Towards Predicting Nano-Biointeractions:
An International Assessment of Nanotechnology Environment, Health and Safety Research Needs
# Table of Contents

**Foreword** .......................................................................................................................... 5
**Executive Summary** ............................................................................................................ 6

**Workshop 1: Towards Nanomaterial Classes** ..................................................................... 7

- **Key findings** ....................................................................................................................... 7

**Workshop 2: Towards Predicting Nano-Biointeractions** ...................................................... 8

- **Key findings** ....................................................................................................................... 8

**Cross-Cutting Issues** .......................................................................................................... 8

**Next Steps** ........................................................................................................................... 9

**Workshop Recommendations** ............................................................................................ 10

- **Research to Predict Nano-Biointeractions** ....................................................................... 10
- **Research to Meet Risk Management Needs** ...................................................................... 11

**Overview: Nanotechnology and its Implications** ................................................................ 11

**Related Reports** .................................................................................................................. 13

## 1. Workshop 1: Towards Nanomaterial Classes ................................................................. 1-14

### 1.1. Workshop Overview ....................................................................................................... 1-14

### 1.2. Summary of Workshop Findings .................................................................................. 1-15

### 1.3. Next Steps ..................................................................................................................... 1-16

### 1.4. Workshop Steering Team and Sponsors ........................................................................ 1-16

### 1.5. Workgroup Summaries ................................................................................................. 1-16

#### 1.5.1 Oxide Workgroup Summary ..................................................................................... 1-16

1.5.1.1 Introduction ................................................................................................................... 1-16
1.5.1.2 Common Oxide Particles .............................................................................................. 1-17
1.5.1.3 Nanomaterial Properties and Biointeraction ............................................................... 1-17
1.5.1.4 Synthesis, Formulation and Manufacture ................................................................. 1-18
1.5.1.5 Potential Hot Spots in the Nanomaterial Life .............................................................. 1-18
1.5.1.6 Research Priorities ....................................................................................................... 1-19
1.5.1.7 General Questions and Concerns ................................................................................ 1-19
1.5.1.8 Backup Information .................................................................................................... 1-19

#### 1.5.2 Metals Workgroup Summary .................................................................................... 1-20

1.5.2.1 Introduction ................................................................................................................... 1-20
1.5.2.2 Common Metallic Nanomaterials and Applications ............................................... 1-20
1.5.2.3 Nanomaterial Properties and Biointeraction .............................................................. 1-20
1.5.2.4 Synthesis, Formulation and Manufacture ................................................................. 1-21
1.5.2.5 Potential Hot Spots in the Nanomaterial Life .............................................................. 1-22
1.5.2.6 Research Priorities ....................................................................................................... 1-22

#### 1.5.3 Semiconductor Workgroup Summary ....................................................................... 1-22

1.5.3.1 Introduction ................................................................................................................... 1-22
1.5.3.2 Synthesis ....................................................................................................................... 1-22
1.5.3.3 Applications .................................................................................................................. 1-23
1.5.3.4 Hot Spots ...................................................................................................................... 1-23

#### 1.5.4 Carbon Workgroup Summary ................................................................................... 1-24

