO_4$

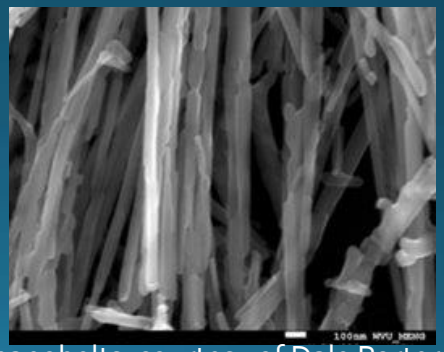
Copper Oxide
Quantum Dots – ZnS/CdSe



Si nanowires: Roberts et al., 2012



TiO2 nanospheres: courtesy of Dale Porter

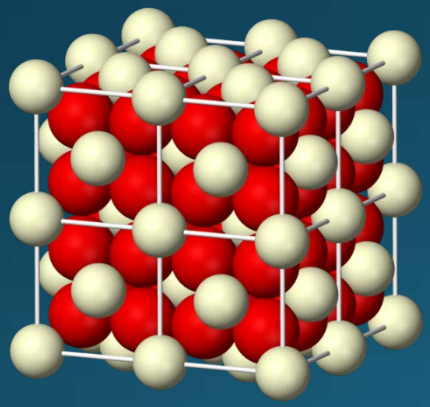


TiO2 nanobelts: courtesy of Dale Porter

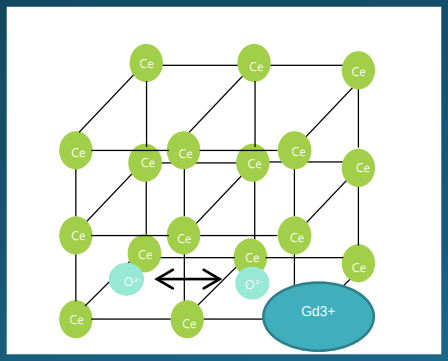
Nanomaterials Investigated at NIOSH

Functionally Modified Nanoparticles – Prevention through Design:

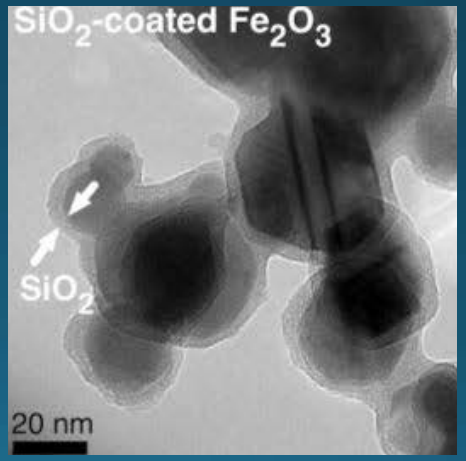
- Carboxylated and Humics Acid Titanium Nanobelts
- Nitrogen-doped MWCNT
- Carboxylated MWCNT
- Amine Functionalized MWCNT
- Heat-Treated MWCNT
- Amorphous silica coated Iron Oxide and Cerium Oxide
- Gadolidium-doped and SiO_2 coated cerium oxide



