

Concept Clearance

Branch: Exposure, Response and Technology Branch

Council Period: 201501

Concept Title: Nanotechnology Environmental Health and Safety

The Nanotechnology industry is recognized as a major economic force in the 21st century with an estimated output of about \$1.5trillion with the use of engineered nanomaterials (ENMs) in thousands of consumer products. Projections are that the field will continue to grow at a very high rate with the continued development of new engineered nanomaterials with subtle variation in physicochemical properties. This widespread use of ENMs in consumer products is a concern for potential unintended exposure to ENMs. The NIEHS centers for Nanotechnology Health Implications Research (NCNHIR) consortium was formed in 2010 as a central part of an inter-agency effort to assess the potential toxicities associated with exposure to nanomaterials; focusing on understanding the correlation between chemical and physical properties with toxicity to allow predictions of toxicities for emerging materials. The research findings from NCNHIR over the past four years suggested that ENMs, based on their physicochemical properties can initiate oxidative stress, acute inflammation and ultimately cell death. Limited sub-chronic studies indicated development of pulmonary fibrosis in animal models. The research output from these efforts clearly demonstrated toxicity of a variety of ENMs and how diverse physicochemical properties influence the toxicological outcomes. The research in this program studied a small library of ENMs with a focus on the pulmonary route of exposure and investigated acute to sub-acute effects. The inter-agency National Nanotechnology Initiative has recently published a stakeholder review of Nano EHS strategic plan progress. This effort identified the need to continue support for an integrated research program by member agencies to investigate a representative set of ENMs based on production and use in consumer products, gain understanding on molecular and biological mechanisms involved in the observed toxicological effects. The proposed concept outlines an effort to refine our Nano EHS effort to address potential human health issues due to unintended or intended exposure to ENMs in alignment with the overall federal effort.

This research program also addresses components of NIEHS Strategic Goals 1, 3 and 5.

The overarching goals of the NIEHS Nano EHS program are to gain a fundamental understanding of the molecular and pathological pathways involved in the toxicity of ENM-biological interactions and to develop a database of ENM toxicology-associated physicochemical properties that allows in silico hazard ranking of ENMs and guides the development of benign, next generation, ENMs. The knowledge gained from these efforts will also contribute to human health risk characterization and potential intervention or remedial measures.

The goals of the present funding opportunity are twofold. The first is to expand our basic understanding of ENM-biological interactions by expanding the library of ENMs and physicochemical properties focusing on specific materials with high production and use in consumer products as well as recently emerging two-, and three-dimensional ENMs containing new transitional metals and whose toxicology is unknown. Towards this goal a set of ENMs to be studied will be identified with input by federal partners (regulatory agencies) of National Nanotechnology Initiative (NNI). The materials to be used in this solicitation will be produced and characterized by a central infrastructure which will be established. This resource center will also work with investigators of the research projects and develop analytical methods for in situ characterization of ENMs as the program evolves.

The second goal of the program is to develop a comprehensive toxicological profile for these ENMs surveying a wide range of systems reflecting more physiologically relevant models. These projects will be solicited to cover a wide range of systems including integrated in vitro and in vivo studies and a wide range of factors influencing susceptibility. In this component of the program ENM-biological interactions will be investigated focusing on route of entry (inhalation, dermal, oral and ocular) and both acute and chronic effects. Where appropriate, efforts utilizing an integrated high throughput system and in silico approaches will be sought. The animal studies using ENMs investigated by the NCNHIR consortium for which a clear toxicity profile is established will be targeted to understanding the underlying molecular and pathological mechanisms using relevant exposure methods to understand chronic effects. Research projects that aim to explore potential common mechanisms of action across classes of ENMs and properties are also encouraged. Studies focused on validating the relevance and specificity of acute response pathways (inflammation, fibrogenic) in sub-chronic and chronic exposures to identify potential biomarkers of response will also be encouraged.

As in the past ENM characterization and toxicity data generated from the current funding efforts will be deposited in the CEBS database and will be made accessible to investigators performing in silico and modeling studies.

Mechanism and Justification

This funding opportunity will utilize U24 and U01 mechanisms to support two different components of the program. The materials core and resources center will be established with U24 Cooperative Research Resource mechanism. This resource will design, procure, characterize, and supply defined ENMs to research program investigators. Along with intellectual and scientific leadership in ENM characterization, this center will also provide logistical and administrative support for steering committee and grantee meetings.

The second component of this program is to support basic research to investigate ENMs-biological interactions at molecular, cellular, and organ system scale using state of the art research approaches and physiologically relevant model systems. This will use U01 cooperative agreement mechanism. The investigators will propose an independent research plan to investigate ENMs-biological interactions guided by physicochemical properties to identify molecular and biochemical pathways involved in their toxicity mechanisms using ENMs provided by the ENMs core and coordinating center. The investigators have to demonstrate their research focus and expertise that will contribute to comprehensive understanding of the toxicity profile(s) for ENMs. This program will be designed as an independent research effort with opportunities to support potential collaborative research among investigators throughout the funding period.

A consortium will be formed with the U24 and U01 investigators to promote collaborative research across the program and also to facilitate exchange of expertise, tools and assays among members of the consortium. The steering committee established for the consortium will meet twice a year for exchange of research information and one of these meetings will be a face to face meeting.