A. Vision and Strategic Plan

The emergence and rapid expansion of nanotechnology has generated concern about the environmental health and safety (EHS) of engineered nanomaterials (ENMs). In response to this apprehension, the University of California Center for Environmental Implications of Nanotechnology (UC CEIN) was established in October 2008 with a long-term vision of developing a multidisciplinary and quantitative framework for assessing the potential environmental impact, hazard and exposure to ENMs, in both their primary as well as commercial nano-enabled formulations. The Center also provides feedback and guidance for the safer implementation of nanotechnology, including risk reduction and safer design strategies. The multidisciplinary approach of the Center involves materials science, environmental chemistry and engineering, toxicology, ecology, social science, computer science and modeling, statistics, public health and policy formulation. Collectively, these fields of expertise are necessary to address the complexity of the ENM physicochemical properties involved in hazard generation, establishment of structure-activity relationships (SARs), and use of exposure assessment to evaluate ecosystems impact. The UC CEIN’s vision is to generate predictive tools for environmental hazard and exposure assessment as well as to develop strategies to ensure the safe implementation of nanotechnology to the benefit of society, the environment and the economy. These tools and knowledge are disseminated through vibrant and impactful educational and outreach programs.

Our strategic plan for implementing this vision over the next five years involves four overarching goals:

i. To develop hazard ranking and structure-activity relationships (SARs) that relate the physicochemical properties of compositional and combinatorial ENM libraries to toxicological responses in cells, bacteria and multi-cellular organisms, with a goal to develop predictive toxicological paradigms to understand the environmental impact of nanotechnology;

ii. To estimate environmentally relevant exposure concentrations of high-volume and potentially high-impact ENMs (primary nanoparticles as well as commercial nano-enabled products) using life cycle assessment (LCA) and fate and transport modeling to obtain quantitative information about the uptake, bioaccumulation, and hazard of nanoparticles in terrestrial and estuarine ecosystems;

iii. To determine the potential of ENMs, selected through high throughput screening (HTS), SAR analysis, LCA and multimedia modeling, to impact ecosystem services in model ecosystems. These include terrestrial mesocosms with food crop plans and bacterial populations that control nutrient cycles, and estuarine mesocosms comprised of a representative natural food web;

iv. To use UC CEIN knowledge acquisition and environmental impact assessment tools to educate the next generation of nano EHS scientists as well as to inform and engage academic, government, industrial and societal stakeholders involved in risk perception, regulatory decision-making, policy development, risk management and safe implementation of nanotechnology.

The multidisciplinary UC CEIN team addresses these goals through four major thrusts. The first thrust (Structure-Activity Relationships) involves nanomaterial acquisition and characterization with a view to perform high-content screening (HTS) of ENM libraries to understand SARs at the nano/bio interface. This task is carried out by material scientists and chemists who acquire and synthesize compositional and combinatorial ENM libraries that are used to assess the physicochemical properties that could contribute to hazard generation in cells, bacteria, yeast, zebrafish embryos, terrestrial and aquatic life forms. Where possible, the hazard assessment is carried out by automated high throughput screening (HTS) in the California NanoSystems Institute (CNSI). The rich data sets emerging from the HTS are deposited into the CEIN data repository, enabling computer scientists and engineers to develop a computational framework for assessing the environmental impact of ENMs through the use of knowledge extraction and machine learning methods for data visualization (e.g., heat maps and Self-Organizing Maps), hazard ranking and establishment of quantitative SARs (QSARs). The second major thrust (Ecosystems Impacts) looks at the impacts of selected materials, identified through hazard ranking and exposure modeling, on terrestrial and aquatic ecosystems. The terrestrial theme emphasizes the ENM impact on microbes and plants, while the aquatic theme looks at estuarine species that are chosen based on the likelihood of suspension (pelagic organisms) or sedimentation (benthic organisms) exposures. Both environmental themes are focused on ENM impacts on ecosystem services (e.g., nutrient cycling, food webs, and biodiversity) and ecological processes (e.g., growth, primary production, and trophic transfer). The
ecosystems studies also include development of dynamic energy budget (DEB) models that quantify and integrate the ecosystem impacts across scales and life stages. The third major thrust examines environmental modeling through the lens of environmental fate and transport as well as lifecycle analysis. In combination with multimedia modeling tools developed by the first thrust, this research is used for ENM environmental decision analysis and modeling of the environmental exposure scenarios. The fourth thrust (Societal Outputs) is engaged in societal implications, education and outreach activities that generate new knowledge about societal contexts for ENM risk and also translates our research, knowledge acquisition and decision-making science to students, experts, the public and industry stakeholders.

B. Intellectual Merit
The science, education and outreach activities in the UC CEIN are planned around national nano EHS research needs, as expressed by the National Nanotechnology Initiative (NNI)\(^1\) and the 2012 PCAST reports.\(^2\) Accordingly, we address key NNI-targeted environmental research areas such as: (i) "Understand[ing] environmental exposures through the identification of principal sources of exposure and exposure routes" - by conducting lifecycle analysis of environmentally relevant material categories as described in the Environmental Modeling Thrust; (ii) "Determin[ing] factors affecting the environmental transport of nanomaterials" and understanding "the transformation of nanomaterials under different environmental conditions" by conducting fate and transport studies, including performance of case studies on nano-Cu and -ZnO materials; (iii) "Understand[ing] the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects" by studying terrestrial and estuarine species as addressed in the Ecosystems Thrust, in which we also demonstrate the use of mechanistic approaches for safety assessment of simple organisms, which are then used for prediction making, dynamic energy budget modeling and testing of trophic effects in more advanced organisms, populations, and communities; (iv) "Develop[ing] computational models of ENM structure–property-activity relationships to support the design and development of ENM with maximum benefit and minimum risk to .... the environment" by the acquisition of compositional and combinatorial ENM libraries that are used for high throughput screening and development of computational methods to establish SARs, hazard ranking and safer design of ENMs; (v) "Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation" of ENMs by using environmental fate and transport analysis, lifecycle analysis, multimedia modeling tools, computational and HTS approaches for establishing SARs, and predictive \textit{in vitro} \textit{→ in vivo} toxicological approaches for performing comprehensive and integrated analyses of the environmental impact of ENMs, including how to use this fundamental information for risk reduction. The emphasis on these NNI-targeted areas is reflected in our goals and strategic plan.

Through the pursuit of interdisciplinary, predictive and high throughput approaches, the UC CEIN has made, and will continue to make, a transformative impact on nano EHS assessment. The cornerstone of this impact is our ability to use an interdisciplinary approach for acquisition and synthesis of ENM libraries, which are assessed by high throughput and facilitative test strategies that inform about nanomaterial hazard and potential impact across a broad range of nano/bio interfaces, from cells to ecosystems. Coupled with our computational analysis tools and fate and transport modeling, this allows environmental impact analysis of broad material categories, including the use of this information for safety assessment, safer design and regulatory decision-making. The paradigm shift in nano EHS assessment in UC CEIN is reflected in the major research progress over the first five years, including: (i) development of an interdisciplinary and harmonized approach to study nanosafety across a wide range of disciplines; (ii) development of environmental decision making tools that consider the importance of ENM physicochemical properties in determining multimedia distribution, hazard ranking and development of nano-SARs; (iii) demonstration of the utility of compositional and combinatorial ENM libraries to understand what makes these materials hazardous and bioavailable; (iv) ENM hazard assessment through innovative HTS technology at cellular and organism level; (v) use of \textit{in vitro} hazard ranking and nano-SARs for making predictions in more complex organisms; (vi) ranking of oxide nanoparticles for regulatory decision-making, risk reduction, and dosimetry calculations; (vii) pioneering studies on trophic transfer of toxic ENMs from primary producers to grazers; (viii) demonstration of the importance of sunlight exposure and photoactivation in the toxicity of TiO\(_2\) in phytoplankton; (ix) safer design of ZnO by iron doping and demonstration of this effect across multiple ecosystems; (x) development of dynamic energy budget modeling to predict ENM impacts within populations and across multiple species in a
mesocosm or natural environment; (xi) the implementation of a nanotoxicology teaching course; (xii) analysis of legislative approaches to nano EHS governance; and (xiii) the development of laboratory safety guidelines for nanotechnology research personnel. The four thrusts described in our strategic plan will further strengthen our approach.

C. Broader Impacts
UC CEIN has demonstrated how to use an interdisciplinary approach to establish a science platform that addresses the major nano EHS challenges by using a predictive toxicological approach that links ENM properties to environmental hazard generation through the implementation of well-characterized ENM libraries, high throughput screening, computational analysis (to establish SARs), and using this fundamental knowledge together with fate and transport studies to make predictions about the possible impact on essential ecosystem services and ecological processes. Moreover, our study approaches, protocols, data and foundational knowledge have been widely disseminated to academia, industry, regulatory agencies and the public through our outreach capabilities and education tools (discussed below). Collectively, the Center's work product has had a major impact in shaping national and international nano EHS research directions. This includes a prominent role in the development and dissemination of harmonization study approaches for nanomaterial safety assessment. We will continue the predictive scientific approach to accelerate ENM hazard assessment commensurate with the rate of expansion of nanotechnology. We will also demonstrate how this knowledge can be used for the implementation of risk reduction strategies and safer design of ENMs. Members of the Center will continue to play leadership roles nationally and internationally in developing a predictive toxicological approach to ENM safety assessment, high throughput screening, nano informatics and development of QSARs, understanding how the impact on terrestrial organisms could influence the food supply, societal and stakeholder risk perception, nano EHS policy formulation and developing effective nano EHS teaching tools.

By using the Center's research to educate a new generation of interdisciplinary scientists and nano EHS decision-makers, UC CEIN plays an important role in developing a future nano EHS workforce for the US. Our educational programs have been developed to broaden the knowledge base of the environmental implications of nanotechnology through academic coursework, research, and training courses for industrial practitioners, public outreach, and a journalist/scientist communication program. UC CEIN educational programs have also broadened informal science education of K-12 audiences, the general public, and specialized stakeholder groups. We will continue to develop educational materials for a variety of academic audiences, including improvement of our environmental nanotoxicology capstone course by lectures that are made available through the web and workshops nationally and internationally. We will also incorporate UC CEIN research advances into existing undergraduate and graduate level courses across the Center's disciplines and institutions. Academic instruction is supplemented by the development of online training modules and the development of standardized methods and protocols that can be used for nano EHS assessment and decision-making. Theme 7 will continue playing an active role in disseminating UC CEIN research results and knowledge to experts involved in nano EHS policy making, governance and anticipatory decision-making.

As UC CEIN expands the development of safe handling of nanomaterials, we will engage industrial partners that can benefit from our research in the safety assessment and safer-by-design approaches for CNTs, nano-Ag, metal oxides, semiconductors, and silica nanoparticles. We also use workshops and roundtable discussions to inform industry about alternative safety assessment approaches, encourage information sharing, and conduct assessment of product life cycles. The broader impact of our societal outreach has resulted in safe implementation of nanotechnology practices in research laboratories, soliciting the opinion of the public, industrial stakeholders and policymakers.
PROJECT DESCRIPTION

A. Vision and Strategic Plan

The emergence and rapid expansion of nanotechnology, now reaching a large number of consumers in products such as personal care products, food additives, pharmaceuticals, electronics, energy harvesting, coatings, and paints, has generated considerable concern about the environmental health and safety (EHS) of engineered nanomaterials (ENMs). In response to this concern, the University of California Center for Environmental Implications of Nanotechnology (UC CEIN) was established in October 2008 with a long-term vision of developing a multidisciplinary and quantitative framework for assessing the potential environmental impact, hazard and exposure to nanomaterials, in both their primary as well as consumer product formulations. The Center also provides feedback and guidance for the safer implementation of nanotechnology, including risk reduction and safer design strategies. The multidisciplinary approach involves materials science, environmental chemistry and engineering, toxicology, ecology, social science, computer science and modeling, statistics, public health and policy formulation. Collectively, these fields of expertise are necessary to address the complexity of the ENM physicochemical properties involved in hazard generation, establishment of structure-activity relationships (SARs), and use of exposure assessment to evaluate ecosystems impact. The CEIN’s vision is to generate predictive tools for environmental hazard and exposure assessment as well as to develop strategies to ensure the safe implementation of nanotechnology to the benefit of society, the environment and the economy. These tools and knowledge are being disseminated through vibrant and impactful educational and outreach programs. This vision is clearly aligned with the National Nanotechnology Initiative’s (NNI) and national research needs, as echoed by the 2012 PCAST report.

Towards continuing the implementation of this vision over the next five years, our strategic plan includes the use of a multidisciplinary approach to achieve four overarching goals, namely:

i. To develop hazard ranking and structure-activity relationships (SARs) that relate the physicochemical properties of compositional and combinatorial ENM libraries to toxicological responses in cells, bacteria and multi-cellular organisms, with a goal to develop predictive toxicological paradigms to understand the environmental impact of nanotechnology;

ii. To estimate environmentally relevant exposure concentrations of high-volume and potentially high-impact ENMs (primary nanoparticles as well as commercial nano-enabled products) using life cycle assessment (LCA) and fate and transport modeling to obtain quantitative information about the uptake, bioaccumulation, and hazard of nanoparticles in terrestrial and estuarine ecosystems;

iii. To determine the potential of ENMs, selected through high throughput screening (HTS), SAR analysis, LCA and multimedia modeling, to impact ecosystem services in model ecosystems. These include terrestrial mesocosms with food crop plans and bacterial populations that control nutrient cycles, and estuarine mesocosms comprised of a representative natural food web;

iv. To use UC CEIN knowledge acquisition and environmental impact assessment tools to educate the next generation of nano EHS scientists as well as to inform and engage academic, government, industrial and societal stakeholders involved in risk perception, regulatory decision-making, policy development, risk management and safe implementation of nanotechnology.

The multidisciplinary UC CEIN team addresses these overarching goals through four major thrusts, which include eight research themes (Figure 1). The first thrust (Structure-Activity Relationships) involves nanomaterial acquisition and characterization with a view to perform high-content screening (HTS) of ENM libraries to understand structure-activity relationships at the nano/bio interface. This task is carried out by material scientists and chemists who acquire and synthesize compositional and combinatorial ENM libraries that are used to assess the physicochemical properties that could contribute to hazard generation in cells, bacteria, yeast, zebrafish embryos, terrestrial and aquatic life forms. Where possible, the hazard assessment is carried out by automated high throughput screening (HTS) in the Molecular Shared Screening Resource (MSSR) in the California NanoSystems Institute (CNSI). The rich data sets emerging from the HTS are deposited into the UC CEIN data repository, enabling computer scientists and engineers to develop a computational framework for assessing the environmental impact of ENMs through the use of knowledge extraction and machine learning methods for data visualization (e.g., heat maps and Self-Organizing Maps), hazard ranking and establishment of quantitative structure-activity relationships (SARs). The second major thrust (Ecosystems Impacts) looks at the impacts of selected materials, identified through hazard ranking and exposure modeling, on terrestrial and aquatic ecosystems. The terrestrial theme emphasizes the ENM impact on microbes and plants, while the aquatic theme looks at estuarine species that are chosen based on the likelihood of suspension (pelagic...
B. Overview of Research Program

B.1. Introduction and Outline of the Integrated Research Activities in the UC CEIN Themes

Building on an extensive and impressive library/repository of >150 commercial and UC CEIN-synthesized ENMs varying in composition, morphology, crystalline structure, coatings, and dopants, the studies in Theme 1 over the next 5 years will expand our multidisciplinary framework to address a series of major questions concerning the environmental implications of ENMs. Emerging toxicological paradigms based on our world-class HTS studies in Theme 2 have provided a wealth of hypotheses to apply to this study of the impact of commercial and high-volume ENMs in vivo and in situ hazard generation at the ecosystem level in the next 5 years, as well as for possible design of safer materials by tuning critical properties involved in hazard generation. The first four years of HTS have generated volumes of data on the interactions of dozens of ENMs and cells and embryos (e.g., bacteria, zebrafish) at a wide range of concentrations. The work to date has identified ~10 major mechanisms of ENM toxicity, which will be further enhanced by proteomics discovery. Theme 6 has developed numerical and visualization tools to assess prediction making and studying of ecosystems impact in Themes 4 and 5. The wealth of organisms or sedimentation (benthic organisms) exposures. Both environmental themes are focused on ENM impacts on ecosystem services (e.g., nutrient cycling, food webs, and biodiversity) and ecological processes (e.g., growth, primary production, and trophic transfer). The ecosystems studies also include development of dynamic energy budget (DEB) models that quantify and integrate the ecosystem impacts across scales and life stages. The third major thrust examines Environmental modeling through the lens of environmental fate and transport lifecycle analyses. In combination with multimedia modeling tools developed by Theme 6, this research is used for ENM environmental decision analysis and modeling of the environmental exposure scenarios. The fourth thrust (Societal Outputs) is engaged in societal implications, education and outreach activities that generate new knowledge about societal contexts for ENM risk and also translates our research, knowledge acquisition and decision-making to students, experts, the public and industry stakeholders. For more comprehensive information on the organization and integration of UC CEIN, please refer to our website: http://www.cein.ucla.edu
information generated via HTS and captured in SARs address the NNI’s research needs to “understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects”, providing a predictive toxicological framework. Moreover, the computational framework and data repository in Theme 6 will actively contribute to the newly established nano informatics initiative in the NNI community. Addressing impacts to key ecosystems services provides the means of using the predictive framework for reducing environmental harm.

