The United States
Environmental Protection
Agency

Office of Research and
Development
Washington, DC 20460

EPA/600/F-96/003
April 1996

EPA

The United States Environmental Protection Agency

Announces
the Availability of

1996 Grants for Research

on

Endocrine Disruptors
Role of Interindividual Variation in Human Susceptibility to Cancer
Risk-Based Decisions for Contaminated Sediments

APPLICATION SUBMISSION CLOSING DATE: MAY 1, 1996

Introduction

The U.S. Environmental Protection Agency (EPA) invites research grant applications in the following areas of special interest to its mission:

11. Endocrine disruptors

12. Role of Interindividual Variation in Human Susceptibility to Cancer

13. Risk-Based Decisions for Contaminated Sediments

This invitation provides relevant background information, summarizes EPA's interest in the topic areas, and describes the application and review process.

Background

During fiscal year 1995 EPA increased funding for its investigator-initiated research grants program. For fiscal year 1996, EPA anticipates a second increase, subject to the 1996 Federal appropriation process. In December 1995 EPA issued a Request for Applications (RFA) which summarized its interest in 9 programmatic areas. This announcement supplements that RFA and solicits research proposals in 3 additional topical areas. Additional programs involving cooperation with the National Science Foundation and other agencies were announced separately.

EPA Mission and R & D Strategy

The mission of EPA — and its unique role — is the protection of both environmental quality and human health through effective regulations and other policy implementation. Achievement of this mission requires the application of sound science to the assessment of environmental problems and evaluation of possible solutions. A significant challenge is to support both long-term research that anticipates future environmental problems as well as to fill significant gaps in knowledge relevant to meeting current Agency goals. This Request for Applications and the joint solicitations with other agencies are important steps toward ensuring that EPA can provide a sound scientific foundation as the country enters a new generation of environmental protection.

EPA recently reorganized its research programs to focus on the reduction of uncertainty associated with risk assessment and reduction of risks to human health and ecosystems. Through its laboratories and through grants to universities and other not-for-profit institutions, EPA will promote research in both domains, according the highest priority to those areas where risk assessors are most in need of new concepts, methods, and data. At the same time, EPA will foster the development and evaluation of new

risk reduction technologies across a spectrum, from pollution prevention, through end-of-pipe controls, to remediation and monitoring. In all areas, EPA is interested in research that recognizes issues relating to environmental justice, the Agency's effort to achieve equal protection from environmental and health hazards for all people without regard to race, economic status, or culture.

Research Programs of Interest

11. Endocrine Disruptors

Reports have been accumulating that both humans and wildlife species have experienced adverse health consequences resulting from exposure to environmental pollutants that interact with the endocrine system. These pollutants are collectively referred to as "endocrine disruptors," a term broadly defined as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of reproductive and developmental processes." The Agency is concerned with potential effects posed by environmental agents that act as hormones or anti-hormones, as well as chemicals or mixtures which perturb components of the endocrine system through as yet uncharacterized modes of action.

To date, problems have been identified primarily in domestic or wildlife species with high exposure to organochlorine compounds, including DDT and its metabolites, PCBs and dioxins, some organometals, unidentified components of certain types of complex effluents and emissions, and/or to naturally occurring plant estrogens. Whether similar effects are occurring in the general human or wildlife population is unknown. Several reports of declines in the quality and quantity of sperm production in humans over the last four decades and reported increases in incidence of certain cancers (breast, prostate, testicular) have led to speculation about environmental etiologies. Correlational evidence suggests that specific populations of animals such as birds, fish, reptiles, and mammals have been, or currently are being, adversely impacted by exposure to environmental contaminants that may manifest effects through the endocrine system.

The objective of EPA's Endocrine Disruptor research program is to evaluate potential health effects associated with endocrine disruptors and to determine the extent of current exposures. Investigator-initiated grant proposals are sought in four broad areas: (1) human health effects, (2) ecological health effects, (3) human exposure evaluations, (4) ecological exposure evaluations.

Examples of research topics of interest to EPA include:

- Refinement of methods to monitor and characterize exposure of humans and/or wildlife to endocrine disruptors, including aspects such as exposure half-life, speciation, uptake, and phase equilibrium.

- Development and validation of models to estimate exposure to endocrine disruptors from different sources via multiple pathways.

- Development and validation of biomarkers of endocrine disruptor exposure and effect.

- Development and validation of in vitro and short-term in vivo test systems to screen for chemicals with specific mechanisms of action expressed via different endocrine pathways; test systems that are applicable across multiple phylogenetic levels are of particular interest.

- Development of Physiologically-Based Pharmacokinetic (PB-PK), Physiologically-Based Toxicokinetic (PB-TK), and Biologically-Based Dose-Response (BBDR) models that incorporate key species-specific parameters critical to the extrapolation of effects across phyla.

