NIEHS Nanotechnology Research Update: Current Activities and Future Plans

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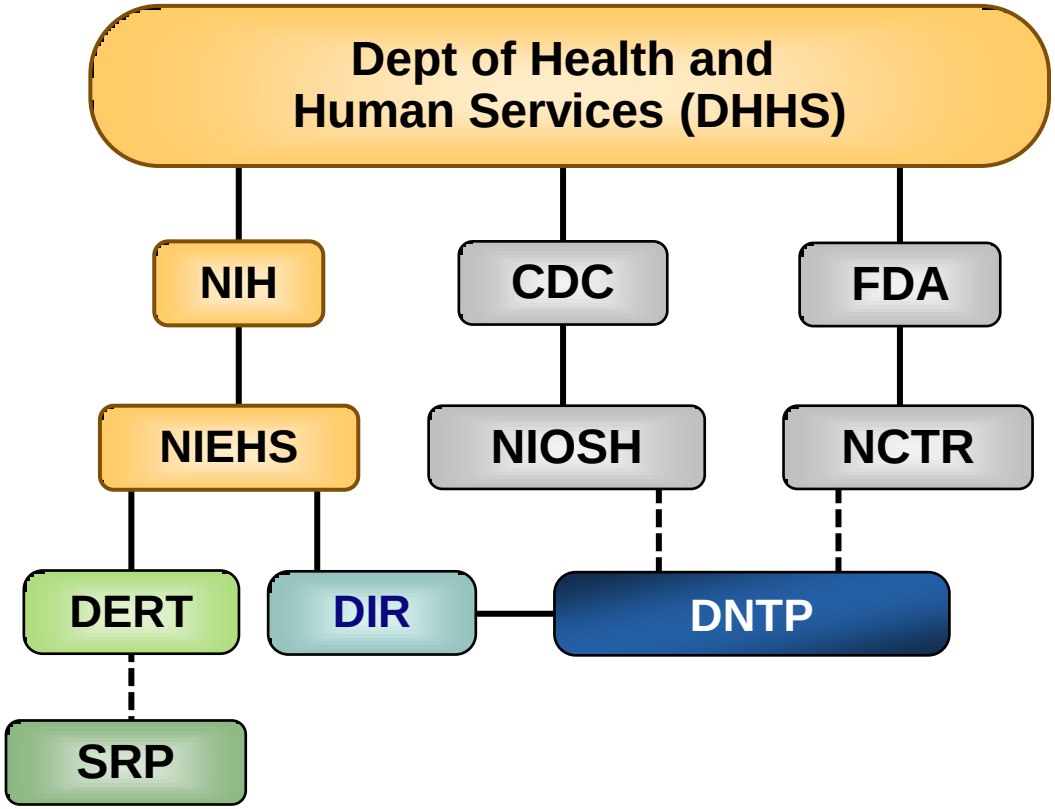
Program Director

ERTB/DERT/NIEHS

Organization

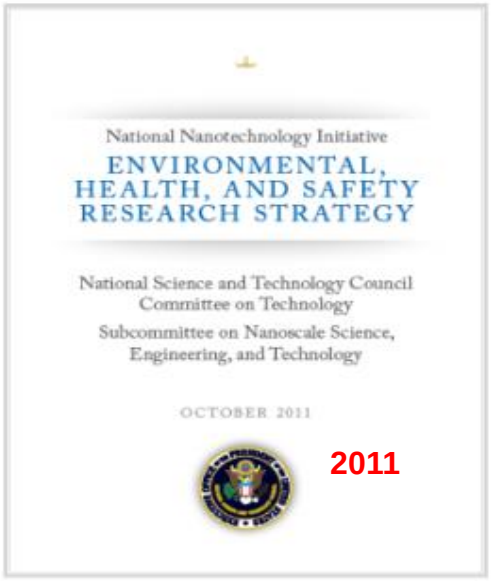


Mission: Reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

NIEHS Nanotechnology Research program

- Division of Extramural Research and Training
- Nano EHS
- Nanotechnology applications
  - Sensors (environmental)
  - Personal monitoring (point of contact)
- Investigator-initiated research
- Request for Applications (RFA)
- Division of National Toxicology Program
  - Contract research
  - Peer reviewed research reports
- Division of Intramural Research
- Laboratory and clinical research

