Why a Prevention-Based Approach to Managing the Risk of Engineered Nanomaterials Makes Sense and How to Get There

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Adaptive Iterative Approach to Nanoregulatory Policy

Stage 1: Short-term Approach	**Stage 2: Longer term approaches**
Changes we could implement with existing information and statutes through coordination:	Shift to risk prevention paradigm
• Data collection (e.g., commerce chain, life cycle) • Safe management practices (e.g., occupational exposures) • Best practices • Hazard assessment • Exposure assessment • Streamlined risk reduction practices	• <u>Proof</u> of hazard, exposure reduction • Effective control measures • Continuously improving best practices • Restrict specific ENM if risk is compelling • Safe-by-design and green nanotechnology • Statuary reform to promote collection • Active role for industry

Future Stages

Evidence-Based Decision Making

Sustainable Decision Making

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Traditional Framework for Regulatory Decision Making

Hazard Identification

- Epidemiology
- Lifetime rodent bioassays
- Short-term, in vitro/in vivo tests
- Structure/activity

Risk Characterization

- Potency (dose/response)
- Exposure analysis
- Variation in susceptibility

Risk Reduction

- Information
- Substitution
- Regulation/prohibition

Figure adapted from: “The Risk Assessment-Risk Management Paradigm” by G. S. Omenn in *Risk Assessment for Environmental Health,* M. G. Robson & W. A. Toscano, Eds. John Wiley & Sons, Inc. 2007.

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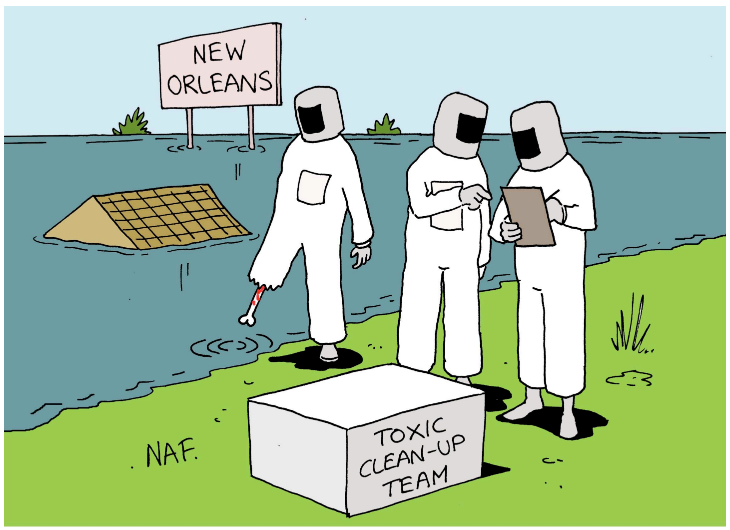
Limitations of traditional approach:



"Put a tick under 'very toxic'."

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~50,000 chemicals registered for commercial use in the US