1.5.4.1 Introduction ................................................................................................................... 1-24
1.5.4.2 Carbon Nanomaterials ............................................................................................... 1-24
1.5.4.3 Exposure Scenarios During Manufacture/Synthesis ................................................. 1-24
1.5.4.4 By-Products and Contaminants .................................................................................. 1-25
1.5.4.5 Applications and Uses for Carbon Nanomaterials .................................................. 1-25
1.5.4.6 Exposure Scenarios During Use of Carbon Nanomaterials ..................................... 1-25
1.5.4.7 Improving Exposure Assessment ............................................................................... 1-26
1.5.4.8 Prioritization of Research Needs ................................................................................ 1-26
2. Workshop 2: Towards Predicting Nano-Biointeractions ........................................ 2-38
   2.1. Workshop Overview ............................................................................................. 2-38
   2.2. Summary of Workshop Findings ........................................................................... 2-40
       2.2.1 Next Steps ........................................................................................................ 2-42
   2.3. Summary Research Needs and Timetables ............................................................ 2-42
       2.3.1 Research to Predict Nano-Biointeractions ....................................................... 2-42
           2.3.1.1 Characterization of Nanomaterials ................................................................ 2-42
           2.3.1.2 Standard Terminology .................................................................................. 2-43
           2.3.1.3 Standard Reference Nanomaterials ............................................................... 2-43
           2.3.1.4 Techniques for Detecting Nanomaterials in Biological Media ...................... 2-43
           2.3.1.5 In Vivo Tests and Correlation to In Vitro Tests ................................................. 2-44
           2.3.1.6 In Vitro Testing .............................................................................................. 2-44
           2.3.1.7 Model Development ...................................................................................... 2-45
       2.3.2 Metrology for Risk Management ...................................................................... 2-45
           2.3.2.1 Assessment of Bioavailability throughout the Lifecycle ................................. 2-46
           2.3.2.2 Characterization of Potential Mobility of Embedded Nanomaterials ............ 2-46
   2.4. Common Themes ................................................................................................. 2-46
       2.4.1 Need to Correlate Nanoparticle Physicochemical Properties with Interactions in Organisms and the Natural Environment ........................................ 2-46
       2.4.2 Importance of Dose and Dose Rate in Understanding Biointeractions ............ 2-47
       2.4.3 Need for Well-Characterized Reference Materials and Standardized Assays, and New Assay Development ................................................................. 2-47
       2.4.4 Reproducibility of Research and Better Documentation of Methods to Improve the Quality and Comparability of the Science ............................................... 2-47
       2.4.5 Methods for Predicting Potential Long-Term Effects ...................................... 2-48
       2.4.6 Metrology for Locating and Characterizing Nanomaterials in Biological Organisms and Samples .............................................................................................. 2-48
       2.4.7 Metrology for Exposure Characterization ........................................................ 2-48
   2.5. Workshop Steering Team and Sponsors ............................................................... 2-48
   2.6. Charge to the Breakout Groups—Session 1: Mechanisms for Interaction of Nanoparticles with Biological Organisms ......................................................... 2-49
       2.6.1 Breakout Group 1A: Oxidative Stress, Inflammation, and Immune Response 2-49
           2.6.1.1 Background ................................................................................................. 2-49
# International Council on Nanotechnology 2007 Workshop Report

## Appendix C: Workshop 2 Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7.1 Breakout Group 2A: Nanoparticle-Biofluid Interactions/Target Cell Interactions</td>
<td>2-65</td>
</tr>
<tr>
<td>2.7.2 Breakout Group 2B: Cell Signaling and Communication</td>
<td>2-67</td>
</tr>
<tr>
<td>2.7.3 Breakout Group 2C: Whole Animal Interactions—Biokinetics</td>
<td>2-68</td>
</tr>
<tr>
<td>2.7.4 Breakout Group 2D: Ecotoxicology</td>
<td>2-70</td>
</tr>
<tr>
<td>2.6.2 Breakout Group 1B: Protein Misfolding/Biomolecules</td>
<td>2-53</td>
</tr>
<tr>
<td>2.6.3 Breakout Group 1C: Apoptosis and Necrosis</td>
<td>2-56</td>
</tr>
<tr>
<td>2.6.4 Breakout Group 1D: Genotoxicity and Mutagenicity</td>
<td>2-59</td>
</tr>
<tr>
<td>2.6.5 Breakout Group 1E: Developmental Effects</td>
<td>2-62</td>
</tr>
<tr>
<td>2.6.1 Breakout Group 1A: Interactions of Nanoparticles with Living Organisms</td>
<td>2-64</td>
</tr>
</tbody>
</table>