NNI Nano EHS Research Strategy : Focused areas



- ❑ Human Health
- ❑ Human Exposure Assessment
- ❑ Nanomaterial Measurement Infrastructure
- ❑ Environmental Effects
- ❑ Risk Assessment and Risk Management Methods
- ❑ Informatics and Modeling for Nano EHS Research

NIEHS Nano EHS Overarching Goals

- Gain fundamental understanding on the interactions between engineered nanomaterials (ENMs) – biology
  - Physicochemical characteristics
- Develop comprehensive toxicological data
  - Prioritize ENMs
    - Production, use, and physicochemical properties
    - Integrated approaches for hazard ranking
- Serve as reference data to address
  - Public health issues
  - Regulatory needs

ARRA Nano Grand Opportunity Consortium

Develop reliable and reproducible methods to assess biological response/toxicological endpoints for ENMs.

- Utilize ENMs with well defined physicochemical properties
- Develop standardized protocols and methods for ENM dispersal and characterization in cell culture media.
- *In vitro* and *in vivo* models that can reliably predict biological response and reproducible data across labs using well characterized ENMs

NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR)

Administrative & Scientific Core

Project #1*: In Vitro*
Understand basic ENM-biological interactions (molecular, cellular, organelle, organ level). Diverse cell phenotypes, representing portals of entry

Project #2*: In Vivo*
Investigate how ENM PCPs influence physiological pathological outcomes in target/secondary organs; ADME, translocation across different organs

Nanotechnology Characterization Laboratory

Consortium ENMs:
Silver (20, 110; citrate, PVP)
MWCNTs (3 AR)

33 ENMs, 18 sizes, 12 surface modifications
Metals (27), carbonaceous (6), QDs (3)

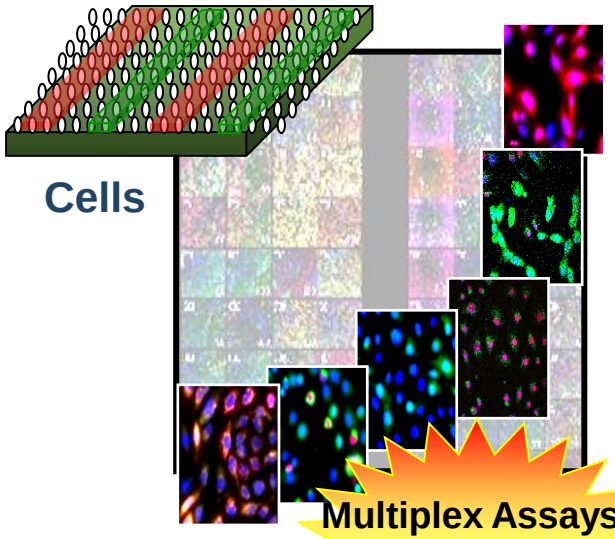
Risk Assessment

Project#3:
Risk Assessment Translation: Develop RA framework
In Two phases:
Phase1: conceptual framework
Phase2: Collaborative/integrated

NCNHIR Consortium Highlights

- In vitro studies using four silver ENMs indicated:
  - Cell-specificity in acute toxicity responses
  - Role of protein corona
- High throughput screening of metals and metal oxides clearly suggested:
  - Initiation of acute pulmonary inflammation
  - Susceptibility to pulmonary infection

High throughput screening



Multiplex Assays:
Cytokines
Chemokines

Dissolution

CuO
ZnO

Fe_2O_3
Fe_3O_4
WO_3

CoO
Co_3O_4
Cr_2O_3
Mn_2O_3
Ni_2O_3

Reactive surface

Al_2O_3, CeO_2,
Gd_2O_3, HfO_2,
In_2O_3, La_2O_3,
NiO, Sb_2O_3,
SiO_2, SnO_2,
TiO_2, Yb_2O_3,
Y_2O_3, ZrO_2

