⊕EPA

Research Plan for Arsenic in Drinking Water

As (III) oxidation As (V)
reduction

Inorganic soluble Arsenic
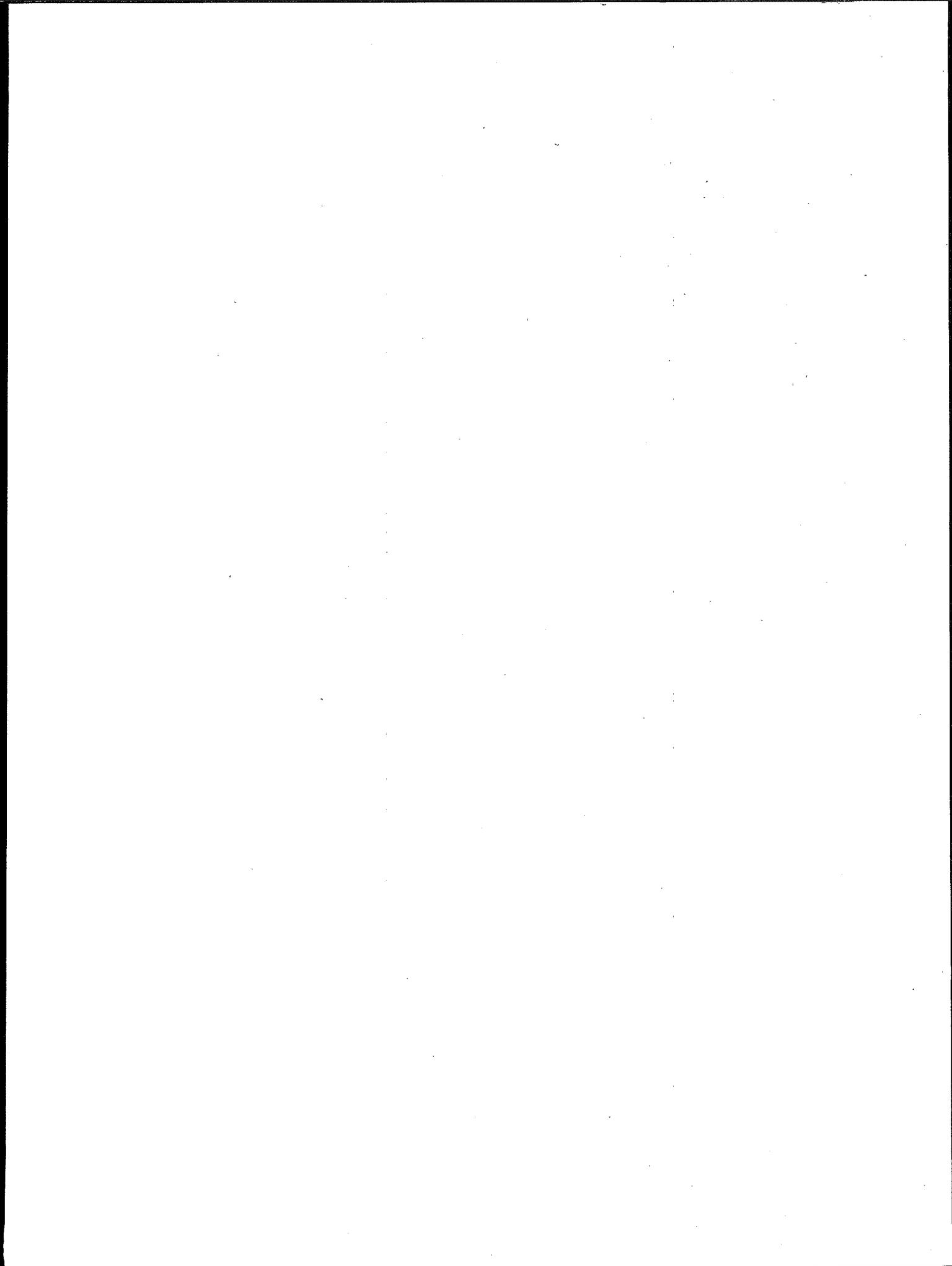
Research Plan for Arsenic in Drinking Water

Notice

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Foreword

The 1996 Strategic Plan for the Office of Research and Development (ORD) sets forth ORD's vision, mission, and long-term research goals. As part of this strategic process, ORD used the risk paradigm to identify EPA's top research priorities for the next several years. The ORD Strategic Plan thus serves as the foundation for the research strategies and research plans that ORD has developed, or is in the process of developing, to identify and describe individual high-priority research topics. One of these high-priority research topics is arsenic in drinking water.

The Research Plan for Arsenic in Drinking Water was developed through a process involving EPA-wide research activities and research partnerships with stakeholders. In 1992 EPA's Science Advisory Board (SAB) reviewed EPA's 1991 Arsenic Research Recommendations, and advised EPA to consider several additional research projects. In 1995, an Expert Workshop on Arsenic Research Needs was sponsored by the American Water Works Association (AWWA) Research Foundation, the AWWA Water Industry Technical Fund, and the Association of California Water Agencies; the workshop's final report prioritized research in mechanisms, epidemiology, toxicology, and treatment. In addition, the 1996 Safe Drinking Water Act Amendments directed EPA to develop a research plan to reduce the uncertainty in assessing health risks from low levels of arsenic, and to conduct the research in consultation with the National Academy of Sciences, Federal agencies, and interested public and private entities. EPA held arsenic in drinking water stakeholder meetings in 1997 that addressed, among other things, research activities for arsenic.

A research plan is different from a research strategy. While a research strategy provides the framework for making and explaining decisions about program purpose and direction, a research plan defines the research program that EPA is pursuing. The research strategy, as an overarching view of research needs and priorities, thus forms the basis for the research plan and provides a link between the ORD Strategic Plan and the individual research plan. In turn, the research plan links the research strategy to individual laboratory implementation plans (which serve as the blueprints for work at ORD's national laboratories and centers) by defining the research topic(s) at the project level.

This research plan describes the research that can contribute to the development of an arsenic drinking water regulation. Areas covered in the plan include both short-term and long-term studies to:

- improve our qualitative and quantitative understanding of the adverse human health effects of arsenic;

- understand mechanisms of arsenic health effects, using a variety of research tools, including PBPK and BBDR models;

- measure exposures of the US population to arsenic from various sources (particularly diet), thereby permitting better definition of cumulative exposures to arsenic;

- development of biomarkers of effects and exposure;

- improve methods for assessing and characterizing the risks from arsenic exposures and health effects; and

- refine treatment technologies for the removal of arsenic from water supplies.

To address these issues, the plan prioritizes arsenic research within the following broad research areas: analytical methods, exposure assessment, risk assessment, metabolism, health effects and dose-response for cancer and non-cancer endpoints, mechanisms of action, human susceptibility characteristics, and potable water treatment modalities.

This research plan is an important tool for measuring accountability because it makes clear the rationale for, and the intended products of, EPA's arsenic in drinking water research. By specifying up front how EPA will manage its scientific data and information products, EPA can effectively communicate the results of its aresenic in drinking water research to its clients, stakeholders, and the public. This research plan is also an important budget tool, enabling EPA to clearly track progress toward achieving its arsenic in drinking water research goals, as required by the 1993 Government Performance and Results Act.

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Peer Review

Peer review is an important component of research plan development. The peer review for the Research Plan for Arsenic in Drinking Water was conducted by an Ad Hoc Subcommittee of ORD's Board of Scientific Councilors (BOSC) during January 1997. In addition, the draft research plan was discussed with stakeholder groups prior to the plan's finalization.

