

ARSENIC HEALTH EFFECTS RESEARCH

BACKGROUND

The Environmental Protection Agency (EPA), American Water Works Association Research Foundation (AWWARF), and Association of California Water Agencies (ACWA) are jointly requesting grant and contract applications for research on human health effects associated with low level arsenic exposure via ingestion. The Safe Drinking Water Act Amendments of 1996 directed EPA to develop a comprehensive study plan to reduce the uncertainty in assessing health risks associated with exposure to low levels of arsenic. This request for applications (RFA) will provide some of the early research in support of that plan. Congress also directed EPA to propose a revised arsenic standard by January 1, 2001. When issuing National Primary Drinking Water Regulations, Section 1412(b)(3)(A) of the amendments specify that EPA use the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices.

While there are several possible approaches to improving our understanding of arsenic risks, additional data on the baseline exposure, metabolism of arsenic, mechanisms of arsenic carcinogenesis, and early endpoints of arsenic toxicity in human populations are key research priorities. Exposure data on arsenic from dietary sources other than drinking water will help determine the relative significance of arsenic exposures from drinking water and aid in comparisons of current United States (U.S.) arsenic exposures with exposure levels at which human health effects have been observed. Understanding the mechanism of arsenic carcinogenesis, the variability in arsenic metabolism, and early endpoints of arsenic toxicity may ultimately contribute to determining the shape and slope of dose-response curves, including possible linear or nonlinear effects, and reduce the uncertainty in these curves.

Risk management policies for arsenic in the U.S. have changed with increases in knowledge, as evidenced by EPA's divergent guidance for arsenic under the Safe Drinking Water Act and the Clean Water Act. EPA's drinking water standard, or maximum contaminant level (MCL), of 50 µg/l was developed by the Public Health Service in the mid-1940s. In 1980, EPA established a human health water quality criterion for arsenic at 0.018 µg/l for a one in a million (10^{-6}) cancer risk level under the Clean Water Act. Researchers have since developed a substantial amount of data (toxicologic, epidemiologic, and some mechanistic) about the potential human health effects of arsenic following ingestion.

The EPA's 1988 Special Report on Ingested Inorganic Arsenic: Skin Cancer; Nutritional Essentiality (EPA/625/3-87/013) developed a risk assessment for arsenic based on existing data. This document has undergone peer review, inside and outside the Agency. The risk assessment addressed the strengths and weaknesses of the database and identified several areas of uncertainty. Given existing human exposure to low levels of arsenic in the U.S., the high costs associated with reducing the level of arsenic in drinking water systems, and specific legislative requirements, additional research on arsenic is warranted. As part of this effort, this RFA encompasses several areas where additional research may contribute to a fuller understanding of arsenic's risk and to reduction of uncertainties in the risk assessment.

PRINCIPAL AREAS OF INTEREST IN THIS RFA

The four research areas presented below provide opportunities for exposure, human health, tissue, and animal research. Proposals may address one or more than one research area, and supplements to existing human studies are encouraged. Large-scale epidemiology studies of arsenic's chronic health effects are not included under this RFA due to limited available funds. Ongoing epidemiological feasibility studies being funded by EPA and AWWARF, among others, may lay the groundwork for future epidemiological investigations. However, proposals for studies with human participants are appropriate under each of the four research areas.

1. Contribution of Arsenic From Dietary Sources

In order to understand the possible health impacts of exposure to arsenic from drinking water ingestion, it is important to know the relative contributions from different media. Since air exposures typically are low, the amount and variability of exposures from food and beverages need to be quantified for various populations, taking into account demographic variabilities. This could be done by using techniques such as market-basket surveys and duplicate diet surveys for U.S. populations. At a minimum, such surveys need to distinguish between inorganic and organic arsenic. In conducting these studies it is also desirable to address bioavailability of arsenic absorption from ingested foods. Information on specific food sources should be determined in addition to total dietary contributions.

