Suggested Research Topics for Superfund Basic Research and Training (P42)

This document contains suggested research topics for the Superfund Basic Research and Training (P42) RFA ES-08-005 (http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-08-005.html). These examples are meant to stimulate thinking by illustrating interdisciplinary linkages between scientific disciplines, and, ultimately, how this knowledge enhances public and environmental health. These examples are not intended to be exhaustive, and investigators may study these and many other topics that meet the objectives of the RFA.

Specific Research Needs

There are some specific research needs and new directions within the Program that applicants may wish to consider. These include:

- the study of asbestos (and related mineral fibers or elongated mineral particles) including determinants of fiber toxicity; mutagenicity; fiber dosimetric and its relation to adverse health effects (including autoimmune and cardiovascular diseases); toxicological effects on multiple organ systems; effect of variable levels of exposure (low dose effects); early life exposures - children's exposure to asbestos and susceptibility factors; fiber mechanisms leading to disease; and biomarkers of exposure and disease
- the study of contaminated sediments including development, demonstration, and validation of technologies or methods to monitor the effectiveness of contaminated sediment remediation in reducing contaminant exposures or adverse biologic effects to receptors of concern at Superfund sites
- the application of "green technology" to current remediation practices to improve energy-efficiency and reduce waste generation, thereby increasing the usability and sustainability of otherwise effective remediation technologies
- the study of the mechanisms and health consequences of exposure to trichloroethylene (TCE) and the development of remediation strategies to mitigate exposure
- the optimization of sequential, compatible remediation strategies for different phases of a clean-up process, also known as "combined remedies" or "treatment train," to maximize the degradation/removal of hazardous substances at complex sites
- the investigation of effects of multiple stressors (radionuclide and chemical contaminants) on humans or biota in order to identify patterns of synergism, antagonism, or cumulative effects
- the development and application of methods to assess processes leading to vapor intrusion and resultant potential health effects
- the incorporation of high throughput screening methods to develop detailed dose-response studies leading to identification and validation of sensitive biomarkers of biological response anchored to a phenotypic characteristic
- the development and application of bioengineered devices to study the exposure – response – disease paradigm in living cells and tissues

Broad Research Themes

In addition to the specific research needs listed above, examples of broad scientific themes relevant to the SBRP are provided. These examples are meant to stimulate the thinking of potential applicants by illustrating interdisciplinary linkages between scientific disciplines, and, ultimately, how this knowledge enhances public and environmental health. These examples are not intended to be exhaustive.

Mechanistically-based Biomedical Research. Understanding the mechanisms whereby toxicants induce adverse human health effects is central to the SBRP. It is believed that environmental factors contribute to the etiology of most human diseases/dysfunctions (e.g., reproductive, immune competence, pulmonary/cardiovascular, cancer, neurodevelopment, neurobehavioral, congenital defects, renal, etc.). Therefore, the SBRP seeks to support mechanistic research that includes laboratory-based and population-based studies for unraveling critical biological pathways that contribute to disease when perturbed by environmental contaminants. Research should focus on environmentally related diseases and pathways of toxicological significance in the exposure-disease paradigm. Examples include but are not limited to the following:

- dissecting the molecular, genetic and biochemical events that describe the normal physiological processes that contribute to good health and the roles hazardous substances play in its disruption by studying these issues at multiple system levels, from in vitro cell, tissue or organ culture, to non-mammalian model organisms to whole animals (including genetically manipulated), and to humans
- using high throughput cell-based assays ("omics techniques") to create mechanistically based toxicity profiles for hazardous substances in order to assess risk
- employing integrative or systems biology approaches to study the effects of environmentally relevant levels of hazardous substances on the dynamic nature of biological systems in order to understand cellular homeostasis; to appraise "biological noise"; and to identify biologically relevant events that lead to disease and dysfunction
- incorporating bioengineering and synthetic biology to study the regulation, control and modulation of biological processes by small molecules and environmental chemicals
- developing and validating mathematical and computational approaches for physiologically-based mechanistic models for predictive toxicology that incorporate high data content information (e.g., the virtual cell)
- integrate knowledge derived from basic mechanistic research by identifying, developing and validating biomarkers – key molecular or cellular events that link specific environmental exposures to health outcomes - in population, clinical and ecological-based studies
- developing biomarkers as prognostic indicators of human diseases, as well as therapeutic efficacy
- developing novel diagnostic or pre-clinical markers of exposure and biological responses
- the study of the interplay between exposure and epigenetics, genetic variability (single nucleotide polymorphism or "SNPs"), somatic mutations on influencing the biological processes
- applying bioengineering principles to develop therapeutic approaches to mitigate biological consequences of chemical exposures
- developing biologically-based risk models that incorporate mechanistic data (see Risk Assessment section)