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Research Plan for Arsenic in Drinking Water
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Abstract

The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) develops research plans to guide its research direction pertaining to specific environmental issues over a 5- to 10-year time frame. This research plan addresses opportunities to enhance the scientific basis for understanding the health risks associated with arsenic in drinking water as well as research to support improved control technologies for water treatment. Better understanding of arsenic health risks will provide an improved science base for arsenic risk assessment and regulatory decisions in the U.S. Further evaluation of control technologies will support cost-effective implementation of future regulatory requirements.

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Introduction

Purpose

The Environmental Protection Agency's (EPA) Office of Research and Development (ORD) develops research plans to guide its research direction pertaining to specific environmental issues over a 5- to 10-year time frame. This research plan addresses opportunities to enhance the scientific basis for understanding the health risks associated with arsenic in drinking water as well as research to support improved control technologies for water treatment. Better understanding of arsenic health risks will provide an improved science base for arsenic risk assessment and regulatory decisions in the United States. Further evaluation of control technologies will support cost-effective implementation of future regulatory requirements. This research plan is expected to be of interest to scientists, risk managers and decision makers in government, industry, and academia as well as members of the public interested in arsenic exposure. The issue of arsenic research needs and the basis for current risk assessments have been the subject of several reviews and expert panels (AWWARF, 1995; U.S. EPA, 1988, 1991, 1992, 1996c). Therefore, this document stresses the implications of recent research findings and emphasizes identification of key strengths and sources of uncertainty and variability[1] in the arsenic risk assessment. This document will also explain how information gained through research can:

- impact the methods used in new investigations to assess the risks of arsenic, and

- support or suggest changes in the assumptions and methods used in arsenic risk assessments.

The risk assessment/risk management paradigm was chosen as the format for the plan because risk assessment provides a systematic approach to analyze sources of scientific uncertainty and variability which can influence research directions more effectively (NRC, 1994). The risk assessment/risk management paradigm involves four types of scientific analyses followed by risk management decisions. The risk assessment analyses consists of *hazard identification, dose-response assessment, exposure assessment* and *risk characterization* (NRC, 1983, 1994). Hazard identification involves descriptions of the potential adverse effects (e.g., short-term illness, cancer, reproductive effects) that might occur due to exposure to the environmental stressor (e.g. arsenic). Dose-response assessment determines the toxicity or potency of the stressor by describing the quantitative relationship between the amount of exposure to a stressor and the extent of injury or disease in

humans. Exposure assessment describes the nature and size of the populations exposed to a stressor and the magnitude and duration of exposure. Exposure assessment also includes descriptions of the pathways (e.g. air, water, food supply) by which the stressor travels through the environment along with the potential routes of exposure (oral, dermal, or inhalation). Risk characterization uses the data collected from the three preceding analyses which are integrated to convey the overall conclusions about potential risk, as well as the rationale, strengths and limitations of the conclusions. It provides an estimate of the likelihood that individuals in a population will experience any of the adverse effects associated with the stressor, under known or expected conditions of exposure. Risk management decisions for drinking water involve setting maximum contaminant levels (MCLs), based on minimizing adverse health effects considering the available technologies. In the context of this plan, risk management research involves identifying treatment technology options and evaluating their performance, cost, and effectiveness.

This Arsenic Research Plan addresses the protection of human health, especially the research needed to implement the 1996 Safe Drinking Water Act Amendments (SDWAA). It is intended to serve as a blueprint that will be discussed with parties interested in addressing key strengths and uncertainties in the arsenic risk assessment. The research needs are broader than those that EPA can address alone, and it is anticipated that other entities will be involved in conducting some of the needed research.

Background on Arsenic

Arsenic occurs widely in the earth's crust and is a natural contaminant of water. Elevated levels of arsenic in water and soil can be found in certain areas of the country as a result of leaching from rock into ground water and possible geothermal activity, depending on the geologic make-up of the area. In addition, nonferrous mining and smelting operations, refining operations, wood preservative use, contaminated pesticide manufacturing sites, and past use of pesticides on crops (e.g., cotton) may add to elevated concentrations of arsenic in water and soils. Humans are exposed to arsenic in a variety of forms from sources such as food and water. Arsenic has also been used for medicinal purposes.

Arsenic is a transitional, reactive element that forms complexes with other metals, as well as carbon and oxygen (Gorby, 1994). There are three biologically important arsenic valence states: elemental arsenic As(0), arsenite As(III) and arsenate As(V). Arsine gas

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[1] The terms uncertainty and variability, as used here, have distinct meanings (NRC, 1994). Uncertainty refers to gaps in knowledge, and variability to interindividual differences (heterogeneity) in both exposure and personal dose-response relationships (susceptibility).

is considered the most acutely toxic; inorganic arsenic compounds are generally considered to be more toxic than organic arsenic compounds. Elemental arsenic is the least toxic. The inorganic arsenicals are the predominant forms found in water.

Although the general toxicity of arsenic is widely known through poisoning incidents and its medical use, epidemiological reports of arsenic-related cancers in Taiwan and other populations have raised public health concerns about effects arising from chronic exposure. In Taiwan, an association between arsenic levels in drinking water and increased skin cancers and internal cancers in the exposed populations was observed (Tseng et al., 1968; Tseng, 1977; Chen et al., 1986). Effects other than cancer were also noted in this population such as effects on the peripheral vasculature leading to Blackfoot's disease and noncancerous skin lesions such as altered pigmentation and skin thickening (hyperkeratosis). Animal studies suggest the possibility of other noncancer effects occurring under certain conditions of exposure.

Regulatory Background

EPA's authorities and responsibilities are mandated primarily by a number of environmental statutes. These statutes direct EPA to perform a wide variety of activities with the underlying goal of protecting human health and the environment. This research plan for arsenic specifically emphasizes research issues related to arsenic in drinking water. Therefore, the discussion in this section will focus on mandates under the Safe Drinking Water Act (SDWA), with some consideration of other statutes affected by the SDWA, in particular the Clean Water Act (CWA). Nevertheless, it is important to consider the risk from water in context of the total risk from exposure resulting from other pathways to ensure that control strategies will achieve adequate reduction in risk.

The SWDA mandates that EPA identify and regulate drinking water contaminants that may have adverse human health effects and that are known or anticipated to occur in public water supplies. EPA's drinking water standard, or maximum contaminant level (MCL), under SDWA is 50 µg/L for arsenic. This level was developed in 1942 by the Public Health Service and was not based on risk assessment methodology. Since that time, revision of the drinking water standard has been considered a number of times, but no change was made. In February 1995, OW decided to delay proposals for the revision of the arsenic MCL pending additional health research to reduce uncertainties and to conduct research on arsenic removed by small system treatment technologies. The 1996 Amendments of SDWA require the development of an arsenic research plan, a proposal to revise the MCL by January 2000, and a final rule by January 2001.

The EPA's Office of Water (OW) has also established guidance for arsenic under the CWA. The U.S. EPA's 1992 National Toxic Rule established a human health water quality criterion for arsenic of 0.018 µg/L. Water quality criteria are used as guidance to states in establishing surface water quality standards and discharge limits for effluents. However, actual implementation of the surface water standards has depended on measurability criteria for arsenic at a level of several µg/L.

Having two very different criteria for arsenic (0.018 µg/L in ambient water vs. 50 µg/L in drinking water) to protect human health is very confusing to the public. These different values have been difficult to explain, defend, and implement in EPA and State programs.