2. Arsenic Metabolism

Further characterization of arsenic metabolism in humans would strengthen the arsenic risk assessment. Two distinct, but related, needs are improved characterization of dose dependency in arsenic metabolism and characterization of the interindividual and intraindividual variability in human populations. Metabolic indicators and biomarkers of exposure (such as urinary arsenic measurements) may fluctuate substantially from day to day. Accordingly, a quantitative evaluation of the impact of such fluctuations is key to the interpretation of the biomarker data. For these studies to be interpretable, total exposures from various sources should be considered. Studies of the dose response for arsenic metabolism should examine exposure levels ranging from those received by high-dose groups to the lower levels typical of the U.S. population. Included in this area are studies to improve mass balance data for differing chemical forms of arsenic at various doses. With regards to population variability, studies could investigate variations in metabolism or other factors affecting human susceptibility to arsenic that might be associated with exposure, genetic factors, age, sex, nutritional status, etc.

3. Mechanisms of Arsenic Carcinogenesis

A mechanistic understanding of carcinogenesis would facilitate a fuller qualitative and quantitative understanding of cancer risks. In order to understand how arsenic causes cancer, it is necessary to have model biological systems relevant to humans. Data collected at the molecular, cellular, tissue, animal, and epidemiological level can contribute to an understanding of arsenic carcinogenesis. As scientific information about arsenic risk is based on direct observations of human tumors, it is particularly important for mechanistic research to establish how findings in

any model biological system would relate to human carcinogenesis. Understanding of mechanisms may also be useful in the identification of biomarkers for developing dose-response relationships and for detecting human populations sensitive to arsenic.

4. Early Endpoints of Arsenic Effects in Humans

Studies to characterize early endpoints of arsenic-associated pathology would enhance knowledge of the effects of low doses of arsenic in human populations. These studies should consider dose-response patterns, with an emphasis on effects at low doses. Specific effects that could be addressed in prevalence studies include hyperkeratosis, neurological effects, and other endpoints. Investigators should state the statistical power anticipated by their proposed research given the number of people surveyed and endpoints investigated. Total exposure to relevant chemical forms of arsenic is also an important factor in study design.

FUNDING

Funding for this joint solicitation is provided by the U.S. EPA, AWWARF, and ACWA for a total of approximately \$3 million. Any proposal submitted will be considered for an EPA grant or AWWARF contract, unless the proposal stipulates otherwise. EPA will fund approximately \$2 million worth of grants, and AWWARF/ACWA will fund approximately \$1 million worth of contracts. Recipients will be funded entirely by one agency or the other. It is expected that three to six applications, each with a project period of up to 3 years, will be funded under this joint solicitation.

ELIGIBILITY

Academic and not-for-profit institutions located in the U.S. and state or local governments are eligible under all existing EPA authorizations. Profit-making firms are not eligible to receive assistance from EPA under this program, but are eligible to receive funding from AWWARF. Researchers in federal agencies other than EPA may submit applications, but federal employees may not request salary reimbursement. Federal employees may cooperate or collaborate with other eligible applicants within the limits imposed by applicable legislation and regulations.

Researchers who are late in any ongoing AWWARF-sponsored studies without an approved no-cost extension will not be eligible for funding by AWWARF; however, they may be eligible for funding by EPA. Potential applicants who are uncertain of their eligibility for an AWWARF contract should contact their AWWARF project manager.

AWWARF and EPA have a policy of nondiscrimination and abide by all laws, rules, and executive orders governing equal employment opportunity. All entities receiving funding under this solicitation will be required to agree not to discriminate on the basis of age, sex, race, religion, color, national origin, disability or veteran status. AWWARF expects its contractors to be equal opportunity employers who accept the goal of having a workforce that generally reflects the minority composition of the community in which it is located. It is the policy of AWWARF to encourage proposals from qualified minority owned or directed institutions.

STANDARD INSTRUCTIONS FOR SUBMITTING AN APPLICATION

This section contains a set of special instructions related to how applicants should apply for this EPA/AWWARF/ACWA joint request for applications. Proposed projects must be for research designed to advance the state of knowledge in the research areas described in this solicitation.

Sorting Codes

In order to facilitate proper assignment and review of applications, each applicant is asked to identify the topic area in which their application is to be considered. **The sorting code for this program is 97-NCERQA-14.** At various places within the application, applicants are asked to identify this topic area by using the Sorting Code. The Sorting Code must be placed at the top of the abstract (as shown in the abstract format), in Box 10 of Standard Form 424 (as described in the section on SF424), and should also be included in the address on the package that is sent to EPA (see the section on how to apply).