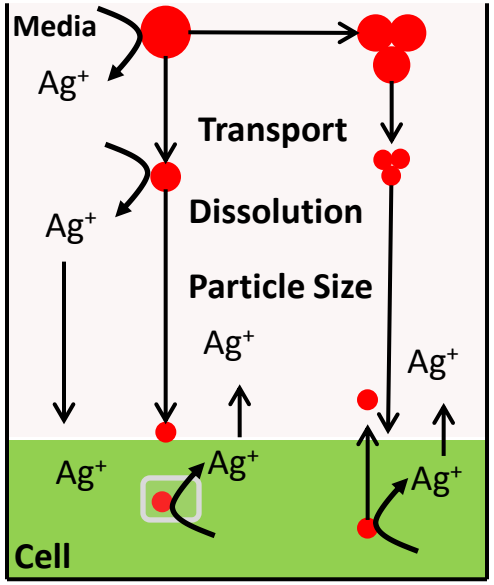
Nel's group, UCLA

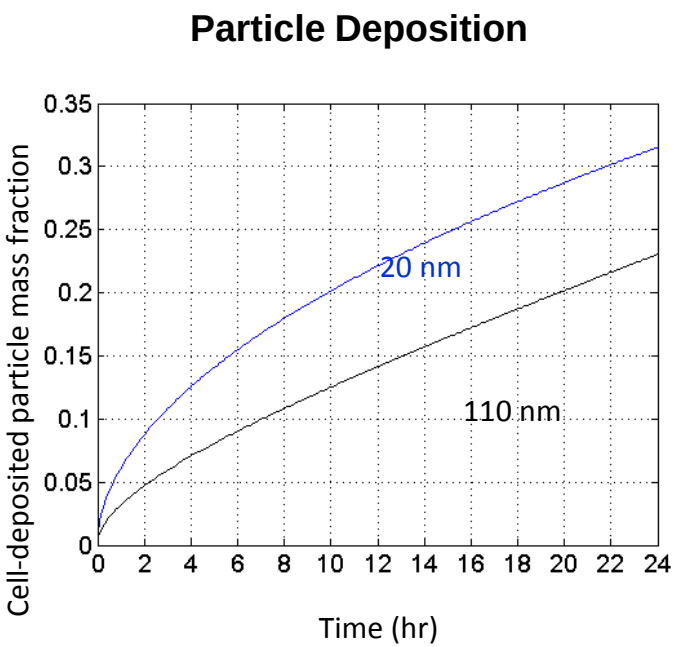
NCNHIR Consortium Highlights (2010-2015)

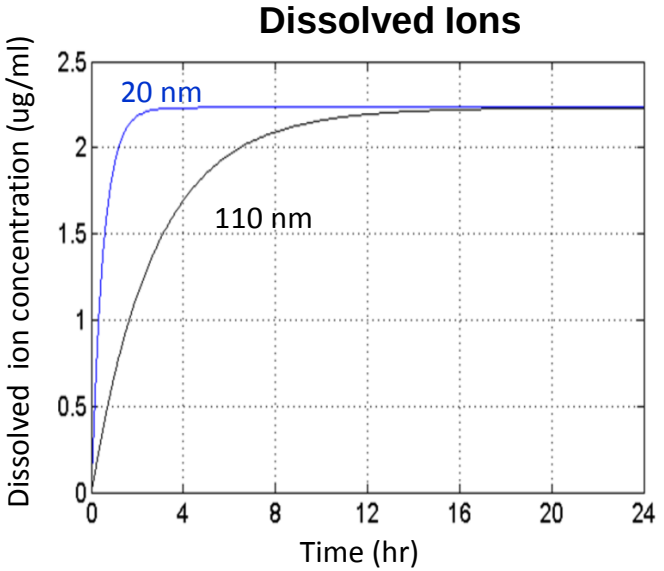
- In vitro studies using four silver ENMs indicated:
  - Cell-specificity in acute toxicity responses
  - Role of protein corona
- High throughput screening of metals and metal oxides clearly suggested:
  - Initiation of acute pulmonary inflammation
  - Susceptibility to pulmonary infection
- Studies with MWCNTs predicted fibrinogenic effects
- Species and strain specific acute pulmonary effects
- Acute vascular toxicity of Ag and MWCNTs
- Computational models (ADME, ISD3, BMD and QSAR)