Estimating the likelihood of exposure requires analyzing potential releases to the environment during ENM manufacturing, applications, and end-of-life fate. Building on the identification of potential high-impact ENMs on the environment, Theme 3 is developing an LCA framework for estimating emissions that, in combination with our evolving multimedia fate and transport model, will estimate exposure concentrations in different environmental media (e.g., soil, freshwater, sea water) being used in these models. In the next five years, we will address the NNI’s research focus on understanding environmental exposures through identification of principal sources, routes of exposure, key receptors, as well as the development of tools to predict exposure concentrations. We will conduct case studies for coated, uncoated and doped ZnO nanoparticles (being used in sunscreens and lotions) as well as nano-Cu formulations (used as antibacterial agents fungicides and other environmental applications) to determine environmental exposure via atmospheric deposition, storm water runoff, direct water contact, and wastewater effluent and biosolids. Our integrated research approach reduces this complexity stepwise by first evaluating the dominant emissions of ENMs to different environmental media, their transport pathways, and expected exposure concentrations. Once exposures to each medium are ranked, we ask: What are the potential ecological impacts, and how can they be minimized or eliminated? This approach directly responds to NNI’s research needs and provides actionable information for regulators.

The broader impact of high-risk materials identified through cellular and zebrafish HTS, exposure and case studies are used to further evaluate the impact on ecosystem services via in-situ case studies using model ecosystems: natural soils with crop plants and microbial communities (Theme 4), and a simulated estuary comprising a natural but simplified food web (Theme 5). Concurrent fate & transport experiments in Theme 3 utilizing the same model ecosystems are used to determine transformation, mobility, bioavailability and bioaccumulation of the ENMs. Ecotoxicity and fate & transport research generates results that include modeling parameters for our predictive mathematical models, and thereby refine environmentally relevant risk ranking. Themes 4-6 also integrate ENM toxicity data via Dynamic Energy Budget (DEB) modeling to predict effects at higher ecological levels and to provide mechanism-based dose-response expressions that are transferable to other cells and organisms. The combination of DEB and exposure modeling provides predictive tools for estimating population, community, and ecosystem-level effects. This work connects directly with NNIs research needs to “Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels” as well as to understand other ecosystem-level effects.

The UC CEIN is committed to leveraging our scientific discoveries to serve the broader society. Theme 7 will expand the translation of our research for multiple stakeholder groups and integrate our science to assist the development of new policy approaches and science translation. By partnering with experts in academia, law, policy, industry, and civil society organizations, the Center's outreach activities will identify priority areas for targeted engagement and science translation. One of the key goals of Theme 8 is to educate the next generation nano EHS scientists, engineers, and policy makers to anticipate and mitigate potential future environmental hazards associated with nanotechnology. In addition to continuation of our Center-wide mentoring and career development programs for students and postdoctoral fellows in years 6-10, we intend to broaden the scope of UC CEIN’s mentoring, public education programs, and activities to increase participation of underrepresented minorities, and also engage more undergraduate science majors and a broader range of students at UCLA, UC Santa Barbara, UC Riverside, UC Davis, and UTEP in our research and education programs.

The rest of section B provides a theme by theme outline of the work to be undertaken by UC CEIN. The numerical order is for ease of description purposes only, as well as to outline the intellectual contribution of key faculty participants.

B.2. Theme 1: Synthesis of ENM Libraries for Property-Activity Analysis
Faculty Investigators: Jeffrey I. Zink, UCLA (Theme Leader); C. Jeffrey Brinker, University of New Mexico and Sandia National Laboratory; Mark Hersam, Northwestern University; Lutz Mädler, University of Bremen (Germany); Galen Stucky, UC Santa Barbara.
Scope of Theme 1 Activities and Integration in the Center: Libraries of nanomaterials will be synthesized, commercially acquired and characterized. The primary goal of Theme 1 is to develop SARs that relate fundamental ENM physical/chemical properties to biological outcomes, using these relationships to develop predictive toxicological models. The development of ENM libraries during the past four years has been one of the key factors in the Center's success towards understanding fundamental principles of nanotoxicity. We will continue with this fundamental exploration for the newly nominated materials and will also use the SARs towards "safer-by-design" strategies that will attempt to lessen the impact of those materials in ecosystem studies. The new nanomaterial compositions will be premised on materials that are likely to be used in commercial products and determined to have an environmental impact potential based on volumes of production and lifecycle analysis. The fundamental understanding that we want to develop will be to predict the potential deleterious environmental impact as well as to inform about possible design strategies to lessen the hazardous impact.

Core B, which is integrally linked to Theme 1 and overseen by the team leader, will obtain and characterize commercially available nanomaterials. Core B will also catalog, store and disseminate nanomaterials for use in Themes 2-5. Moreover, Core B will also provide Theme 6 with nanomaterial physicochemical characteristics for computational analysis. The activities of Core B as a Center-wide resource are described in more detail in the management section. The ENM libraries are essential for the HTS in Theme 2 and the development of nano-SARS and environmental modeling in Theme 6. Traceable and collectable nanoparticles will assist the fate and transport studies in Theme 3. Feedback about the biological results from Theme 2 and the terrestrial and aquatic results from Themes 3-5 will help guide the design of new compositions and synthesis of materials with new safety features (e.g., addition of surface coatings of metal oxide doping that lead to decreased dissolution).

Goals and Outline of Theme 1 Research: The primary goals of Theme 1 are to synthesize, purify, characterize and disperse in relevant media libraries of nanomaterials that are chosen in order to develop SARs that relate fundamental physicochemical properties to biological responses in cells, bacteria and organisms (overarching goal 1 of the Center). An important subsidiary goal is to identify and test new materials that are being developed for commercial applications before they are in widespread production in order to pre-empt environmental danger. In addition to these goals, the theme will develop and synthesize new nanomaterials with useful properties for investigation in estuarine and terrestrial ecosystems.

Research Plan and Deliverables: The proposed research program in Theme 1 is presented from the viewpoint of the physical properties of the nanomaterials and is organized into four major Projects that will each contribute to one major study per year. Each project is focused on a key set of properties or material characteristics that will be studied by using materials with a variety of chemical compositions. The research projects are designed first and foremost to develop a fundamental understanding of relationships between properties of ENMs and biological responses. This insight will allow us to predict whether a material could be harmful, why it would be harmful, and thus allow us to develop new safer-by-design materials that will also be investigated for maintenance of their useful characteristics. We also intend to acquire or synthesize and measure biological responses to new ENM compositions that are increasingly being used in commercial products in order to pre-empt deleterious environmental impacts. These include two broad categories of metal oxides (ZnO and CuO) that will be used for the environmental case studies described in Themes 2-6.

(a) Project 1: Relationships between ENM Electronic Structure and Biological Outcomes. Prior studies have demonstrated that there is a good correlation between the conduction band energy of metal oxide semiconductor nanoparticles and adverse biological responses. The correlation was attributed to electron transfer from redox-active biomolecules (redox couples) to the nanoparticles. However, since the observed correlations were good but not perfect more refined studies are needed, including fine-tuning of the band energies, correlation with catalytic activities of nanoparticles, and correlation with inter-band states. We propose to carry out detailed studies by tuning band energies using libraries of mixed metal oxides, performing p and n doping (i.e. adding electron acceptors and donors, respectively) of metal oxides, and establish p-n junctions between different metal oxides. These materials will be synthesized by pyrolytic (Mädler), hydrothermal and sol-gel methods (Zink). Novel syntheses including 2-flame spray pyrolysis (Mädler) and ink-jet multi-metal methodology (Stucky) will also be used to develop libraries for HTS. Copper and zinc oxides will be emphasized in the case studies in Themes 3-6.
Boundary effects caused by interactions of two dissimilar materials may also play a role in their toxicity. Mixed metal oxides containing interactions ranging from intimate contact (p-n junctions in individual semiconductor particles) through non-covalent interactions between nanoparticles will be deliberately synthesized (Mädler, Zink).

(b) Project 2: Relationships between ENM Shape/Size and Biological Outcomes. Commercial nanoparticles (for example silver and ceria) often contain non-spherical particles that are overlooked when studying toxicity. For instance, nano-rods and nano-wires with large aspect ratios generate inflammatory responses and cell death even when nanospheres of the same chemical compositions are nontoxic. Libraries of metal oxide nanorods and wires (Zink) and of carbon nanotubes (Hersam) will be prepared and biological responses to these materials will be measured by the proposed new assays in Theme 2. Moreover, controlled aggregation of fumed silica into “chain-of-beads” (Brinker) will also be studied to better define the relationships between nature and degree of aggregation and specific toxic effects.

(c) Project 3: Relationships between ENM Surface Structure/Chemistry and Biological Outcomes. Surface functionalization is a critical factor in influencing nano/bio interactions. Many synthetic preparations require surface coatings, many commercial nanoparticles are surface-coated, and most nanoparticles acquire a corona of biomolecules in tissue culture and aqueous environmental media. Carbon nanotubes will be coated with a variety of polymers for HTS (Hersam). Metal oxide nanoparticles will be deliberately coated with nonpolar and polar (cationic, anionic and neutral) molecules (Zink) to determine their toxicological potential. Metal and metal oxide coatings ranging from one to several atoms thick will be applied using atomic layer deposition (Brinker) and the effects of these highly controlled coatings will be studied. We will also acquire commercially coated ZnO and CuO nanoparticles for the case studies that will be used in Themes 3-5. The prior history of nanoparticles, including the temperature at which they were synthesized, calcined or annealed, affects their effects on cells and organisms. For instance, fumed silica synthesized at high temperature is toxic whereas silica synthesized at low temperatures is not. Libraries of silica and metal oxide nanoparticles made by flame-spray pyrolysis (high temperature, Mädler), hydrothermal methods (moderate temperatures, Zink) and sol-gel or aerosol methods (low temperature, Brinker, Zink) will be synthesized. The synthesis methods affect the surface structure. HTS will determine for which materials the synthesis temperature affects biological response. Selection of the appropriate synthesis temperature could constitute a safer-by-design approach.

(d) Project 4: Relationships between Novel ENM Properties and Environmental Outcomes. The largest groups of nanomaterials that will be studied in this project are layered materials such as clays (Stucky) and certain metal oxides (LiCoO$_2$) and chalcogenides (MoS$_2$) (Hersam). The former are ubiquitous natural (geological) materials (and were suggested by the review committee), and the latter are in use in batteries and solar energy conversion. These materials can exfoliate (strip off layers) to expose new surfaces, or can intercalate ions (such as Li$^+$) that change their charge and electrochemical properties. A physical property that will be useful for tracing, collecting and recovering nanoparticles from microcosms, mesocosms and the environment is magnetism. Metal oxide nanoparticles of interest will be synthesized around a super paramagnetic or ferromagnetic core (Stucky, Zink). The exterior of these particles retain most of the properties of the pure oxide nanoparticle but the core/shell particles can be manipulated or captured using a permanent magnet. This library of magnetic nanoparticles will be useful for studying the coatings that they collect during transport in artificial or natural aqueous environmental media, since these magnetic particles can be recovered and separated from background media, i.e. soils (Themes 3 and 4) and sediments (Themes 3 and 5).

B.3. Theme 2: High Throughput Screening to Establish Predictive Toxicological Paradigms

Faculty Investigators: André Nel, UCLA – Professor, (Theme Leader); Kenneth Bradley (MSSR Director), UCLA; Hilary Godwin, UCLA; Patricia Holden, UC Santa Barbara; Shuo Lin, UCLA; Tian Xia, UCLA; Huan Meng, UCLA.

Scope of Theme 2 Activities and Integration in the Center: The implementation of HTS approaches to assess mechanistic injury responses at the biomolecular and cellular level has allowed UC CEIN to develop hazard ranking and SARs that can be used to predict the ENM properties that could lead to the generation of toxicity in organisms in the environment. Moreover, this in vitro HTS platform was strengthened by the development of zebrafish HTS, in which robotic handling of embryos and automated imaging equipment has allowed large numbers of ENMs to be assessed in a single experiment. The rich data content and hazard ranking has allowed Themes 1, 2 and 6 to establish predictive toxicological
paradigms and SARs to assist in the planning of the ecosystems studies in Themes 4 and 5. This will include the selection of commercial nano-ZnO and -CuO to develop environmental case studies in which the HTS data will be used together with life cycle analysis (Theme 3) and environmental exposure modeling (Themes 3 and 6) to study ENM impact on terrestrial and estuarine ecosystems. Theme 2 will also develop new screening approaches to allow SAR analysis of the contribution of novel electronic, shape, size, aspect ratio, surface properties, inter-particle interactions, and catalytic properties in the new generation of ENMs that will be acquired or synthesized by Theme 1. Collectively, the interaction of Theme 2 with other UC CEIN themes will help to establish a broad-based analysis of the environmental impact of important categories of ENMs over the next 5 years, including commercial materials that go beyond primary OECD-selected nanoparticles. These materials are described in Theme 1.

**Goals and Outline of Theme 2 Research:** The overarching goal of Theme 2 is to use high throughput discovery of the hazard potential of ENM properties at cellular (mammalian, fish, bacterial cells) and organism (zebrafish) levels to develop predictive toxicological paradigms, SARs and hazard ranking to prioritize our environmental studies and identify opportunities for hazard reduction. HTS of industrially important metal, metal oxides, mixed metal oxides, chalcogenides, metal fluorides, and carbon allotropes as well as in-house synthesized combinatorial ENM libraries (that include a systematic variation of the major physicochemical property) will be used for the high volume data generation and quantitative SAR analysis. HTS will also assist the environmental case studies in Themes 3-5 in which selected materials with commercial applications (e.g., nano-ZnO and nano-Cu) will be used for life cycle analysis and exposure modeling to study specific environmental receptors in terrestrial and estuarine ecosystems. In addition to our established mechanistic toxicological paradigms that address oxidative stress, membrane disruption, interference in bacterial growth and membrane function, hatching interference and developmental abnormalities in zebrafish embryos, we will introduce new HTS platforms that delineate: (i) the role of shape, aspect ratio, and surface properties in the ability of newly selected materials to induce lysosomal damage, inflammasome activation, and the generation of subacute and chronic inflammatory responses; (ii) the role of metal liganding by the active center of a metalloprotease (which is involved in zebrafish embryo hatching and expressed in homologous enzymes in more than 500 environmental species) as a predictive paradigm to screen large numbers of metals, metal oxides and chalcogenides that are used in semiconductor, insecticide, and antibacterial products; (iii) the induction of stress gene responses (e.g., heat shock and oxidative stress) by redox active and cytotoxic ENMs in transgenic zebrafish that can be used for acute and subacute studies in zebrafish embryos and larvae. While our choice of mechanistic screening platforms is premised on the molecular and cellular injury pathways that contribute to adverse outcomes in whole organisms, we will also implement the site visit recommendations of using discovery platforms such as proteomics to explore novel ENM biological responses that can be used for high throughput discovery. We will also follow the panel's recommendation to develop more cost-effective HTS analysis by developing lab-on-a chip technology for screening of cellular injury responses.