## 2.8. References Cited

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix C: Workshop 2 Agenda</td>
<td>2-76</td>
</tr>
<tr>
<td>Appendix D: Workshop 2 Attendees</td>
<td>2-78</td>
</tr>
</tbody>
</table>
About the International Council on Nanotechnology (ICON)

ICON is an international, multistakeholder organization whose mission is to develop and communicate information regarding potential environmental and health risks of nanotechnology, thereby fostering risk reduction while maximizing societal benefit. ICON was founded in 2004 as an extension of the U.S. National Science Foundation Center for Biological and Environmental Nanotechnology (CBEN) at Rice University in Houston, Texas. ICON is a knowledge-driven organization. It does not engage in advocacy or commercial activities. More information about ICON can be found at http://icon.rice.edu.

Sponsorship

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Foreword

“Imagine you had the intellectual capital of all the nations on earth, strong support, and a large—not infinite—budget to fund research that led to a deeper understanding of the impacts of nanotechnology. What would you do?”

This was the fundamental question posed to the participants in two international workshops aimed at defining a set of research needs for the nascent area of nanotechnology. The creation of new knowledge has long been associated with technological innovation—without new ideas, how can society expect to benefit from creative solutions to its most pressing problems? Perhaps less apparent is the critical role that the research enterprise plays in defining and managing the possible environmental and health risks of its inventions. No new technology has zero risk, and decision-makers, whether they are in a corporation, supermarket, or government agency, understand this reality. But for them to take full advantage of the potential of new technologies, they must have access to solid research results that permit them to understand, quantify, and manage any risks.

Coordinated research into the risks of emerging technology, particularly nanotechnology, is uncharted territory. Historically, the risks are assessed after technologies are deployed, when specific risks are documented in defined settings and use patterns. Proactive research into risk is not about assessing a single documented risk, but rather about filling out a more complex risk landscape that addresses a range of possible scenarios of technology use and settings. Understanding how to construct and develop a research program to accomplish this aim was the motivation for the work described in this report.

Nanotechnology was the specific focus area for the participants who helped define this report. Good strategy depends critically on defining a desirable end goal, and as noted by groups before ours, there are several overarching outcomes for nanotechnology and research into its impacts. To focus these workshops, we oriented around one particular outcome: a framework for predictive models for nanotechnology’s impacts. With the “what” being firmly established prior to the events, the groups were free to focus on the “how”—that is, 2-, 5-, and 10-year goals that when taken together would result in tools to help all stakeholders characterize the impacts of emerging nanotechnologies possibly even before they are created. I hope that the specific recommendations for strategy contained in this report can be used to structure various research programs around the world.

I also hope that readers of this document appreciate the “how” by which this document was produced—with open, equal, and truly shared ownership by stakeholders from many groups at all steps—because the diversity of the participants and collaborative process in which they engaged could have significant implications for the future. Whether and how nanotechnology is used will not be the result of a single decision made by a monolithic group. Rather it will be shaped by a thousand smaller decisions made by individuals in academia, industry, government, and nongovernmental organizations (NGOs). Creating common understanding, shared vision, and coordination among these diverse groups is thus essential to defining a path for nanotechnology commercialization that earns the confidence of and acceptance by many, if not all, international stakeholders.

The leadership of the International Council on Nanotechnology (ICON) in these workshops facilitated the engagement of multiple stakeholders—73 in all—that will be essential to the success of a coordinated international research effort. All of ICON’s programs use diverse teams that follow transparent processes to generate, plan, and ultimately implement projects of shared interest. The workshops whose results are reported here were conceived in 2005, arising naturally out of other ICON activities toward international coordination and research priorities for nanotechnology’s risk research. This report synthesizes the discussions, presentations, and identified research needs from these efforts.