Modeling Silver Nanoparticle Dissolution and Cell Dosimetry

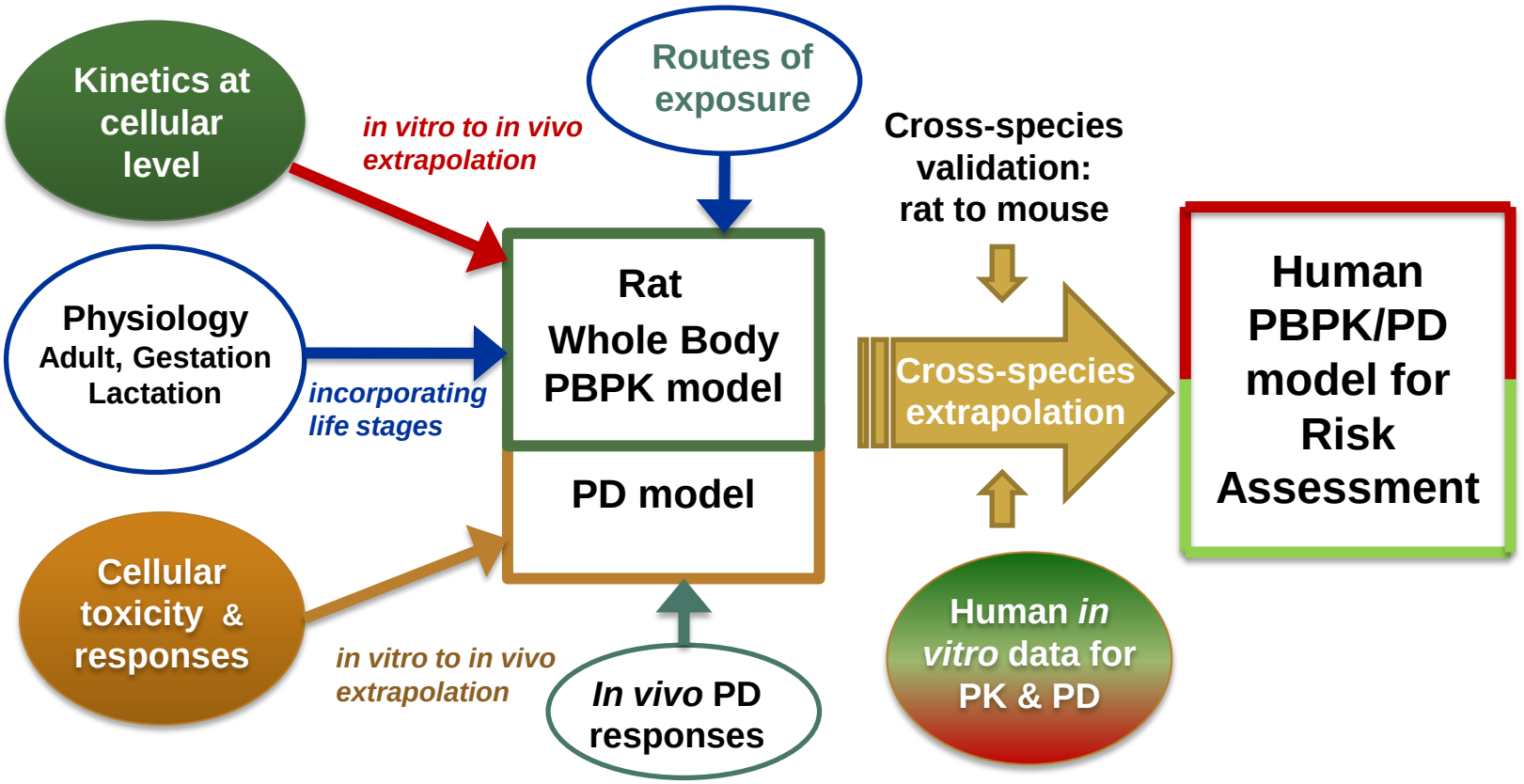
- To understand the role of cellular dose in the differential toxicity of silver NP, the consortium extended a NP dosimetry model to treat dissolution and transport of particles and ions into cells (**ISD3 Model**).
- Capturing the time-dependent dissolution of silver NP and transport of silver into cells in culture allows improved dose response and enables extrapolation to animal models and humans.