**Research Plan and Deliverables:** The projects in Theme 2 will be carried out in the shared CEIN lab and the high throughput screening (Molecular Shared Screening Resource or MSSR) facility at UCLA. The MSSR, under the direction of Bradley, serves as a UC CEIN core facility (Core D). This fee-service facility performs automated screening in which automated, robotic equipment is used for epifluorescence screening, luminescence-based reporter gene activity, multiplex quantification of cytokines and biological response markers as well as automated bright field and fluorescence image analysis of zebrafish embryos and larvae. We expect to execute 3 projects per year, each requiring 12-24 months for completion under the oversight of a project leader who works with one graduate student or postdoctoral fellow. The projects that are envisaged over the next five years include: (a) Project 1 that will perform zebrafish HTS under the direction of Lin. The successful implementation of HTS in zebrafish embryos and larvae will allow comparative analysis, hazard ranking and establishment of dose-response profiles of multiple metals, metal oxides, mixed metal oxides, and some metal-contaminated CNT formulations. One toxicological paradigm addresses interference in metalloprotease activity of ZHE1, a zebrafish hatching enzyme, by specific metal ions. We have developed an abiotic assay that accurately predicts the dissolving metal oxide nanoparticles leading to hatching interference in intact embryos. A ZHE1 peptide homology search has identified >500 aquatic species, including fish embryos, in which homologous metalloproteases are expressed that could be impacted by metal oxides. Theme 5 will include at least one of these fish species (Fundulus) in their assessment of estuarine ecosystem impact.
The availability of a collection of transgenic fish lines will allow the assessment of additional toxicological paradigms, including the induction of heat shock responses, oxidative stress, inflammation, and developmental abnormalities (e.g., vascular development). The studies will be performed by automated embryo picking, fluorescence microscopy and image analysis in larvae and adult animals. We will also use adult zebrafish to assess organ-specific toxicological injury of the gill, gut, liver and vasculature. (b) Project 2, under the direction of Nel, will conduct cellular and bacterial HTS analysis. The multi-parameter screen for oxidative stress (ROS production, cellular calcium flux, mitochondrial perturbation and cytotoxicity) allows high content data generation and comparative analysis of up to 24 materials that, depending on their ability to generate ROS abiotically and biotically, have the potential to induce a series of oxidative stress injury responses in several environmental organisms. Use of this assay will allow high content data generation, hazard ranking and establishment of quantitative SARs for semiconductor, photoactive, surface reactive and metal shedding nanoparticles. The collaboration between Godwin and Holden will lead to the development of high content and HTS in bacteria to determine the effect of redox-active and metal shedding ENMs on the growth, ROS production, membrane electron transduction and membrane integrity of the terrestrial bacteria. The studies will be used by Theme 4 to model the impact of the same materials on nutrient cycling and food production in plants. (c) Project 3, under the direction of Xia, will develop new HTS assays and collaborate with the UCLA Proteomics core to expand the scope of ENM biological responses that can be assessed by HTS. An example of a new HTS assay is to assess lysosome damage and activation of the NALP 3 inflammasome by long aspect ratio materials such as nanowires, nanorods, and CNTs. The proteome analysis will be undertaken in tissue culture cells and will concentrate on identifying proteins that are involved in cell stress responses (e.g., the protein unfolding response) as well as cellular signaling transduction pathways. (d) Project 4, under the direction of Meng, will collaborate with Chu in the UCLA School of Engineering to develop lab-on-a-chip technology for rapid and cost-effective assessment of oxidant injury and the release of cytokines and growth factors by cells. The technology is based on the assessment of impedance measurements.

B.4. Theme 3: Fate & Transport, Exposure, and Life Cycle Assessment
Faculty Investigators: Arturo Keller, UC Santa Barbara (Theme Leader); Sharon Walker, UC Riverside; Sangwon Suh, UC Santa Barbara; Ponisseril Somasundaran, Columbia University.

Scope of Theme 3 Activities and Integration in UC CEIN: Theme 3 provides the UC CEIN with quantitative information on the fate and transport of NPs selected by the Center, the life cycle implications of ENMs, and experimental methods to measure and estimate likely NP exposure concentrations in different environmental media. The development of quantitative information on NP aggregation and dissolution in synthetic and natural waters has allowed Theme 6 to develop and evaluate a quantitative ENM fate and transport (F&T) web-based model that is used by Theme 3 researchers. Combining screening Life Cycle Assessments (LCAs) with F&T modeling, Theme 3 generates predicted exposure concentrations (PECs) for planning toxicological studies by Themes 2, 4 and 5. The performance of LCA by Theme 3 is also used for prioritizing the commercial materials that Core B acquires, characterizes and distributes to the CEIN. We will implement the recommendation from the 2012 Site Visit for Theme 3 to enhance LCA research by using case studies, for which we have selected coated and functionalized nano-ZnO and nano-Cu ENMs.

Goals and Outline of Theme 3 Research: The overarching goal of Theme 3 is to address the likely range of ENM exposure concentrations in specific aquatic and terrestrial environments. Previously, Theme 3 assessed the key environmental conditions that control mobility and bioavailability in natural waters for more than 15 types of NPs, including metals, metal oxides and CNTs, elucidating the role of natural organic matter (NOM) in providing NP stabilization through control of surface charge, as well as the destabilizing effects of suspended clay particles. In collaboration with Themes 1 and 2, relationships were established between NP physicochemical characteristics that determine aggregation vs. characteristics that determine bioavailability and toxicity. Working with Theme 4, we demonstrated the effect of surface coating on the uptake of NOM-coated CeO2 by corn plants, and with Theme 5 we elucidated the differential bioprocessing of CeO2 and ZnO by mussels due to the intrinsic material properties. Also, Theme 3 collaborated with Theme 6 on the conceptual approach for ENM F&T modeling framework. Recently, we developed screening LCAs for over a dozen ENMs to estimate likely emissions to different environmental media. Building on this F&T and LCA knowledge base, our goals are to: (i) develop innovative approaches to address LCA information gaps, including developing experimental methods for determining actual release of ENMs; (ii) elucidate the transformation (fate) of
Research Plan and Deliverables: Theme 3 goals will be achieved through three main project areas. Each project will be carried out under the supervision of a faculty PI over a 12-18 month time period and executed by a graduate student or postdoctoral researcher.

(a) Project 1: Life Cycle Assessment (LCA). To estimate the potential release of ENMs to the environment, an LCA approach will be developed. While the various steps in LCA analysis will be organized into a computational LCA tool (Theme 6), establishing release estimates at various life cycle stages require carefully designed case studies. Accordingly, LCA methodology will be developed based on case studies with ZnO and Cu NPs, selected based on the criteria of high use, environmentally relevant applications, and differences in F&T behavior (e.g., dissolution rates). These ENMs are utilized in a variety of applications that include (but are not limited to) broadband UV blockers in sunscreens, cosmetics, paints, automotive coatings, light emitting diodes, solar panels, and polymers. The above ENMs may be released to the environment via various pathways during their life-cycle (e.g. wash off of personal care products during swimming/showering, wastewater discharge treatment, storm water runoff, biosolid applications, and outdoor use). Storm water runoff from agricultural and urban areas may transport pesticide residuals, paint and coating flakes from weathered surfaces to receiving waters (e.g. rivers, estuaries, lakes). Suh’s group will develop detailed LCAs for ENMs being considered across the UC CEIN as having the potential for high environmental impact (e.g., as determined by HTS studies Theme 2 and exposure assessment in Themes 3 and 6). Interviews of manufacturers, surveys and market research studies will be used to refine the estimated release of ENMs during various applications. Emission estimates will be refined with targeted experimental weathering studies (e.g., marine paints in estuarine conditions, ENM-laden biosolids applied to soil) to determine the release from commercial products under realistic but controlled conditions. Based on the LCA methodology developed by the case studies, a general computational framework will be developed in collaboration with Theme 6 to enable generalization of the approach to other ENMs. The goal is to develop an LCA model that will seamlessly integrate with the cloud-computing environmental impact assessment (EIA) framework in Theme 6.

(b) Project 2: Transformation of ENMs. ENMs age as they pass through wastewater systems on their path to the environment, acquiring oxide, sulfide and natural organic coatings, as well as partially dissolving. Their commercial coating may dissolve or biodegrade, further modifying the original surface chemistry. The rate of transformation is expected to depend on redox conditions, pH, ionic strength and the concentration of various ions suspended in simulated wastewater conditions. In order to evaluate the fate of ENMs in this setting, a physical model of a wastewater treatment developed in the Walker Lab (UCR), will be used. This model allows tracking and analysis of the transformation of different ENMs at various stages in the system by XRD, TGA, TEM and other surface chemistry analytical methods. These studies allow control of the residence time, and generate good predictions of the physicochemical state and range of likely ENM exposure concentrations in the waste that is applied to agricultural soils (Theme 4) or discharged as treated effluents into estuaries and other waterways (Theme 5). Walker will develop quantitative models to predict the rate of transformation as a function of environmental conditions to be incorporated in the Theme 6 F&T framework. Moreover, the inclusion of ZnO and Cu nanoparticles for the case studies will support the LCA analysis of the same materials by providing data on release pathways and concentrations in the aqueous versus solid matrices.

(c) Project 3: F&T in model ecosystems. Keller’s group will use LCA estimates and F&T assessment (e.g. aggregation, sedimentation, suspension stability, dissolution, filtration, chemical transformation) to generate predictions about the distribution (e.g. soils, pore water, estuary water column, suspended sediments, sediment bed, biota), exposure concentrations, dissolution rates, and transformation of a wide range of ENMs in modeled terrestrial (Theme 4) and estuarine (Theme 5) environments. The models are comprised of: (i) a soil irrigation and waste water treatment model in which the soil conditions, pH, ionic strength, NOM concentrations, irrigation rates, rate of biosolid application, etc are systematically varied; (ii) a dynamic estuarine model in which cycles of flow reversal, salinity gradients, NOM loading, and
sediment resuspension are systematically varied. We also test our modeled predictions by sampling soil and estuarine mesocosms during actual organism exposures to the case study materials (ZnO and Cu) for temporal-spatial assessment of ENM concentrations, aggregation state and transformation products. These concentrations will be used by Themes 4 and 5 as the actual exposure levels against which ENM effects can be reconciled. In addition to chemical analysis of different media and biological tissues, XANES/EXAFS, SEM/EDX and TEM will be used to determine the chemical state, presence and localization of these case study materials. The information in these studies will be used to understand: (i) NP transport to the root zone of crop plants; (ii) interactions between different NPs and suspended sediment fractions and types, as a function of environmental conditions; (iii) NP stability under dynamic estuarine conditions; (iv) NP uptake and bioprocessing by plant roots, soil microbes, phytoplankton, other biota in the estuarine system; and (v) systematic exposure reduction to reduce bioavailability via destabilization and increased attachment. Keller will be assisted in these studies by Somasundaran’s group who will perform electrostatic separation, magneto separation, flotation, gravimetry, and selective (bio)leaching followed by precipitation to determine ENM concentration in soils and sediments. These separation methods will be adapted and combined with standard spectroscopic techniques, as well as nonconventional spectroscopic and microscopic methods such as electron paramagnetic resonance (EPR), and fluorescence spectroscopy under environmental conditions. The results of the fate and transport studies during the mesocosm exposures will improve the predictive value of Theme 3 analytical models under real-life exposure conditions and will enable validation and refinement of the integrative Theme 6 modeling framework.

B.5. Theme 4: Terrestrial Ecosystems Impact and Hazard Assessment

Faculty Investigators: Patricia A. Holden, UC Santa Barbara (Theme Leader); Roger M. Nisbet, UC Santa Barbara; Joshua P. Schimel, UC Santa Barbara; Jorge Gardea-Torresdey, University of Texas El Paso; Erik B. Muller, UC Santa Barbara.

Scope of Theme 4 Activities and Integration in the Center: Theme 4 assesses the impacts and fates of ENMs in terrestrial ecosystems, including plants and bacteria, and evaluates ENM property-variants for improving terrestrial environmental compatibility. ENMs that are projected by Themes 3 and 6 to accumulate in terrestrial environments are characterized and provided by Theme 4. ENM effects on bacterial population growth are mechanistically modeled using dynamic energy budget (DEB) theory, and model efficacy is experimentally tested against other ENMs of concern. Methods for low throughput screening of hypothesized effects in ecologically-important, sensitive bacteria are developed by Theme 4, and then promoted for Theme 2 HTS using ENM property (e.g., solubility and band gap) variants from Theme 1, to provide sufficient data for hazard ranking by Theme 6 and for DEB model validation. Ecologically-important bacterial populations are identified through hazard assessment of soil microbial communities, in planted and unplanted mesocosms; planted mesocosms are also used to assess ENM bioavailability in soil and ENM ecosystem-level effects to plant and bacterial populations, including plant-microbe interactions that affect soil fertility and plant growth. As we enter this next 5 years, Theme 4 focuses on N₂-fixing bacterial populations—previously identified as sensitive to high production MOx (TiO₂, ZnO and CeO₂) ENMs—to determine if effects mechanisms originate at bacterial membranes (as previously shown for gram negative bacteria), using a toxicity assay system developed by Theme 4 that is promotable to HTS in Theme 2. We extend a prior DEB model of ENM effects on bacterial population growth to N₂-fixing bacteria, and validate the new model using experimentation (growth curves and cell damage indicators). We assess ENM property variants (e.g., coating charge, solubility, band-gap) on N₂-fixing and other ecologically-important bacteria, and on agriculturally-relevant plants under hydroponic conditions for which effects mechanisms and ENM fates in plants are thereby determined. Armed with population-based and DEB model predictions for ENMs that appear harmful, we further advance DEB modeling to describe ecosystem-level processes. We then conduct mesocosm studies to determine if harm manifests at the community and ecosystem levels, and then evaluate these results against population-based screening, hazard assessments, and DEB models that are intended to predict higher ecological impacts. Because the terrestrial environment is biogeochemically reactive, we also measure biotransformation endpoints and rates for select ENMs such that Themes 3 and 6 can inform fate and transport predictions, and further parameterize multimedia models. Taken together, Theme 4 will demonstrate how experimentation and DEB modeling of ENM-exposed environmentally-relevant bacteria and plants can measure and predict population-level effects whose magnitudes forewarn testable and ultimately predictable ecosystem impacts.
Goals and Outline of Theme 4 Research: Theme 4 seeks to understand ENMs in terrestrial environments, with the overarching goals of predicting terrestrial ecosystem and food supply hazards, providing environmentally-relevant HTS approaches, and guiding safe ENM design. A further objective is to forward a validated, hierarchical approach for terrestrial ecosystem hazard assessment for use by others. The hierarchy involves: parallel bacterial and plant population-level growth and effects mechanism assessments; DEB model development for expressing bacterial population-level effects; ENM hazard ranking and DEB model validation by HTS using bacteria; ecosystem model development; model testing using planted agricultural mesocosms; ENM stability assessments in population and mesocosm studies. Focal industrial ENMs for this research are those likely to build up in soils exposed to wastewater treatment plant biosolids and those intentionally used in agriculture, with exposure expectations reconciled against Theme 3 LCA and Theme 6 multimedia models. ENM property variants are selected to test specific hypotheses related to ENM effects to soil bacteria, hydroponic plants, and plant-microbe interactions in soil. At the renewal onset, focal ENMs include: industrial and laboratory-synthesized nano-ZnO, and Fe-doped variants that dissolve relatively slowly, plus capped (polar, nonpolar, neutral, and cationic or anionic) variants used in personal care products; industrial and laboratory-synthesized nano-TiO₂ and Fe-doped band-gap variants; commercial, coated and uncoated, nano-CeO₂, nano-CuO, and -Cu(0) used in market bactericides /fungicides (agricultural and commercial). ¹⁴C-MWCNTs synthesized by NIST collaborators³⁶ (Petersen) and “cold” analogs are specifically tested for biotransformation.