http://goo.gl/vWa6HO



Courtesy of Stephen Leonard

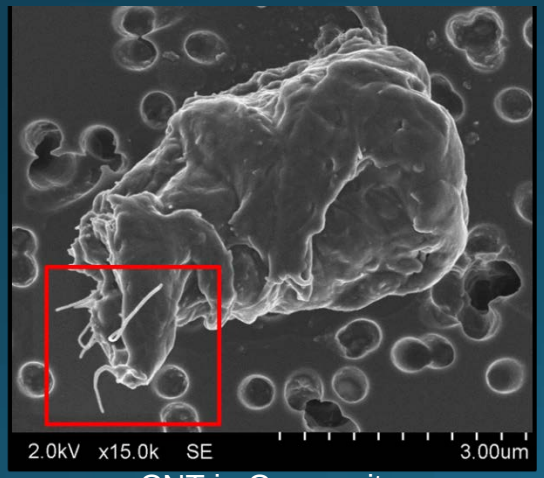


Gass et al., 2013

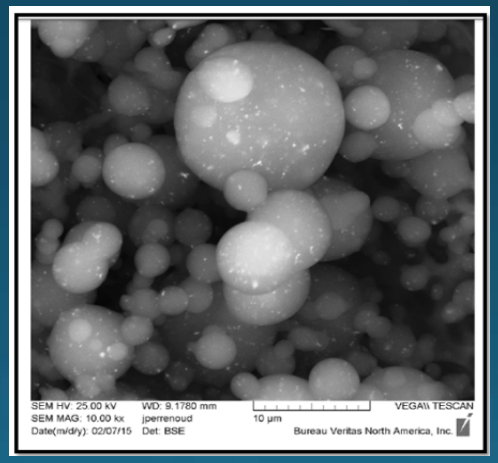
Nanomaterials Investigated at NIOSH

Exposure with Nanoparticle Components – NanoRelease/Life Cycle:

Crushed Preparation MWCNT
CNT Polymer Composites – Construction operations – Sanding/Sawing
Printer-Emitted Particles – Toners and Inks (CPSC and Harvard University)
Three Dimensional Printing Emissions (CPSC and West Virginia university)
Copper-Treated Wood – Dust from Construction Operations (CPSC)
Suncreen Spray – ZnO nanoparticles (FDA)
Disinfectant Sprays – ZnO or Silver Nanoparticles
Wood Sealant/Stain Aerosol – Spraying Operations – ZnO Nanoparticles (CPWR)
Stain-Treated Wood Dust – Construction Operations – ZnO Nanoparticles (CPWR)
Welding Fume Exposure – mixture on metal nanoparticles



CNT in Composite
– Courtesy of A. Erdely



ZnO particles on paint droplets
– Courtesy of CPWR, B. Lippy

Nanotoxicology Program Highlights

- Generating Occupationally Relevant Aerosols for In Vivo Studies
- CNT – A Model Toxicity Assessment
- Into the future with a life cycle approach

Inhalation Exposure Systems

Monitoring Equipment: Feedback to computer regulated control of environmental conditions

