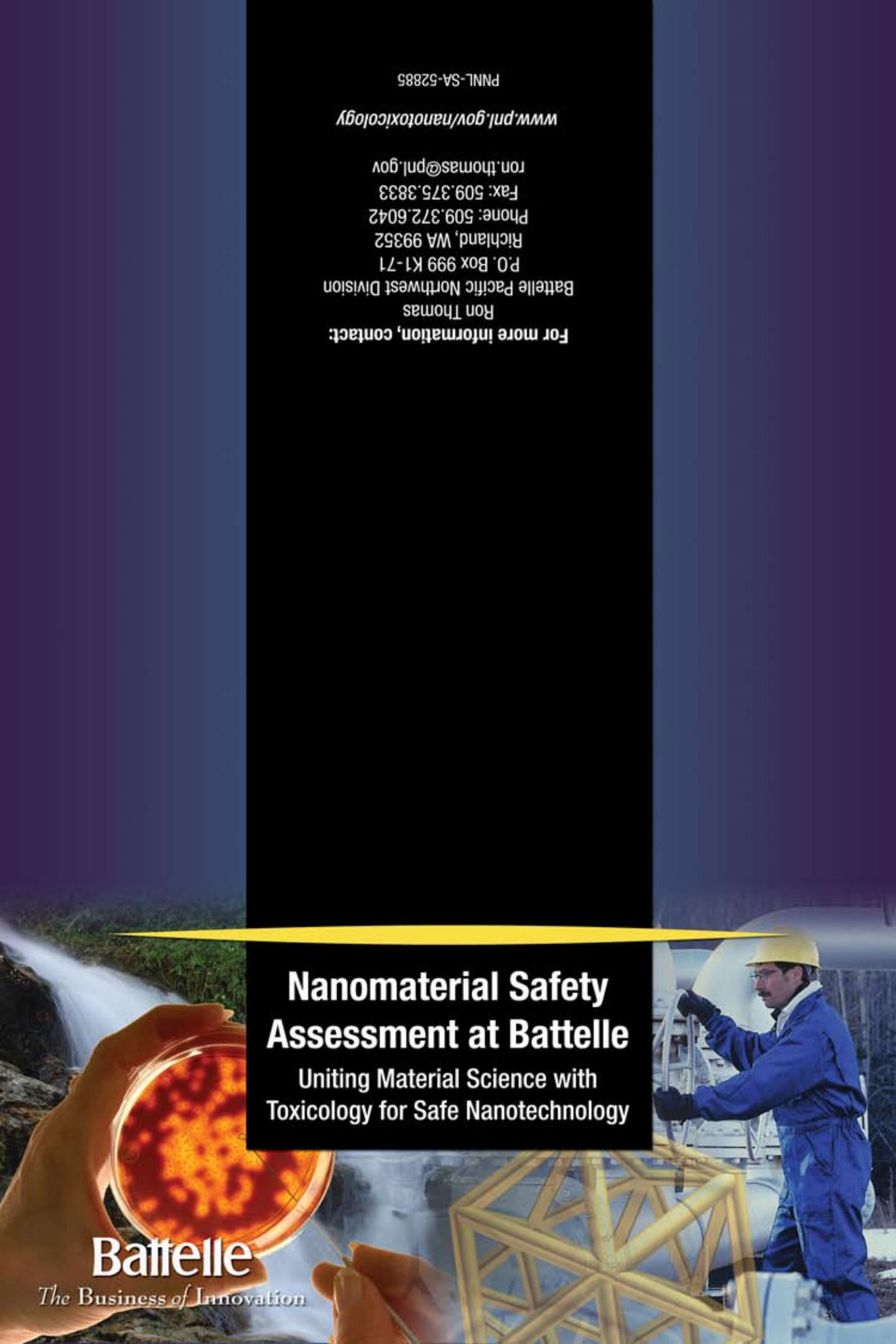
Nanomaterial Safety Assessment at Battelle

Uniting Material Science with Toxicology for Safe Nanotechnology



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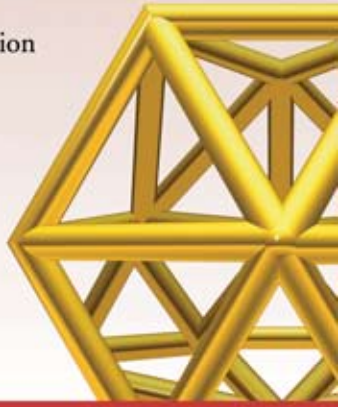
Nanoscience is revolutionizing products in many industries—from consumer products and drug delivery to solar cells and aerospace materials. In recent years, questions surrounding the safety of these products have companies looking for answers as they seek to protect their employees, consumers and the environment.