Treatment efficiency is another major concern for risk managers since removal of arsenic from water and soil can cost billions of dollars. Previous EPA estimates indicate that national cost estimates for implementing revisions range from $140 million to $6.2 billion, for MCLs of 20 down to 5 µg/L. However, a variety of strategies for implementation of an MCL could substantially reduce cost. Further cost estimates will be conducted pursuant to the new SDWAA provisions. Treatment costs are of particular concern for small communities. Since the MCL must be set as close to the health goal as feasible, there continues to be considerable scrutiny placed on the health effects data and resulting risk assessments for ingested arsenic. The potential cost impacts of a revision of the arsenic MCL have served to highlight the arsenic risk assessment and its associated strengths and uncertainties.

Risk Management Decisions Required for Arsenic in Drinking Water

To meet the January 1, 2001, target for a final arsenic drinking water regulation, EPA's risk managers will rely on scientific results that are available, at the latest, by mid-1999. However, longer-term research will also be important because every 6 years EPA must review and revise, as appropriate, each national primary drinking water regulation promulgated. Key issues for risk management decision-making in developing a drinking water standard are described below.

1. Determine the Maximum Contaminant Level Goal (MCLG)

In the development of national primary drinking water regulations under SDWA, EPA is required to promulgate a health-based MCLG for each contaminant. The MCLG is set at a level that will not result in adverse health effects, incorporating a margin of safety. In setting MCLGs, EPA's policy has been to distinguish between carcinogens and non-carcinogens as follows:

- For contaminants with strong evidence of carcinogenicity via drinking water, considering weight of evidence, pharmacokinetics, potency and exposure, the MCLG is set at zero.

- For contaminants with limited or no evidence of carcinogenicity including many Group C agents, the

MCLG is based on noncancer effects using the Reference Dose (RfD). The RfD is derived from a no- or- lowest- adverse- effect level identified from a sensitive endpoint of toxicity from a relevant human or animal study and adjusted to account for uncertainty of the findings. A relative source contribution factor (RSC) is applied to the RfD to determine the maximum amount of the RfD allocated to drinking water (U.S. EPA, 1994b). If the contaminant shows limited evidence of carcinogenicity, an additional factor of 10 is applied to the RfD to account for possible carcinogenicity.

2. Determine the Maximum Contaminant Level (MCL)

An MCL is set as close to the MCLG as "feasible". The SDWA (section 1412(b)(4)(D)) characterizes "feasible" as follows: "feasible with the use of best technology, treatment techniques, and other means which the Administrator finds available (taking costs into consideration) after examination for efficacy under field conditions and not solely under laboratory conditions".

- When setting an MCL, EPA lists the best available technology (BAT) as feasible technologies based on cost assessments for large public water systems.

- Under the new SDWAA , EPA must also identify affordable technologies that will meet the MCL for small water systems in three population size categories: 25-500; 501-3,300; and 3,301-10,000.

- EPA will establish a standard analytical method(s) to be used for compliance monitoring of the contaminant.

3. Determine if the Benefits of the MCL will Justify the Compliance Costs

The new SDWA Amendments expand upon the cost-benefit analysis previously required for drinking water regulations. Under the Amendments, EPA must:

- Analyze quantifiable and nonquantifiable health risk reduction benefits likely to occur as a result of treatment of the contaminant and co-occurring contaminants, including health risk reduction benefits for infants, children, pregnant women, the elderly. and ill.

- Analyze the quantifiable and nonquantifiable costs of compliance, including monitoring and treatment costs.

- Determine if the benefits justify the costs.

- If the benefits do not justify the costs, identify a higher MCL that maximizes health risk reduction benefits, where the costs are justified, unless the cost to large systems would justify the benefits.

However, if the contaminant is found exclusively in small systems that are unlikely to receive a variance, a higher MCL can be established.

Scope of this Research Plan

This research plan describes the research that can contribute to the development of the arsenic drinking water regulation, both in the near and longer terms.[2] Areas covered in the research plan include both short-term and long-term studies to:

- improve our qualitative and quantitative understanding of the adverse human health effects of arsenic;

- understand mechanisms of arsenic health effects, using a variety of research tools;

- measure exposures of the U.S. population to arsenic from various sources (particularly diet) thereby permitting better definition of cumulative exposures to arsenic;

- improve methods for assessing and characterizing the risks from arsenic exposures and health effects; and

- refine treatment technologies for the removal of arsenic from water supplies.

The relationship of the exposure and health effects research to the development of the risk assessment and integration into the final risk characterization is depicted in Figure 1. An overview of how the arsenic research and assessment will be implemented in developing drinking water regulations is illustrated in Figure 2.

Research Planning and Implementation Process

U.S. EPA's Office of Research and Development (ORD) has implemented a new planning process where representatives from each ORD research organization (covering all disciplines) meets regularly with representatives of the Office of Water to discuss programmatic needs and time-lines for needed research. EPA Regional representatives also participate in these activities to ensure that results from ORD research, and subsequent program office decisions, can be maximally and practically utilized. More recently ORD, working with all EPA program offices, has prioritized its entire research program from top to bottom using a two-step process of first making a difference with the best science only perspective and then modifying the rankings because of programmatic needs/deadlines, Congressional man-

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[2]However, this plan does not describe all the regulatory assessment and monitoring studies needed to support arsenic regulation. Such assesments would include studies of the prevalence of different levels of arsenic contamination in water supplies in the US and economic evaluations of regulatory costs. Such data collection and analysis falls outside the scope of resesrach planning and is addressed directly by EPA's Office of Water.
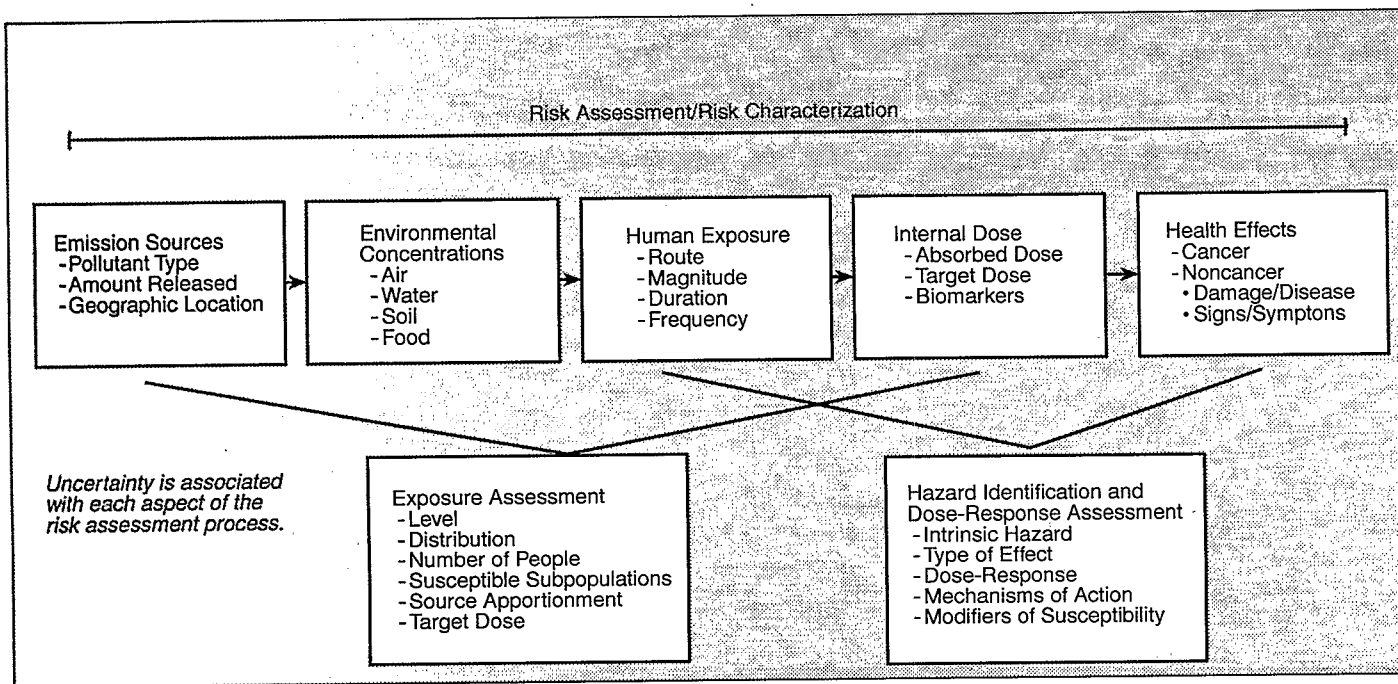
Adapted from: Sexton et al. (1992)

Figure 1. Risk Assessment/Characterization: Relationship of Exposure and Effects Research.