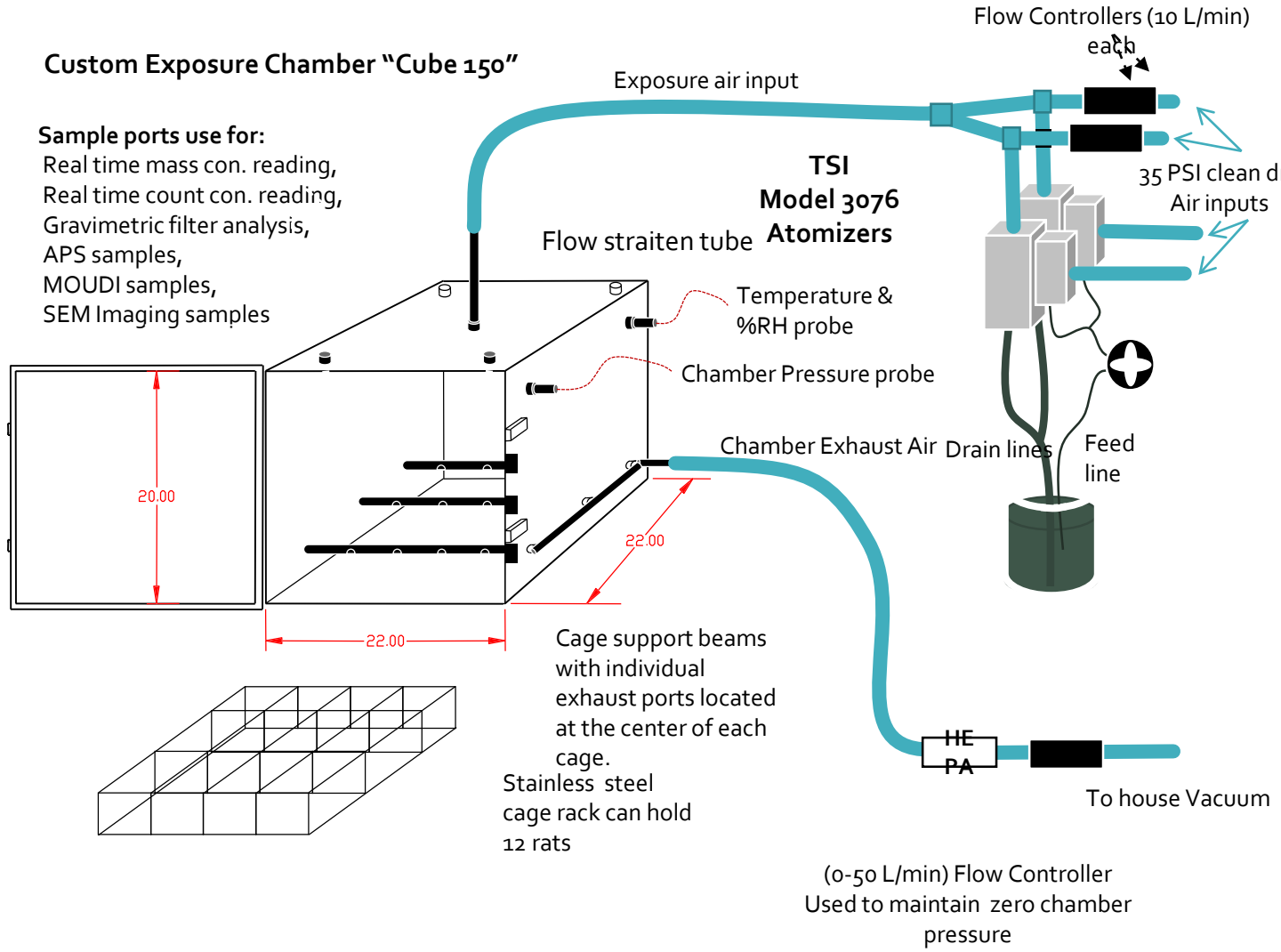
Animal Exposure Chamber

Dry Dust Chamber

Speaker – Subwoofer

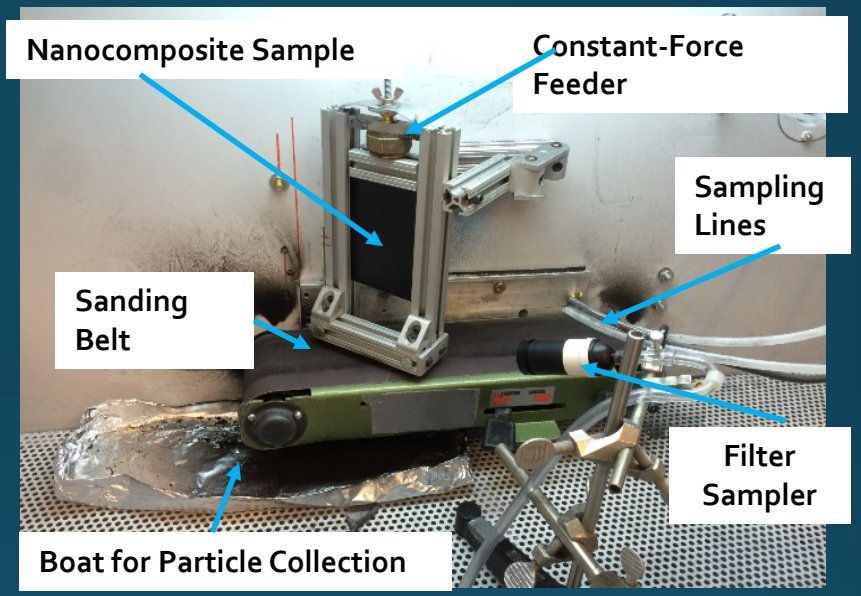
Dry Dust Acoustical Generator

Inhalation Exposure Systems: Wet Aerosols



Processing and Characterizing Aerosols from Nano-Enabled Materials

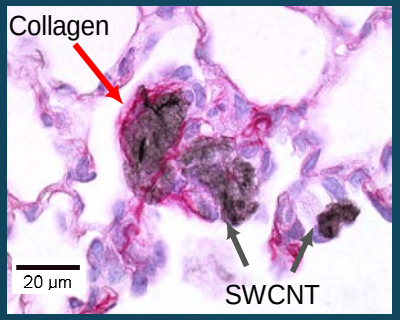
Internal View



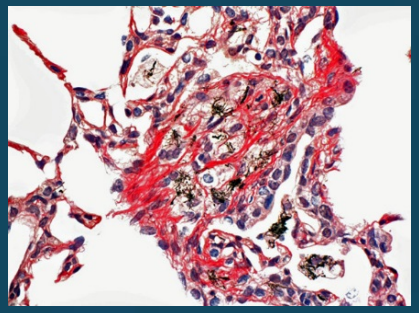
Courtesy of A. Erdely, L. Cena and A. Afshari

CNT – A Model Toxicity Assessment

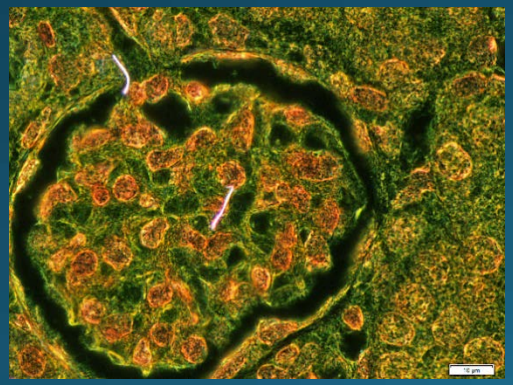
- Initial Hazard Identification Studies – SWCNT and MWCNT (Mitsui-7)
  - Dose-response time course studies in mice – aspiration of single bolus dose