Safety assessment of nanomaterials requires unprecedented levels of collaboration between scientists of multiple disciplines. The traditional fields associated with safety assessment—toxicology, pathology, molecular & cellular biology, pharmacokinetics and biochemistry—must work closely with experienced material scientists and others to ensure safety and biocompatibility studies produce conclusive, interpretable data for safety assessment.

Battelle, one of the world's largest private science and technology organizations, has one of the nation's most experienced, multidisciplinary nanotoxicology teams. Its Pacific Northwest Division is located on the Richland, Washington campus of Pacific Northwest National Laboratory, one of five national laboratories managed by Battelle for the U.S. Department of Energy. Here, a comprehensive suite of instrumentation and talented staff is changing nanomaterial assessment for industry. We perform all aspects of nanomaterial safety assessment—from exposure assessment and in vitro toxicity screening to full Good Laboratory Practice (GLP) chronic bioassays in AAALAC*- accredited animal research facilities and extrapolation of findings to humans.

Whether improving product biocompatibility, conducting toxicity testing or designing product stewardship research strategies, Battelle researchers partner with client experts to understand the issues and create innovative solutions. We offer an unequaled breadth of experience in a variety of nanomaterial safety assessment related disciplines, including:

- Nanomaterial Exposure Assessment
- Physicochemical Characterization
- Aerosol Physics and Particle Exposure Engineering
- Particokinetics and Particokinetic Modeling
- Toxicity Screening and Hazard Assessment
- Structure Activity Relationship Modeling
- GLP Inhalation, Dermal & Oral Toxicity Studies
- Animal to Human Extrapolation
- In Vitro to In Vivo Extrapolation
- Product Stewardship
- Risk Assessment