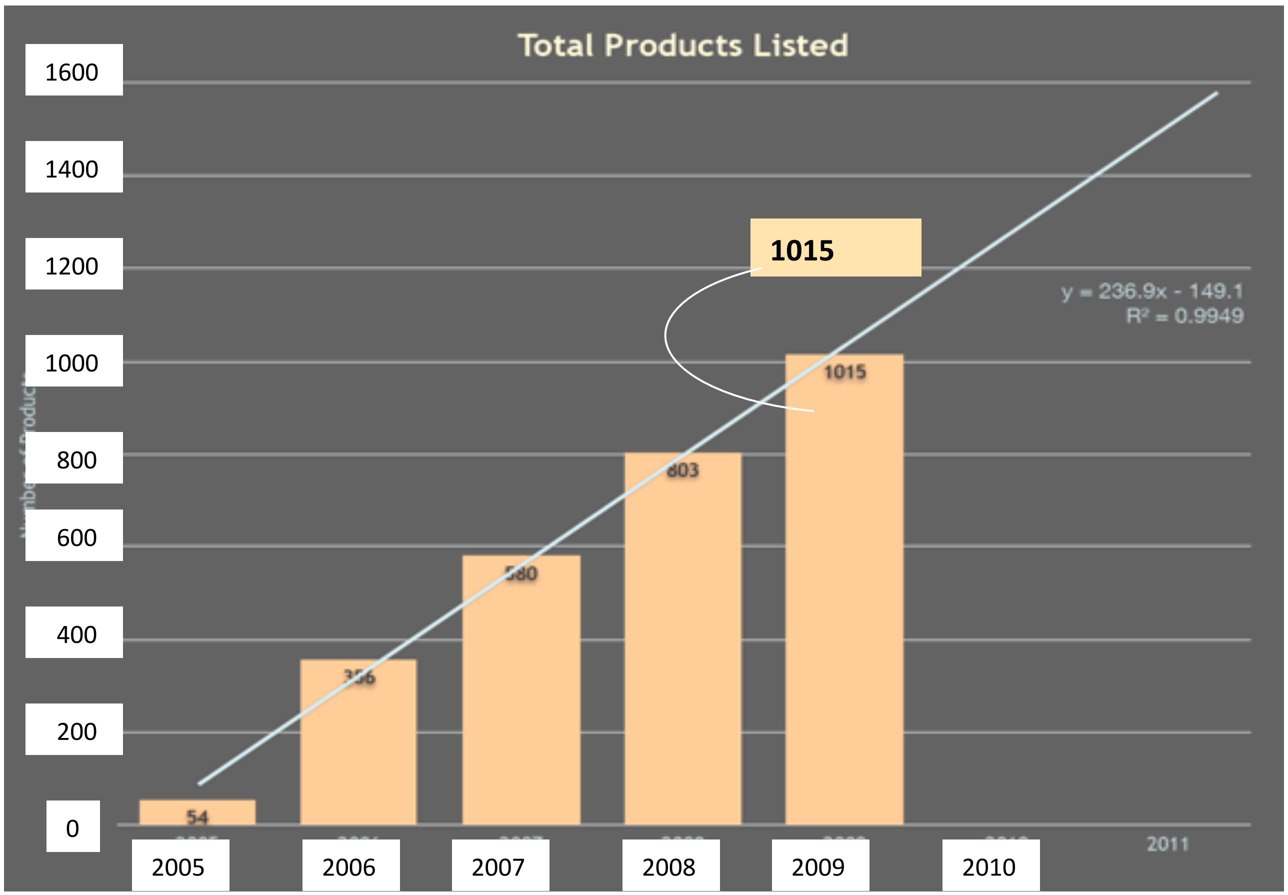
< 2500 have undergone toxicity testing

Resources required are overwhelming; each test requires:

- $2-$4 million (for in vivo studies)
- > 3 years to complete

New nanomaterials being introduced into marketplace at rate that greatly exceeds that for conventional chemicals

Prolific Growth of Nanotechnology



Source: Project on Emerging Nanotechnologies

What we need….

- More effective linkage of hazards research to research on primary prevention & safer technological options
- Integrative approach to science & policy, including integration of quantitative and qualitative data sets
- Innovative methods for analyzing cumulative & interactive effects, impacts on populations & ecosystems, impacts on vulnerable groups
- Systems for monitoring for early warning of risks
- More comprehensive approach to analyzing and communicating potential hazards

2001 Lowell Statement on Science and the Precautionary Principle

"Why Risk Assessment Is Not Enough To Protect Public Health" by J. A. Tickner in *Risk Assessment for Environmental Health,* M. G. Robson & W. A. Toscano, Eds. John Wiley & Sons, Inc. 2007.

Steps in Alternatives Assessment

- Examining and understanding of the impacts and purpose of the activity
- Identification of a wide range of options
- Comparative analysis of alternatives
- Alternatives selection/alternatives plan

"Why Risk Assessment Is Not Enough To Protect Public Health" by J. A. Tickner in *Risk Assessment for Environmental Health,* M. G. Robson & W. A. Toscano, Eds. John Wiley & Sons, Inc. 2007.

Risk Assessment versus Alternatives Assessment

initial reports suggesting triclosan

may pose threat to environment

RA

More completely assess possible hazard(s) and exposure(s)

AA

Determine whether effective, safer alternatives exist

Developing Rapid Screening and Assessment Tools

- Indentifying intrinsic hazards of chemicals (or ENMs)
- Identifying use categories and other surrogates for exposure
- Identifying classes of chemicals (ENMs) with similar characteristics or risk profiles
- Identifying design criteria for safer chemicals (ENMs) and products
- Assessing risk rapidly with flexibility to quickly modify assumptions

"Why Risk Assessment Is Not Enough To Protect Public Health" by J. A. Tickner in *Risk Assessment for Environmental Health,* M. G. Robson & W. A. Toscano, Eds. John Wiley & Sons, Inc. 2007.