The research is predicated upon the following ENM property-based hypotheses: dissolving ENMs exert toxicity according to solubility characteristics and ion release (e.g. into bacterial growth media, hydroponic plant growth media, and the soil solution); redox-active ENMs can inflict particle-associated sublethal depletion of electron transport chain activity and/or generation of membrane-damaging ROS; ENM dissolution is enhanced by specific ligands; toxicity mechanisms (i.e. specific ion toxicity vs. ROS-mediated damage vs. sublethal electron-scavenging) vary with media complexity, such that in bacterial cell and hydroponic plant exposures, both ionic and ENM effects manifest, whereas in soil (where exopolymers and soil matrices slow mass transfer of ENMs to cells and roots), dissolving metal-based ENMs exert impacts primarily through specific ion effects. To test Theme 4 hypotheses, using focal ENMs we will quantify population growth and membrane-associated damage mechanisms for terrestrial bacteria, including N₂-fixers. Using DEB, we will develop a mechanistic population-level model of bacterial growth as a function of ENM structure and dose. With Theme 2, bacterial HTS will be conducted to assess effects of ENMs on membrane function and ROS generation in environmental bacteria for developing hazard ranking and SAR analysis. To enable population-scale predictions of ENM-related hazards to terrestrial plants and the food supply, we will assess ENM surface chemistry on ENM uptake, transformation, and damage in plants. We will quantify ENM translocation into reproductive (edible) plant parts and inter-generational ENM transfer, and quantify aerial (i.e. via leaves) ENM uptake. We will quantify effects of ENM properties on the nutritional quality of plants, and determine the impact of ENMs on plant-microbe symbioses that promote plant growth and soil fertility. To enable development of hazard predictions at the ecosystem scale, over which Earth’s biogeochemical processes and food crop production manifest, we will develop an ecosystem-level³⁷ model of ENM impacts to soil-grown food crops that rely on natural N₂-fixation and execute an additional mesocosm-scale experiment to test and validate the model for plant growth, yield, and microbial processes related to soil fertility. To enable incorporation of microbial biotransformation into ENM transport and fate models (i.e. by Themes 3 and 6), we will quantify bacterial electron transport activity and concomitant reduction of transition metals within doped MOx ENMs. We will also quantify and describe bacterial acceleration of ENM dissolution in solution and in unsaturated (soil and plant) biofilms, and quantify microbial biotransformation, including mineralization, of carbonaceous ENMs, using ¹⁴C-MWCNTs (in collaboration with NIST).

Research Plan and Deliverables: The four projects in Theme 4 will be carried out at UCSB, UTEP, and in collaboration with Theme 2 at UCLA, each primarily led by one of our four PIs with an associated postdoc or advanced graduate student substantially performing the research. (a) Project 1, under the co-direction of Holden and Schimel involves screening soil (including N₂ fixing) bacterial growth and sublethal effects in laboratory cultures exposed to focal ENMs to determine dose-sensitivity and the mechanistic basis for toxicity including membrane damage and associated processes. (b) Project 2, under the direction of Gardea-Torresdey, exposes hydroponic and soil-grown, agricultural and native, plants to focal ENMs via roots and leaves. The deliverables are delineated toxicity mechanisms and an understanding of the potential for ENMs to transfer in plants inter-generationally. Project 2 also assesses
plant-microbe symbiosis changes from ENM exposure and estimates impacts on soil fertility. This project also assesses how ENM core chemistry, band gap, and dissolution and surface characteristics affect plant nutritional quality alterations, and how such ENM properties affect ENM translocation and transformation in planta (using X-ray synchrotron methods advanced by Gardea-Torresdey). (c) Project 3, under the cooperation of Holden and Gardea-Torresdey, delivers rate parameters for Theme 6 and Theme 3 mathematical fate and transport models that account for microbial transformation (oxidation/reduction, dissolution, and mineralization) of metal oxides and MWCNTs. The parameters are measured using bacterial monocultures and complex communities, under redox control, based on hypothesized biotransformation pathways (e.g., involving direct electron transfer, ligand binding, and co-metabolism). (d) Project 4, under the direction of Holden, Schimel, Nisbet, Gardea-Torresdey, and Muller projects and extends DEB bacterial population modeling and plant hazard assessment into a model of planted agricultural crop growth, then conducts a mesocosm study to test model efficacy for predicting hazard effects to select food crops. Through project 4, the cumulative advantages of tiered testing are realized, and ENM hazards to food crops are quantified.

B.6. Theme 5: Marine and freshwater ecosystems impact and toxicology
Faculty Investigators: Hunter Lenihan, UC Santa Barbara (Theme Leader); Gary Cherr, UC Davis; Robert Miller, UC Santa Barbara; Erik Muller, UC Santa Barbara; Roger Nisbet, UC Santa Barbara.

Scope of Theme 5 Activities and Integration in the Center: Theme 5 addresses the impact of ENMs on estuarine ecosystems. We have chosen estuaries because they provide important ecosystem services (e.g., nursing ground and habitat for many seafood species) and also act as possible sinks for anthropogenic pollutants. Estuaries are also characterized by distinct spatial gradients in salinity, sediment types, and hydrodynamics, thus providing an excellent environment that can be modeled by applying our foundational work on freshwater and marine ecosystems in the first five years to demonstrate how ENMs provided by Theme 1 may impact a sensitive environment that is also assessable to LCA. Theme 5 will use estuarine mesocosms, combined with model, targeted smaller-scale in vitro and in vivo studies, to examine the toxic effects and mechanisms of injury that can be related to the physicochemical properties of ENMs. Since the physicochemical behavior and toxicity of ENMs will be affected by the salinity gradients estuarine conditions, Theme 5 will collaborate extensively with Themes 3 and 6 to quantify the ENM exposure concentrations, state of aggregation and bioavailability in the mesocosm matrices (i.e., water, sediment, and organismal tissues). The toxicological analysis in cells, bacteria, and zebrafish embryos in Theme 2 and 4 and SAR analysis in Theme 6 will help in prioritizing the materials that will be studied in Theme 5, which will employ high content discovery of estuarine species to be included in the study. Ultimately, these predictions will be confirmed in mesocosm case studies that will be conducted with nano-ZnO and Cu as discussed in Themes 3 and 4. The overarching goal of Theme 5 is to systematically evaluate the degree to which ENMs are bioavailable and toxic under environmentally realistic variable conditions characteristic of estuarine ecosystems.

Goals and Outline of Theme 5 Research: We will: (i) conduct high content screening (HCS) to link mechanisms of injury to specific ENM properties, (ii) perform individual- and population-level microcosm exposures to assess the impact of specific injury mechanisms on organisms and populations, (iii) use predictions based on HCS and microcosms to evaluate ENMs with the highest-risk properties in mesocosm and case studies to quantify ecosystem-level effects, and (iv) develop predictive computational models of ENM impacts to estuaries using DEB modeling. Specifically, HCS will be used to identify mechanisms of injury, including ROS production, mitochondria injury, lysosomal stability, and plasma membrane integrity, for estuarine plankton, benthic invertebrates, and fishes, organisms which will be used in estuarine microcosms and mesocosms, as a function of varying ENM properties (e.g., shape, size, conduction band energy level, catalytic properties) to generate hazard ranking and SARs relevant to environmental species. The hazard ranking and SARs, in turn, will be used to study the prediction making potential in terms of the impact on the growth, survival and reproduction of individual species or the growth rates and dynamics of communities included in our microcosms. Subsequent experiments in mesocosms will test the influence of ENMs on a simplified estuarine food web to demonstrate how species interactions influence toxicity through trophic transfer, bioaccumulation, and alteration of competition and predation. These studies will be guided by and contribute to the collaborative Themes 3 and 6 predictive modeling of ENM exposure concentrations for chronic and acute (hot-spot) conditions. DEB modeling will use the output of HCS and individual organism-based models to predict
impacts in population microcosms and mesocosms under varying environmental conditions, and these model results will be scaled up in the estuarine mesocosm study to produce a predictive model of toxic effects in an estuary that can be used to predict real-world impacts. This predictive model will be evaluated and refined using field experiments in a salt marsh estuary. Outputs from both mesocosm and field studies will enable Theme 6 to both validate and further refine fate and transport and exposure models, while also providing input for Theme 6 environmental impact assessment tools.

Research Plan and Deliverables: Theme 5’s proposed research program is organized into four projects that will each contribute to one major study per year. Each Project is focused on a specific ecological scale, from the individual (HCS) to the ecosystem (mesocosm and field experiments) that will be exposed to materials with a variety of chemical compositions. In accord with the rest of the center, each project will be executed under the supervision of a PI by a postdoctoral fellow graduate student. The projects are designed to produce an assessment of risk at increasingly complex ecological scales and to connect mechanisms of injury with specific properties of ENMs, allowing general predictions of toxicity risk a priori, based on properties of ENMs. In addition to testing new ENM compositions that are increasingly being used in commercial products, we will focus on two broad categories of metal oxides (ZnO and CuO) that will be used for the environmental case studies described in Themes 2-6. (a) In Project 1 Cherr will use mechanistic injury paradigms to conduct HCS, hazard ranking and dose-response profiling in phytoplankton (diffusion exposure), polychaete worms (omnivore), Macoma clams (deposit-feeding), Olympia oysters (suspension feeding), and killifish (predation). The materials that will be prioritized will be selected based on the hazard ranking and SAR analysis in Theme 2 HTS, the bioavailable studies in Themes 3 and 6, and the emission estimates from LCA in Theme 3. The mechanisms of injury will overlap with those in Theme 2, but will also be specifically adapted for estuarine organisms. For instance, the effects on ZHE1 metalloprotease activity in Theme 2 have inspired the inclusion of Fundulus (killifish) in our estuarine studies, but our studies on the phytoplankton will specifically demand looking at ROS production and photo activation, as demonstrated by our earlier studies. We will also include studies on clam, oyster and worm hemocytes/coelomocytes to address the effect of long aspect ratio materials and the possible impact on the lysosomes. (b) Project 2: Miller will use microcosms for population growth experiments for estuarine phytoplankton (primary production and photosynthesis) that vary in their tolerance to salinity and nutrients. Using one-stage chemostat microcosms, the hypotheses will be tested that multi-species phytoplankton mixtures exposed to ENMs will: (i) confer competitive advantage to an ENM-resistant species, and (ii) cause synergistic negative effects to less ENM-tolerant species by adding competition to toxic effects. Multi-stage chemostat microcosms will be used to quantify the effect of ENM-contaminated phytoplankton on growth, fecundity, and survival of clams and oysters to isolate and quantify the effects of trophic transfer to benthic estuarine consumers and predict outcomes of mesocosm and field experiments. (c) In Project 3, Lenihan will use the estuarine model ecosystem developed in collaboration with Theme 3 to test the hypotheses that: (i) bioavailability/uptake of ENMs will increase for deposit feeders, but decrease for suspension feeders, with increasing salinity due to increased ENM deposition, (ii) increased current speed will re-suspend ENM increasing uptake by suspension feeders, and (iii) key ecosystem processes (benthic respiration, N/P cycling, and community productivity) will decrease with ENM bioavailability and uptake. We will utilize state-of-the-art 300-L estuarine mesocosms to control environmental parameters influencing ENM physicochemistry, including salinity, sediment grain-size, TOC, and current speed/resuspension. In collaboration with Theme 3 and 6, we will develop exposure models that include inter-media transport (e.g., sedimentation) and ENM uptake. Mesocosms will contain the same organisms tested in Projects 1 (HCS) and 2 (microcosms), exposing them to the case study materials (ZnO and Cu) through contaminated phytoplankton. Exposure in sediments and water will be measured in collaboration with Theme 3. To test the predictive model generated using estuarine mesocosm results, Lenihan’s group will also use long-term field experiments to test whether case study materials influence estuarine communities that assemble in ENM/TOC-laden sediment trays placed in an estuarine environment. (d) Project 4: Nisbet and Muller will develop predictive DEB models of toxic effects on an estuarine ecosystem. Model equations and parameters will be inferred from microcosm studies (Project 2) and information on injury mechanisms (Project 1). Connecting injury mechanisms to changes in population growth rates will be accomplished using modeling techniques recently validated for Theme 4 bacteria exposed to quantum dots. The planktonic microcosms will provide data on the dynamics of single populations and on species interactions. The microcosms with larger animals (oysters, killifish) will allow parameterization of the DEB model of individual organisms from which population dynamic implications can be projected using techniques developed during years 1-5.
An ecosystem model for the more complex mesocosms will be developed by coupling the microcosm-based representations of individual mesocosm components and estimating exposure based on Theme 3 and 6 modeling. The model will support mesocosm experimental design and will generate detailed hypotheses on community impacts under a range of environmental conditions. Finally, the models will be used to interpret the field studies (Project 3) on impacts on estuarine species diversity by testing quantitatively whether mechanisms operating in mesocosms are consistent with field data.

B.7. Theme 6: Analysis of the Environmental Impact of Nanomaterials

**Faculty Investigators:** Yoram Cohen, UCLA (Theme leader); Donatello Telesca, UCLA; Robert Rallo, Universitat Roviri i Virgili; Sharon Walker, UC Riverside; Kenneth Bradley, UCLA; Andre Nel, UCLA.

**Scope of Theme 6 Activities and Integration in the Center:** Theme 6 integrates knowledge regarding ENM properties (Themes 1 and 3), toxicity (Themes 2, 4 and 5) and fate and transport (F&T) behavior in aquatic and terrestrial environments (Themes 3, 4 and 5) for the purpose of developing a computational framework for assessing the environmental impact of ENMs. Knowledge extraction from the HTS data and the use of machine learning methods have led to successful development of quantitative SARs, data-driven hypotheses regarding cellular toxicity and signaling pathways, hazard ranking, and decision boundaries considering data uncertainties. UC CEIN expansion of high content databases (Themes 2, 4, and 5) will enable development of a new generation of multi-parametric nano-SARs, based on a multiplicity of receptors and toxicity assays, for integrative hazard ranking. In this regard, new integrative machine learning methods will be introduced for hazard ranking based on combined multi-parametric HTS (Theme 2) and low throughput screening (LTS) (Themes 4 and 5) toxicity data. Multi-parametric Nano-SARs will allow establishment of decision boundaries with respect to “safe” ENM properties and environmental conditions; these will support “safer by design” efforts by the UC CEIN and suggest needed experimental validations. In order to estimate the environmental distribution of ENMs (MendNano), Theme 6 developed a first generation multimedia compartmental F&T model (with Theme 3 support) to assess the impact of various environmental release scenarios. The above approach is the foundation for a comprehensive modeling framework to be developed for exposure assessment of nanomaterials (ExpNano). Since emission estimates are central to estimating environmental exposure concentrations, Theme 6 will collaborate with Theme 3 life cycle analysis studies to develop environmental ENM emission estimates for ENMs being evaluated by the UC CEIN. New ENMs F&T sub-models will then be incorporated based on Theme 3 data on ENM-surface interactions, aggregation and transformation and the mesocosm studies (e.g., soil infiltration and sediment resuspension) in Themes 4 and 5 simulating environmental exposure conditions. Moreover, data on ENMs uptake rates by ecological receptors (Themes 4 and 5) will allow construction of ENM uptake models for use in ExpNano. Estimation of exposure concentrations, based on the fundamental description of ENM F&T processes, will provide input to Themes 4 and 5 dynamic energy budget models in support of UC CEIN toxicity studies and for environmental impact analysis (EIA). The overall mission of the effort will be to integrate toxicity predictions with exposure analysis into an in silico environmental impact analysis (EIA) platform for evaluating ENM risk management and safe-by-design options.

**Goals and Outline of Theme 6 Research:** Theme 6 aims to develop a rigorous approach to identify and rank ENMs that could be of environmental concern. This task will be accomplished through integration of knowledge derived from high volume data generated via HTS (Themes 2 and 4) and other toxicity studies (Themes 4 and 5), assessment of the environmental distribution of ENMs (based on experimental F&T and mesocosm studies in Themes 3-5) and models. The premise of the approach is that environmental impacts are governed by toxicity and ENM exposures. Therefore, EIA requires estimates of potential ENM exposure concentrations, receptor dose, toxicity information and an analysis platform for decision making regarding the safe design and use of ENMs. Accordingly, for the next 5 years, Theme 6 will focus on developing: (i) an advanced modeling platform (implemented for cloud-based computing) for EIA of nanomaterials (EIA-Nano), and (ii) case studies to elucidate the potential environmental impact of ENMs. As an integral component of the above effort, Theme 6 will explore (via machine learning and standard statistical methods) voluminous ENM toxicity data (Themes 2, 4 and 5) to develop hazard ranking considering various aggregation methods and multi-parameter ENMs toxicity assays. Theme 6 will also develop (with Theme 3) emission estimates for use with multimedia F&T modeling to assess various potential exposure scenarios, and integrate the above information/models into an EIA-Nano framework and case studies. The specific goals of Theme 6 are to: (i) develop advanced quantitative multi-
parametric Nano-SARs based on integration of multiple ENMs toxicity assays/platforms; (ii) develop a framework for exposure analysis for nanomaterials (ExpNano) integrating an ENM emission model(s) (Theme 3) with an expanded F&T model (MendNano) to estimate individual receptor ENM dosage for varying exposure scenarios; and (iii) develop an in silico (computational) platform for EIA of nanomaterials (EIA-Nano) that integrates ExpNano with quantitative Nano-SARs, and the ENMs database for carrying out case studies with selected ENMs including nano-ZnO and Cu that will be evaluated across the center.

