

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Division of Extramural Research and Training

Susceptibility and Population Health Branch

and

The National Toxicology Program

Biomolecular Screening Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

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Concept Clearance

for

The Environmental Health Sciences Centralized KnowledgeBase

In *New Frontiers in Environmental Sciences and Human Health: The 2006-2011 NIEHS Strategic Plan*, seven overarching goals are described that focus on identifying and preventing hazardous exposures associated with an increased risk for disease, with the ultimate goal of improving human health. Included among these goals are

- using environmental exposures to understand and better characterize common, complex diseases;
- developing improved research models for human diseases with the knowledge gained from environmental sciences and human biology, especially in regard to defining signal transduction pathways that influence disease outcomes; and
- developing sensitive markers of environmental exposures, early (pre)clinical biological responses, and genetic susceptibility.

Elucidating the mechanisms by which exposures to environmental stressors result in disease outcomes is a complex, data-intensive process. Numerous interacting factors are involved, including exposure scenarios, chemical/gene interactions, resulting signal transduction changes, and perturbations exceeding homeostatic controls that ultimately lead to overt disease. Research conducted in these areas is published in an ever increasing number of journal articles; even with the best of research teams, it is difficult to keep informed of all the current reported research findings for all of the interdependencies required to synthesis a comprehensive concept relating environmental exposure to disease outcome.

In order to facilitate data collection relating exposure to disease outcome, the NIEHS is proposing to use a contract mechanism to support the maintenance and expansion of a comprehensive, centralized resource (The Environmental Health Sciences Centralized KnowledgeBase or EHS KB). This resource, freely available to the environmental health science community, would contain well annotated data and analysis tools that could be used to inform the design and interpretation of environmental health studies and promote the understanding of underlying mechanisms resulting in environmental diseases. The EHS KB will be populated with information from the peer-reviewed literature relevant to environmental health sciences, integrating chemical exposures, “-omics”-related data (genes and chemical-gene/protein interactions), as well as phenotypic changes, including molecular, biochemical and

Centralized KnowledgeBase for Environmental Health Sciences

physiological changes resulting in disease outcomes. In addition, tools will be available to determine, either directly or inferred (with a confidence estimate) chemical- and gene-disease relationships.

The EHS KB is consistent with the vision outlined in the National Research Council's recent publication *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy*¹, which calls for a new approach to understanding the relationship between exposure and disease that takes advantage of the substantial recent scientific progress in elucidating cellular-response networks, and specifically the mechanisms through which environmental agents perturb biologic pathways and induce disease. Critical to the elucidation of the relationship between "toxicity" pathways and disease is the establishment "of a data-storage, -access, and -management system that would enable broad use of the data being generated to facilitate the understanding of the toxicity pathways and research and knowledge development in later phases." Contents of the database should be accessible to a broad audience and reported in a readily comprehensible fashion. The organization of the database will require both data analysis and exploration; understanding of the relationships between pathways and adverse endpoints will involve a large volume of data analysis. The EHS KB is envisioned as critical tool to achieve this goal, populated with information curated from the scientific literature and presented in a context of chemical-gene/protein-disease outcome interactions and freely available to the scientific community for hypothesis generation and testing.

Purpose and Project Plan:

The objective of this contract is to provide a centralized, publicly available and user-friendly, web-based tool for entry, query, display, and communication of existing environmental health science information, including information related to the etiology of environmentally relevant diseases. EHS KB will also provide access to the existing and emerging relational information describing interactions between exposure, genetic variation, and disease through linkages to existing publicly available databases supported through the National Library of Medicine (NLM) and other groups.

The contract will have five primary tasks:

- 1) Identification, prioritization, and curation of toxic chemicals of concern, their exposures, mechanistic effects, gene-environment interactions, and associations with phenotypic and disease endpoints;
- 2) Creation and maintenance of links to publicly available information resources as they become available in other, complementary fields; a bidirectional link will be required to access the information housed in NIEHS' CEBS (Chemical Effects in Biological Systems) database;
- 3) Development and application of appropriate statistical, analytical, and visualization tools to provide capacity for prediction, analysis, and interpretation of environment-disease networks across studies, chemicals, genes, and diseases;
- 4) Maintenance and expansion of the EHS KB infrastructure; and

¹ NRC Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. P2.
<http://www.nap.edu/catalog/11970.html>

Centralized KnowledgeBase for Environmental Health Sciences

5) Outreach, marketing, and evaluation activities.

Project Management:

This is a joint effort to be supported through NIEHS Division of Extramural Research and Training (DERT) and the National Toxicology Program (NTP). The NIEHS has identified a contract mechanism as the optimal choice in implementing the goals of this effort as it allows for the control necessary to meet the needs of both Divisions in a directed fashion. Through bidirectional links to the EHS KB, NTP will make available to the environmental health science community data residing within CEBS. CEBS, originally developed by NIEHS Division of Intramural Research to house data of interest to toxicologists and environmental health scientists, contains studies of chemical test articles, environmental agents (e.g., ozone and hyperoxia), responses of genetic changes (knockout models), and effects of physical agents (e.g., magnetic fields). Oversight of CEBS has been transferred to NTP and the database is being expanded to include historical toxicological data generated by the NTP, as well as the mid- and high-throughput screening data related to NTP's Tox21 Initiative and the animal models of disease data generated by the NTP host susceptibility program. Screening results produced by NTP's Tox21 effort will be linked through the EHS KB to pathways and the pathways to human diseases; these relationships will be readily accessible by the extramural research community. It is anticipated that this information will be instrumental to the extramural community in generating plausible hypotheses to study novel exposure–disease paradigms that could be pursued through the NIH grant process. Having access to a knowledgebase that computationally evaluates linkages between exposures and disease will provide an unprecedented resource for hypothesis generation exploration in areas of interest to the NIEHS and for the environmental health science community as a whole.

Budget:

\$2,000,000 annually for 5 years (to be cost-shared between NIEHS DERT and NTP)