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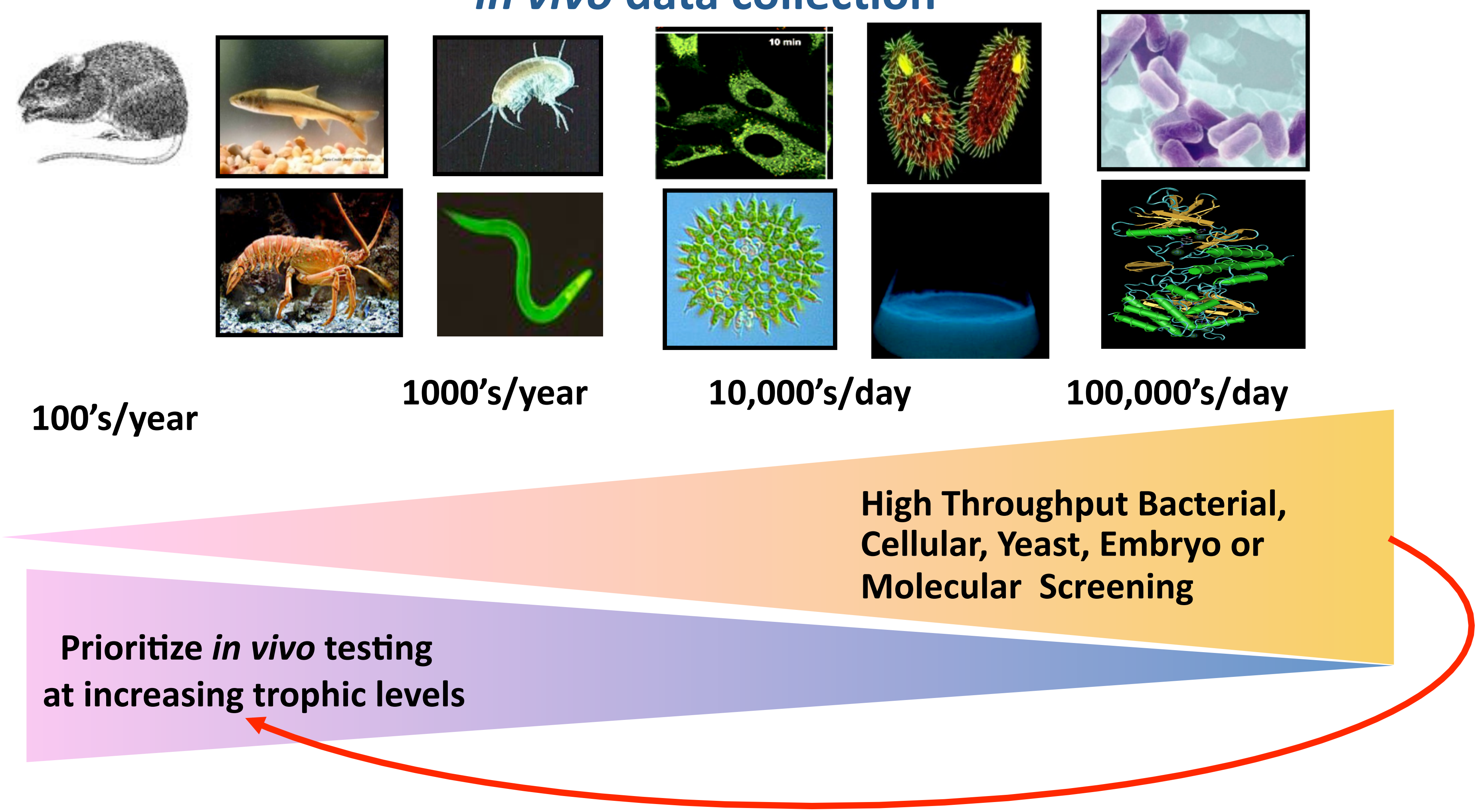
Knowledge generation and Data Mining at molecular and cellular level to rank NM hazard and prioritize *in vivo* data collection