Research Plan and Deliverables: The goals of Theme 6 will be achieved via three main project areas. Each project area will consist of defined 12-18 month projects supervised by a faculty member and executed by a graduate student or postdoctoral fellow.

(a) Project 1: Development of advanced quantitative Nano-SARs based on integration of multiple ENM toxicity assays/platforms. Developing predictive models for toxicity metrics, over an applicability domain suitable for EIA, requires integration/aggregation of the body of evidence from multi-parameter HTS assays and experimental platforms. The development of advanced quantitative nano-SARs that are based on multiple toxicity endpoints would represent a significant leap forward relative to single-point nano-SARs - the latter providing a narrow applicability range for decision-making. Solving the problem of nano-SAR development based on multi-parameter HTS requires new machine learning algorithms/methods to construct the rank aggregation as an optimization problem. Theme 6 is well-positioned to build on its nanoinformatics and machine learning expertise to develop further suitable computational models/algorithms that can be used for nano-SAR development based on multi-parameter CEIN toxicity data (both in vivo and in vitro high and low throughput studies). Theme 6 will explore the use of a variety of methods (for handling multiple endpoints) including the traditional Borda's and Footrule methods, Markov chain methods, Cross-Entropy Monte Carlo algorithm, Genetic algorithm, and supervised rank aggregation. The goal is to expand the applicability domain of multiple endpoint nano-SARs (relative to single toxicity end-point nano-SARs) by integrating evidence across different experimental platforms and multiple-assay toxicity studies by Theme 2 (e.g., different cell types and zebra fish), Theme 4 (e.g., soil microbial communities and model food crops) and Theme 5 (e.g., oysters, clams, crabs, worms, bacterial communities, phytoplankton).

(b) Project 2: Environmental Exposure Analysis for Nanomaterials (ExpNano). Exposure assessment of ENMs (ExpNano) is critical for EIA of nanomaterials. Accordingly, as part of EIA-Nano, an ExpNano model will be developed integrating: (i) ENM emission model, based on the life cycle analysis approach in Theme 3, (ii) multimedia environmental distribution of nanomaterials (MendNano) model expanded to include near-source emissions, (iii) Intake model to estimate ENM dose for selected ecological receptors (e.g., based on uptake studies with plants and aquatic organisms by Themes 4 and 5, respectively), and (iv) capabilities for near point-source exposure (due to atmospheric dispersion and dispersion in flowing water bodies). ExpNano will be developed as a cloud-computing accessible simulator that is publically available. In accordance with the recommendation from the 2012 Site Visit, case studies for validating various model transport components (i.e., inter-media transport modules) will be undertaken making use of available field monitoring data for particle-bound pollutants (e.g., PAHs, PCBs). Subsequently, experimental data from simulated estuarine mesocosms studies of Theme 5 will serve to evaluate the significance of a variety of processes including, but not limited to, diurnal cycles of flow reversal, salinity gradients, organic matter loading, and sediment resuspension. In addition, data from terrestrial mesocosm studies of Theme 4 will enable assessment of the degree of ENM uptake in plant roots. The above mesocosm studies will provide invaluable data to validate ExpNano modules for ENM infiltration into the soil and sediment matrices.

(c) Project 3: In silico (computational) platform for environmental impact analysis (EIA) of nanomaterials (EIA-Nano). Assessment of the potential environmental impact of ENMs is a major challenge given the rapid rate of growth of nanotechnology and the scarcity of environmental monitoring data. Therefore, Theme 6 will develop an in silico environmental impact analysis (EIA) platform in order to enable evaluation of risk management and safe-by-design options for ENMs considering a multi-criteria analysis process. In this approach, toxicity information and estimates of environmental exposure concentrations will serve as input for environmental hazard ranking. Toxicity information regarding ENMs (e.g., from in vivo or in vitro toxicity screening data stored in the rapidly growing CEIN database and library of nano-SARs) will be used to define suitable risk metrics. Propagation of uncertainties throughout the EIA process will be tracked considering data and modeling uncertainties, in addition to various toxicity end points (e.g., ranking of ENMs with respect to exposures, dosage, and associated toxic...
end-points). The overall EIA-Nano approach will make use of a Bayesian network to enable decision making while estimating, tracking and aggregating uncertainties throughout the analysis process. Theme 6 EIA-Nano models and data analysis tools will be developed for remote execution (i.e., cloud computing). In this regard, Theme 6 will continue its collaboration with government regulators and the broader scientific and commercial communities, as well as through its participation in Nanoinformatics 2020, to make its nanoinformatics tools/models available for open-source use and to encourage a community-based effort to improve and standardize tools for ENM environmental impact assessment.

B.8. Theme 7: Using UC CEIN Knowledge Generation to Engage and Impact Multiple Stakeholders

Faculty Investigators: Hilary Godwin and Andre Nel, UCLA (Theme Leaders); J.R. DeShazo, UCLA; Barbara Herr Harthorn, UC Santa Barbara; Fred Klaessig, Pennsylvania NanoBio Systems; Timothy Malloy, UCLA; JoAnne Shatkin, Conservation Law Foundation Ventures.

Scope of Theme 7 Activities and Integration in the Center: Whereas in the first 5 years, Theme 7 focused on goals of generating new knowledge about the ethical, legal, and societal implications of nanotechnology, Theme 7 is now proposing to further integrate and translate CEIN research among multiple stakeholder groups to assist the development of new policy approaches, safety assessment and safe implementation approaches for ENMs. This will require enhancing relationships across stakeholder groups as well as recognizing the sensitivities facing industry (e.g., confidential business information) with respect to engaging in open dialogue. In addition, by partnering with experts in academia, law, policy, industry and civil society organizations (CSOs) we will identify priority areas for engagement and science translation. Thus, in the second funding period, UC CEIN will continue to expand its science translation and outreach efforts by using the knowledge generated in the Center to engage national and international thought leaders in the areas of nano EHS policy, governance and anticipatory decision-making. Theme 7 will be intricately linked to the work of each of the scientific research Themes 1-6 as its efforts are informed by the scientific results emerging from those cores. The outreach activities of Theme 7 are complementary to the public education goals of Theme 8 and Theme 7 will play an active role in aspects of student and postdoctoral scholar mentoring and leadership workshops that focus on skills development for translation of science to multiple non-academic audiences.

Goals and Outline of Theme 7 Research: The overarching goals of Theme 7 are to encourage the use of UC CEIN’s body of knowledge to inform multiple stakeholder audiences about the potential adverse impact of nanotechnology in the environment; to integrate salient scientific results into existing and developing nanotechnology environmental decision frameworks; and to elevate UC CEIN as a key thought leader on the contributions of predictive toxicological paradigms that can assist nano EHS policy and decision making. To accomplish this, we have established three specific goals: (i) Use nano EHS science accomplishments to engage multiple stakeholders: Use research across the Center to identify key scientific accomplishments for translation and engagement of the public, industry and academia. This includes collaboration with the Center for Nanotechnology in Society at UC Santa Barbara for access to formative research findings on multiple stakeholders’ concerns and needs. (ii) Conduct research on existing or new nano EHS policy models: identify and evaluate how the scientific advances developed in UC CEIN and elsewhere provide a basis for new regulatory models that provide risk reduction or can influence adaptation of existing state, national and/or international regulations and/or policies that affect nano EHS. (iii) Engage industry, Chief Scientific Officers (CSOs) and regulatory agencies: work across sectors to bring together experts in academia, law, policy, industry, CSOs and the general public who can identify priority areas for dissemination of the Center’s science with the goal of improving regulatory frameworks and deepening the understanding of diverse perspectives on safe implementation of nanotechnology in the environment.

Research Plan and Deliverables: UC CEIN will work with regulators, policy makers, industry, CSOs, standard setting organizations and other key stakeholders to determine the role of science in standard setting and policy making. UC CEIN is well poised to be the convener of stakeholders who have historically faced challenges coming together. Methodologies developed in the first five years of the UC CEIN have helped to improve the safety assessment of ENMs and have helped to develop a number of the scientific underpinnings that are required for a comprehensive Nano EHS enterprise. UC CEIN has also forged partnerships with a broad range of stakeholder groups and will continue to use its evolving knowledge base in years 5-10 to engage and offer nano EHS solutions to industry, the public and the
regulatory community. We will deepen our understanding by examining a focal set of ENMs and associated industry segments that could lead to environmental impact and are of regulatory concern. For each focal set of ENMs and its associated regulatory and stakeholder groups, we will establish an annual “Assessment and Solutions” workshop, a forum for assessing challenges, issues and proposing solutions relating to the use and regulation of ENMs as well as a “Decision-Support” workshop intended to provide support to regulators on the ENM-related issues deemed to be most critical to the safe and effective emergence of the focal ENMs.

(a) Project 1 will translate scientific accomplishments in the Center to broad audiences under the direction of Godwin, Harthorn and Nel. This effort will enhance partnership opportunities with the public, industry and the regulatory community and develop two-way communication critical for goals 2 and 3. This goal will be accomplished by identifying opportunities from our research for integration in multi-year structured activities that will result in the development of published white papers, multi-stakeholder roundtable discussions, and press and media products. As one example, convening the workshop on alternative testing strategies (varying from those in use by regulators) will raise awareness of a key CEIN research accomplishment that could impact regulatory decision-making through the implementation of evolving science in the area of nano EHS.

(b) The research focus of Project 2, research on new or existing policy models, is critical to assisting regulatory agencies in improving existing regulatory frameworks to enable a nimble response to ENMs through the use of new and emerging data. DeShazo and Malloy will focus on adapting or transforming regulatory approaches (including soft law, adaptive regulation, and prevention-based approaches) that leverage the range of predictive toxicological methods, management protocols and decision-analysis tools under development at UC CEIN. Both will work to implement the annual “Assessment and Solution” and “Decision-Support” workshops as well as co-author policy and regulatory white papers and research publications.

(c) Project 3 will engage industry, CSOs and regulatory agencies to develop opportunities for intellectual exchanges between diverse stakeholders across sectors working within the ENM field. As a leader in the study of nano EHS, UC CEIN is poised to facilitate discussions about how emergent scientific discoveries in this field can be made more useful and accessible to regulatory agencies in improving existing regulatory frameworks to enable a nimble response to ENMs through the use of new and emerging data. DeShazo and Malloy will focus on adapting or transforming regulatory approaches (including soft law, adaptive regulation, and prevention-based approaches) that leverage the range of predictive toxicological methods, management protocols and decision-analysis tools under development at UC CEIN. Both will work to implement the annual “Assessment and Solution” and “Decision-Support” workshops as well as co-author policy and regulatory white papers and research publications.

C. Broader Impacts

C.1 Education - Hilary Godwin (Theme Leader): The UC CEIN educational program seeks to broaden knowledge of the environmental implications of nanotechnology beyond our Center through a range of academic coursework and training materials based on UC CEIN science, training courses for industrial practitioners, and informal education and public outreach. The UC CEIN is committed to educating and training the next generation of interdisciplinary scientists and engineers needed to advance the field of nanotechnology, which can also anticipate and mitigate any potential future environmental hazards associated with this important technology. Activities within the Center are designed to enhance professional development of Center trainees and broaden participation of underrepresented groups in the sciences. At the same time, we are committed to engaging members of the general public (from K-12 through adult populations) on topics related to the environmental implications of nanotechnology. In years 6-10, the UC CEIN’s mentoring, public education programs, and activities to broaden participation of underrepresented minorities will be expanded to encompass both undergraduate science majors as well as a broader range of students at UCLA, UC Santa Barbara, UC Riverside, UC Davis, and UTEP. The UC CEIN Education program reaches across all themes and cores of the Center and directly influences every Center member. Under the leadership of Education and Outreach Director Godwin, UC
CEIN will continue to focus on: (i) student/postdoctoral mentoring and professional development; (ii) the development of educational outputs based on UC CEIN research; (iii) synergistic/integrative Center activities; and (iv) informal science education (ISE) and public outreach. Over the course of the next five years, each project area will evolve and expand based on ongoing evaluation and feedback, and new areas of focus will be introduced as dictated by the priorities of our members and the scientific findings generated by the Center.

**Student/Postdoctoral Fellow Mentoring and Professional Development:** CEIN will continue to provide participant-centered professional development workshops and one-on-one professional development/job skills support for Center students and postdoctoral fellows to improve their skills in the areas of public speaking, professional presentations, and writing. Topics for the workshops and individual mentoring are determined by input from the Center's Student Postdoc Advisory Committee (SPAC) as well as priority areas identified by Center faculty. Details can be found in the Postdoctoral Mentoring plan in the Supplemental Proposal Materials.

**Course Development, Workshops, and Learning Tools:** In the first five years of the award, UC CEIN has played a major role locally, nationally and internationally in developing educational materials about the environmental implications of nanotechnology for a wide variety of academic audiences. In years 6-10, we propose to update the online Nanoecotoxicology course; a 13 lecture course based on the research of the UC CEIN developed in years 1-5 and made available to other Universities nationally and internationally. The course will be updated to reflect the evolving state of the science, and new lectures (both integrated into the course and stand alone) will be developed and made available over the next five years. Additionally, the science of the UC CEIN will continue to be continuously integrated into existing undergraduate and graduate level academic courses across the Center's disciplines. Strategies for the creation of supplemental learning materials, including online training modules and textbook chapters, are currently being discussed by Center faculty.

To supplement our public education activities, we are developing a middle school level science fair project based on the research being conducted in the Center. The project will be made available to the public through Science Buddies (http://sciencebuddies.org/), an award-winning, non-profit organization that enables K-12 students, parents, and teachers to find free science fair project ideas. Partnering with Science Buddies will enhance the Center’s ISE efforts through website exposure, allowing us to reach thousands of children and teenagers. On average, each project on the Science Buddies website is accessed 14,000 times a year by a very diverse population. The Center’s initial project, “How Nano-sized Silver Particles from Antibacterial Socks Affect Bacterial Growth,” focuses on the effects of different nano-sized silver particles concentrations on the growth of bacteria and will be the website’s first nanoscience project. Additional projects will be developed based on UC CEIN science in Years 6-10, depending on the feedback we receive from Science Buddies and their user base on the original project. ISE outreach to high-school students will continue in partnership with local high schools (the Brentwood School and Thousand Oaks High School) and in collaboration with the UCLA CNSI’s summer residency programs. Additionally, the UC CEIN will continue to interact with consortiums of academic nano science education programs (i.e., NISENET) to share our experiences in developing public education tools and relationships.

**Synergistic/Integrative Center Activities:** The UC CEIN education group works to increase the integration of activities and provide opportunities for synergism across the Center. In addition to coordinating annual Center retreats, workshops, and seminars, the education program also coordinates a series of cross-disciplinary integrated meetings focused on topics identified by the Executive Committee and our researchers as critical. In the first five years, the Protocols Working Group developed, validated, and finalized for dissemination a range of standard laboratory protocols for key processes within the Center that are now publically available on our website. This activity will continue in the next 5 years. Seminars on special topics are convened (i.e., development of high throughput screening strategies, ecotoxicology, risk management, data analysis and interpretation) to allow researchers from all levels in the Center to explore in greater detail the discipline-specific science and to discuss how these specific areas of research affect other areas of Center research. These integrative meetings will continue on topics as defined by the Center leadership.