    - Rapid Onset of Fibrosis

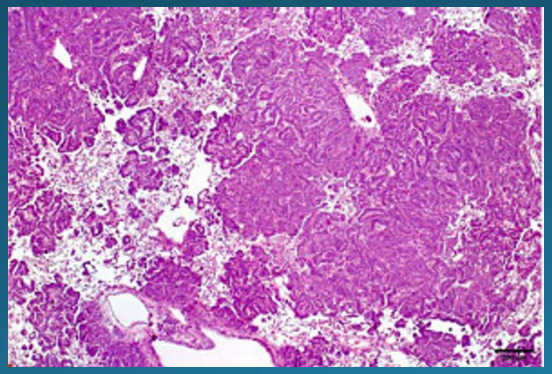


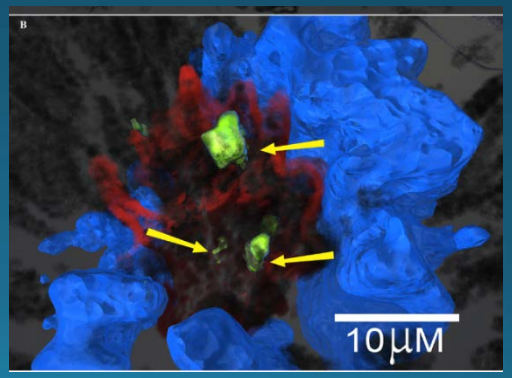
Shvedova et al. 2003 - SWCNT


Mercer et al., 2010- MWCNT

    - Extrapulmonary Effects: effects in cardiovascular, immune, and nervous system
  - Inhalation Studies (Mitsui-7) - 1st Studies Conducted – 5 mg/m^3
    - Rapid development of pulmonary fibrosis (Porter et al., 2013)
    - Pleural penetration and translocation to other organ systems (Mercer et al., 2013)
    - Lung adenocarcinoma tumor promotion (Sargent et al., 2014) – Basis for IARC ruling on Mitsui-7 and other CNT