Strategic Research Plan for UC CEIN

- Develop a predictive scientific model that links bio-physicochemical interactions at cellular and organism level to effects on populations, ecosystems and at different trophic levels in the environment
- Develop compositional and combinatorial ENM libraries to demonstrate how key physicochemical properties determine fate and transport as well as a wide range of interactions at the nano-bio interface
- Develop high content and high throughput screening to perform hazard ranking that prioritizes and facilitates mesocosm studies in terrestrial, seawater and freshwater environments
- Develop a computational expert system that integrates data generation in above environments for quantitative property-activity relationships, multimedia modeling and risk ranking
- Utilize above knowledge domains to inform the public, academia, industry and government agencies how nanotechnology can be safely implemented in the environment

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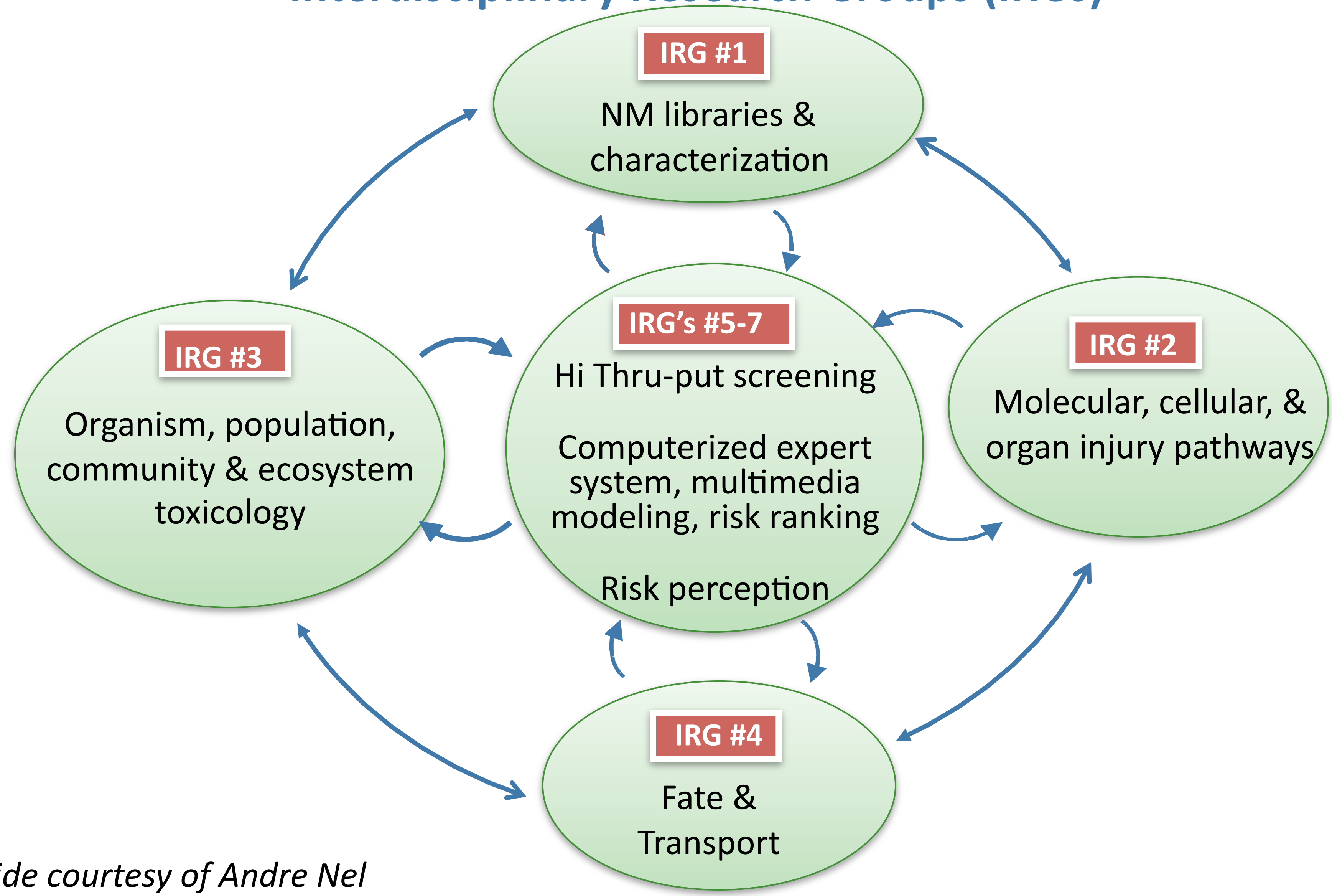
Interdisciplinary Research Groups (IRGs)