Predictive Modeling: PBPK

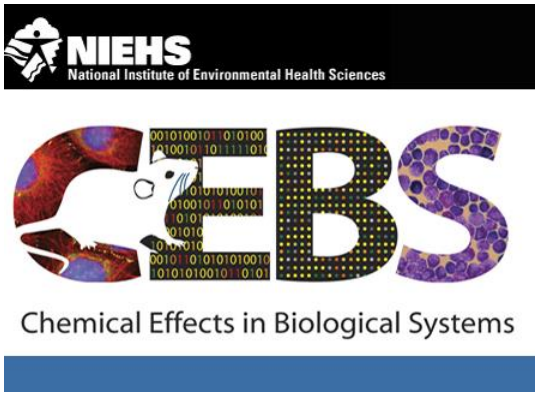


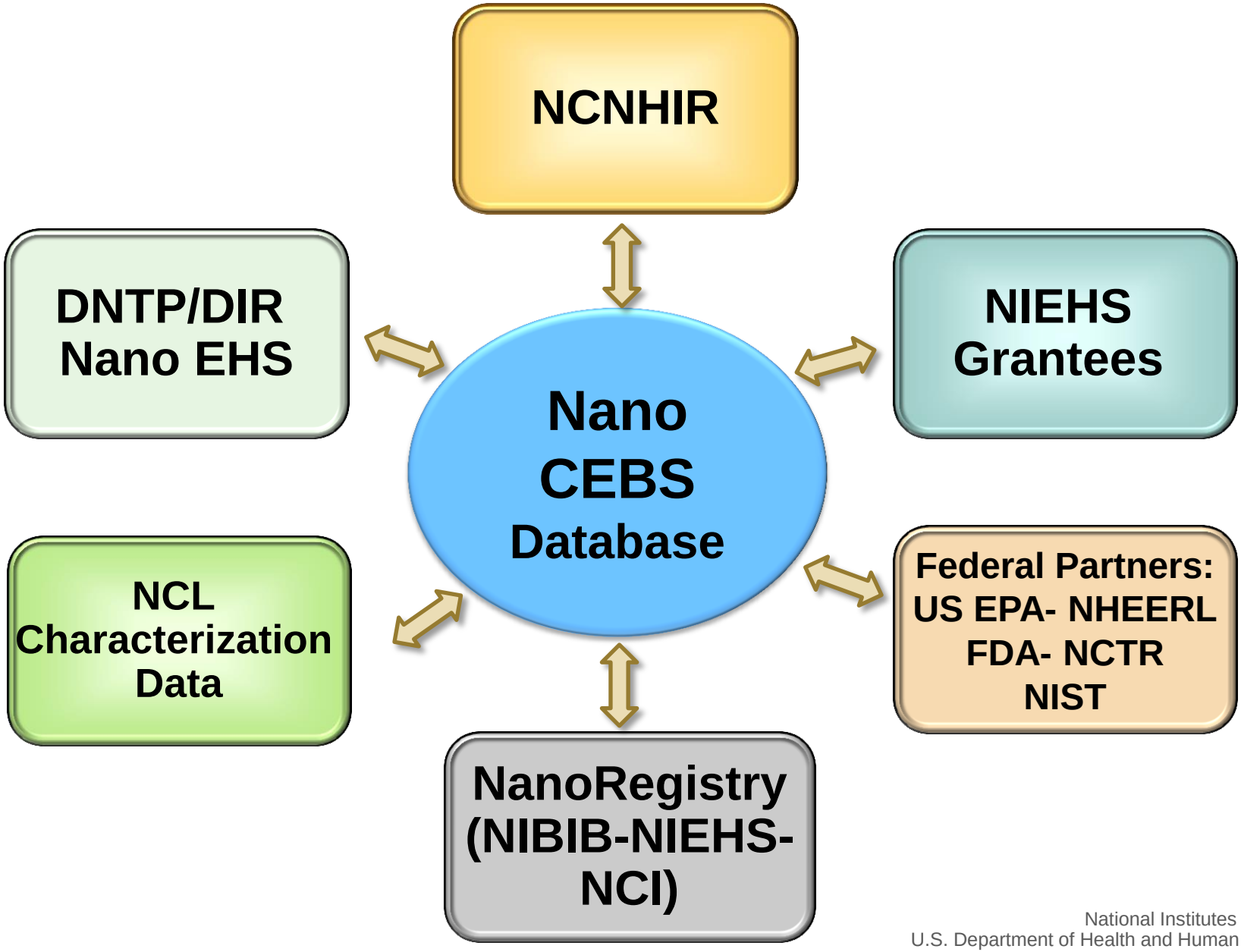
NTP Nano EHS Efforts

- C60 fullerenes Sub-chronic toxicity and immunotoxicity of Inhalation (50nm and 1um) and oral route- reports in prep
- Nano silver sub-chronic studies and toxicokinetics (completed), reports in preparation
- MWCNTs
  - PCPs of 24 commercial CNTs (Levine et al 2014)
  - Sub-chronic inhalation toxicity and clearance of a selected MWCNT completed and report is in preparation
  - 30 day functional immunotoxicity (inhalation) study will be initiated in spring 2015; NCNHIR consortium investigators will participate in these studies
  - Two-year chronic studies with MWCNTs to be initiated in late 2015

Nano EHS in CEBS

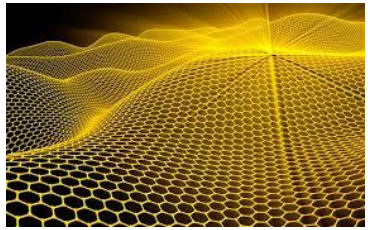
- Chemical Effects in Biological Systems database (CEBS) houses toxicological information of interest to health scientists.
- CEBS has a public and a private component.
- The public component houses over 9000 toxicological studies containing raw study data and metadata.
- Data from NTP Nano EHS and NCNHIR consortium efforts are being moved into CEBS and will be accessible to investigators/partners
  - Access to public as deemed fit
- http://cebs.niehs.nih.gov




NCNHIR
DNTP/DIR
Nano EHS
NIEHS
Grantees
Nano
CEBS
Database
NCL
Characterization
Data
Federal Partners:
US EPA- NHEERL
FDA- NCTR
NIST
NanoRegistry
(NIBIB-NIEHS-
NCI)

Research Gaps and Needs to Be Addressed…

- Expand knowledge base to gain insights into ENMs-biological interactions
  - Diverse classes of ENMs, material properties, biological endpoints