Professor Vicki Colvin, Executive Director of ICON
Executive Summary

This report presents the results and recommendations from two international workshops centered on a global research strategy for understanding nanotechnology’s environmental and health impacts. More specifically, the overarching goal of the workshops was to develop a framework for predicting the interactions between engineered nanoparticles and biological systems at the molecular level so that biocompatible nanomaterials can be developed and applied safely. Convened by ICON, the workshops were held in Bethesda, Maryland, USA in January 2007, and in Rüschlikon, Switzerland in June 2007. Each workshop brought together more than 50 experts, mostly scientists, representing diverse stakeholder groups including academia, industry, governments, NGOs, and 13 countries. All participants are involved in fields relevant to the workshop topics, including biology, computational modeling, toxicology, materials science, biophysics, and environmental science. Cosponsors of the workshop included ICON and the National Science Foundation (NSF) of the USA, with significant in-kind support provided by the U.S. National Institutes of Health (NIH) and Swiss Reinsurance Company.

The grand challenge of producing computational models that predict interactions of engineered nanoparticles with organisms is a long-term challenge of at least 10 years. The ICON Research Needs Assessment workshops were structured to approach the challenge systematically, breaking it down into component areas that will ultimately produce predictive models that will enable all users of nanotechnology to better characterize its impacts, improve risk mitigation processes, and rationally design biocompatible nanomaterials. Fundamental to the challenge, as defined by workshop organizers, is the identification of the physicochemical properties of nanomaterials and establishment of links between such properties and their biological impacts. Accordingly, the goals of the first ICON workshop (Towards Nanomaterial Classes) were to identify preliminary classes of nanomaterials with common properties and to identify for these classes potential “hot spots” in their life cycle. The results from Workshop 1 served as input to Workshop 2 (Towards Predicting Nano-Biointeractions), which had as its goal to define research strategies for developing predictive models of engineered nanomaterials’ interactions with biological systems.

No other research effort on potential nanotechnology risks has taken up this challenge, nor has any other research strategy been a product of collaboration among such a diverse group of international participants. The workshop participants were charged with defining the research needs, or milestones, required to produce predictive models of an engineered nanoparticle’s biological effects. The research needs were constrained not to be so large as to require a decade or more of funding from multiple sources. They were also written not to be so detailed as to define single investigator or even larger collaborative programs. In many ways, these research needs were developed to be at the level of (but not to serve as actual) requests for proposals (RFPs) that could be developed by agencies worldwide—topically focused with terms of several years, and engaging multiple investigators in distantly related activities.

The identified research needs and activities comprise recommendations for progressive research within specific timeframes largely toward predictive models for nanomaterial risks. Altogether, 26 research needs for predicting nano-biointeractions were identified (Figure 1, page 10). In addition, a second set of six research needs was identified for risk management (Figure 2, page 11). Such research is necessary to inform policy makers about the adequacy of current detection and protection measures in workplaces where engineered nanomaterials are present and to inform researchers as to the potential magnitude of exposure related to these materials. Identified research needs from the various workgroups were combined and refined to avoid redundancy. Each research need in Figures 1 and 2 provides a link between the grand challenge and actionable programs for the near-term (2-year), mid-term (5-year), and long-term (7- to 10-year). Details on research needs and milestones are contained in the workshop reports that start on page 14.
The workshops were intended to explore and express the general views of a broad group of individuals rather than to achieve a consensus position. Drafts of the workshop report were generated by the workshop steering teams, facilitators, and scribes, and then circulated among the participants for review. The final product is a reflection of the wide-ranging discussions that occurred over the course of the two events and should not be construed as expressing official positions of the organizations employing the workshop participants.

The outputs of the ICON Research Needs Assessment workshops build on previous work toward research agendas for biointeractions of nanomaterials. Several reports on such work are included in this document’s references, among them Maynard et al.\textsuperscript{10} and Balbus et al.\textsuperscript{12}

**Workshop 1: Towards Nanomaterial Classes**

Participants in this workshop began by discussing what is known about key classes of nanomaterials and exploring whether physical and chemical properties are adequate for determining biointeractions. The participating experts explored options for classifying the physical and chemical properties of engineered nanomaterials that could affect biointeractions; assessed these properties for nanoparticles composed of oxides, semiconductors, metals, carbon, macromolecules, and self-assembled materials; and identified potential areas of concern (“hot spots”) for current and future applications, volumes, exposure, and hazard throughout the nanoparticle life cycle.