Key: PQL = Practical Quantiation Limit
RSC = Relative Source Contribution
RA = Risk Assessment
BAT = Best Available Technology

Figure 2. Arsenic Research to Support Regulation Development.

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dates, etc. This has resulted in an ordinal ranking of nine broad arsenic research areas being developed. This activity allowed EPA to further develop the prioritization of the arsenic projects found within this revised research plan into three broad categories. These categories are High, Medium, and Low. The Arsenic Research Plan contains project priority rankings using this approach.
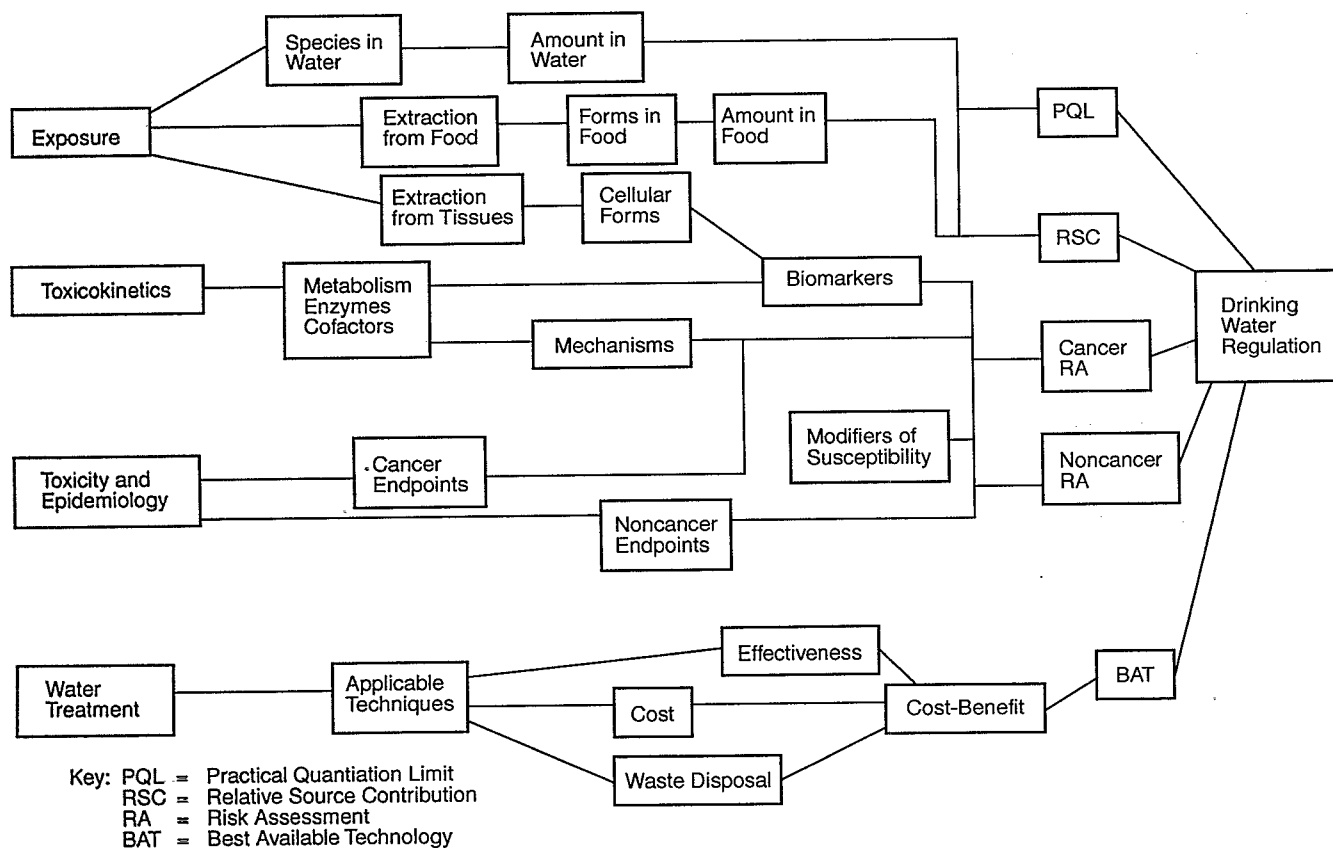
The research implementation process involves utilizing the results of the research planning for identification of arsenic related High Priority Research and comparing these priorities to other High Priority Research Needs identified by EPA. Decisions on when and to what levels EPA will conduct research related to these arsenic research needs will be made on a yearly budgetary basis. Ultimately, decisions to implement planned research depend on the priority set from within this research plan, the relative priority of arsenic research compared to other EPA High Priority Research Needs, and the resources provided to EPA to conduct research. The ability for EPA to leverage the research interest of other parties to conduct portions of this arsenic research also plays an important part in the implementation process.

Prioritization Criteria

Decision-making criteria for use in priority-setting within this research program have been developed. The primary arsenic specific prioritization criteria involves meeting the following short-term and long-term criteria. In addition, the sequence of needed research and feasibility of accomplishing research goals was taken into account in prioritizing tasks. Through application of these criteria, resources have been and will be allocated in the most effective and efficient manner.

Short-Term Criteria

1. Will the research improve the scientific basis for risk assessments needed to propose a revised arsenic MCLG by January 1, 2000?

2. Will the research improve the scientific basis for risk management decisions needed for proposing a revised arsenic MCL by January 1, 2000?

Long-Term Criteria

1. Will the research improve the scientific basis for risk assessment and risk management decisions needed to review and develop future MCLs beyond the year 2001?

2. Is the research essential to improving our scientific understanding of the health risks of arsenic?

Within each proposed research area, the plan summarizes the primary focal area for the research, indicates whether the activity is targeted primarily toward the intramural or extramural (or both) components of the EPA research program and to the extent possible other

research programs, and the planning year in which the research is proposed to be undertaken. The arsenic research plan also specifies whether the research area will satisfy the short-term or long-term needs of the Agency. While, in general, EPA has given the highest priority to meeting short-term objectives, longer-term high-priority research has been initiated in order to address requirements for future regulations in 2006. In some cases, EPA expects the research to be conducted by other entities. While these tables also propose the research sequence, this strategic plan is likely to be refined as the program progresses and new research results emerge. The full scope of the program will likely exceed available resources. In this context, it is anticipated that selections of particular projects within the scope of the issues will be determined by scientific peer reviews and programmatic relevancy reviews. Peer review will help ensure the high quality of projects selected, which is of critical importance to both the regulatory application of the resulting information and the overall credibility of the Agency. Additionally, EPA will coordinate its efforts with other interested parties. After further peer review of this research plan, EPA will prepare more laboratory-specific implementation plans for selected areas of research. This plan has been used and will continue to be used to guide the development of solicitations under EPA's extramural grants program as well as other interested parties.