Slide courtesy of Andre Nel

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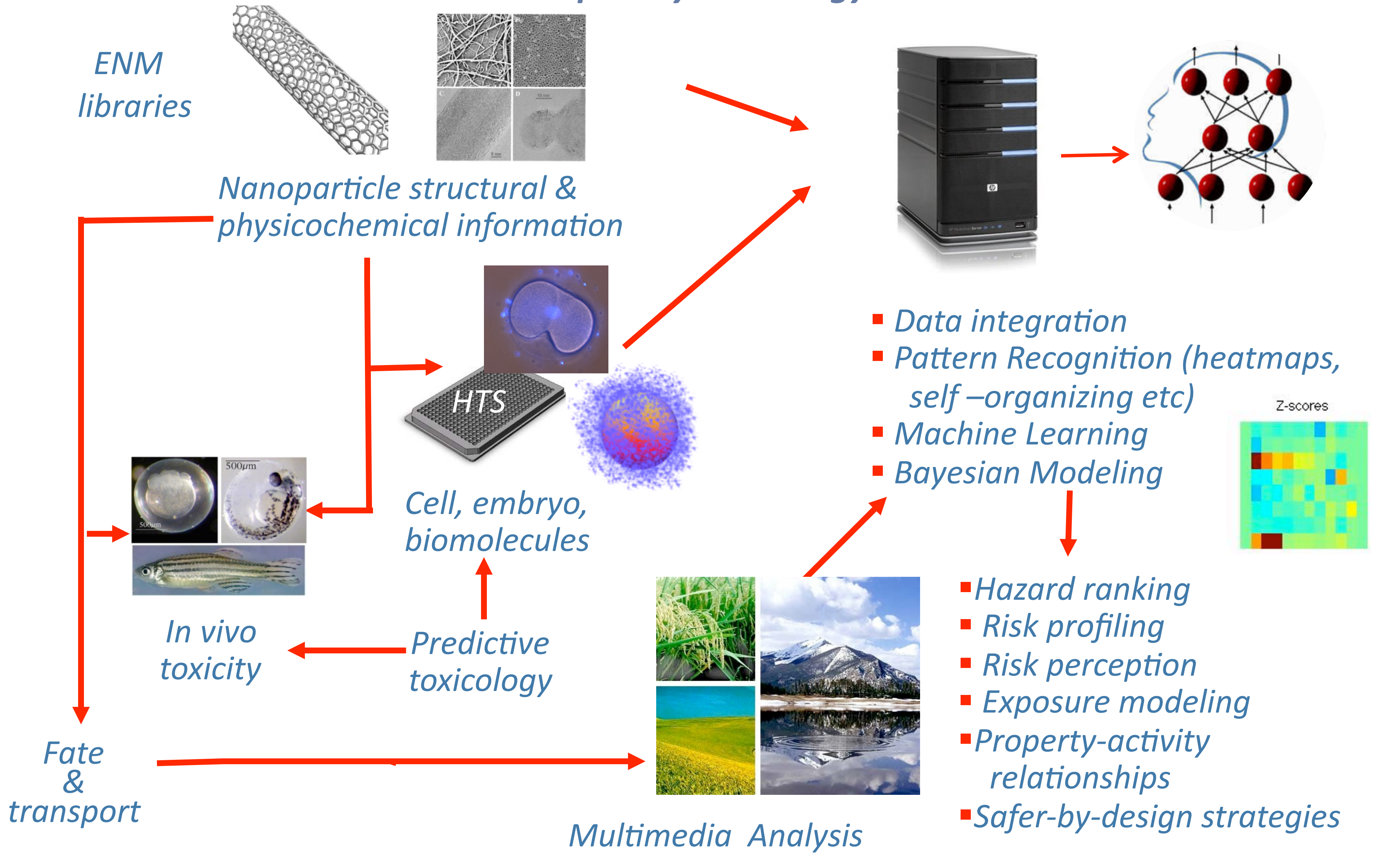
UC CEIN Predictive and Multi-disciplinary Toxicology model