Letter of Intent

A letter indicating the intention of the applicant to submit an application should be sent by April 18, 1997 via regular or express mail to:

U.S. Environmental Protection Agency
Peer Review Research Division (8703)
Sorting Code: 97-NCERQA-14
Room 2411
401 M Street, SW
Washington, D.C. 20460
Phone: (202) 260-0563 (for express mail applications)

The letter of intent to submit an application should include a tentative title of the research project, names and affiliations of all principal investigators and important coworkers, and a brief abstract of the proposed project. This information will assist us in selecting peer reviewers. Applications will be accepted from investigators who do not submit a letter of intent.

The Application

The initial application is made through the submission of the materials described below. **It is essential that the application contain all the information requested and be submitted in the formats described.** If it is not, the application may be rejected on administrative grounds. If an application is considered for an award (i.e., after external peer review and internal review), additional forms and other information will be requested by the Project Officer. **The application should not be bound or stapled in any way.** The Application contains the following:

A. Standard Form 424: The applicant must complete Standard Form 424 (see attached form and instructions). This form will act as a cover sheet for the application and **should be its first page.** Instructions for completion of the SF424 are included with the form. The form must

contain the original signature of an authorized representative of the applying institution. Please note that both the Principal Investigator and an administrative contact should be identified in Section 5 of the SF424.

B. Key Contacts: The applicant must complete the Key Contacts Form (attached) as the **second page** of the submitted application.

C. Abstract: The abstract is a very important document. Prior to attending the peer review meetings, some of the reviewers may read only the abstract. Therefore, it is critical that the abstract accurately describe the research being proposed and convey all the essential elements of the research. Also, in the event of an award, the abstracts will form the basis for an Annual Report of awards made under this program. The abstract must be limited to one page and should include the following information:

1. **Sorting Code:** Use the code that corresponds to this topic: **97-NCERQA-14.**
2. **Title:** Use the exact title as it appears in the rest of the application.
3. **Investigators:** List the names and affiliations of each investigator who will significantly contribute to the project. Start with the Principal Investigator.
4. **Project Summary:** This should summarize: (a) the **objectives** of the study (including any hypotheses that will be tested), (b) the experimental **approach** to be used (which should give an accurate description of the project as described in the proposal), (c) the **expected results** of the project and how it addresses the research needs identified in the solicitation, and (d) the estimated improvement in risk assessment or risk management that will result from successful completion of the work proposed.

D. Project Description: This description must not exceed fifteen (15) consecutively numbered (center bottom), 8.5x11 inch pages of single-spaced standard 12-point type with 1-inch margins. The description must provide the following information:

1. **Objectives:** List the objectives of the proposed research and the hypotheses being tested during the project and briefly state why the intended research is important. This section can also include any background or introductory information that would help explain the objectives of the study (one to two pages recommended).
2. **Approach:** Outline the methods, approaches, and techniques that you intend to employ in meeting the objective stated above (five to 10 pages recommended).
3. **Expected Results or Benefits:** Describe the results you expect to achieve during the project and the benefits of success as they relate to the topic under which the proposal was submitted. This section should also discuss the utility of the research project proposed for addressing the environmental problems described in the solicitation (one to two pages recommended).

4. **General Project Information:** Discuss other information relevant to the potential success of the project. This should include facilities, personnel, project schedules, proposed management, interactions with other institutions, etc. (one to two pages recommended).

5. **Important Attachments:** Appendices and/or other information may be included but must remain within the 15-page limit. References are in addition to the 15 pages.

E. Resumes: The resumes of all principal investigators and important co-workers should be presented. Resumes must not exceed two consecutively numbered (bottom center), 8.5x11 inch pages of single-spaced standard 12-point type with 1-inch margins for each individual.

F. Current and Pending Support: The applicant must identify any current and pending financial resources that are intended to support research related to that included in the proposal or which would consume the time of principal investigators. This should be done by completing the appropriate form (see attachment) for each investigator and other senior personnel involved in the proposal. Failure to provide this information may delay consideration of your proposal.