1. Arsenic Risk Assessment/Characterization

1.1. Background

The research plan is broadly organized according to a modified risk assessment/ risk management paradigm in which the risk characterization serves to formulate the critical questions, identifies uncertainties and research needs and provides a bridge from the scientific data to risk management options. The Risk Assessment/Characterization Chapter is intended to provide a broad perspective on the scope and nature of the problem. It provides a discussion of the current risk assessments for ingested inorganic arsenic. This discussion also describes the strengths and uncertainties and identifies data gaps surrounding these assessments. Secondly, this chapter outlines research opportunities that can improve the scientific basis for refining the current risk estimate and its sources. The research projects to address data gaps are discussed in the subsequent chapters on Exposure, Health Effects and Risk Management Research. Thirdly, this chapter discusses the ongoing and future risk assessment research, models, and assessments that should be developed in order to fully understand the risks associated with ingestion of arsenic and support refinement of existing regulations.

1.2. Characterization of Arsenic Risks: State of the Science

This section reviews the risk assessment foundations of the current regulatory standards for arsenic in water and discusses the strengths and uncertainties in the interpretation

of our current knowledge about arsenic exposures, health effects, and risks. It also summarizes the approaches used to develop existing exposure and health risk assessments to support existing regulations and guidance under the Safe Drinking Water Act (SDWA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and Resource Conservation and Recovery Act (RCRA). The overarching risk assessment issue is determination of the risk associated with levels of arsenic to which people in the United States are exposed in drinking water. The evaluation of these risks includes consideration of the following issues:

- Regulatory levels for arsenic in drinking water and ambient water;

- Data on levels of human exposure to arsenic through drinking water and other major pathways;

- Exposure levels at which adverse effects are observed and the closeness of those levels to levels found in U.S. drinking water;

- An understanding of the variety of cancer and noncancer effects induced by arsenic;

- Supporting biological and mechanistic data that may aid in understanding arsenic risks; and

- Quantitative risk estimates and their strengths and uncertainties.

1.2.1. Current Exposure Data.
1.2.1.1. Arsenic in Drinking Water — Presently, water utilities are only required to report arsenic concentrations that exceed the MCL of 50 µg/L. To develop a national picture of arsenic exposures from public drinking water supplies, data have been derived from four national surveys: 1) Community Water Supply Survey, 2) Rural Water Survey, 3) National Organics Monitoring Survey, and 4) National Inorganics and Radionuclides Survey (U.S. EPA, 1983, 1989, 1988). Detection limits ranged from 2-5 µg/L. Arsenic was detected in both groundwater and surface waters. Concentrations ranged from 0-100 µg/L. However, there is uncertainty associated with the analytical methods used for these measurements and the analytical detection limits. In less-comprehensive surveys, results were more variable; for example, concentrations ranging up to 393 µg/L in Hidden Valley, CA, have been reported. The Metropolitan Water District of Southern California has estimated that about 2% of the U.S. population is exposed to arsenic drinking water concentrations exceeding 10 µg/L, about 5% is exposed to concentrations above 5 µg/L, and about 15% is exposed to concentrations above 2 µg/L (Davis et al., 1994). The U.S. EPA is currently evaluating and analyzing new databases received from states, public water utilities and associations and will establish revised occurrence and exposure distributions before beginning to draft the MCL. Additional data from ORD's National Human Exposure Assessment Survey will be available in early 1999.
1.2.1.2. Dietary Arsenic Exposures — Dietary exposures are also of concern because diet may contribute significantly to arsenic exposure. Since 1961, the U.S. FDA has systematically collected and analyzed food for arsenic as part of the Total Diet Study, also known as the Market Basket Study. Most recent data sets include food analyses conducted from April 1982 to April 1988 and June 1988 to April 1990 (U.S. FDA, 1992). A total of 234 foods were analyzed for arsenic content; foods were classified into one of 11 separate categories and total dietary intake averaged for three age groups (infant, toddler and adult). Using average daily consumption rates for each food group, total arsenic intakes of 21.5, 27.6. and 52.6 µg/day were estimated for infants, toddlers, and adults respectively. These data address total arsenic content of foods. Because some common organic forms of arsenic are thought not to present toxicity concerns, this data should not be directly compared with drinking water intake information. Using some limited data on inorganic arsenic in foods (which can be more directly compared with water intake), Borum and Abernathy (1994) estimated that inorganic arsenic comprises about 20-25% of total dietary intake of arsenic.

1.2.2. Current Health Risk Estimates.
Arsenic has been recognized as a potent human toxicant since ancient times, and reports of human cancers associated with ingestion date to the last century. In recent decades, arsenic has been found to be carcinogenic by both ingestion and inhalation routes in multiple epidemiological studies (U.S. EPA, 1980a, 1984, 1993; Tseng, 1977; Tseng et al., 1968). Indeed, arsenic is the only known substance for which there is adequate evidence of carcinogenic risk by both inhalation and ingestion routes of exposure. Arsenic is also the only carcinogen where exposure through drinking water has been clearly demonstrated to cause human cancer. Thus U.S. EPA has classified arsenic as a Group A carcinogen, i.e., a known human carcinogen, based on the 1986 Cancer Assessment Guidelines. This designation is used when there is sufficient evidence, generally from epidemiologic studies, to support a causal association between exposure to an agent and cancer in humans.

1.2.2.1. Foundations of the Current Arsenic Regulations in Water — As discussed previously, the regulatory and guidance levels under the SDWA and CWA vary widely. In 1975, EPA adopted 50 µg/L as a maximum contaminant level (MCL) for arsenic in drinking water under the SDWA. This level was developed by the Public Health Service in 1942 based on the acute or short-term toxicity associated with consuming high levels of arsenic (U.S. EPA, 1995). The arsenic MCL is not supported by a health-based risk assessment; rather it was adopted from the U.S. PHS standard with the consideration of water intake of arsenic relative to total intake of arsenic from food. Using the information that was available then (dietary arsenic was estimated to average 900 µg/day), a consumption of 2 L/day of drinking water containing 50 µg/L was estimated to contribute ~10% of the total ingested arsenic (U.S. EPA, 1975). Controlling water intake to less than 10% of the total intake was considered public health protective. As discussed above, more recent FDA data indicate much

lower dietary arsenic intake than was assumed in this calculation.

More recently, a water quality criterion (WQC) of 0.018 µg/L for arsenic was established to protect humans consuming arsenic-contaminated water and 6.5 g of fish and shellfish/day under the CWA (U.S. EPA, 1980a, 1989, 1992). The WQC was calculated based on the recommendations and findings from U.S. EPA Risk Assessment Forum Technical Panel (1988) and the Ambient Water Quality Criteria Methodology (U.S. EPA, 1980b). It represents an intake associated with an upper bound incremental cancer risk of on-in-a-million. The WQC reflects the dose-response data for skin cancer from the Taiwan study (Tseng, 1977; Tseng et al., 1968), use of age-specific prevalence rates for dose, and a linear-quadratic dose-response model to estimate lifetime risk of cancer. The use of a one-in-a-million risk level represents an EPA policy decision.