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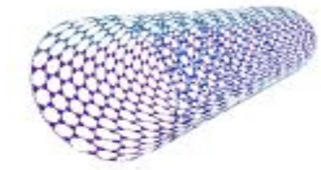
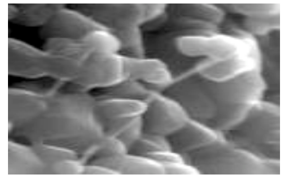
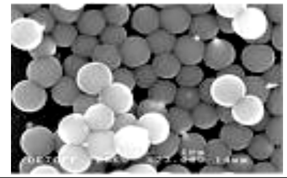
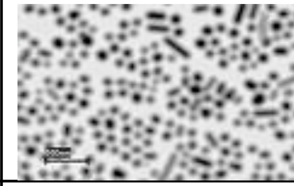
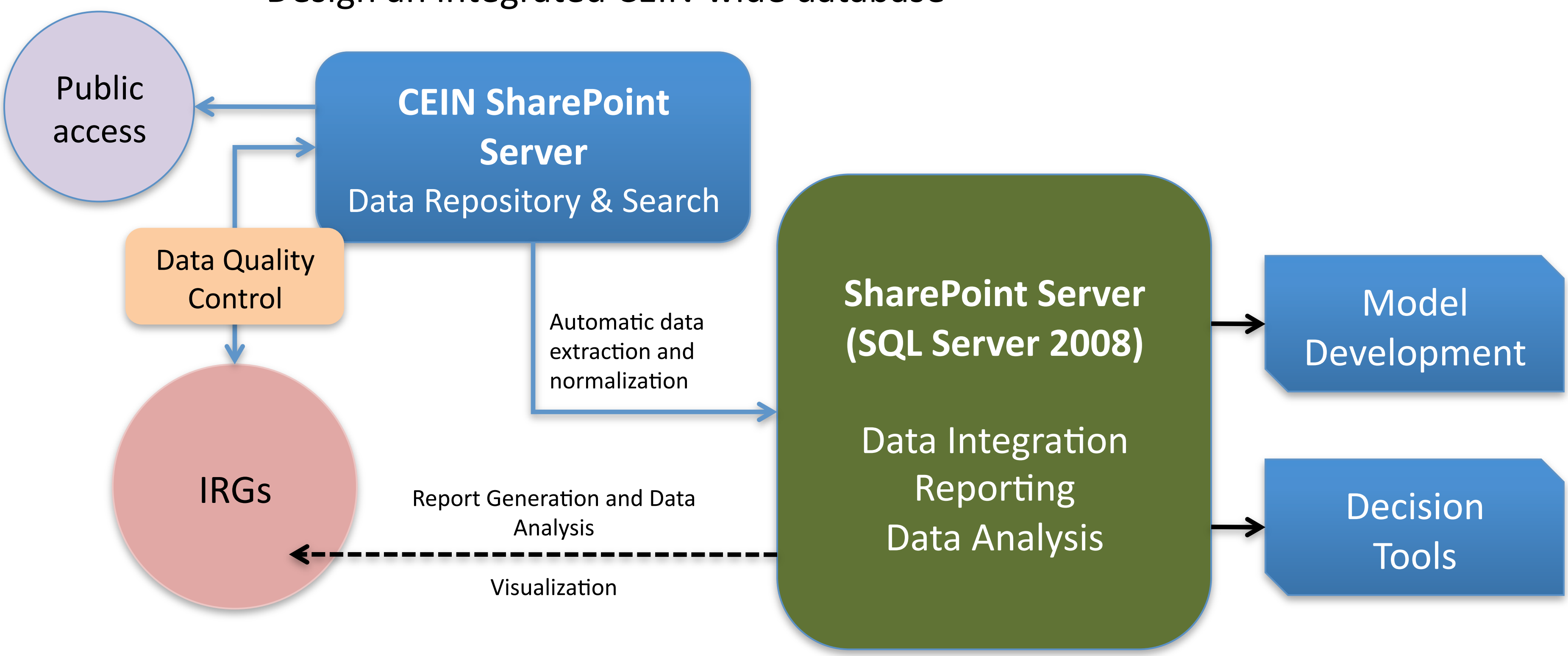
ENM Toxicological Profile	Property-activity relationships
ZnO extremely toxic: • mammalian cells • zebrafish embryos • oyster embryos • phytoplankton	NP dissolution and Zn^{++} shedding dominates in fresh and seawater environments • lysomal and mitochondrial damage • oxidative stress • disrupt hatching enzymes • bio-concentration in chorion
TiO_2 potentially toxic: • UV photo-activation • anatase > rutile Stimulates algal growth	Photo-activation with: • e^- hole-pair formation • ROS production Possible interaction with membrane e^- transduction processes and photosynthesis
CeO_2 relative lack toxicity In mammalian cells and organisms	Possible antioxidant effects in surface defects due to cycling between 3^+ and 4^+ valent states
Nano-Ag relative lack toxicity in mammalian cells but toxic in acquatic organisms	Mechanisms being explored