**Key findings**

- While participants of this workshop were asked to classify nanomaterials based on the physicochemical properties that could affect bioactivity, it became clear that this was not possible with the available body of knowledge. As the experts noted, subtle changes in structure, surface structure, and composition could dramatically affect electronic and chemical properties over the material’s life cycle. Many properties can be dramatically altered during nanomaterial synthesis, functionalization, or at other points during the product-manufacturing process. Furthermore, because nanoparticles change as they interact with living systems, it is unlikely that their physicochemical properties at any one stage in the life cycle alone will predict biological behavior. Therefore, the first recommendation from Workshop 1 was that tools and models must be developed that can describe the dynamic nature of nanomaterials throughout their lifestyle.
- The best potential mechanisms to characterize nanomaterial properties at various stages of the life cycle would be physical/chemical screens and select \textit{in vitro} tests to determine chemical reactivity, surface charge, surface composition, and solubility. These screens would need to be correlated to transport properties and biointeractions in full biological tests in order to identify nanomaterials that need detailed testing. \textit{In short, a set of screening tools is needed to correlate the functional properties of nanomaterials with their potential for biological interaction.}
- Current information suggests some general conclusions regarding exposure potential to nanomaterials. For nanomaterials in a dry powder form, potential for exposure to high concentrations is greatest during the cleaning of synthesis reactors, bagging operations, surface functionalization, and formulation areas of manufacturing. Nanomaterials in liquid form present possible topical application or inhalation exposures during manufacturing or product applications. Nanomaterials bound in a liquid or solid matrix would have a lower potential for exposure than an unbound nanomaterial. Little is known, however, about whether the physical form of a nanomaterial or its chemical composition is most important in evaluating net dose for its various biointeractions. Therefore, \textit{exposure assessment studies are needed to lead to predictions about physicochemical properties and their implications for net dose}. 

Executive Summary 7
Workshop 2: Towards Predicting Nano-Biointeractions

The second workshop focused on identifying the research needs and milestones to inform predictions of an engineered nanoparticle’s biological effects, and on defining strategies to develop predictive models of engineered nanomaterials’ interactions with biological and environmental systems. The first breakout session focused on the mechanism of an organism’s response to stress induced by a nanomaterial, and identified additional interactions of the nanomaterial with the recovery pathway. The second breakout session identified the research needed to develop predictive models of interactions with biofluids, cells and tissue, whole animals, and the environment. Detailed discussions focused on nano-biological interaction mechanisms such as oxidative stress, inflammation and immune response, protein misfolding, apoptosis and necrosis, genotoxicity and mutagenicity, and developmental effects at cell-free, cellular, tissue and whole-animal levels. Research needs were identified for all of the areas of understanding and for determining interactions between in vivo and in vitro research to develop predictive models. Many of the needs are not unique to nanomaterials but are required for progress in predictive chemical toxicology.

Key findings

- When a nanoparticle is put into a biological fluid or the environment, it becomes coated with biomolecules in a complex and dynamic manner that is not well understood. For predictive modeling, nano-environmental, health, and safety (nano-EHS) researchers must be able to identify what biomolecular interactions will dominate in a given environment and what the particle “identity” likely will be. To gain this information, quantitative models are needed to describe how the physicochemical properties of nanoparticles control the nature and extent of biomolecular interactions at their surface.

- With nanoparticles’ large ratio of surface area to mass, the traditional mass-based measure of dose may result in higher than expected concentrations of nanoparticles at a cell membrane or other biological structure. These high concentrations could result in new types of interactions that would not occur at lower concentration. Therefore, it will be important to establish thresholds of interaction and to validate concentration measurements against them. Dose and dose rate may need to be validated independently for nanomaterials.