1.2.2.2 Weight of Evidence Discussion of the Cancer Data—
EPA has identified arsenic as a group A "known" human carcinogen (U.S. EPA, 1993, 1998). Other organizations such as the International Agency for Research on Cancer (IARC) have also classified arsenic as a human carcinogen (IARC, 1987). This classification is based on sufficient evidence of carcinogenicity from human data involving occupational and drinking water exposures. This Tseng et al. (1968) epidemiological study in Taiwan has played a central role in the current EPA and IARC cancer assessments. The Tseng et al. (1968) Taiwan study evaluated a large population (over 40,000), in comparison to other studies. Each participant was evaluated by a physician to identify skin lesions. Pathology was conducted on tissues collected from a affected individuals. Older individuals were determined to have had long-term exposure, and there was a large control population for comparison. The population studied was characterized by age and covered a full range. Drinking water arsenic levels in the population studied by Tseng et al. (1968) were classified into three concentration strata 0-290 µg/L, 300-600 µg/L, and 600 µg/L over) and showed a clear dose-response relationship with elevated skin tumor prevalence rates in all three strata. Skin tumor prevalence rates were elevated in both males and females, with the males showing a larger increase. With regard to the U.S. regulatory concern with drinking water, the Tseng et al. (1968) study provide data on risks for levels much closer to those of regulatory concern. In the Risk Forum report, an estimation of skin cancer in a Mexican population exposed to arsenic was consistent with the results observed in the Taiwan study and supported the credibility of the risk estimates based on the Taiwanese data (Cebrian et al., 1983).

The EPA Risk Assessment Forum report upon which EPA's current risk assessment is based was prepared by a Technical Panel convened in 1986 (U.S. EPA, 1988). The purpose of the panel was to address issues relating to the qualitative and quantitative carcinogenic risk assessment for ingested arsenic. In particular, the panel examined issues relating to the validity of the Taiwan study and its application to U.S. populations, use of arsenic-induced skin lesions and the role of arsenic in human nutritional status (i.e., essentiality). The panel also evaluated information on genotoxicity, metabolism, body burden, tissue distribution, and the possibility for a cancer threshold. With regard to the Taiwan data, the panel evaluated validity of the study and applicability of the dose-response assessment to the U.S. population, the interpretation and use of arsenic-associated skin lesions, and the role of arsenic in human nutrition. The panel concluded that: 1) the epidemiologic studies demonstrated that arsenic was a human carcinogen by the oral route; 2) the Taiwan studies provided a reasonable basis for quantifying the risks of skin cancers associated with the ingestion of inorganic arsenic in U.S. population; 3) an estimated unit risk range for water is $3\text{-}7\times10^{-5}$/µg/L; 4) the slope of the dose-response curve at doses below the range of observation may be less than linear, therefore the calculated unit risk could overestimate the true risks[3]; and 5) arsenic may be a possible but not proven nutritional requirement in humans. Based on the peer-reviewed findings of this panel, the Risk Assessment Council recommended and EPA adopted the group A classification for ingested inorganic arsenic with a potency estimate of 0.0015/µg/kg/day and a unit risk for water of 5×10^{-5}/µg/L.

There continues to be debate among the scientific community on the shape of the dose-response curve at low doses. Scientific information has been developed that supports both linear, i.e., shallow slopes at very low doses, and nonlinear responses. ORD is working through its own research program and in cooperation with the grants program to gather more information relevant to the dose-response assessment. To further address this issue, on May 21 and 22, 1997, EPA convened an expert panel and workshop to evaluate the body of available data regarding arsenic's mode of action and recommend whether data are sufficient to support a linear versus nonlinear response. The charge to the panel was: 1) examine the data on the direct and indirect effects of arsenic and its metabolites on DNA, DNA repair, DNA methylation and regulation, mutagenesis and carcinogenicity; 2) comment on possible mechanisms and modes of action, including whether there is clear evidence for a mode of action; 3) comment on the confidence level for any one particular mode of action and 4) provide guidance on the weight of evidence supporting the use of linear or nonlinear responses in extrapolating to low-dose arsenic exposures. The panel concluded that more than one mode of action for arsenic may be operating at different dose levels or even at the same dose level. It also stated that although there does not appear to be any direct interaction of arsenic with DNA, this does not rule out a linear dose-response relationship at lower doses. The panel concluded that the modes of action they considered would lead to nonlinear responses for cancer. However, the panel

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[3]Additionally, it should by noted that a Maximum Liklihood Estimate (MLE) rather than upper bound linear quadratic model was fit to the Taiwan data: thus there was also potential for underestimation of the true low-dose slope.

also observed that at very low doses the curve might effectively be linear. The panel stated that the low-dose linear component of response would likely be very shallow. However, data to allow an evaluation of the low dose-response were not identified because the mode of action for arsenic is still uncertain and an area of needed research. It should be noted that in using the term "linear models", EPA has focused on the low-dose region and what is more precisely described as "models that are linear at low doses". As discussed, EPA has shared the findings of this panel with National Academy of Science (NAS) for consideration in its risk assessment of arsenic.

As can be anticipated with a large and complex epidemiological study, a number of specific issues have arisen concerning the evaluation and interpretation of the Tseng et al. (1968) study. Several of these issues have been identified as areas of uncertainty and further research to improve the risk characterization of arsenic.

Water concentration estimates in the Tseng study were made at the village, rather than the individual level. Grouped measurements are commonly employed in epidemiological studies (for example, use of area concentration rather than personal measurements in many occupational studies). However, arsenic concentrations in individual wells varied within villages; person-specific concentration data, were they available, might have allowed increased resolution of dose-response patterns. Similarly, well concentrations exhibited temporal variability, and a larger number of measurements per well, using an improved analytical method that can reliably measure low concentration (i.e., <50 µg/L), would have increased the precision of exposure estimates.

The potential for concomitant exposures to other contaminants in the Taiwan drinking water study has also received attention. The arsenical water in Taiwan also contained humic substances. It has been speculated that these substances may be carcinogenic. However, humic substances are found in water supplies in many areas of Taiwan without observed elevations of cancer rates, and the data for Taiwan show that cancer prevalence was correlated with arsenic concentrations in well water.

In a nutritional study, Yang and Blackwell (1961) suggested that the Taiwanese diet in the endemic Blackfoot area was deficient in methionine and fat. However, a recent reexamination of these data by Engel and Recevuer (1993) reported that the Taiwanese intakes for protein and methionine were within the now-current recommended levels. It has been suggested that individuals with low intake of methionine may be less able to methylate arsenic and are potentially at higher risks of cancer.[4] However, diets low in animal fat are widely recommended as a preventative measure to reduce cancer risks. This suggests that the risks observed in the Taiwanese population (including internal cancer mortality reported in later studies) might have been higher if they consumed a more typically western diet. There also exists uncertainty regarding the contribution of arsenic in food to total arsenic intake for individuals in the arsenic endemic areas.

The U.S. and Taiwanese populations differ in genetic characteristics, diet, and exposures to other environmental chemicals. Therefore, there is some uncertainty in the quantitative extrapolation of arsenic risks from one population to the other. However, for perspective, these uncertainties need to be compared with the greater degree of uncertainty involved when experimental animal results are applied to estimate human risks.

At the time of the 1988 Risk Forum report, the available data addressed primarily skin tumors resulting from the ingestion of arsenic. While some data on the relationship between arsenic and internal cancers were available in 1988, that data had not been fully assimilated into Agency risk assessment or management discussions. The fact that arsenic skin cancers are usually nonfatal led to Agency discussions of whether cancer risk estimates for arsenic should be managed less stringently. However, further data on arsenic carcinogenesis at internal organ sites has become available in the intervening years.