G. Budget: The applicant must present a detailed, itemized budget for the entire project. This budget must be in the format provided (see attachment) and not exceed two consecutively numbered (bottom center), 8.5x11 inch pages with 1-inch margins. If desired, a brief statement concerning cost sharing can be added to the budget justification. Please note that institutional cost sharing is not required and, therefore, does not have to be included in the budget table. Note: AWWARF does not generally provide funding for equipment purchases.

H. Budget Justification: This section should describe the basis for calculating the *personnel*, *fringe benefits*, *travel*, *equipment*, *supplies*, *contractual support*, and *other* costs identified in the itemized budget and explain the basis for their calculation (special attention should be given to explaining the *travel*, *equipment*, and *other* categories). This should also include an explanation of how the indirect costs were calculated. This justification should not exceed two consecutively numbered (bottom center), 8.5x11 inch pages of single-spaced standard 12-point type with 1-inch margins.

I. Schedule: This description should not exceed two pages. Estimate the duration of the project, giving the proposed starting and completion dates, milestone dates, and explain the importance of any specific starting date. Estimate the amount of time needed to complete each task.

J. Quality Assurance Narrative Statement: For awards that involve environmentally related measurements or data generation, a quality system that complies with the requirements of ANSI/ASQC E4, "Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs," must be in place. This statement should not exceed two consecutively numbered, 8.5x11 inch pages of single-spaced standard 12-point type with 1-inch margins. This is in addition to the 15 pages permitted for the Project Description. The Quality Assurance Narrative Statement should, for each item listed below, either present the required information or provide a justification as to why the item does not apply to the proposed research.

1. The data collection activities to be performed or the hypothesis to be tested (reference may be made to the specific page and paragraph number in the application where this information may be found); acceptance criteria for data quality (precision, accuracy, representativeness, completeness, comparability).
2. The study design including sample type and location requirements and any statistical analyses that were used to estimate the types and numbers of samples required.
3. The procedures for the handling and custody of samples, including sample identification, preservation, transportation, and storage.
4. The methods that will be used to analyze samples collected, including a description of the sampling and/or analytical instruments required.
5. The procedures that will be used in the calibration and performance evaluation of the sampling and analytical methods used during the project.
6. The procedures for data reduction and reporting, including description of statistical analyses to be used.
7. The intended use of the data as they relate to the study objectives or hypotheses.
8. The quantitative and/or qualitative procedures that will be used to evaluate the success of the project.
9. Any plans for peer or other reviews of the study design or analytical methods prior to data collection.

ANSI/ASQC E4, "Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs" is available for purchase from the American Society for Quality Control, phone 1-800-248-1946, item T55. Only in exceptional circumstances should it be necessary to consult this document.

K. Postcard: The Applicant must include with the application a self-addressed, stamped 3x5 inch post card. This will be used to acknowledge receipt of the application and to transmit other important information to the applicant.

How to Apply

The original and ten (10) copies of the fully developed application and five (5) additional copies of the abstract (15 in all), must be received by NCERQA no later than **4:00 P.M. EST**, May 16, 1997.

The application and abstract must be prepared in accordance with these instructions. Informal, incomplete, or unsigned proposals will not be considered. The application should not be bound or stapled in any way. The original and copies of the application should be secured with paper or

binder clips. Completed applications should be sent via regular or express mail to:

U.S. Environmental Protection Agency
Peer Review Research Division (8703)
Sorting Code: 97-NCERQA-14
Room 2411
401 M Street, SW
Washington, D.C. 20460
Phone: (202) 260-0563 (for express mail applications)

Guidelines, Limitations, and Additional Requirements

If you wish to submit more than one application on this topic, you must ensure that the research proposed is significantly different from any other you submitted to this solicitation or from any other grant/contract you are currently receiving from any other source.

Awardees of this joint solicitation will be expected to budget for and participate in an annual All-Investigators Meeting with EPA grantees, AWWARF contractors, and other scientists to report on research activities and to discuss issues of mutual interest.

