Pacific Northwest NATIONAL LABORATORY

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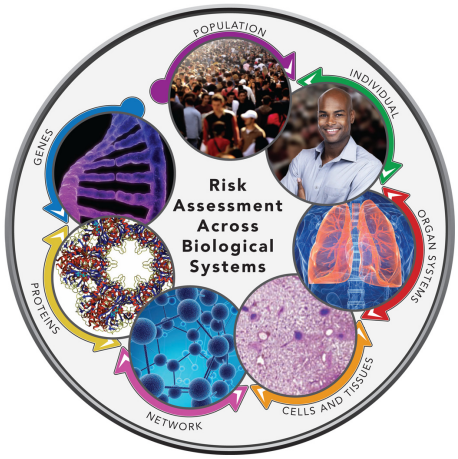
A Systems Approach to Nanotoxicology

NANOMATERIAL SAFETY ASSESSMENT CAPABILITIES

Biocompatible design of nanomaterials requires unprecedented levels of collaboration between scientists of multiple disciplines. Traditional fields associated with safety assessment—toxicology, pathology, biology, pharmacokinetics and biochemistry—must work closely with material science, modeling and others to ensure nanomaterial toxicity and biocompatibility studies produce conclusive, interpretable data for risk assessment.



Pacific Northwest National Laboratory's systems approach integrates responses of multiple levels of biological processes, and enables an understanding of the effects of nanomaterials on cell and organism function.

COORDINATED, INTEGRATIVE AND SYSTEMS-LEVEL APPROACH AND CAPABILITIES

Pacific Northwest National Laboratory (PNNL) has one of the nation's most experienced, multidisciplinary nanotoxicology teams, as evidenced by federal funding and participation in national workshops. The combination of talented staff and a comprehensive, state-of-the-art suite of instrumentation is changing nanomaterial assessment.

Our capabilities include:

- *Design, synthesis and characterization of custom nanomaterials*
- *Comprehensive dosimetry assessment: molecular, cellular and systemic dosimetry*
- *Elucidating mode-of-action from integrated 'omics: proteomics integrated with transcriptomics, biological pathway analysis and computational statistics to identify biosignatures and discover biomarkers*
- *Systems biology and bioinformatics: computational biology, proteomics, data visualization, molecular and cellular imaging*
- *Respiratory tract imaging and simulation*
- *Inhalation toxicology and pulmonary pathology*
- *Atmospheric chemistry and physics.*

FOUNDATIONS FOR NANOMATERIALS EXPERTISE

The Environmental Molecular Sciences Laboratory (EMSL), a world-class Department of Energy scientific user facility at PNNL, provides a broad range of capabilities for molecular studies including those associated with synthesis, characterization, theory and modeling, dynamic system properties and environmental testing relevant to a wide range of environmental and health related issues and topics.

U.S. DEPARTMENT OF ENERGY

CUTTING-EDGE MOLECULAR AND CELLULAR NANOTOXICOLOGY

PNNL's molecular and cellular toxicologists have nanomaterials experience including metals, metal oxides, fullerenes, silicates and carbon nanotubes. Working closely with material scientists, high-throughput methods can be used to assess the potency of nanomaterials as stimulants of inflammation, oxidative stress and other important endpoints of toxicity. For instance, multiplexed assays for inflammatory cytokines are used to assess multiple markers of inflammation.

Global genomics, proteomics and metabolomic profiling are applied when broader measures of response are necessary to define a toxicity profile or mode of action. Many of these assays are performed in parallel with real-time visualization of nanoparticle deposition, cellular uptake and trafficking. This broad set of capabilities is particularly important when testing multiple surface chemistry modifications for biocompatibility.

LEADING DOSE EXTRAPOLATION FOR HAZARD AND RISK ASSESSMENT

Researchers at PNNL are leading development of experimental and computational tools for predicting cellular dose of particles and nanomaterials in rodents and humans that include:

- *An anatomically correct 3D computational fluid dynamic model of rodent and human respiratory tracts to predict nanomaterials dose to specific lung regions and extrapolate from delivered doses in animals to humans*
- *A computational model of cell culture system particle kinetics and dosimetry to select doses for in vitro toxicity screening studies normalizing delivered doses across particle types and reflecting reasonable human exposure scenarios.*

These tools and our associated expertise in particle dosimetry offer unequalled capability to extrapolate the results of nanoparticle toxicity studies across dose, study type, species and sensitive populations.

SELECTED PUBLICATIONS

Orr GA et al. 2010. "Cellular Recognition and Trafficking of Amorphous Silica Nanoparticles by Macrophage Scavenger Receptor A." *Nanotoxicology.* Published online September 17, 2010.

Orr G et al. 2009. "Syndecan-1 Mediates the Coupling of Positively Charged Submicrometer Amorphous Silica Particles with Actin Filaments Across the Aveolar Epithelial Cell Membrane." *Toxicology and Applied Pharmacology* **236**(2):210-220.

Waters KM et al. 2009. "Macrophage Responses to Silica Nanoparticles are Highly Conserved Across Particle Sizes." *Toxicological Sciences* **107**(2):553-569.

Teeguarden JG et al. 2007. "Particokinetics In Vitro: Dosimetry Considerations for In Vitro Nanoparticle Toxicity Assessments." *Toxicological Sciences* **95**(2):300-312.

CURRENT NANOTOXICOLOGY PROGRAMS AT PNNL

- ***NIEHS Center for Nanotoxicology.*** *In 2010, the National Institute of Environmental Health Sciences (NIEHS) established the multidisciplinary Center for Nanotoxicology at PNNL. The Center houses research projects that will lead to quantitative understanding of how engineered nanomaterial properties interact with biological systems. The goal is to ultimately understand the role of nanomaterials in tissue disposition, physiological responses and risk of initiating or promoting disease. Program Director: Dr. Joel G. Pounds*
- ***Battelle Institute for Fundamental and Systems Toxicology.*** *PNNL is a partner in the multi-institutional Battelle Institute for Fundamental and Systems Toxicology. This program includes collaborative research by PNNL, Battelle, Oak Ridge National Laboratory, Brookhaven National Laboratory and Lawrence Livermore National Laboratory focused on applying modern systems toxicology approaches to identify preclinical markers of adverse biological responses to emerging pharmaceutical agents, including nanomaterials. The goal is to identify early and predictive markers of potential toxicity pathways to advance safe nanotechnology and pharmaceutical development. PNNL Technical Lead: Dr. Brian Thrall.*

ABOUT PNNL

Pacific Northwest National Laboratory, a U.S. Department of Energy Office of Science laboratory, solves complex problems in energy, the environment, and national security by advancing the understanding of science. PNNL employs more than 4,600 staff, has a business volume exceeding $800 million, and has been managed by Ohio-based Battelle since the Lab's inception in 1965.

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