More recent studies in the same area of Taiwan have reported a strong association between arsenic ingestion and increased mortality and incidence of internal cancers including cancers of the liver, bladder, kidney, colon, and lung (Chen et al., 1986). Chen et al. (1986) calculated standardized mortality ratios (SMRs) for each of these cancers. The authors found the SMR for cancers of the liver, lung, colon, bladder and kidney to be significantly elevated ($p<0.05$). A recent study in Argentina (Hopenhayn-Rich et al., 1996) has provided evidence that arsenic exposures in drinking water are associated with bladder cancer in a population that is very different from that studied in Taiwan. The contrast between the Argentine and Taiwanese studies in terms of ethnic background, dietary patterns, and potential for other constituents to be present in drinking water also serves in resolving concerns that some special characteristics of the Taiwan population or environment might have been responsible for the findings in the Tseng et al. (1968) study. Specifically, Hopenhayn-Rich et al. (1996) observed elevated rates of bladder cancer in an arsenic exposed population that consumed large amounts of animal protein and where humic substances were not identified in the water. Studies in England (Cuzik et al., 1992) and Japan (Tsuda et al., 1990) also contribute to the weight of evidence that ingested arsenic causes bladder cancer. Studies conducted in the United States have not demonstrated an association between arsenic in drinking water and skin or internal cancers. While there was no demonstrated elevated cancer incidence in some limited U.S. populations, the population sizes were too small and/or exposure times too short to expect to detect an effect.

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[4]Hsueh et al. (1995) also found for individuals in the arsenic endemic area an association with high consumption of sweet potatoes with chronic carriers of hepatitis B surface antigen liver disfunction and an increased risk of skin cancer. The relevance of these findings for arsenic risk assessment is not clear.

While there are a number of relevant issues that warrant consideration regarding quantitative extrapolation of the Taiwanese findings, there are also considerable strengths that provide validity to the data. As noted in U.S. EPA (1988), the study and comparison group were large enough to provide reliable estimates of skin cancer prevalence rates. The skin cancer risks were statistically, significantly increased many years after the initial exposures in the exposed group versus the comparison group. These increases were dose-related. The exposed and comparison groups were matched by occupation and socioeconomic status. Finally, the observed skin cancer were confirmed by clinical pathology in over 70% of the reported cases.

1.2.2.3. Noncancer Assessment

In addition to the cancer effects observed in epidemiologic studies, arsenic exposures have also been reported to result in adverse noncancer health effects in humans. These effects include skin lesions such as hyperpigmentation and hyperkeratosis and cardiovascular effects. A risk assessment for noncancer effects associated with exposures to inorganic arsenic has been developed using data from the Tseng (1977) study considering the drinking water and potential dietary arsenic intake for that population. An oral RfD of 0.3 µg/kg for inorganic arsenic was developed based on the absence of hyperpigmentation, keratosis or documented vascular complications in the study control group (U.S. EPA, 1997). The RfD was based on a no-observable-adverse-effect level (NOAEL) of 0.8 µg/kg-day that included intakes of 9 µg/L of arsenic in water and 2 µg/day in food. The RfD was calculated using the NOAEL of 0.8 µg/kg-day and applying an uncertainty factor of 3 and medium confidence. This confidence ranking reflected a weakness in the data regarding actual exposure levels from water. Agency risk assessors identified a range of values as candidates for the RfD, depending on the particular assumptions made about arsenic exposures in the study group where adverse effects were not observed and with different potential choices of a data base uncertainty factor. There was not a consensus among workgroup scientists on a single value for an RfD. The EPA Risk Assessment Council selected a RfD of 0.3 µg/kg/day for total inorganic intake and concluded that strong scientific arguments could be made for various values within a factor of 2 or 3 of the recommended RfD value, i.e., 0.1 to 0.8 µg/kg/day. If exposures were solely from water, this would amount to 28 µg/day for adults (or 14.0 µg/L, assuming consumption of 2 L/day). The discussion on dietary exposures above in Section 1.2 suggests that background dietary exposures are already 50-100% of that value.

The risk assessments for arsenic that are discussed above have been peer reviewed, adopted by the Agency, and appear as Agency consensus opinions on IRIS (U.S. EPA, 1997).

1.2.2.4. Metabolic and Mechanistic Data — Current Contribution to Risk Assessment

In recent years, research has provided significant information about the biological effects of arsenic, including its genotoxicity (chromosomal and DNA changes) and metabolism. The "state of the science" of our current understanding of arsenic mechanisms is addressed in some detail in Chapter 3. Our understanding of the mechanism of action of arsenic carcinogenesis (and other toxicity) is very limited. See the discussion of the expert panel report regarding mode of action in Section 1.2.2.2. The recommendations from this workshop are expected to help shape future research directions.

Some scientists, including a panel of the EPA SAB, have focused on evidence for dose-dependent methylation as potentially supporting changes in the dose-response modeling for arsenic or suggesting that "apparent thresholds" exist. Currently, our understanding of the role that methylation plays in the induction of toxicity is limited; methylation may either reduce or potentiate toxicity. Data indicate that substantial quantities of both inorganic and methylated arsenic are excreted in urine at both high- and low-exposure levels. This observation suggests that potential dose dependencies in metabolism may not be of a magnitude to support major revisions to the arsenic risk estimate. Further research is being conducted to determine if the toxicity of arsenic at low doses is reduced or potentiated.

Further research into the mechanisms of arsenic toxicity may make important contributions to arsenic risk assessment, as suggested by EPA's recently proposed cancer risk assessment guidelines (U.S. EPA, 1996d). Mechanistic information has application in both hazard identification and understanding dose-response relationships, potentially reducing the reliance on the use of default assumptions. However, the current U.S. standard for drinking water is within an order of magnitude of concentrations at which cancers and other health effects have been seen in epidemiological studies. The closeness of arsenic "effect levels" and levels of regulatory concern limits, until further data are available, the potential changes in current regulatory and treatment options resulting from slight alterations in risk estimates. Data identifying nonlinear effects in fundamental biological processes will provide additional information on the range of arsenic risks. Such an assessment must take into account the expected diversity of human responses to arsenic and the substantial "background" dietary exposures to arsenic. These factors suggest that mechanistic findings may support refinements to the arsenic risk characterization within the range of current regulatory concern.

1.3. What are the Research Opportunities to Improve/Refine Current Risk Assessments?

This section identifies and briefly discusses the research opportunities associated with improving the existing risk and exposure assessments and potential significance in refining the current assessment. The information is organized by key research questions that relate to the uncertainties in the risk assessments previously described. Research has been delineated as being either short-term or long-term research. In general, higher priority has been given to research that has the potential to be completed by 2000. While there seems to be general recognition that substantial changes (order of magnitude or greater) to the fundamental health risks assessment for arsenic are not to be expected for the proposal in 2000, useful short-term research has been identified on arsenic health effects, and exposure and treatment

technology. It is anticipated that this short-term research could lend additional support for arsenic exposure and risk assessment currently being undertaken and would impact treatment options and risk policy decisions especially for small systems. In addition, long-term studies have been identified and initiated to develop data for future risk assessments. This section identifies key research opportunities in order to set the direction for both the short-term and long-term research that is discussed in the following chapters on Exposure, Health Effects and Risk Management Research.

1.3.1. Exposure Assessment.

Most available data on arsenic address total arsenic concentrations and do not distinguish between arsenic valence states or inorganic versus organic forms of arsenic (U.S. FDA, 1982, 1990, 1992). In a number of the research efforts discussed in this plan, it is important to distinguish between different chemical forms of arsenic, that is to "speciate" arsenic during chemical analysis. This is important for assessing risks because the arsenic species can influence the dose-response and exposure assessments. The importance of data on the chemical form of arsenic depends on the environmental media being addressed and the intended application of the data. Arsenic present in water is primarily in the form of inorganic arsenic (III and V); arsenic (III) is oxidized during water treatment to arsenic (V). In this research strategy, distinguishing between the inorganic forms of arsenic in water is not considered to be important for assessing arsenic risks, but can be important for treatment removal. However, a particular concern is the need to distinguish between inorganic and organic arsenic forms in assessment of dietary exposure. To be comparable with data on drinking water (which contains inorganic arsenic), dietary assessments need to measure levels of inorganic arsenic present in food, and differentiate them from organic arsenic. Food and water are thought to be the main contributors to arsenic exposures; dermal exposures from soil and water and inhalation exposures are believed to be minor contributors to arsenic exposure (ATSDR, 1993; Borum and Abernathy, 1994).