ENM	Cytotoxicity mechanism	Design features to mitigate toxicity
TiO_2	• Electron/hole-pair ROS production • Glutathione depletion and toxic oxidative stress	• **Iron-doping** to slow dissolution • **Capping** with surfactants, polymers or complexing ligands • **Coating** with low-molecular-weight antioxidants • **Altered chemical composition** that, for example, eliminates crystalline states and material defects (e.g., rutile in place of anatase TiO_2)
ZnO	• ROS generation • Dissolution and Zn^{++} release • Lysosomal damage • I nflammation	
Ag NPs	• Dissolution and Ag^{+} release • ROS production • Disrupt membrane integrity and transport processes	
CdSe	• Dissolution and release of Cd and Se ions	• **Coating** the toxic core with biocompatible polymers/inorganic shells
SiO_2 and quartz (crystalline silica)	• ROS generation by surface hydroxyls/impurities • Membrane disruption	• **Particle aggregation** or modification of size and/or surface charge • **Surface modification** with aluminium lactate or polyvinylpyridine *N*-oxide
Magnetite, Fe_3O_4	• ROS production and oxidative stress • Liberation of toxic Fe^{2+} • Disturbance of electronic and/or ion transport in cell membrane	• Fuctionalization with biocompatible shell • Polymer coating (e.g., alginate, chitosan)

	Carbon nanotubes	TiO_2 nanoparticles	ZnO nanoparticles	Ag nanoparticles
				
Consumer, occupational & human risk	Regarded as pulmonary toxicant by NIOSH; effective. workplace prevention feasible	Among best characterized ENM since the '80's; effective workplace risk management	High-volume material with reasonably safe consumer profile; inadvertent lung exposure leads to metal fume fever	Modest risk to workers and consumers but some concern to developers
End-of-life and environmen-tal risk	Uncertain: capping agents promote spread Nano-composites may disintegrate	Ultimate disposal risk uncertain but likely not more than micron sized pigments	Reasonably high concern because Zn^{++} regarded as extremely toxic in the environment	Possible high environmental impact, especially aquatic systems
Perceptual risk	Relatively high based on analogy to asbestos	Sunscreen ingredient but no clinical data indicating toxicity	Same as for TiO_2 in sunscreens; Does it reach the environment and in what quantities?	High perceptual risk due to environmental concerns
Regulatory position	Under TSCA, CNT are new chemicals requiring a PMN. EPA regulating with consent order/SNUR.	Existing chemical under TSCA. EPA developing a SNUR for nano forms of existing chemicals.	Existing chemical under TSCA. EPA developing a SNUR for nano forms of existing chemicals.	EPA uses FIFRA for antibacterial claims.

CEIN's Data Management Architecture

- Collaboration server
- Development of metadata for CEIN data sets
- Design an integrated CEIN-wide database



Slide courtesy of Yoram Cohen, leader of UC CEIN IRG6

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Future Stages

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Sustainability Decision Making

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- Exposure assessment
- Streamlined risk reduction practices

California Department of Toxic Substances Control

•January 2009: CA DTSC served notices to CNT manufacturers in CA requiring information about:

- value chain
- analytical test methods for monitoring CNTs in workplace
- Knowledge of potential hazards of CNTs
- EH&S practices
- Waste disposal practices

•. Manufacturers had one year from that date to respond. DTSC received 22 responses.

California Department of Toxic Substances Control. *Chemical Information Call-In*. 2007 http://www.dtsc.ca.gov/PollutionPrevention/Chemical_Call_In.cfm#Specific_Chemical_Call-Ins.