- Many of the research challenges for this area overlap with the larger needs of the toxicology community. The workshop participants noted that for screening, especially given the sheer diversity of nanoparticles, in vitro assays would be essential. However, there was a strong recognition that such datasets may not predict outcomes in animals. Specific research designed to develop better biomarkers, or sets of biomarkers, is thus essential to address the vast diversity of nanoparticle types and to develop strong correlative models for predicting in vivo data based on in vitro results.

Cross-Cutting Issues

Researchers in both workshops agreed that the most immediate barrier to realizing the grand challenge of creating predictive models for interactions between engineered nanoparticles and biological systems is the lack of defined and shared research practice. Toward this, researchers must agree on a common language and general good practices for engineered nanoparticle characterization—especially with respect to purity, biological endpoint assessment, and data-reporting structures. Reference materials were widely discussed by participants as one way to address these issues; others recognized the importance of workshops and face-to-face meetings of scientists to develop standard practices. Without agreement on
definitions and common experimental practices, research across the world will be difficult to integrate and interpret.

While not formally on the agenda, risk management practices emerged repeatedly in both workshops, especially as they relate to potential exposures and exposure assessment. Identified by participants were needs for metrology and tools to characterize and measure nanomaterials, and to monitor their presence in the environment and in biological media used in research. Test methodologies to characterize the potential mobility of embedded nanomaterials also were called for, as was the basic need for characterizations of nanomaterials, evaluation of the appropriateness of *in vitro* tests to characterize nanomaterial interactions more broadly, standardization for biological materials used in testing, and the creation of a data-sharing framework to accelerate development of models. Further discussion of these crosscutting issues can be found in Common Themes section of Workshop 2 (page 46). Because time frames for research needs also were addressed in Workshop 2, please refer to page 42 for further discussion and detail related to risk management.

**Next Steps**

A coordinated international research effort will be needed to formulate tools for predicting engineered nanoparticle interactions with organisms. The scope of the materials under consideration, the diversity of possible exposure scenarios, and the quantification of biological response are all daunting challenges to achieving this outcome. Furthermore, efforts should be established to coordinate the collection and dissemination of biointeraction knowledge from research in such diverse areas as medical diagnostics and treatment applications and interaction studies for consumer applications.

Workshop 1 participants noted that further deliberative efforts with similar programming would be required to provide detail for many of the specific research needs identified as significant obstacles to producing predictive models (Figure 1). Among the areas that need further investigation are 1) reviewing the individual workgroup research priorities to assess their broader applicability, 2) identifying screening strategies to measure physical (size, shape, nanostructure) and chemical (composition, chemical reactivity, particle surface charge, solubility, surface composition) properties, 3) establishing agreement on a set of functional screens and identifying tests to determine whether these properties correlate to biointeraction potential, 4) assessing potential for nano-biointeractions with a wider range of biological systems, and 5) identifying research needed to develop predictive models of nano-biointeraction.

At the end of the second workshop, participants also brainstormed on the subject of potential future directions. Some of these recommendations were for activities that ICON might be in a position to organize, including future workshops that begin to address one or more specific needs identified by the group, and others for activities that might be taken up by other groups or organizations. The following activities were advanced as potential future directions:

- an international effort to identify promising metrology and methodologies for monitoring nanomaterials in the workplace and the environment
- an international effort to identify tools for detecting the presence and characteristics of nanomaterials in biological systems
- an effort to develop a minimum set of experimental data to be submitted with a technical manuscript (such as the Minimum Information About a Microarray Experiment [MIAME] protocols) to allow for greater reproducibility and comparison of nano-biointeractions research
- an effort to identify model biological systems and model nanoparticles for nano-biointeractions research
- a workshop to identify a number of functional materials properties, including chemical screens, reactivity, charge, and solubility.
## Workshop Recommendations

### Research to Predict Nano-Biointeractions

**10-Year Goal:** Computational models that predict nano-biointeractions and estimate safety and hazard with validation screens