**C.2. Diversity:** UC CEIN is dedicated to increasing diversity at levels of participation in the Center (from Faculty, to student, to public education participants). Open positions within the Center are advertised widely, and efforts are made to recruit a diverse employment pool from the list of qualified applicants. An important shift in years 6-10 is that we will expand our mentoring mission to incorporate strategies for
engaging undergraduate science and engineering students at four main campuses within the Center (UCLA, UBSB, UCR, and UTEP) and include our graduate students and postdoctoral fellows in these mentoring activities. Specifically, we propose to develop new leadership workshops specifically targeted at undergraduates (e.g., on how to apply to graduate school and on funding opportunities for interdisciplinary science) and to adapt some of the leadership workshops previously developed within the Center (e.g., how to give an effective scientific presentation) for the needs of undergraduates. We will offer these workshops at the minority-serving institutions within our Center (UCR and UTEP) and will partner with undergraduate science and engineering societies (e.g., SACNAS) at our main campuses (UCLA and UCSB) and UC Davis. By connecting early with undergraduates – particularly those from underrepresented groups – on our campuses, we will build relationships that will make it more likely that these students will want to participate in both summer research experiences at institutions across our Center and to apply for graduate programs that feed our Center. As a result, these workshops will both promote the professional development of undergraduates and help to broaden participation of underrepresented individuals in the sciences and engineering general and in our Center more specifically.

C.3. Outreach: The UC CEIN has developed a broad range of outreach activities to ensure that the science performed and discoveries made within the Center are leveraged to serve broader societal needs in accordance with national directives. Through the combined efforts of our Education team and Theme 7, we have developed a range of outreach activities targeted across stakeholder groups including academia, adults in the public sector, K-12 students, industry practitioners, policy makers, and government stakeholders.

Seminar Series: The UC CEIN coordinates an annual academic seminar series where experts in the field of environmental nanotechnology are invited to UCLA and/or UC Santa Barbara to discuss the state of the science. In years 6-10, we will expand this series to ensure that other institutions within the Center are hosting seminars on topics related to Center research. UC CEIN will host annual conferences to present research and encourage academic discourse on topics directly related to the Center's themes. The conferences will feature presentations of Center research alongside invited leaders in the field internationally, and will be advertised widely to the nanotechnology research community. Finally, the UC CEIN will continue to organize and/or co-sponsor academic workshops on selected topics related to the Center's research and its broader societal implications, as discussed in Theme 7.

Informal Science Education: UC CEIN has developed partnerships with the California Science Center, the Santa Monica Public Library, and CalPoly Pomona to conduct public informal science education (ISE) focusing on the environmental relevance of nanotechnology. These partnerships will continue, and additional partnerships will be identified on an ongoing basis, based on the alignment of our Center's education goals with potential partners, the potential audiences, and the proposed range of informal science education activities. The current roster of annual public events includes (but is not limited to): Exploring your universe (UCLA), NanoDays (California Science Center), Nanotechnology: Small is big! (Santa Monica Public Library), and additional as-needed public events at the California Science Center. In the second funding cycle, our ISE events will be expanded to include active participation by UTEP and UCR Center members, with Center students and postdocs in these institutions actively engaged to participate in public education activities to complement their research. To facilitate these interactions, we will run training sessions on how to conduct effective outreach events and demonstrate NISEnet activities for faculty, students and postdocs at UTEP and UCR, similar to the training sessions that we already run for UCLA, UCSB, and Cal Poly Pomona. For instance, students at UTEP who are trained in how to perform outreach activities and to use NISENet materials will then be able to partner effectively with local institutions (e.g., Insights El Paso Science Museum) to conduct outreach activities in conjunction with NISENet's Nanodays event.

Translation and Dissemination of CEIN Research for Policy: Theme 7 will conduct outreach to multiple stakeholder groups (industry, regulators, academia, the general public) through identification of key research findings within the Center for translation into white papers, press releases, blog entries, and other media products. The message of the translation outputs will be tailored for specific target audiences and will help raise awareness of key CEIN research findings and bring momentum to important changes in policy and decision-making, guided by relevant and evolving science in the area of nano EHS.
REFERENCES CITED


2. Report to the President and Congress on the Fourth Assessment of the National Nanotechnology Initiative. President’s Council of Advisors on Science and Technology. 2012.


SHARED FACILITIES

UCLA: (1) CEIN Laboratory(1000sq+): housed in the California NanoSystems Institute (CNSI) building, centrally located on the UCLA campus. The CEIN has recently installed a Perkin-Elmer Analyst Graphite Spectrometer and a Shimadzu ICP-9000 to expand characterization. This equipment joins our existing CEIN characterization and HCS equipment: Quadrasorp SI to analyze surface area and pore size of our library NMs; Wyatt DynaPro Plate Reader Dynamic Light Scattering instrument; a Brookhaven Zeta Potential analyzer; and an Elisa Plate. Bench space has also been outfitted to accommodate approximately 10 working bays. (2) Molecular Screening Shared Resource (MSSR): houses two fully integrated HTS systems: (i) Automated liquid handling, multiple plate reading, plate filling and washing, deshielding, and delidding, and online incubators for cell-based assays using a Beckman/Sagian system equipped with an Orca robotic arm that delivers plates to individual work stations; Beckman Biomek FX liquid handling robot (96-well pipetting, 96- or 384-pin transfer); Perkin-Elmer Victor3(V) plate reader (96–1536 well plates) to assess luminescence, fluorescence, fluorescence polarization, time-resolved fluorescence, UV–Vis absorbance modes; Molecular Devices FlexStation II plate reader equipped with an integrated pipetter and general fluorescence and luminescence plate applications in 96- or 384-well format; Cytomat 6001 incubator: CO2 incubator; Multidrop 384: manifold liquid dispensing into 96- or 384-well plates; ELx 405 plate washer: well washing, aspiration, dispensing. The current capacity of cell-based assay is ca. 10⁵ wells (conditions)/day. Multiple plate readers allow fluorescence, FRET, BRET, time-resolved fluorescence, fluorescence polarization, luminescence, and UV–Vis absorption assays. (ii) A second Beckman/Sagian Core system for HCS using automated microscopy with an Orca arm; Molecular Devices ImageXpress (micro) automated fluorescence microscope and a Cytomat 6001 incubator. (3) Zebrafish Facility: under the direction of Dr. Shuo Lin, this state of the art facility in the UCLA Life Sciences Building facilitates the use and quick access of common mutations, genetically engineered transgenic zebrafish and routine techniques of zebrafish manipulations. The core provides four major categories of service: i) space for housing and performing larger scale genetic or chemical genomic screens; ii) assistance in development of zebrafish experiments; iii) generation of transgenic zebrafish; and iv) cryostorage of zebrafish sperm and re-derivation of live fish. (4) Molecular Instrumentation Center is a state-of-the-art campus-wide facility dedicated to molecular characterization housed in the Department of Chemistry. With focus on Magnetic Resonance, Mass Spectrometry, Materials Characterization, and X-Ray Diffraction, equipment includes SEM, differential scanning calorimetry, thermogravimetric analysis, magnetic resonance imaging, X-ray diffractometers, mass spectrometry for proteomics and biochemistry instrumentation, ICP-AES for elemental analysis and speciation. (5) CNSI Core Facilities provide additional equipment not found in the above laboratories on a recharge basis. Nano-electronics Research Facility includes scanning electron microscopy (SEM) with energy-dispersive analysis of X-rays; transmission electron microscopy; surface profilometers and ellipsometers. UCLA’s Environmental Nanotechnology Research Laboratory includes a programmable oven, furnace, and microwave systems for NM synthesis, bench-top micro-centrifuge and stirred filtration cells for NM isolation, BET analyzer for powder surface area and pore size analyses, equipment for polymer phase inversion, interfacial polymerization, and solution casting. Nano-Bio Interfacial Forces Laboratory includes a contact angle goniometer for powder/substrate wetting and surface energy analyses; particle micro-electrophoresis system for particle electrophoretic mobilities (zeta potentials); dynamic and static light scattering for evaluating particle sizes and polymer molecular weights; upright optical and epifluorescence microscope; and AFM integrated with inverted optical microscopy.

UC Santa Barbara: Four clusters of laboratories are available to CEIN: (1) CNSI-UCSB provides recharge access to the Microscopy and Microanalysis Facility: three transmission electron microscopes (FEI Titan FEG and two FEI Tecnai G2 Sphera), three SEMs (FEI XL40 Sirion FEG, FEI XL30 Sirion, FEI Inspect S), five scanning probe STMs/AFM microscopes (Digital Multi-mode Nanoscope, Digital Dimension 3000, Digital Dimension 3100, Asylum MFP-3D SL, Asylum MFP-3D Bio), a secondary ion mass spectrometer (Physical Electronics 6650 Quadrupole), X-ray Photoelectron Spectroscopy Kratos Axis Ultra System, Focused Ion Beam System (Model DB235 Dual Beam). The Spectroscopy Facility has seven state-of-the-art spectrometers (Nicolet Magna 850 IR/Raman, Varian Cary Eclipse Fluorimeter, Bruker D PX200 SB NMR for solutions, D SX300 WB NMR for solids, DMX500 SB NMR for solutions, Bruker IPS0500 WB NMR for solids, Bruker EMX Plus EPR spectrometer). (2) Bren School of Environmental Science and Management. The School Infrastructure Lab (2350 sf) includes a Shimadzu HPLC with fluorescence and diode array detectors, Shimadzu GC/FID, Beckman scintillation counter, total-carbon analyzer, –80 °C Revco freezer, high-speed refrigerated Sorvall centrifuge, two static incubators for cultivation at 37 and 41 °C, refrigerator, water baths, spectrophotometers, hybridization oven, UV crosslinker, Nanopure water system, autoclave,
icemaker, laboratory microwave, two multi-user walk-in 4 °C rooms for sample storage and two walk-in freezers, and two variable-temperature rooms. **Holden’s lab** (930 sf) includes: HP 6890 GC/MS with autosampler; Baker biological control cabinet; Sorvall microcentrifuge; New Brunswick shaker/incubator; analytical balances; Nikon E-800 epifluorescent microscope equipped with a CCD camera and NIS-Elements acquisition and analysis software; BioTek Synergy2 microplate shaker/incubator/reader with UV/Vis/TRF detectors; PCR and qPCR thermal cyclers and other equipment related to electrophoresis, PCR product quantification, and analyzing terminal labeled restriction fragment length polymorphisms. **Micro-Environmental Imaging and Analysis Facility (MEIAF)**, an environmental SEM with a cryo-stage for imaging frozen materials and an X-ray detector for elemental analysis (300 sf). The MEIAF is available to the public on a recharge basis. **Keller’s lab** (940 sf) includes: Malvern Zetasizer nano series Nano-ZS90; and QSonica Misonix Sonicator S-4000; Shimadzu high performance liquid chromatography (HPLC) system (SPD-M10AVP); Varian Saturn 2100T GC/MS with autosampler; Nikon Optiphot-M epi-fluorescence microscope with CCD camera; Thermo Cahn Radian 315 dynamic contact angle analyzer; Brookfield viscometer; column transport pumps and controllers. (3) **Department of Ecology, Evolution, and Marine Biology. Schimel’s lab** includes: two Finnegan MAT Delta Plus MS systems equipped with elemental analyzer, gas bench, pyrolysis, and GC inlet systems (available through MSI analytical lab); two multichannel Lachat autoanalyzers for dissolved nutrients; C/N analyzer for solid samples; Shimadzu GC 14 for simultaneous CO2, CH4, and N2O analyses; microtiter plate reader (UV/Vis) for enzyme and chemical assays. **Nisbet’s lab** has high-end PCs for DEB modeling, additional access to a high-performance computing multi-node facility at UCSB is available on a recharge basis; Leica Dissecting scope with digital color camera; Leica inverted microscope, fully motorized, with monochrome camera; Molecular Devices Gemini EM scanning spectrophotometer (top and bottom reads); C/N Analyzer for solid samples; Ocean Optics Jazz portable spectrophotometer; four peristaltic pumps; Mettler-Toledo Ultra-microbalance; Millipore Elix water system; bath sonicator; two incubators. (4) **MRL Facilities** provide access on a recharge basis: Thermo iCAP 6300 Inductively Coupled Plasma ICP Spectrometer; Shimadzu UV3600 UV-Nir-NIR Spectrometer; Mettler 851e TG coupled to a Pfeiffer ThermoStar Mass Spectrometer TGA-MS for thermo gravimetric analysis; Quantum Design MPMS 5XL SQUID Magnetometer; Bruker D8 Theta-Theta XRD; MicroMeritics TriStar Porosimeter for surface area, pore volume, and pore size distribution measurements; Perkin Elmer LS 55 Luminescence Spectrophotometer.

**UC Davis**: Bodega Marine Laboratory (BML) houses 16 specialized wet labs. Equipment includes state-of-the-art fluorescence imaging facility, ultracentrifuges, ultra-cold freezers, autoclaves, a 28-ft flow-visualization water tunnel/flume, OES mass spectrometer, and experimental climate change laboratories. Support buildings include terrestrial and marine greenhouses, animal resources, marine operations (diving, vessels and ocean observing), and an industrial shop (engineering, fabrication, and maintenance). **Seawater Laboratory Sensor Network**: a sophisticated computer-controlled, up to 1,000,000-gallon/day seawater system that provides seawater to the wet labs, classrooms and public displays. Specialized laboratories on the Seawater Sensor Network include a marine pathology laboratory (the only State-approved facility for marine pathology studies) and salt and freshwater laboratory for studies of threatened and endangered species. **Cherr’s laboratory** houses BML’s Fluorescence Imaging Facility, which includes a Photon Technology spectrophotometer with ratiometric and ion quantitation software; high-speed fluorescence video imaging system on a fixed stage microscope controlled by Metamorph software; three epifluorescence microscopes; UVP Epic hem II fluorescence/chemiluminescence gel documentation system; Tecno Genios time-resolved fluorescence/ and luminescence/absorbance plate reader; Olympus Fluoview 500 confocal scanning laser microscope with temperature controlled stage and water immersion objective lenses; Expert Vision System motion analysis software; and a Nikon AZ100 fluorescence stereo zoom microscope with a computer controlled stage HCS software capabilities.

**UC Riverside**: **Walker’s laboratory** is equipped with an inverted Olympus IX70 microscope (phase contrast or fluorescent mode), used to image bacterial cells or particle attachment to test surfaces within a parallel plate flow cell or a radial stagnation point flow cell. The lab is also equipped with an Electrokinetic Analyzer for streaming potential measurements and a ZetaPal machine for particle electrophoretic mobility and dynamic light scattering (both pieces by Brookhaven Corp.).

**Columbia University**: shared resources in the MRSEC and Chemistry Departments for work on this project: Hitachi 4700 SEM; JEOL SEM and TEM; Inel X-ray diffractometer; Bruker NMR spectrometer; PHI 5500 XPS; ellipsometer. **Somasundaran’s laboratory** includes: Horiba Aramis Raman microscope with four lasers; Digital Instruments AFM; PenKem 3.0+ Zeta meters; Perkin–Elmer Spectrum100 FTIR spectrophotometer; Horiba Jobin Yvon Fluorolog fluorescence spectrophotometer (steady state); Horiba Jobin Yvon IBH5000F fluorescence spectrophotometer (time-resolved); Quantachrome Instruments
Quantasorb surface area analyzer; Bruker EMX EPR spectroscope; Perkin–Elmer Plasma 400 ICP spectrophotometer; Perkin-Elmer UV-Vis Lambda-25 Spectrophotometer, Kruss K12 surface and interfacial tensiometers; NIMA Tech DST9005 dynamic surface tension analyzer; Nikon optical microscope; Beckman–Coulter Optima XL-1 analytical ultracentrifuge; SORVALL RC-5B bench-scale and temperature-controlled centrifuge, HF scientific turbidity meter, flotation equipment.