- Refinement and validation of methods and models that relate effects observed at subcellular levels to adverse impacts in individuals (both human and wildlife species) and in wildlife populations.

Funding: Up to $3.5 million is expected to be available in fiscal year 1996 for awards in this program area. The projected award range is $100,000 - $200,000/year for up to 3 years.

12. Role of Interindividual Variation in Human Susceptibility to Cancer

Background

In 1994, the National Academy of Sciences released the report, Science and Judgment in Risk Assessment. This report, which was produced in response to the Clean Air Act Amendments of 1990, evaluated risk assessment methods at EPA and drew a series of conclusions and recommendations. Included was the issue of variation in human susceptibility. On this issue, the report concluded that EPA's consideration of interindividual variability has been limited largely to noncarcinogenic effects, such as asthmatic responses to sulfur dioxide exposure, and suggested that EPA include consideration of interindividual variability in its cancer risk assessments. The NAS recommended that:

(1) Federal agencies should sponsor molecular, epidemiological, and other types of research to examine the causes and extent of interindividual

variability in susceptibility to cancer and the possible correlations between susceptibility and such covariates as age, race, ethnicity, and sex. Results should be used to refine estimates of risks to individuals and the general population.

(2) EPA should increase its efforts to validate or improve the default assumption that humans on average have the same susceptibility as humans in epidemiological studies, the most sensitive animals tested, or both.

The NAS report stated that human beings vary substantially in their inherent susceptibility to carcinogenesis, both in general and in response to any specific stimulus or mechanism. Point estimates of carcinogenic potency of a substance will not apply to all individuals in the population. They further stated that variability affects each step in the carcinogenic process (e.g., carcinogenic uptake and metabolism, DNA damage, DNA repair and misrepair, cell proliferation, tumor progression, and metastasis) and that the variability arises from many independent factors, some inborn and some environmental. NAS stated that it appeared that some of the individual determinants are distributed bimodally or perhaps trimodally in the population (e.g., hypersusceptible people such as those with germ-line mutations in tumor suppressor genes) while other determinants seemed to be distributed more or less continuously and unimodally with either narrow or broad variances (e.g., the kinetics or activities of enzymes that activate or detoxify particular pollutants).

Description

In this RFA, EPA is interested in: (1) the identification of human genetic polymorphisms which can affect carcinogenic risk from environmental agents, (2) the quantitative relationship of these polymorphisms to the risk of cancer from environmental agents, and (3) the distribution of such polymorphisms in the general population. Response to this RFA should address human variation in susceptibility with regard to polymorphisms and a specific chemical carcinogen of concern to the Agency.

Funding: Up to $2.0M is expected to be available in Fiscal Year 1996 for this program area. The projected award range is $100,000 - $200,000/year for up to 3 years.

13. Risk-Based Decisions for Contaminated Sediments

Many persistent chemical contaminants in aquatic ecosystems eventually accumulate in sediments where they may adversely affect the benthic biota, become a source of contamination in the water column, accumulate in biological tissues, and enter pelagic and human food chains. Contaminated sediments now appear to be the main source of toxic contaminants in many bays, lakes, and rivers. For example, of the Great

Lake's 42 Areas of Concern, 33 have degraded water quality problems associated with contaminated sediments. Because of their potential adverse impacts, the long periods of time associated with natural assimilation of many in-place contaminants, and the high costs of mitigation, sediments have become a focus of concern for EPA.

The following areas of research provide the framework for the competition:

Risk-Based Assessments

Hazard Identification

All assessment techniques, either biological or chemical, need validation of their ability to predict impacts on indigenous aquatic communities. When laboratory data and test systems are being used to predict contaminated sediment impacts, there needs to be a strong lab-to-field association. Research is needed to validate these techniques using a risk-based approach. Validation efforts must consider the uncertainty associated with the assessment and the degree of protection offered to the aquatic community.

The effects of contaminants associated with sediments is often manifested through aquatic food chains. Research and mathematical modeling is needed to accurately characterize the transfer of toxic substances from their source to the sediments, from sediments to organisms, and organism to organism.

Dose-Response

Short-term sediment toxicity test methods to examine aquatic life effects using laboratory animals exist. In addition, there are some theoretical models to predict whether certain single chemical concentrations will have an adverse impact on benthic communities. Most contaminated sediments contain mixtures of chemicals; thus, mixture toxicity research and modeling both for organic substances and trace metals are needed to complement single chemical assessments. Further research is needed to expand the number and kind of species being tested.

Exposure Assessment

Knowledge of the fate and bioavailability of toxic substances in sediments is sometimes highly speculative. Additional knowledge is needed on: (1) the fate of toxic substances during resuspension, especially during severe events, and biological, chemical and physical factors controlling resuspension of sediments, (2) the spatial (horizontal and vertical) and temporal extent of sediment contamination, and (3) biogeochemical partitioning between sediments, water, and biota to better predict bioavailability of chemicals believed to have adverse impacts.