  - Emerging ENMs (2D-, and 3D)
  - Identified based on input from NNI (regulatory agencies) and state of science
- Comprehensive toxicity profiles
  - Molecular predictive toxicological approaches
  - Animal models using multiple routes of exposures
  - Chronic- and sub-chronic studies
  - Develop predictive biomarkers- target and secondary organ response
  - Identify common mechanism(s) of action across ENMs and routes of exposure



Moving forward - Basic Research

- Focused approach
- A limited set of ENMs
  - Pre-identified with input from regulatory agencies
- Two components
  - Materials resource core center
  - Research projects
    - Utilize diverse routes of exposure, target organs
    - Molecular, pathophysiological approaches for comprehensive toxicity profile(s)
- Form consortium
  - Annual meetings
  - Opportunities for collaborative efforts

Future Plans - Exposure Assessment

- Support development of tools for measurement and monitoring ENMs and Nanoenabled products
- Detection
  - Particle number, size, surface area
- Quantification and speciation
  - Real-time and archived samples
  - Metals, metal oxides, CNTs
- Spatial and temporal distribution
- Discrimination from ambient combustion generated nanoparticles

Opportunities for Collaborations

- Mechanisms for sharing materials
- Inclusion of additional experiments
- Specific data needs of regulatory agencies
- Promote partnership with international collaborators
- Participation at consortium annual meetings
- External advisory committee
- Access to CEBS- Nano

Thank You