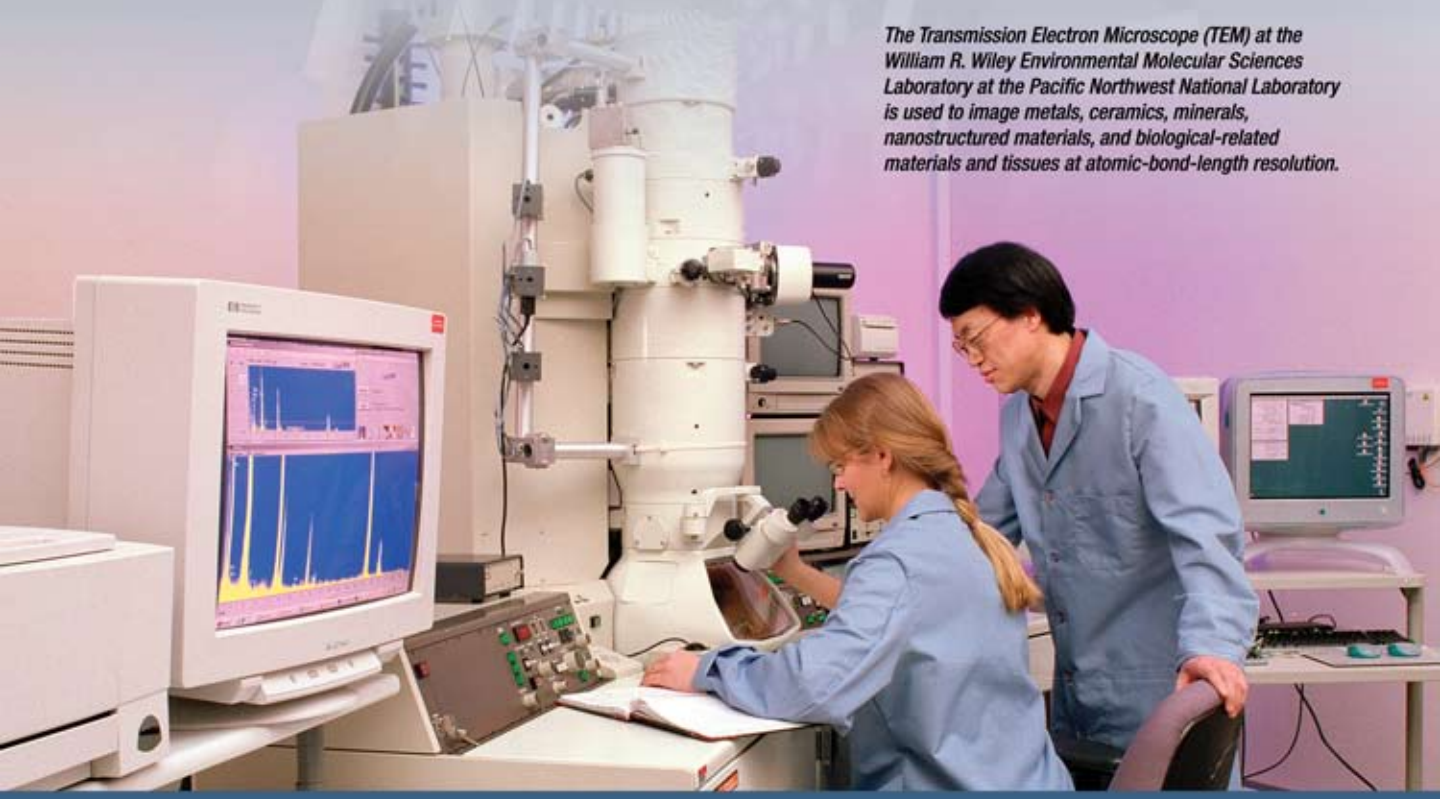


**Association for Assessment and Accreditation of Laboratory Animal Care*

PROGRAM OVERVIEW

Nanomaterials pose no risk to humans when exposures are near zero. Manufacturers are investing in assessment of workplace exposure to nanomaterials during product manufacturing and application to determine if the potential for health risks exist. Battelle researchers, working with manufacturers, have designed approaches to exposure assessment that overcome some significant technical challenges.

To eliminate the confounding affects of natural background concentrations of nanoparticles, Battelle has developed the capability to simulate manufacturing processes in a controlled environment. This enables accurate characterization of exposures through real-time measurement of particle concentrations and sample collection for determination of size-class distribution, number and particle physicochemistry. These capabilities combined with unique simulation capabilities at PNNL, including particle physics and lung dosimetry, reduce the uncertainty in assessing exposure and determining human risk during the production and manufacturing process.



The Transmission Electron Microscope (TEM) at the William R. Wiley Environmental Molecular Sciences Laboratory at the Pacific Northwest National Laboratory is used to image metals, ceramics, minerals, nanostructured materials, and biological-related materials and tissues at atomic-bond-length resolution.

Toxicology Northwest, located on Battelle's Richland, Washington campus is the nation's leader in inhalation toxicology of vapors, particulates, nanomaterials, and fibers. Here, aerosol scientists realized their most recent innovation—the first controlled generation and real time monitoring of micron and nanoscale C_{60} fullerenes for chronic inhalation exposure to rodents.

This important advancement in inhalation exposure technology overcame significant technical challenges and limitations of other systems to create the state of the art for conducting in vivo exposures to nanomaterials. This ideal exposure system for human hazard and safety assessment is being utilized by the National Toxicology Program and illustrates our unmatched experience conducting chronic toxicity studies of ultra-fine particulates and fibers.

The LSL II building houses Toxicology Northwest for Battelle and several new systems biology laboratories for the Pacific Northwest National Laboratory. As part of the Biomolecular Systems Initiative, scientists will use the facility to further their understanding of systems biology and their work with DOE's Genomes to Life Program.

Nanomaterials present particular characterization challenges because of their small size, sensitivity to time and environment, and their often complex structure. Many characteristics are important in assessing their interaction with biological systems and the environment—size, structure, chemical composition and surface chemistry—to name a few. No single characterization method provides enough information to completely assess the potential risk for a particular material.

Battelle's general approach is to combine measurements that average over a large ensemble of nanoparticles with those that probe single particle characteristics to obtain a useful picture of both average particle properties and the extent of variation. Some of the specific capabilities include unique electron and light microscopies, advanced nuclear magnetic resonance (NMR) and mass spectroscopy methods, and optical atomic force microscope (AFM) spectroscopies. These characterization approaches have been honed over many years by researchers working on a variety of research and development projects with nanoscale materials including metal oxide catalysts, fluorescent quantum dot labels, and functionalized carbon nanotube-based materials.