**Northwestern University: The Hersam Laboratory** (3000 sq. ft.) houses five fume hoods and the following major pieces of instrumentation: (i) 2 Thermomicroscopes CP Research Atomic Force Microscopes (AFMs): characterize mechanical (force-distance spectroscopy) and electronic (electric force microscopy and scanning potentiometry) properties of materials at the nanometer scale in ambient, controlled atmosphere, and liquid environments; (ii) 2 Room Temperature Ultra-high Vacuum (UHV) Scanning Tunneling Microscopes (STMs): These home-built multi-chamber systems are used to prepare pristine surfaces, which are then characterized at the atomic-scale with STM and scanning tunneling spectroscopy. Feedback controlled lithography has also been implemented to isolate and pattern individual molecules on surfaces in atomically precise geometries. The UHV chambers (base pressure ~ 2×10⁻¹¹ Torr) are directly interfaced to a controlled atmosphere glove box (oxygen and water concentrations < 1 ppm) to enable combined UHV and wet chemical processing with minimal contamination; (iii) 1 Cryogenic Variable Temperature UHV STM; this system controls the temperature of the sample and the microscope between 10 K and 400 K, ideal for cryogenic studies and high resolution scanning tunneling spectroscopy; (iv) 1 Nanoelectronic Charge Transport Measurement Apparatus: Enables electrical characterization of nanoscale devices and sensors. The apparatus includes a wafer prober, hall measurement apparatus, high sensitivity source-measure unit, spectrum analyzer, current preamplifier, lock-in amplifier, and 4-channel digital oscilloscope. (v) 3 Density Gradient Ultracentrifugation (DGU) Apparatuses: Used to sort carbon nanotube and graphene samples by their physical and electronic structure. Each apparatus includes a horn ultrasonicator, a Beckman Coulter Optima L-90 K Preparative Ultracentrifuge, and a BioComp Piston Gradient Fractionator.

**University of New Mexico/Sandia National Lab:** Brinker's Biocharacterization laboratory integrates biological organisms/components with engineered platforms. Capable of handling Biosafety Level 2 organisms and cell lines and the isolation and analysis of DNA, RNA, and proteins. Methods used to incorporate biological organisms/components onto engineered platforms: vesicle fusion; multiple tethering schemes; and plugged flow packing. Other capabilities include: ellipsometry for film characterization; electrochemistry; a PCR instrument for DNA amplification; a laser connected to an inverted microscope for fluorophore interrogation; and a hyperspectral microarray scanner for microarray analysis. The AML facility contains standard microbiological and biochemical equipment and supplies for handling the microbiorganisms and cell lines proposed for use on this project: Class II flow bench; standard and CO₂ incubators; cryostorage; freezers and refrigerators; autoclave; and a fluorescence microscope. The laboratory includes a new Asylum Research MFP-3D-BioAFM integrated with a Nikon TE2000-U inverted fluorescence microscope; Nano-ZS 90, Malvern; Fisher XRF. Additional shared resources: Bruker 250-MHz NMR spectrometer; Bruker 300-MHz multi-nuclei NMR spectrometer; Electroscan 2020 environmental SEM; Kevev omicron X-ray microfluorescence spectrometer; Hitachi S-4800-II SEM with EBSD; EDAX/TSL X-ray analyzer and electron backscatter diffraction imaging equipment; Zyvex Nanomanipulator and Nanoprobe; Hitachi H-8000 TEM; Fluorescence microscope; confocal microscope; conductivity meter; AFM. The XAS studies planned for this project will be performed at Stanford Synchrotron Radiation Laboratories (SSRL), Stanford, CA, where Gardea-Torresdey has received beam time the duration of this project.

**University of Texas, El Paso:** Gardea-Torresdey's laboratory: 3100 Perkin–Elmer flame atomic absorption spectrometer; 4100 ZL Perkin–Elmer Zeeman graphite furnace atomic absorption spectrometer; 4300 DV Perkin–Elmer ICP OES; Perkin–Elmer Elan DRC llle Laser ablation/HPLC/ICP-MS; EG&G Model 394 electrochemical trace analyzer; Hewlett–Packard 5890 GC; Hewlett–Packard 5972 GC/MS; Perkin–Elmer Spectrum 100 FTIR spectrometer coupled to a Perkin–Elmer Spectrum spotlight 300 FTIR microscope; Nano-ZS 90, Malvern; Fisher XRF. Additional shared resources: Bruker 250-MHz NMR spectrometer; Bruker 300-MHz multi-nuclei NMR spectrometer; Electroscan 2020 environmental SEM; Kevev omicron X-ray microfluorescence spectrometer; Hitachi S-4800-II SEM with EBSD; EDAX/TSL X-ray analyzer and electron backscatter diffraction imaging equipment; Zyvex Nanomanipulator and Nanoprobe; Hitachi H-8000 TEM; Fluorescence microscope; confocal microscope; conductivity meter; AFM. The XAS studies planned for this project will be performed at Stanford Synchrotron Radiation Laboratories (SSRL), Stanford, CA, where Gardea-Torresdey has received beam time the duration of this project.
DATA MANAGEMENT PLAN

Data/Cyber Infrastructure: CEIN has developed and maintains a data management server, a CEIN web portal and a web-based data repository. The CEIN hardware infrastructure includes two servers, four high-end workstations and an in-house computational cluster. One server uses Microsoft SharePoint for data management, data analysis tool development and research collaboratory. This platform has customized features for file storage with metadata, data sharing, web tool development and file versioning. It also offers built in user access management and private/public content controls. Each research team within the center as well as external CEIN collaborating groups/centers are provided dedicated private research websites which has strict access and permission controls. This server, which will be expanded over the new CEIN cycle, hosts a data repository where data from various CEIN and CEIN partner studies/projects are stored. The second server is a storage node with 24TB of raw storage capacity, which also provides space for the daily backup of CEIN server and the computational cluster. The CEIN maintains a high performance 10-node computational cluster which hosts various computational tools and simulators (e.g., analysis of high throughput toxicity data, environmental impact analysis, life-cycle analysis, image analysis, etc.). The servers and cluster are physically located at the CEIN data management facility in a temperature controlled dedicated data lab which has access to fire protection and power backup services. In addition to the daily backup to the on-site storage node, all server content is also backed up to an off-site location.

Data Format: Data are collected in various forms, depending upon the type of study. In toxicity studies, the data are generally in text, pdf or spreadsheet format, while data from some nanomaterials characterization studies consist of images (e.g., nanoparticle TEM images and images of zebrafish embryo/larvae) in various formats (e.g., JPEG, TIFF etc.) and files of various numerical and text formats. Data are stored along with metadata according to a strictly enforced metadata template and a workflow for submission, review and approval of data for acceptance to the data repository. All submitted metadata files that accompany submitted project data must contain the names of data owner, data generator, identify all endpoints, organisms, type of experimental systems, summary of nanomaterial properties, description of instrumentation used, specification of calibration methods calibration files, etc. Given the heterogeneity of experimental systems, the data repository handles both unstructured and structured data sets of the following broad categories: (a) Raw Data in numerical form from various analytical instruments or systems such as from high throughput screening (HTS) of toxicity of nanoparticles, characterization of nanoparticles via dynamic light scattering (DLS) and zeta potential measurements, (b) Images derived from HTS studies of whole organisms, mesocosm and field studies with plants and aquatic species, (c) Processed data which consists of raw data refined through various processing of data via various machine learning and statistical methods, data processing, (d) Published data which are in various publisher formats. Given the growing significance of image generation in CEIN studies, specialized image management will be developed aiming for consistency with other NSF BIO centers such as iPlant.

Data Tools: CEIN will continue with its program of making various modeling and HTS analysis tools available via cloud computing. Tools for environmental impact analysis will be made available for public use and building on the NSF iPlant “Atmosphere” cloud infrastructure platform. A CEIN-developed simulator for nanoparticles fate and transport and analysis of high throughput data have already been released for public use, with users able to access such tools via standard web browsers and make use of allocated storage space on the CEIN computational cluster. CEIN will continue to refine its data analysis tools, as well as adding new life-cycle analysis and hazard ranking platforms, for use by CEIN researchers as well as the broader nanotechnology and nano-EHS communities.

Data Archiving: Once study data are collected and published in the CEIN data repository, CEIN researchers are required to submit (online or via email) accompanying completed metadata forms to the CEIN data repository. The metadata field list has been developed to balance search criteria needs with convenience and flexibility for use by researchers and for data searching and mining. Submitted data files are moved to the CEIN data repository only after a metadata quality check and approval by the responsible project/study leader and the CEIN data manager. It is expected that the CEIN data repository (which has both publically accessible and secure areas) would be operational for at least the next six years (i.e., until the end of 2019) of the CEIN, after which the content will be transferred to either a CEIN public site or to UCLA managed data repository sites such as Merritt, eScholarship and EZID. It is also possible that the data will be transferred to one of the emerging public nanoinformatics sites that are
currently under development as envisioned by the Nanoinformatics 2020 Roadmap (DOI: 10.4053/rp001-110413).

**Data Access:** CEIN affiliates and the public will have direct access to the data repository via the CEIN public web site. In addition, request for access to specialized data that is in the stages of analysis and continuing research can be requested (via email). Moreover, consistent with NSF recommendations, all the data will be made available through the CEIN public website within a reasonable time after data publication.

**Collaborations and Migration towards Open Source:** In order to reduce the costs of infrastructure and to bring its offerings of tools and know-how to a broader community, the CEIN has made plans to collaborate with the NSF iPlant which is a center focusing on data sharing, storage, community access and tool development for plant scientists. This collaboration will be mutually beneficial as it will enable the CEIN to leverage the iPlant cloud infrastructure service platform, while providing the iPlant community with seamless access to CEIN HTS analysis tools and inclusion of the plant compartment in CEIN Fate and Transport simulators.

**Centralized Data Management:** The CEIN will migrate its current data repository and collaboratory platform which is built on Microsoft Share Point server to a centralized data management site using open source technologies. This will be accomplished through a recently established collaboration with iPlant that has developed extensive experience with the use of Open Source platforms for data management. The planned data management platform would feature web based forms for data and metadata upload, cloud storage and easy export to metadata exchange standards such as ISA-TAB Nano. The Central Data Management System (Fig. 1) would allow drag and drop file uploads to the repository as well as online metadata forms for each file. It would also feature pre-submission error checking and verification as well as automatic receipt generation. To increase compatibility, the site would be designed using free web and data packages (e.g. MySQL), computer languages (e.g. PHP, jQuery/JavaScript) and data exchange protocols (e.g. XML, JSON). Additional benefits include simpler integration with centers that use or support such packages.

**Personnel/Departure Contingency Plan:** PI/Co-PIs will jointly define data management policy, with the day-to-day data management (software and hardware) handled by a full-time data/systems manager. In the unlikely event of departure of PI or Co-PI principally responsible for the CEIN data management, the data/systems manager will assume temporary oversight until a new PI/Co-PI are assigned. When the CEIN ceases to exist, CEIN data will be migrated to and be made available through a public UCLA maintained data repositories (see Item 4).

**Copyright and Privacy:** CEIN collects organisms and laboratory animal data, but no human subject data. Therefore, privacy constraints/issues are not expected. The CEIN public website reserves the right to disseminate the data as dictated by the rules and standards of Intellectual Property set forth and approved by the Regents of the University of California.

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Figure 1: Proposed Central Data Management System
POSTDOCTORAL MENTORING PLAN

The UC CEIN is committed to educating and training the next generation of interdisciplinary scientists and engineers needed to advance the field of nanotechnology who can also anticipate and mitigate any potential future environmental hazards associated with this important technology. To enhance the professional development of our Center trainees, the UC CEIN Education program conducts a coherent and effective series of annual leadership and mentoring activities within the center designed to further the professional development of all Center trainees (postdoctoral fellows AND graduate students). UC CEIN conducts participant-centered professional development workshops and provides one-on-one professional development/job skills support for Center students and postdoctoral fellows to improve their skills in the areas of public speaking, professional presentations, and writing. Topics for the workshops and individual mentoring are determined by input from the Center's Student Postdoc Advisory Committee (SPAC) as well as priority areas identified by Center faculty. The SPAC includes representatives from all themes and partner institutions. We are committed to providing leadership development opportunities to postdoctoral researchers at all Center partner institutions, and funds are available in the Education budget to fund travel for out-of-state participants.

Additional development opportunities include our cross-campus trainee seminar series. Trainees from the Center are supported to travel to a partner campus to present a seminar and lead a discussion on their ongoing research projects. This program fertilizes cross-disciplinary discussions at the trainee level, and has been extremely popular. In the first round of funding, UCLA and UC Santa Barbara played host to "visiting researcher" graduate students and postdoctoral scholars, and we will expand these opportunities in years 6-10. This is critical to our students and postdocs being able to form substantive interactions with their counterparts at distant institutions within the Center.

Another component to the mentoring provided to our postdoctoral researchers comes in the form of workshops focused on translation of Center research findings for multiple stakeholder audiences. We have conducted four Journalist-Scientist communications workshops, and moving forward, the Center will partner with the Center for Nanotechnology and Society (CNS) at UCSB and with the Luskin Center at UCLA to offer an annual workshop to assist students and postdoctoral fellows in improving their written communication skills, both within academic contexts and also for purposes of communicating science to various external stakeholders. These workshops will be informed by work being performed in Theme 7 and will help to ensure that students and postdocs within the Center are able to comfortably and effectively present their research both to academic and non-academic audiences. A new focus in our mentoring plan for years 6-10 will be the introduction of opportunities for mentoring undergraduate research assistants. As we expand our education programs to offer more research experiences, we will leverage the introduction of undergraduates to provide guidance and experience to postdoctoral researchers in developing their own mentoring skills.

The UC CEIN Education Coordinator conducts formal and informal evaluations of the Student/Postdoctoral Mentoring and Professional Development Program. The Coordinator also offers year-round in person and online sessions on presentation skills, report writing, and proposal writing. The Coordinator is available to all postdoctoral researchers for one-on-one consultation for writing skills, presentation skills, and career development advice. The Center has developed an online course in Nanoecotoxicology based on the scientific integration of our Center's research. This course is made available for all incoming postdoctoral researchers to aid in their understanding of the interdisciplinary integration of the Center's work, as well as provide key scientific background into the Center's mission. Postdoctoral researchers are also given the opportunities to prepare and present lectures and seminars to outside audiences (including high school students, undergraduates, and the public) on CEIN research through our partnerships with the California NanoSystems Institute, the California Science Center, and the Santa Monica Public Library.

In addition to Center-wide mentoring and leadership activities, all postdoctoral researchers across the Center develop a written training plan for their research, and undergo an annual performance evaluation with their mentor. The UC CEIN conducts evaluations of all Center mentoring and workforce development activities, results of which are summarized in our Center's annual reports and are used to influence program development.
INTERNATIONAL PARTNERSHIPS AND ACTIVITIES

UC CEIN has developed a strategy for international collaboration with a focus on identification of partnerships that can best leverage the resources of the Center while contributing to the overall mission and goals of safe design of ENMs. In addition to our funded partnership with the Universitat Bremen (Madler), we have established a strong series of unfunded research and education partnerships across Asia, Europe, and Latin America, which include the establishment of partnerships in a growing number of EU-US Nanosafety efforts. Key partnerships have been formalized through Memorandums of Understanding. The most significant international partnerships reflected in our current research plan are:

Madler’s group (Bremen - Germany) will contribute to the research of Theme 1 synthesizing materials with deliberate characteristics to support the study of relationships between ENM Electronic Structure and Biological Outcomes, as well as the relationships between ENM Surface Structure/Chemistry and Biological Outcomes. Madler’s laboratory has state-of-the-art flame spray pyrolysis reactors for the synthesis of various metal oxide-based ENMs, including their functionalization with noble metals as well as double flame reactors. Bremen will synthesize materials with deliberate structural properties which will undergo in depth chemical characterization (Core B) and introduction across Themes 2-6.

Rallo and Giralt’s group (Universitat Rovira i Virgili - Spain) will continue to contribute its expertise in the development of machine learning techniques for analysis and modeling of high throughput screening data in Theme 6. The knowledge gained from the development of advanced tools for property estimation and toxicity pattern recognition has been applied to European research projects designed to develop novel tools to evaluate chemical risks, and have been adapted to the CEIN materials library as a way to advance the accuracy and range of feature analysis software algorithms. Rallo and Giralt will contribute to the expansion of multiple endpoint nano-SARs through integration of evidence across CEIN experimental platforms (Themes 2-5). Additionally, CEIN is a key partner in the newly established MODERN consortium (led by URV PI Giralt; EU Framework Programme 7) and will provide guidance and input on the development of new models for environmental and human health effects of nanomaterials (unfunded collaboration).