Susceptibility and Predisposition Research. A critical confounding factor underlying the physiological consequences of exposure to hazardous substances is the genetic variability inherent in the population. This variability can lead to sub-populations with unique genetic characteristics that enhance their sensitivity to environmental contaminants or other external insults. The Program recognizes the importance of identifying susceptible populations in order to develop strategies to reduce their burden of environmentally-influenced diseases. It is encouraged that collaborative efforts between biologists, epidemiologists, statisticians, systems engineers, and computer scientists be considered in order to integrate the available information from animal and human studies in such a manner that would inform the risk assessment process. Examples include but are not limited to the following:

- clarifying the contribution of genetic and environmental variables in the risk of developing disease by studying the interplay between exposure and intrinsic factors (e.g., genetic polymorphisms, haplotypes, epigenetic factors, gender and age) and host factors (e.g., nutrition, co-morbid disease/conditions, lifestyle habits; and timing of exposure)
- characterizing altered cellular functions (e.g., metabolic capacity, repair of DNA damage, cell proliferation and apoptosis) critical to modifying susceptibility and predisposition to disease
- adapting molecular, genetic and/or phenotypic approaches into population-based studies to enhance the power to observe associations between exposure and health, or cause and effect relationships
- integrating the factors affecting host susceptibility and resistance into mechanistically-based risk assessment models to identify vulnerable populations
- developing new biostatistical approaches and mathematical algorithms to understand gene-environment, gene-gene or multi-gene-environment interactions
- using of comparative genomics and toxicokinetic approaches to study functional consequences of single nucleotide polymorphisms (SNPs)

Exposure Assessment Research. *A priori*, an environmentally-influenced disease implies that exposure has occurred within some temporal, spatial framework in relation to the development of disease. Unfortunately, exposure is one of the most difficult parameters to measure due, in part, to the lack of precision in the methods to integrate exposure over time, the inability to characterize the attributable risk from multiple exposures experienced over one's lifetime and the lack of statistical and computational approaches to measure complex gene-environment interactions. Because exposure assessment is so integral to decisions related to protecting human health and ecosystems, understanding the complexities that impact exposure is an important research focus for the SBRP. Exposure assessment within the context of the SBRP falls within three interconnected research domains, (a) site characterization, (b) bioavailability and (c) accurate body burden and response measurements. These are further discussed below.

a) *Site Characterization:* The ability to predict the risk of exposure to contaminants at hazardous waste is dependent upon understanding the physical, chemical and geological characteristics of the site. Therefore, site characterization is an integral component of the exposure assessment paradigm. The SBRP seeks to support research that improves site characterization so that the knowledge gained can be incorporated into the exposure assessment paradigm. Examples of research topics include:

- develop advanced technologies that allow for real-time, on site monitoring such as nanotechnology–based sensors and probes, biosensors, new imaging modalities, self-contained miniaturized toxicity-screening kits and miniaturized analytical probes and data analysis tools
- integrate the site environmental data within a contextual framework of how contaminants affect nearby populations (human or wildlife) through modeling approaches
- apply new technologies to study the environmental fate and transport of contaminants such as metals or engineered nanomaterials

b) *Bioavailability:* Bioavailability of a contaminant describes the degree to which it is available for transformation, and transport within environmental media (i.e., soil, sediments and surface and groundwater), as well as the degree by which a contaminant eventually is assimilated by organisms. As an integrating principle, bioavailability crosses all scientific disciplines and is an important factor to consider in understanding the fate and transport of hazardous substances; the ability of hazardous substances to be internalized by microbes, wildlife and humans; and the ability once internalized to be available to tissues and organs. Recent technological advances provide new opportunities to study the complex issues surrounding bioavailability. Research approaches that might be considered include:

- employing an array of multiple, molecular-scale techniques over a range of temporal scales in combination with macroscopic approaches and computational modeling to understand biogeochemical properties and processes important to chemical bioavailability to organisms
- applying state-of-the-art analytical techniques, such as synchrotron-based technologies (e.g., X-ray absorption fine structure spectroscopy), to elucidate reaction mechanisms at a small scale
- characterizing at the molecular scale, the chemical and physical forms and distribution of contaminants in soils, sediments and its interactions with biotic and abiotic systems
- developing nano-enabled and micro-scale platforms to assess the bioavailability of contaminants to biota
- developing science-based bioavailability models to provide additional information for risk assessment
- assessing how the bioavailability of one chemical is affected by other chemicals in a mixture (competitive effects, synergistic effects, co-metabolic effects)
- validating assumptions of bioavailability modeling by incorporating field measurements from hazardous waste sites over multiple time or spatial scales
- developing in vitro systems to mimic bioavailability processes in relevant human systems (i.e. gastrointestinal) that account for parameters such as type of diet, fasting status, susceptibility, co-exposures, etc.

c) *Quantifying body burden and response:* The integration of available data from site characterization and bioavailability studies into exposure and risk assessment models provides a means to predict

potential exposure levels in human populations and ecosystems. The validation of these models requires the development and application of new methods and technologies that can measure the extent of exposure in disparate populations. Many approaches are available that have the requisite sensitivity and specificity to detect current exposures, or measure contaminants that have a long half-life in biological systems. However, the issues of past exposures and exposure to mixtures are still intractable problems. Hence, SBRP seeks research that accounts for concurrent or sequential routes of exposure to a large number of chemicals over varying periods of time. Therefore, some research activities of interest for the SBRP are the following:

- the development of toxicity sensors that rapidly detect and quantify low concentrations of chemicals in cells or tissues
- the development of improved technological methods such as biosensing materials that detect functional changes in only a few cells that might be predictive of exposure and subsequent disease/dysfunction
- the development and application of computational approaches to study temporal and spatial factors associated with timing of exposure, and to detect and assess exposure history within the context of biological relevancy
- the application of advances in miniaturization technology to redefine exposure assessment by improving visualization tools, detection methods (such as biosensors), analytical tools and data mining/data analysis tools that can be used for both environmental media and living biological systems
- the development of mathematical, computational and statistical techniques that integrate exposure and biological information into a holistic model for exposure and risk assessment

Remediation Research. The SBRP supports the application of engineering and microbial sciences as prevention (i.e., remediation) strategies to improve human health by mitigating exposure and reducing toxicity of environmental contaminants at hazardous waste sites. SBRP seeks research that is focused on the scientific principles and underlying processes that drive different remediation technologies as methods to clean-up persistent toxics in groundwater, sediments and soils. Also important is research that focuses on the translation of these basic principles into efficient and cost-effective technologies to reduce the level of contaminants present in the environment. Accordingly, the SBRP encourages a continuum of research that ranges from basic mechanistic research to technology development. Examples include but are not limited to the following:

- the investigation of the mechanistic basis for degradation and sequestration of contaminants by microbial, as well as other biological systems, by assessing the physical, chemical and biological factors that affect movement (or reduction) of site contaminants
- the development of sustainable mining-site remediation
- the incorporation of environmental impact assessments to identify hazards resulting from the use of advanced remediation technologies (such as the use of nanoparticles, bioengineered plants or microorganisms)
- the application of “green technology” to current remediation practices to improve energy-efficiency and reduce waste generation, thereby increasing the usability and sustainability of otherwise effective remediation technologies
- the incorporation of molecular, biochemical cellular and/or engineering tools to understand the basic structural and functional properties of microbial and other populations involved in the bioremediation of hazardous substances
- the development of innovative physical, chemical and biological technologies for the remediation of hazardous substances found at waste sites
- the utilization of visualization and molecular tools to characterize the physical, hydrogeochemical, or biogeochemical properties of sites containing dense non-aqueous phase liquid (DNAPLs) and sites that are typically characterized by extensive, heterogeneous, and persistent source zones of entrapped and pooled organic liquids
- the development of new technologies for in situ remediation of contaminated sediments, soils, and groundwater
- the optimization of combined remedies for clean-up on complex contaminated sites
- the development of innovative approaches to remediate chemical mixtures in environmental media

- the adaptation and application of fate and transport models to predict and assess the influence of chemical mixtures on the efficiency and effectiveness of applied remediation approaches
- the assessment of the health benefits resulting from or related to the clean-up of contaminated sites

Ecological Research. Understanding the ecological impacts resulting from exposure to contaminants found at hazardous waste sites is an important research theme relevant to SBRP and interfaces biology, ecology, microbiology, bioengineering and engineering sciences. An integrated approach is also critical to reducing uncertainty in environmental risk assessments, another important objective of the SBRP. Capitalizing on state-of-the-art methods and genetic approaches that have been primarily applied to human studies provides tools that could be of benefit in advancing the ecological sciences. Accordingly, the SBRP encourages the application of "omics" tools, new sensor technologies and informatics with the goal of enhancing our understanding of ecological succession and biodiversity as a function of exposure to contaminants. Examples include but are not limited to the following:

- the development of molecular, cellular, biochemical and population-level baseline data describing the components that define an ecosystem and how these individual components are affected by hazardous substances
- the establishment of biota dose limits for radionuclides for specific receptor groups including terrestrial animals (e.g., herbivores, omnivores, and carnivores) or aquatic animals (e.g., pelagic fish, bottom feeders and shellfish)
- the identification and validation of genetic markers such as polymorphisms, chromosome inversions, and microsatellites in populations as sensitive indicators of changes in environmental conditions
- the evaluation of the bioavailability/bioconcentration of contaminants in the food web as a basis for predicting bioavailability/bioconcentration in humans
- the development of methods to reduce uncertainty in ecological risk assessment of persistent bioaccumulative toxics (PBTs)
- the assessment of exposure risk (to biota and to humans via the food chain) over time, aging and weathering, at sites where monitored natural attenuation or sequestration is the accepted remediation strategy
- the development of reporter systems and/or biomarkers as integrated measures of uptake and response for ecological assessments of risk
- the development of population level ecological risk assessment models

Mixtures. A critical issue related to hazardous waste sites for remediation or health effects research is that the concentrations at which chemicals occur in the environment are extremely low and exposures are long-term, continual, with simultaneous exposure to multiple chemicals. Whether one considers remediation strategies, exposure to humans or ecosystems, site characterization, bioavailability or the development of risk assessment models, chemical mixtures are an issue of concern. Furthermore, biomedical research, exposure assessments or remediation strategies based on exposures to single substances in isolation are rarely reflected in real-life scenarios. Hence, the SBRP seeks to support research that considers the effects of mixtures. With the continued development and refinement in the available repertoire of advanced tools and approaches, the scientific community may be in a better position to assess the impact of mixtures on all areas of research important to the SBRP. Examples include but are not limited to the following:

- the development of computational toxicology approaches to understand dose/effect relationship in the context of chemical interactions
- the application of high throughput functional assays to define critical mechanistic endpoints associated with potential adverse biological consequences of exposure to chemical mixtures
- the development of new risk assessment methods or frameworks that incorporate chemical mixtures
- the integration of diverse datasets to develop biologically-based predictive models for chemical mixtures
- the application of metagenomics to understand the impact of chemical mixtures on the structure and function of microbial communities involved in site bioremediation

- the assessment of the consequences of interactions such as prior exposure history and vulnerability (i.e., susceptibility), interactions from other stressors of similar/dissimilar mechanisms of action, potentiation or sensitization by chemicals not toxic in themselves, and interaction of chemicals that could lead to synergistic or antagonistic effects

Risk Assessment. The risk assessment process defines exposures of concern and potential threats. Historically, risk assessments are focused on developing models for either human health or ecological health and decisions are made accordingly. However, within the interdisciplinary framework of the SBRP, opportunities to develop integrated models that incorporate both human and ecological effects need to be encouraged in order to assist in making cost-effective and protective decisions. In addition, the translation of the knowledge gained from high data content approaches, which are increasingly being used to obtain mechanistic data, will require the development of a new generation of risk assessment models. These models will need to take into account biological pathways and networks, susceptible populations, low dose effects and mixtures. Therefore, the SBRP is interested in innovative approaches to risk assessment utilizing research focused on the development of: (1) large datasets to be used in model development, (2) tools to integrate diverse datasets and (3) new risk assessment models that incorporate these diverse datasets. Examples include but are not limited to the following:

- the development of robust human and/or ecologically-based genomic, proteomic, metabolomic and functional datasets for model development and validation
- the development of new bioinformatics approaches to bridge data from different disciplines and across scales of biological complexity
- the integration of models that incorporate both human and ecological effects
- the development of multi-dimensional risk models that incorporate exposure data, movement of contaminants within environmental media, bioavailability, uptake by biological receptors (i.e., human or wildlife) and biological responses (e.g., changes in signaling molecules, receptor occupancy, metabolic profiles, etc)
- the development of sophisticated statistical and computational methodologies and improved mathematical algorithms for predictive and computational toxicology to better characterize the lowest dose-response effects that are biologically relevant
- research to assess the uncertainty in risk assessment resulting from differences in species, gender, etc.
- application of human health effects research to risk assessment

Last Update: October 2008