The 7-Tesla Fourier transform ion cyclotron resonance (FTICR) mass spectrometer in the William R. Wiley Environmental Molecular Sciences Laboratory is one of many state-of-the-art tools available to Battelle's nanotoxicology program.

Battelle's molecular and cellular toxicologists have experience with a wide variety of nanomaterials including metals, metal oxides, fullerenes, silicates and carbon nanotubes. Working closely with material scientists, a variety of 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 may be applied when broader measures of response are necessary to define a toxicity profile or mode of action. Many of these assays can be performed in parallel with real-time visualization of nanoparticle deposition, cellular uptake and trafficking. This broad set of capabilities is particularly important when multiple surface chemistry modifications are being tested for biocompatibility.

At the Environmental Molecular Sciences Laboratory, researchers are providing new insight into the molecular basis of disease by developing an advanced proteome analysis capability based upon high-performance liquid chromatograph separations coupled with mass spectrometric technologies.

Researchers at Battelle are leading the development of superior experimental and computational tools for predicting cellular dose of particles and nanomaterials in rodents and humans. An anatomically correct 3-D computational model of the rodent and human respiratory tract are used to predict the dose of nanomaterials to specific lung regions and extrapolate from delivered doses in animals to humans. This unique capability is critical for interpreting the results of animal toxicity studies.

A computational model of particle kinetics and dosimetry for cell culture systems has also been developed for selecting doses for in vitro toxicity screening studies that normalize delivered doses across particle types and reflects reasonable human exposure scenarios. The model can also be used to estimate dose from completed studies to improve data interpretation and extrapolate findings to in vivo exposures. Tools such as these and the associated expertise in particle dosimetry offer unequalled capability to extrapolate the results of nanoparticle toxicity studies across dose (high to low), study type (in vitro to in vivo), species (rodent to human) and sensitive populations (children, asthmatics).

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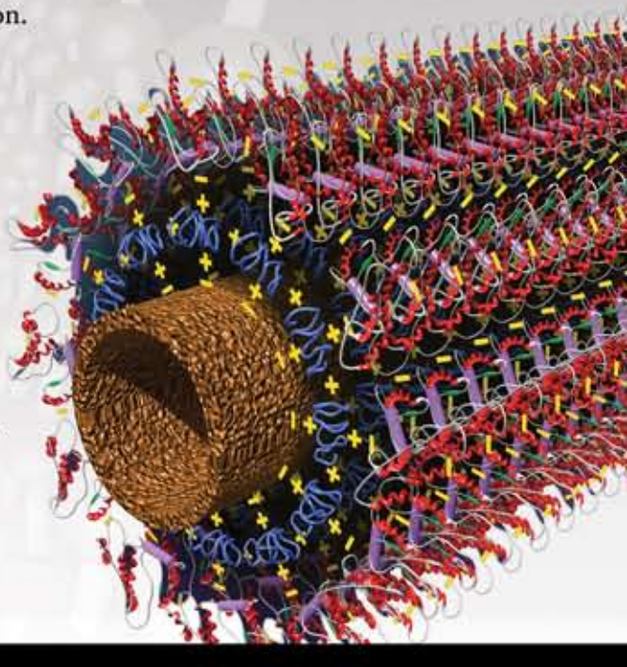
Foundations for Nanomaterials Expertise

Battelle's array of tools and talented staff are the backbone of its nanotoxicology and safety assessment programs. The Environmental Molecular Sciences Laboratory (EMSL) 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. This world-class user facility offers clients a comprehensive array of cutting-edge resources to address important scientific questions.

As one of the world's largest independent research and development organizations, Battelle conducts proprietary research, develops and commercializes technology, and manages national laboratories for its customers. As a non-profit corporation, we manage or co-manage five national laboratories and oversee 19,000 staff in more than 100 locations to conduct $3 billion in annual research and development.

Our internationally-recognized staff provides solutions and helps develop innovative products for commercial customers by leveraging technologies into competitive advantage. We also team with more than 800 federal, state, and local government agencies, providing cost-effective science and technology in the areas of health and life sciences, energy and environment, national security, homeland defense, transportation, and space exploration.

At Battelle, internationally-recognized experts in material science, toxicology and product stewardship access state-of-the-art facilities for biological and material science to implement our comprehensive cross-discipline approach to nanomaterial safety assessment. Together with our industry partners, Battelle employs every tool and expert at its disposal to transform the challenges of today into tomorrow's innovative and safe nanotechnology products.



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