Review and Selection

All applications are initially reviewed by EPA to determine their legal and administrative acceptability. Acceptable applications are then reviewed by an appropriate technical peer review group. This review is designed to evaluate each proposal according to its scientific merit. Each review group is composed of non-EPA scientists who are experts in their respective disciplines and are proficient in the technical areas they are reviewing. The reviewers use the following criteria to help them in their reviews:

1. **Technical Merit.** The originality and creativity of the proposed research, the potential contribution the proposed research could make to advance scientific knowledge about the human health effects of arsenic at low levels in drinking water, the appropriateness and adequacy of the research methods proposed, and the appropriateness and adequacy of the Quality Assurance Narrative Statement will be assessed. Is the research approach practical and technically defensible? Is the proposal well prepared with supportive information that is self explanatory and understandable? Will the research contribute to improving the scientific knowledge base for the risk assessment of arsenic?
2. **Investigators.** The qualifications of the principal investigator(s) and other staff, including knowledge of pertinent literature, experience, and publication records as well as the probability that the proposed research will be successfully completed will be assessed. Will all key personnel contribute a significant time commitment to the project?
3. **Facilities/Equipment.** The availability and/or adequacy of the facilities and equipment proposed for the project will be assessed. Deficiencies that may interfere with the successful completion of the research will be identified.

4. **Responsiveness.** The responsiveness of the proposal to the research needs set forth in the solicitation will be assessed.

5. **Budget.** The reviewers will be asked to evaluate whether the project can be performed within the time period and with the proposed effort. Although budget information is not used by the reviewers as the basis for their evaluation of scientific merit, the reviewers are asked to provide their view on the appropriateness and/or adequacy of the proposed budget and its implications for the potential success of the proposed research. Input on requested equipment is of particular interest.

All proposal evaluation records will be forwarded for review by staff and named representatives of EPA, AWWARF, and ACWA. Proposals considered for funding will be subject to a relevancy review. The purpose of the relevancy review is to develop a balanced research agenda to advance the understanding of the health effects of arsenic at low levels in drinking water. The following criteria will further define which proposals should be selected for funding:

- (1) Which studies have the greatest potential to strengthen the scientific basis for risk assessment/risk management of arsenic in drinking water?
- (2) Which studies have the greatest potential to provide a focus for future arsenic health effects research?
- (3) Do any of these studies duplicate ongoing research?

A summary statement of the scientific review of the proposal will be provided to each applicant. Funding decisions are the sole responsibility of the organization funding the project. Grants and contracts are selected on the basis of technical merit, relevancy to the research priorities outlined, program balance, and budget.

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 returned to the applicant without review.

Funding Mechanism

The funding mechanism for all awards issued under this solicitation will consist of grants from EPA and contracts from AWWARF and depends on the availability of funds. In accordance with Public Law 95-224, the primary purpose of a grant is to accomplish a public purpose of support or stimulation authorized by Federal statute rather than acquisition for the direct benefit of the Agency. In issuing a grant agreement, EPA anticipates that there will be no substantial EPA involvement in the design, implementation, or conduct of the research funded by the grant. However, EPA will monitor research progress, based in part on annual reports provided by awardees.

The mission of AWWARF is to "advance the science of water to improve the quality of life."

Contracts with AWWARF are managed by an assigned AWWARF project manager and a volunteer Project Advisory Committee (PAC). PACs are organized by AWWARF for each funded project to provide guidance, review all reports and significant materials, and generally monitor project performance in behalf of AWWARF and the water utility industry. Periodic reports for AWWARF are required every four months. In addition, a final report and intellectual property rights as outlined in the "Standard AWWARF Funding Agreement" are required under all AWWARF contracts. The "Standard AWWARF Funding Agreement" is available on the AWWARF home page at <http://www.awwarf.com>. For general information regarding the "Standard AWWARF Funding Agreement," contact Kathy Garretson at 303-347-6118 or by E-mail at kgarretson@awwarf.com.

Contacts

Additional general information on the grants program, forms used for applications, etc., may be obtained by exploring the EPA Web page at <<http://www.epa.gov/ncerqa>>. EPA does not intend to make mass-mailings of this announcement. Information not available on the Internet may be obtained by contacting:

U.S. Environmental Protection Agency
National Center for Environmental Research
and Quality Assurance (8703)
401 M Street, SW
Washington, D.C. 20460
Phone: 1-800-490-9194

Contacts have been identified for this topic. They will respond to inquiries regarding the solicitation and can respond to any technical questions related to your application.

- Sheila Rosenthal (EPA) 202-260-7334
rosenthal.sheila@epamail.epa.gov
- Ruth Hund (AWWARF) 303-347-6124
rhund@awwarf.com