<table>
<thead>
<tr>
<th>Research to Predict Nano-Biointeractions</th>
<th>Near-term 2 years</th>
<th>Mid-term 5 years</th>
<th>Long-term 7-10 years</th>
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<tbody>
<tr>
<td>Nanomaterial characterization</td>
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<tr>
<td>1. Establish minimum NM physicochemical properties for characterization.</td>
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<td>2. Establish validated correlation between physicochemical properties and biointeractions.</td>
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<td>3. Establish common vocabulary/terminology for materials and assays.</td>
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<td>4. Establish validated reference NMs that have been tested in vitro and in vivo.</td>
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<td>5. Establish tight control of nanoparticle reference materials.</td>
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<td>6. Develop new techniques for imaging NMs in biological media and organisms to supplement TEM.</td>
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<td>7. Quantitatively determine the fate and interactions of engineered NMs within reference organisms, including dose and dose-rate effects.</td>
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<td>8. Develop a fundamental understanding of NM interaction with cell-signaling pathways.</td>
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<td>9. Identify nano-biointeractions for chronic exposure.</td>
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<td>10. Validate SARs based on in vitro and in vivo data.</td>
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<tr>
<td>In vivo tests and correlation to in vitro tests</td>
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<td>11. Identify standard in vitro biological media and tests based on in vivo tests.</td>
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<td>12. Evaluate interactions of a range of engineered NMs with standard in vitro tests and evaluate vs. in vivo.</td>
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<tr>
<td>13. Establish validated correlation between physicochemical properties and biointeractions.</td>
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<td>14. Validate standard in vitro biological media and assays vs. in vivo tests.</td>
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<td>15. Correlate engineered NMs in vitro and in vivo for model systems.</td>
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<td>16. Explore interactions of a broad range of engineered NMs with complex coatings with standardized in vitro tests.</td>
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<td>17. Complete mechanically based QSAR studies.</td>
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<td>18. Develop engineered NM-specific, high-throughput screening methods with supplemental modeling.</td>
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<td>19. Validate SARs based on in vitro and in vivo data.</td>
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<tr>
<td>Model development</td>
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<td>20. Design framework(s) for data sharing and ontologies.</td>
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<td>21. Explore applicability of established modeling algorithms.</td>
<td>✔</td>
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<td>22. Establish data-sharing structures.</td>
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<td>23. Establish mechanically based QSAR studies.</td>
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<td>24. Validate SARs based on in vitro and in vivo data.</td>
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<td>25. Validate algorithms and training sets for computational models.</td>
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<td>26. Develop engineered NM-specific, high-throughput screening methods with supplemental modeling.</td>
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**Figure 1.**

NIM = Nanomaterial
The ICON workshops identified 26 types of research needed to predict nano-biointeractions. All of these identified areas will contribute to the ultimate, 10-year goal of this effort—also referred to as the grand challenge—to produce computational models for predicting nano-biointeractions.

**Research to Meet Risk Management Needs**

<table>
<thead>
<tr>
<th>Research to Meet Risk Management Needs</th>
<th>Near-term 2 years</th>
<th>Mid-term 5 years</th>
<th>Long-term 7-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metrology for risk management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Identify metrology techniques capable of characterizing the presence of engineered NMs in the workplace and environment.</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Validate the effectiveness of personal protective equipment in limiting exposure.</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Develop portable tools to monitor a wide range of NMs in the workplace and environment.</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Assessment of bioavailability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Determine the bioavailability of NMs throughout the life cycle.</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Characterization of potential mobility of embedded nanomaterials</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. Establish test methodologies to evaluate the stability and mobility of NMs in liquid and solid matrices.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6. Complete evaluation of stability and mobility of NMs in common liquid and solid matrices.</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*NM = Nanomaterial*

Figure 2.

Figure 2 lists the research needed to enable improved risk management of nanomaterials and enable predictive models of nanomaterial biointeractions based on nanomaterial physicochemical properties. Resulting information will inform policy makers about the adequacy of current detection and protection measures in workplaces where engineered nanomaterials are present and will inform researchers as to the potential magnitude of exposure related to these materials, a key component of predictive models.