UC CEIN Unfunded International Research Partnerships
UC CEIN researchers have formulated an extensive network of collaborations across the fields of nanomaterial environmental health and safety. Our partnerships with International collaborators are constantly evolving over time and signify significant intellectual exchanges of knowledge that have and continue to influence our research findings. Examples of current international research partnerships include: Nanyang Technological University, Singapore (Loo) contributes valuable knowledge on the synthesis and chemical characterization of engineered nanomaterials (Theme 1); Chinese Academy of Sciences and the University of Birmingham in the UK (FENAC) are actively engaging UC CEIN in the development of predictive toxicological paradigms for cellular and organismal response to nanomaterial exposures (Theme 2); collaborations with Nanjing University in China, the National Research Council of Italy, and the University of Calgary in Canada (McCauley) help provide insight into the potential terrestrial and aquatic ecosystems impacts of exposures to ENMs (Theme 4/5); and the Catalonia Institute of Nanotechnology in Spain (Puntes) and FENAC at the University of Birmingham in the UK (Lead and Valsalmi-Jones) are involved in ongoing work to validate and expand the use of environmental decision models and their application across data sets (Theme 6). The UC CEIN will also serve as a partner in the U of Birmingham led NanoMile consortium (EU Framework Programme 7), sharing the expertise of across the Center’s themes towards the development of novel experimental platforms for understanding the mechanisms of toxicity.

UC CEIN Unfunded International Education Partnerships
UC CEIN has also established educational partnerships to facilitate to dissemination of our online courses and training materials both nationally and internationally. Currently, the Nanoecotoxicology course is available to toxicology and nanoscientists at the Centro de Investigacion y de Estudios Avanzados del Instituto Politecnico Nacional (CINVESTAV) in Mexico and Nanyang Polytechnic in Singapore. Feedback from international participants has been used to expand the scope of the course and identify future topics for integration into the course. Our educational partnerships have also opened the door to discussing potential research collaboration with both institutions.
MANAGEMENT PLAN

UC CEIN Participating Institutions and Participating Faculty

- **Funded Research Partners:**
  
  **University of California Los Angeles:** André Nel – Professor, Medicine; Chief, Division of NanoMedicine (PI); Yoram Cohen (Co-PI) – Professor, Chemical and Biomolecular Engineering; Hilary Godwin (Co-PI) – Professor, Environmental Health Sciences; Kenneth Bradley – Associate Professor, Microbiology, Immunology, and Molecular Genetics; Robert Damoiseaux - Scientific Director, Molecular Shared Screening Resource; J.R. DeShazo – Associate Professor, Public Policy; Shuo Lin – Professor, Molecular, Cellular, and Developmental Biology; Timothy Malloy – Professor of Law; Huan Meng - Assistant Research Scientist, Medicine, Division of NanoMedicine; Donatello Telesca – Assistant Professor, Department of Biostatistics; Tian Xia - Assistant Adjunct Professor, Medicine, Division of NanoMedicine; Jeffrey I. Zink -- Professor of Chemistry and Biochemistry.

  **University of California, Santa Barbara:** Arturo Keller (Co-Director/Co-PI) – Professor, Bren School of Environmental Science & Mgmt; Patricia Holden (Co-PI) – Professor, Environmental Microbiology; Barbara Herr Harthorn – Professor of Feminist Studies, Anthropology & Sociology; Hunter Lenihan – Professor, Ecology; Robert Miller – Assistant Research Biologist, Marine Ecology; Erik Muller – Associate Research Biologist, Ecotoxicology; Roger Nisbet – Professor, Ecology; Joshua P. Schimel – Professor, Soil Ecosystem Ecology; Sangwon Suh – Associate Professor, Bren School of Environmental Science & Mgmt; Galen Stucky -- Professor of Chemistry.

  **University of California, Davis:** Gary Cherr – Professor, Ecotoxicology.

  **University of California, Riverside:** Sharon Walker – Associate Professor, Chemical Engineering

  **Columbia University:** Ponisseril Somasundaran – Professor, Earth & Environmental Engineering

  **Northwestern University:** Mark Hersam -- Professor of Chemistry

  **University of New Mexico:** C. Jeffrey Brinker -- Professor of Chemical Engineering and Sandia Fellow

  **University of El Paso, Texas:** Jorge Gardea-Torresdey – Professor, Environmental Chemistry

  **University of Arizona:** Nirav Merchant - Cyberinfrastructure Strategist, iPlant

  **University of Bremen (Germany):** Lutz Mädler -- Professor of Production Engineering

- **Unfunded Research Partners:**
  
  **National Institute of Standards and Technology:** Elijah Peterson - Environmental Engineer, Biochemical Sciences Division

  **University of Calgary (Canada):** Edward McCauley - Professor, Ecology, Evolution, Marine Biology

  **Universitat Roviri i Virgili (Spain):** Robert Rallo – Associate Professor, Departament d’Enginyeria Informatica i Matematiques; Francesc Giralt -- Professor, Department of d'Enginyeria Quimica

  **University of Birmingham (UK):** Eva Valsalmi-Jones - Professor, Geosystems Nanoscience

  **Nanyang Technological University (Singapore):** Joaquim Loo - Associate Professor, Materials Technology

  **Catalonia Institute for Nanotechnology (Spain); Chinese Academy of Sciences (China); EPA Computational Toxicology Research (Tox/Cast); Nanjing University (China); National Research Council (Italy); Sandia National Laboratory; Lawrence Livermore National Laboratory; University of Birmingham (UK); NanoMile Consortium (FP7 - Birmingham led); MODERN Consortium (FP7 - URV led).**

- **Educational Partners:**
  
  **Centro de Investigacion y de Estudios Avanzados del Instituto Politecnico Nacional (CINVESTAV-Mexico); Nanyang Polytechnic (Singapore); California Science Center; Santa Monica Public Library**

Management and Organization Strategy

The UC CEIN organizational strategy is to maintain a strong infrastructure that supports and integrates our research, technology development, educational, outreach and diversity efforts. By facilitating communication across our participating communities, our organizational structure allows for selection, prioritization, distribution, and management of resources within a multi-institutional structure. By combining management of our financial operations with our programmatic operations, UC CEIN has been able to create an infrastructure designed to streamline the Center's activities while meeting the reporting requirements of the funding agency and the University.
Leadership
Andre Nel (UCLA) serves as the Center Director and Principal Investigator. As Director, Dr. Nel is responsible for the integration of the Center’s overall research, education, and outreach activities. Arturo Keller (UCSB) is the Associate Director, responsible for coordinating the research integration, seminars, student training, and outreach activities at UC Santa Barbara to provide seamless integration with the activities at UCLA. Focused leadership for the education and outreach components of the Center is provided by Hilary Godwin (UCLA). This faculty management team provides complimentary expertise and strategic leadership to ensure the Center’s vision and mission.

Research Themes. UC CEIN research is organized into seven themes, each under the leadership of a CEIN faculty member. Each theme engages several faculty, postdoctoral researchers, research staff, and graduate students. Key to the success of the CEIN is the integration of research within and across themes. Theme leaders (who are also members of the CEIN Executive Committee) are responsible for setting priorities, allocating resources, and tracking progress towards achievement of the theme’s goals. Frequent formal communication between theme leaders is key to ensuring that progress is made across all groups, and the findings of one theme are rapidly disseminated other themes. Projects submit periodic progress updates to their theme leader, the results of which are shared and discussed by the UC CEIN Executive Committee.
Executive Committee
The Executive Committee (EC) is composed of the Director, Associate Director, Education/Outreach Director, Co-PIs, Theme leaders, and the Center Chief Administrative Officer. The EC meets at least once per month and is responsible for assisting the Director with integration and coordination of research and education, overall resource allocation, and outreach to the scientific, industrial, and policy community. Several times a year, the Executive Committee reviews long-term directions of the Center and possible strategic redirections. Prior to any Research Reviews, Site Visits, and External Science Advisory Committee meetings the EC focuses on strategic planning. Research progress for all projects is reviewed on an ongoing basis, with projects submitting periodic progress updates. Allocation of Center resources is based on the following metrics: (i) contribution of the proposed work to the UC CEIN’s core goals; (ii) productivity, publication, and product delivery record; (iii) novelty; (iv) integration and cooperation with other funded UC CEIN projects; (v) availability of resources and facilities to carry out proposed projects; and (vi) timely delivery of impactful results. Approximately 3% of the Center's annual budget is designated for new and exploratory integrated research seed funding. Proposals for seed funding are reviewed by the EC on an annual basis.

The Executive Committee meets for a day long research retreat 1-2 times per year. The retreat focuses on the review of overall Center priorities and is a forum for discussing and establishing key short and long term goals for the Center, with particular focus on strengthening integration across all Themes.

External Science Advisory Committee
The UC CEIN has convened an External Science Advisory Committee (ESAC) comprised of scientists, technologists, industry members, and policy and education specialists. The ESAC advises the Center's Executive Committee with respect to CEIN strategic directions and management policies. The ESAC provides feedback on the focus and direction of CEIN research, progress made toward achieving Center goals, and illuminating new research and educational opportunities. The diversity of this group provides a comprehensive perspective on the major advances in nanotechnology and key issues with regards to potential environmental implications. In response to the most recent Site Visit comments, we will include more female members of the ESAC over the next five years. The ESAC meets twice a year by teleconference and holds an in-person meeting at UCLA every other year. In addition to the group meetings, UC CEIN Executive Committee members engage ESAC members on an individual basis throughout the year based on their expertise. Additionally, ESAC members are invited to Center public events, including our Outreach workshops and scientific meetings. The composition of the ESAC is reviewed by the Executive Committee every two years.

Student-Postdoctoral Advisory Committee
A Student-Postdoctoral Advisory Committee (SPAC) continues to be active and key role within the UC CEIN. The committee includes graduate student and postdoctoral scholar representatives from each of the Center’s themes. The SPAC provides ongoing input into the development of the UC CEIN education program (including development of undergraduate mentoring opportunities), development of full-day annual leadership workshops, and formulation of goals for future Center workshops and seminar series. With input from the SPAC, the Education/Outreach Director and Coordinator have refined our annual evaluative survey which among other topics, documents educational and training achievements of Center trainees, results of which are discussed with the SPAC.

UC CEIN Core Support Services
The UC CEIN has identified four key Core function areas that form the basis for the Center's research infrastructure and provide support to enable the execution of research of the highest caliber. The Core areas interact across the Center's projects to enable smooth cross-disciplinary integration. The Cores are key in the ability to expand the scope of research within the Center and to maintain the flexibility necessary to conduct complex multidisciplinary research across a range of themes. Each of the Cores is housed within the California NanoSystems Institute (CNSI) facility at UCLA. Each of the Center's Core functions to provide the infrastructure and key support needed to carry out the wide range of multidisciplinary activities within the Center. Each Core serves a unique and necessary function. Cores B, C, and D are all adaptations of previously existing research projects with the Center. The interactions with the Cores and the Themes are essential to the scientific research advances of the Center. As the
Center's mission leads to the exploration of new questions about the environmental implications of nanomaterials, whether that involves new materials, new environmental conditions, or new types of data collected, the Cores will continue to play a key integrated role in the mission of the Center. The Cores are led by research staff who have the technical skills to interact across Center projects. Ideas for future development of Core activities arise through ongoing discussion with theme leaders based on the direction and findings of the Center's overall research agenda.

**Administrative Support - Core A**

An administrative staff has been compiled at UCLA to support streamlined operations of the Center. Since establishment of the Center in September 2008, the administration of the Center has operated under continuous management of the Center's Chief Administrative Officer (CAO). Utilizing experience in managing other large federally funded research, the UC CEIN administration is organized to provide maximized support to all Center projects in the most efficient manner possible. The CAO assists the Director by overseeing the general administration, cooperation, communication, planning, financial implementation, goals setting, and development of Center activities. The CAO is supported by the following dedicated staff:

- Financial/Budget Coordinator – responsible for financial management and reporting systems across partner institutions
- Administrative Assistant – provides general support for all Center activities including meeting coordination
- Education Coordinator – under joint supervision of the CAO and Education/Outreach Director, organizes the training, communication, diversity, and evaluation components of the program (See Education plan for more detail).
- Outreach Coordinator - under joint supervision of the CAO and the Theme 7 Leaders, is responsible for the day-to-day execution of the UC CEIN societal outreach activities, including developing a strategy for interacting with key stakeholders (See Theme 7 plan for more detail)

- To assist in the administrative coordination of the UC Santa Barbara activities, a half time administrative support staff position has been allocated to UCSB.

**ENM Acquisition, Characterization, and Distribution - Core B**

Core B is closely tied to the activities of Theme 1 and operates under the direction of Theme 1 leader Jeffrey I. Zink, who oversees the technical director, Dr. Zhaoxia Ivy Ji. Core B maintains the Centers nanomaterials library and coordinates the synthesis or acquisition and the distribution of ENMs across research projects and themes. This process necessitates close interaction with the toxicity groups to understand the major findings of current ongoing studies and to work with the material synthesis projects to redesign materials as needed to affect material properties. In order to conduct material characterization under relevant exposure conditions, Core B is closely affiliated with the cellular and environmental study investigators to determine the relevant range of characterization procedures and media to be conducted for each material. Characterization parameters that are key to our ongoing studies are: size and distribution analysis in relevant media, agglomeration kinetics, sedimentation studies, and surface charge analysis.

Core B has four main responsibilities:

1. The standard reference and combinatorial nanomaterial libraries are the sources of materials for mechanistic and high-throughput studies designed to probe environmental fate and transport of these materials as well as their cellular, organism, and ecosystem toxicity. Currently more than 100 different nanomaterials, varying from metals, metals oxides, to carbon nanotubes, have been introduced into the library.
2. The major "service" function of Core B involves characterization of the nanomaterials as they are synthesized or acquired. Its goals are to thoroughly characterize nanoparticles of commercial importance and make them available in usable forms and quantities for in vitro and in vivo studies. “Conventional” particles of commercial importance and scientifically-important high value particles are characterized by Core B.
3. Development of methods of dispersing nanoparticles in biologically relevant media is another major service function. Important insight has been gained by the Center, particularly regarding the influence
of cell culture media as they influence dose metrics. For each type of particle introduced into the Center, Core B explores the best method of dispersion and documents these methods.

4. Core B is also responsible for the distribution and tracking of materials across Center projects. The inter- and intra-campus distributions of both the particles and the characterization information associated with them have been very reliable and efficient.

**UC CEIN Data Repository and NanoCollaboratory - Core C**

The UC CEIN Data Management Team, under the supervision of Theme 6 leader Cohen, is responsible for development and maintenance of the computational infrastructure and data management system of the Center. Core C provides core support for data management, data storage, IT support, the web-based collaborative infrastructure and the computational needs of the Center. The technological infrastructure of the Center was developed to keep pace with the data generated by Center projects and to meet the computational needs of the Center's data analysis and modeling projects. Core C has implemented a center-wide file and data repository, hosts the Center's public website, and hosts software that allows for the searching/organizing/mining of research data uploaded to the system. The data manager (Hassan) works with each project's investigators to facilitate the uploading of data and to adapt the data repository system to meet the specific data needs of each project. The CEIN Data Management group plays a key role in the national Nanoinformatics effort. Our computational capabilities have enabled collaborations with external groups, including the EPA's ToxCast Program and NSF's iPlant Collaborative.

**Molecular Shared Screening Resource - Core D**

Core D provides scientific and technical consultation in the planning and execution of high throughput experiments conducted by UC CEIN researchers. The Molecular Shared Screening Resource (MSSR), under the direction of MSSR Director Kenneth Bradley and Scientific Director Robert Damoiseaux, assists in the translation of existing low throughput assays and the de novo establishment of novel assays. The expertise and technical capabilities available through the MSSR make this facility uniquely suited to handle a wide variety of assays, including those aimed at exploring the interaction between nanomaterials and bacteria, yeast, animal cells, and whole animals (zebrafish).

Core D (MSSR) is most closely linked to the research in Themes 2 and 4, working with projects to develop and validate HTS techniques for the screening of cells, bacteria, yeast, and whole animals (zebrafish) for the effects of interactions with nanomaterials. MSSR staff work closely with project researchers to translate existing assays to high throughput format, which includes adaptation of the assays for implementation on the robotics systems and providing assistance in conducting validation studies and data analysis. Once assays have been validated for HTS, screens may be conducted using additional Center library nanomaterials as dictated by the ongoing research project hypotheses.