Mercer et al., 2010- MWCNT


Sargent et al., 2014- MWCNT



Siegrist et al., 2014- MWCNT

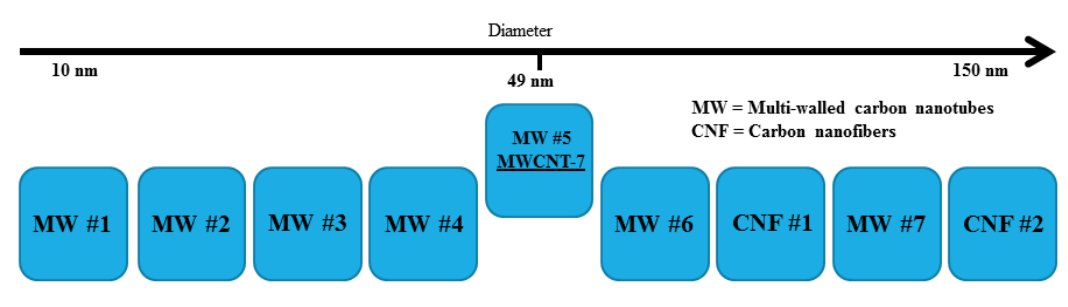
CNT – A Model Toxicity Assessment

- Integration of Exposure Assessment, Epidemiology, and Toxicology – US Facilities Study
  - Dosimetry Study (Mitsui-7) – Aspiration vs Inhalation and Workplace Exposure Assessment
    - Erdely et al., 2013

Estimates based on a worker exposed to an inhalable elemental carbon concentration of **10.6 µg/m^3 for 8 h/d for 250 d/y**

Mouse model	Worker Exposure
5 mg/m3 5 hr/d 19 d = 40 ug deposited	~76 years
0.5 mg/m3 5 hr/d 19 d = 4.0 ug deposited	~7.6 years
0.5 mg/m3 0.5 hr/d 19 d = 0.40 ug deposited	~0.76 years