Risk Management

Sediment Treatment

Contaminated sediments requiring treatment can result from either sediment management operations (e.g., maintenance dredging) or remediation efforts. The environmental risks associated with these sediments need to be reduced. For example, better methods to predict the extent to which dredging operations resuspend and transport contaminants to less contaminated areas are needed. Research is needed to develop innovative treatment options for sites with large volumes of contaminated sediment (e.g., harbors).

Proposals that address the above mentioned needs are invited. Proposals must relate how the research will facilitate better risk assessments and risk management decisions.

Funding: Approximately $2.0 million is expected to be available for awards under this program area. The projected award range is $100,000 - $200,000/year for up to 3 years.

The Application

Proposed research projects must be designed to advance the state of knowledge in the indicated areas. The Application Kit for Assistance contains detailed instructions on how to prepare your application. The application kit is available at most institutional offices of sponsored research or may be obtained from EPA at:

U.S. Environmental Protection Agency
National Center for Environmental Research and Quality Assurance (8703)
401 M Street SW
Washington DC 20460
Phone: (202) 260-3837
Fax: (202) 260-2039

Each application must contain the following:

A. Application for Federal Assistance (Standard Forms 424 and 424A). These forms must have original signature.

B. A detailed, itemized budget for each year of the proposed project.

C. A budget justification describing the basis for calculating the personnel, fringe benefits, travel, equipment, supplies, contractual support, and other costs identified in the itemized budget.

D. An abstract containing the following information: The project title, the names and affiliations of all investigators, and a summary of the objectives, expected results, and approach described in the proposal. The abstract must not exceed one (1) 8.5 x 11 inch page of single-spaced standard 12 point type with 1 inch margins.

E. A Description of the Project. This description must not exceed fifteen (15) pages. All pages must be consecutively numbered, 8.5 x 11 inch, single-spaced standard 12 point type with 1 inch margins. The description must provide the following information (1-5):

1. Objectives: List objectives of the proposed research and/or the hypotheses being tested during the project.

2. Expected Results or Benefits: Describe the results you expect to achieve during the project and the benefits of success.

3. Approach: Outline the methods, approaches, and techniques that you intend to employ in meeting the objective stated above.

4. General Project Information: Discuss other information relevant to the potential success of the project. This might include facilities, project schedules, proposed management, interactions with other institutions, etc.

5. Quality Assurance: A brief narrative statement (not to exceed two consecutively numbered, 8.5 x 11 inch pages of single-spaced standard 12 point type with 1 inch margins) describing the quality assurance procedures proposed for the project (see section of this RFA on quality assurance).

F. Any important attachments, appendices, references, or other information may be included but must not exceed five (5) pages.

G. The resumes of the principal investigator, and co-workers. Resumes must not exceed two consecutively-numbered, 8.5 x 11 inch pages of single spaced standard 12 point type with 1 inch margins.

H. Standard Form (SF) 5700-48 Procurement System Certification (provided in Application Kit).

I. Standard Form (SF) 5700-49 Debarment and Suspension Certification (provided in Application Kit).

J. A list of key contacts (provided in Application Kit) including authorizing representative, payee, administrative contact, and project manager.

K. Disclosure of Lobbying Activities (provided in Application Kit).

L. Copy of State Clearing House Approval Notification (see Application Kit to determine if applicable).

M. In lieu of the Application Receipt Letter provided in some Application Kits, the applicant must include a blank self-addressed, stamped post card with the application.

The application must contain all of the above, in the order listed.

Sorting Codes

In order to facilitate proper assignment and review of applications, applicants are asked to identify the topic area in which their application is to be considered. Applications must be identified by printing the appropriate Sorting Code (see below) in block 10 of the SF-424.

Endocrine Disruptors	96-NCERQA-11
Role of Interindividual Variation in Human Susceptibility to Cancer	96-NCERQA-12
Risk-Based Decisions for Contaminated Sediments	96-NCERQA-13

The Sorting Code must be placed in Block 10 of SF 424 as shown below:

10.	CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:	○	○	●	○	○	○
TITLE:	96-NCERQA-X						

The Sorting Code must also be included in the address on the package that is submitted to EPA (see next section on how to apply).

How to Apply

To be considered, the original and ten (10) copies of the fully developed research grant application and five (5) additional copies of the abstract (fifteen in all), must be received (postmarked if sent by U.S. Mail) by the National Center for Environmental Research and Quality Assurance no later than 4:00 P.M. EST on the closing date assigned to these topic areas, May 1, 1996.