**Overview: Nanotechnology and its Implications**

Nanotechnology is an emerging area of technology development involving structures that measure from 1–100 nm in one or more dimensions. While precise definitions are still somewhat variable, most recognize that nanotechnology involves science and engineering of matter at the nanoscale where properties may change with size or new properties may emerge. Nanoparticles are small pieces of matter within the nanoscale range and constitute an important area of nanotechnology research and development. A subset of this research involves engineered nanoparticles, which are intentionally manufactured to have specific properties or composition, in contrast to incidental nanoparticles, which are generated inadvertently or through natural processes. Engineered nanoparticles include such materials as quantum dots (QDs—semiconductor nanoparticles), nanotubes (carbon nanoparticles), and nanotitania (oxide nanoparticles), among many others. Smaller than microscale particles, yet larger than atoms and many molecules, nanoparticles occupy a transitional regime between classical and quantum physics where physical and chemical properties are somewhat tunable with changes in size, structure, composition, surface structure, and surface composition.

This flexibility presents the nanomaterials scientist with a toolbox for tailoring material properties to a specific application. For example, through some rather rudimentary chemistry we can make a nanoparticle glow one color or another, make it electrically conductive or semiconductive, enable or hinder its
penetration through a cell membrane, or enable multiple properties simultaneously. Thus, engineered nanoparticles are now making their way into the marketplace in familiar consumer products such as sporting goods and personal care products, as well as more high-end applications such as targeted drug therapies. Numerous predictions have been made about the total market for products containing engineered nanoparticles, all of which forecast enormous growth.

The prospect of rapid and massive scale-up of the use of engineered nanoparticles has raised some concerns about the potential for new problems to emerge, in particular with respect to EHS issues. A relatively small but growing body of scientific research has demonstrated that engineered nanoparticles can interact in biological organisms and the natural environment in ways that cannot easily be predicted. Moreover, the very properties that application developers seek to exploit, such as the ability to enhance photocatalysis or cross a cell membrane, may cause unanticipated effects that have yet to be fully documented. If engineered nanoparticles have the potential to impact living organisms or the environment, we must understand better how to maximize the beneficial aspects and minimize undesirable outcomes of these interactions through improved risk assessment and management processes. Doing so will enable technology developers to exploit the full promise of nanotechnology and to solve existing problems in medicine or environmental remediation, as well as other application areas, without introducing new modes of toxicity or contamination.

The unique properties and potential mobility of engineered nanoparticles, along with the lack of mobile monitors to detect their presence, pose significant challenges to the development of best practices for nanomaterial handling throughout the life cycle. Extrapolating from health and safety data available for a larger-scale material may fail to capture the nanoscale analog’s interactions. Nanoparticles’ diversity and tunability make it difficult to predict their behavior. The interaction of an engineered nanoparticle with a cell, for example, can change dramatically with small changes in size, shape, or surface properties, such as may occur during the nanoparticle’s incorporation into a product or as a result of introduction into the body, even if the chemical composition of the base nanoparticle is constant. Testing each different variant of a nanoparticle, even if limited to those of commercial relevance, is impractical. A better understanding is needed of the structure-activity relationships (SARs) of nanoparticles themselves, particularly those with potential for high exposure or high-volume application in current and future products, so that we can proceed with greater confidence that the EHS issues have been identified and can be managed.

As nanoparticles with new properties are discovered and designed with more complex functionality, a scientifically based hierarchy of risk assessment is needed to develop handling protocols that expand in scope as the nanomaterial progresses from research to development to product. Until predictive models are developed, risk assessors will need knowledge of the potential interaction of the nanomaterial with biological organisms and the environment at each stage of the life cycle. Thus, an understanding of the functional properties that correlate with the biological response is needed. There is also a need for metrology and monitoring equipment to readily detect the presence or absence of nanoparticles in the laboratory, workplace, and environment.
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