  - Comparative Toxicity Study: CNT and CNF from those US Facilities

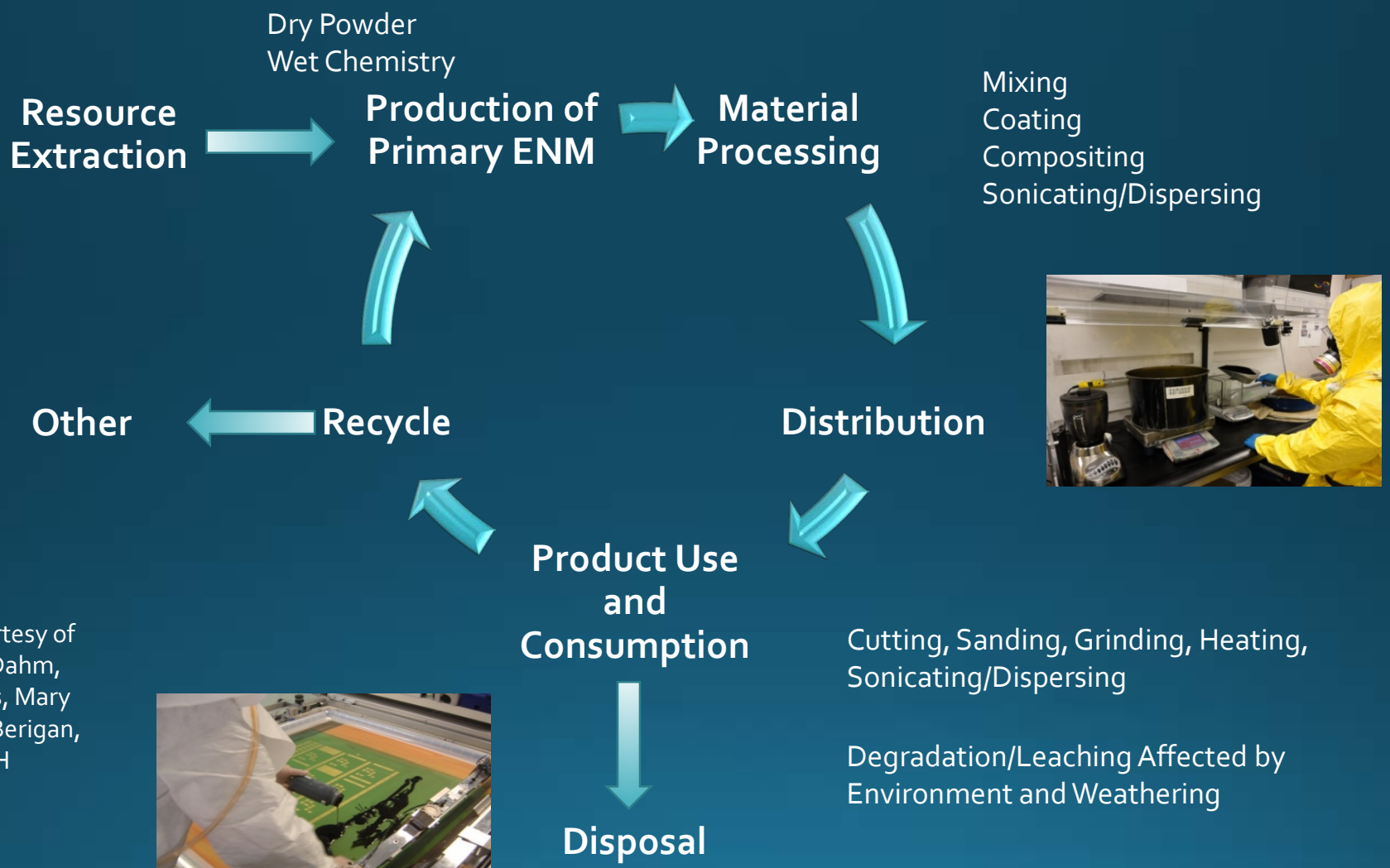


Pulmonary Toxicity
Deposition Pattern and Translocation
Cardiovascular Effects
Neurological Effects
Genotoxicity

  - Biomarkers of Exposure and Disease -
    - ~100 workers – cross sectional study – plasma, serum, sputum
    - Marker were chosen from in vivo and other cohort studies
    - Correlating these markers to ongoing exposure assessment
    - Validates the in vivo biomarker studies

Future Directions

Occupational Material Lifecycle



Images courtesy of Matthew Dahm, Doug Evans, Mary Schubauer-Berigan, NIOSH

Acknowledgements

Don Beezhold
Paul Siegel

Jeff Fedan
Martin Harper
Robert Lanciotti
John Noti
Steven Reynolds

Charles Geraci
Laura Hodson
Paul Schulte
Aleks Stefaniak

James Antonini
Min Ding
Aaron Erdely
Patti Erdely
Jeff Fedan
Ann Hubbs
Pius Joseph
Hong Kan
Elena Kisin
Vamsi Kodali
Stephen Leonard
Qiang Ma
Robert Mercer
Dale Porter
Yong Qian
Jenny Roberts
Liying Rojanasakul
Kristen Russ
Linda Sargent
Tabatha Settle
Anna Shvedova
Krishnan Sriram
Todd Stueckle
Naveena Yanamala

NTRC Critical Area Coordinators: Bean Chen, Kevin H. Dunn, Kevin L. Dunn, Doug Evans, Mark Hoover, Eileen Kuemple, Vladimir Murashov, Mary Schubauer-Berigan, Aleks Stefaniak, Doug Trout, Leonid Turkevich

Vincent Castranova – toxicology and internal dose critical area coordinator 2004-2014

Engineers and Aerosol Scientists

Dave Frazer, Walter McKinney, Travis Goldsmith, Ali Afshari, Bean Chen, Lorenzo Cena

Questions and Challenges:

NTRC and Nanotoxicology version 2.0 – the second decade of research

What is the next emerging material for investigation?

Who is using nanotechnology, nano-enabled materials and how are they being used?

Advanced manufacturing and additive manufacturing

Entrenched in ‘Omics – Compiling all the data for use in predictive modeling (in vitro to in vivo, and mode of action) - Determining the Low Effect and No Effect Dose Level