The application and abstracts must be prepared in accordance with instructions in the Application Kit for Federal Assistance and this RFA. Informal, incomplete, or unsigned proposals will not be considered. Completed applications should be sent via regular or express mail to:

U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Research and Quality Assurance (8703)
Sorting Code: 96-NCERQA-X [X=11, 12, or 13]
Room M2426
401 M Street SW
Washington DC 20460

Applications sent via express mail should have the following telephone number listed on the express mail label: (202) 260-3837

Quality Assurance

Data sets resulting from EPA-funded environmental research often are used by government officials when establishing standards or when making other policy decisions. Explicit indicators of data quality are essential for determining whether a particular data set is appropriate for use in a specific context. To that end, EPA regulations require that grant-funded projects address quality assurance.

The application must include a quality assurance narrative statement, not to exceed two pages, which for each item listed below, either presents the required information or provides justification as to why the item does not apply to the proposed research.

- The intended use of the data and the associated acceptance criteria for data quality (i.e., precision, accuracy, representativeness, completeness, and comparability).

- Project requirements for precision, accuracy, representativeness, completeness, and comparability, and how these will be determined.

- Procedures for selection of samples or sampling sites, and collection or preparation of samples.

- Procedures for sample handling, identification, preservation, transportation, and storage.

- Description of measurement methods or test procedures, with a statement of performance characteristics if methods are non-standard.

- Standard quality assurance/quality control procedures (e.g., American Society for Testing Materials, American Public Health Association, etc.) to be followed. Non-standard procedures must be documented.

- Data reduction and reporting procedures, including description of statistical analyses to be used.

Guidelines and Limitations

Subcontracts for research to be conducted under the grant that exceed 40% of the total direct cost of the grant for each year in which the subcontract is awarded will be subject to special review.

Additional Requirements

Researchers will be expected to participate in an annual All-Investigator's Meeting with EPA researchers and other grantees and cooperators to report on research activities and to discuss issues of mutual interest.

Eligibility

Academic and not-for-profit institutions located in the U.S., and state or local governments are eligible under all existing authorizations. Profit-making firms are eligible only under certain laws, and then under restrictive conditions, including the absence of any profit from the project. Federal agencies and federal employees are not eligible to participate in this program. Potential applicants who are uncertain of their eligibility should contact EPA's Grants Operations Branch at (202) 260-9266.

Review and Selection

All grant applications are initially reviewed by EPA to determine their legal and administrative acceptability and responsiveness to this solicitation. Acceptable applications are then reviewed by an appropriate technical peer review group. This review is designed to evaluate and rank each proposal according to its scientific merit. Each review group is composed primarily of non-EPA scientists, engineers, social scientists, and/or economists who are experts in their respective disciplines. All reviewers are proficient in the technical areas that they are reviewing. The reviewers use the following criteria in their reviews:

- quality of the research plan (including theoretical and/or experimental design, originality, and creativity);
- qualifications of the principal investigator and staff, including knowledge of relevant subject areas;
- potential contribution of the research to advancing scientific knowledge in the environmental area;
- availability and adequacy of facilities and equipment; and
- budget justification — justification for equipment will receive special attention;
- responsiveness to solicitation objectives.

Funding decisions are the sole responsibility of EPA. Grants are selected on the basis of technical merit, relevancy to the research priorities outlined, program balance, and budget.

EPA anticipates making awards from this RFA by September 1996.

Proprietary Information

By submitting an application in response to this solicitation, the applicant grants EPA permission to share the application with technical reviewers both within and outside of the Agency. Applications containing proprietary or other types of confidential information will be immediately returned to the applicant without review.

Funding Mechanism

The funding mechanism for all awards issued under this solicitation will consist of a grant between EPA and the recipient. In accordance with Public Law 95-224, a grant is used to accomplish a public purpose of support or stimulation authorized by Federal statute rather than acquisition for the direct benefit of the Agency. In using a grant instrument, EPA anticipates that there will be no substantial involvement during the course of the grant between the recipient and the Agency.

Contacts

Additional general information on the grants program may be obtained by contacting:

U.S. Environmental Protection Agency
National Center for Environmental Research and Quality Assurance (8703)
401 M Street SW
Washington DC 20460
Phone: (202) 260-3837
Fax: (202) 260-2039

Applicants with technical questions may contact the appropriate individual identified below.

Contacts for Research Topics of Interest

Endocrine Disruptors

- Robert Menzer 202-260-5779
  menzer.robert@epamail.epa.gov

Role of Interindividual Variation in Human Susceptibility to Cancer

- David Reese 202-260-7342
  reese.david@epamail.epa.gov

Risk-Based Decisions for Contaminated Sediments

- David Reese 202-260-7342
  reese.david@epamail.epa.gov

*U.S. Government Printing Office: 1996 - 751-819