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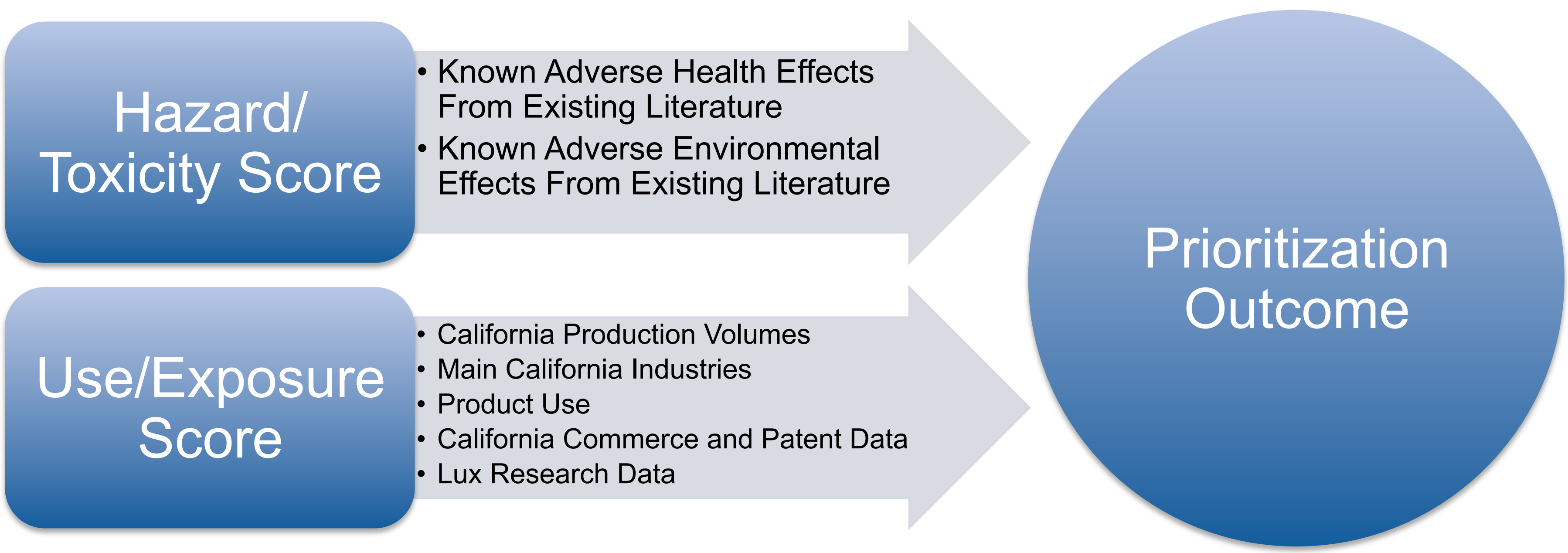
Contract with DTSC in collaboration with UCLA STPP:

- **PROJECT I**: evaluating responses to DTSC's carbon nanotube chemical call-in and providing recommendations for future chemical call-ins under AB 289.

- **PROJECT II**: developing a prioritization methodology that takes into account both exposure potential and existing scientific knowledge on the human toxicology and ecotoxicology of nanomaterials.



Some Insights from Preliminary Analysis of DTSC Call-In

• 11 of the 22 respondents were Universities, National Laboratories, or University-affiliated research centers.

•Analysis of responses to question → how to phrase questions for future call-ins on other ENMs
•Analysis of literature plus letters → large gaps in available information needed for life cycle assessment (e.g., value chain)

• **Good news:** many organizations reported good practices in terms of use and waste protocols for CNTs
• **Bad news:** there appears to be large differences between respondents in:
  • knowledge about CNTs' effects on health and the environment
  • views on how to safely handle CNTs in the workplace.

Nanotechnology Symposium VI

Progress IN Protection

Nanotechnology VI will summarize Engineered Nanomaterial Environmental Health & Safety issues and provide an overview of what EH&S practitioners can do to protect their workers now, where the discipline is heading, and what areas require additional research.

Save the Date:

October 13, 2010

California NanoSystems
Institute (CNSI)
University of California
Los Angeles

For updated symposium information, please visit:
www.dtsc.ca.gov/TechnologyDevelopment/
Nanotechnology/UpcomingSymposium.cfm

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Department of Toxic Substances Control

Training Module on Safe Handling and Disposal of Nanomaterials for Laboratory Workers

- Interactive content in case-study format
- Includes best practices derived from NIOSH and Department of Energy recommendations
- Will be tested for efficacy, modified as appropriate, disseminated to CEIN partner institutions
- Goal to launch test: September 2010

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