More recently, concern has been raised regarding some specific forms of organic arsenic (i.e., mono- and di-methyl forms) found in some foods (ATSDR, 1993) and for which toxicity issues may exist. Pharmacokinetic research also requires data to distinguish between the organic and inorganic forms of arsenic found in biological samples. The strategy for exposure assessment research includes improving methods for the reliable speciation of arsenic. A primary challenge of this research is the reliable extraction of arsenic compounds from complex dietary and biological samples in order to adequately assess intake and tissue levels.

Research Opportunities:

- Arsenic speciation: Improvements in analytical methods for arsenic, particularly for food and biological materials. A primary concern is distinguishing between inorganic and organic arsenic, with specific organic forms of arsenic also warranting attention (short-term). Significance for risk assessment: Improve exposure assessment, improve dose-response assessment, improve risk characterization and aid in design and conduct of future epidemiologic studies.

- Measurement of background exposures to arsenic in U.S. population (general population and susceptible population), particularly addressing inorganic arsenic intake in the U.S. diet. This research should address both the cumulative intake of arsenic and its bioavailability (long-term). Significance for risk assessment: Provide information for interpreting total risks due to arsenic exposure and the contribution that arsenic in drinking water makes to the total risks.

- Development and evaluation of biomarkers of exposures (long-term). Significance for risk assessment: In the assessment of levels of human exposures and contribution to the assessment of arsenic bioavailability.

1.3.2. Cancer Assessments.

Although epidemiologic studies have clearly shown a causal relationship for increased cancer risks in individuals having exposures to arsenic in drinking water, there are a number of areas where further empirical data could broaden and strengthen our ability to assess arsenic risks.

Research Opportunities:

- Further development of data on the several types of internal cancers that have been associated with arsenic exposures (long-term). Significance for risk assessment: Aid in hazard identification and dose-response assessment.

- Dose-response data on hyperkeratosis as a likely precursor to skin cancer, which, due to a higher rate of incidence among arsenic-exposed individuals, can be studied at lower exposure levels (long-term). Significance for risk assessment: Biomarker of effect, define dose-response at lower doses, provide insight into mechanisms of toxicity.

- Research on factors influencing human susceptibility including age, genetic characteristics and dietary pat-terns (long-term). Significance for risk assessment: Provide information on susceptible populations.

- Metabolic and pharmacokinetic studies that can identify the presence of dose dependent metabolism and aid in the evaluation of mechanistic data.

- Mechanistic studies for arsenic-induced genotoxicity and carcinogenicity (for example, induction of genetic damage and tumor promotion in some experimental systems) (long-term). Significance for risk assess-

ment: Mechanistic data, if reliably linked to human carcinogenesis by arsenic, can provide insight into susceptibility and dose-response.

- Laboratory model systems to test dose-response assumptions for cancer.

1.3.3. Noncancer Assessment.

Several epidemiologic studies have observed that arsenic exposures result in adverse effects in addition to cancer. Clear associations were observed for hyperkeratosis, hyperpigmentation, peripheral vascular effects, and a study with a U.S. population reported neurological effects. Other potential effects such as gastrointestinal and liver effects and diabetes have not been clearly defined. Additional studies can better define the potential risks associated with these health effects. In addition, studies can address the influence of other factors on arsenic toxicity.

Research Opportunities:

- Development of human dose-response data for hyperkeratosis, cardiovascular disease, neurotoxicity, and developmental effects (long-term). Significance for risk assessment: Provide data for dose-response assessment.

- Development of additional health effects and hazard identification data on other noncancer endpoints such as diabetes and hematologic effects (long-term). Significance for risk assessment: Provide data for hazard identification and assessment.

1.3.4. Risk Management Research.

Further development of treatment options for the removal of arsenic from drinking water will contribute to informed decision making and can support the development of regulatory standards that are protective of public health. Uncertainty exists as to effectiveness and costs of control technologies for removal of arsenic to levels being considered. Of particular concern is the development of cost-effective treatment options for small systems. Also of high concern for both large and small systems is the increase in costs of residual management that is likely to result from more stringent residual disposal requirements triggered by the lowering of the arsenic MCL.

Research Opportunities:

- Identification of limitations of treatment technologies and impacts on water quality
- Development of treatment technologies for small water systems

- Development of data on cost and performance capabilities of various treatment options

- Consideration of residuals management issues, including disposal options and costs (short-term). Significance of risk management research: Improve controls for implementation of standards, provide cost-benefit information

1.3.5. Research Needs.

Exposure Analysis

Short-Term Research:

- Speciation methods for separation of arsenite from arsenate to support water treatment decisions in large and small utilities

- Refined and evaluated analytical approaches for the speciation of arsenic in urine

- Extraction methods for inorganic and organic arsenicals for separation and detection of individual arsenic species in foods

- National database on arsenic occurrence and concentrations in water constituents

Long-Term Research:

- Exposure studies of populations with high dietary intake of foods associated with toxic species of arsenic

- Biomarkers of exposure in biological media and bioavailability of arsenic

- Speciation methods for biological matrices to support exposure analysis, bioavailability and biomarker research

- Liquid and solid species specific standard reference material for arsenic in water, foods, urine, and tissues

Health Effects

Short-Term Research:

- Feasibility study on various endpoints associated with arsenic exposure

- Directed epidemiologic research on the health effects associated with arsenic exposures

Long-Term Research:

- Factors influencing human susceptibility including age, genetic characteristics and dietary patterns

- Metabolic and pharmacokinetic studies and other laboratory model systems

- Mechanistic studies for arsenic-induced genotoxicity and carcinogenicity and other adverse effects

- Health endpoints in animals

- Biomarkers of effects

- Full-scale epidemiologic studies

Risk Management

Short-Term Research:

• Laboratory and field testing on different arsenic control technologies

• Cost evaluations of arsenic control technologies for small systems

• Arsenic control residual management

Long-Term Research:

• Treatment modifications to reduce residuals and residual disposal options to meet more stringent residual disposal requirements

Risk Assessment

Short-Term Research:

• Risk characterization guidance for States and local communities

• Assessment of arsenic mode of action for understanding biological mechanisms and future research needs

• NAS reassessment of arsenic data

Long-Term Research:

• Predictive tools and statistical models for assessing bioavailability, interactions, and dose-response

• Assessment of exposure levels and incorporation of data into risk estimates

• Assessment of noncancer risks and appropriate modeling tools for quantitative estimation of noncancer risks

1.4. Risk Characterization Research: Health and Exposure

As noted above, there are several strengths, issues, and uncertainties associated with the arsenic database and current risk assessments. In particular, issues exist with the interpretation of human studies, shape of the dose-response at doses below the range of observed effects, toxicity of specific arsenic species, and extrapolation of dose to arsenic exposures in food and water of U.S. populations. Concern also exists regarding the level of protection associated with the drinking water MCL of 50 µg/L which was developed from presumed high exposure to "total" arsenic in the 1940s.

This section discusses the research issues and activities that address improving the current health and exposures assessments and risk estimates. In addition, it describes research projects in the areas of risk assessment methods and model development that are either ongoing or needed to address data gaps in developing or refining current risk assessments for arsenic (i.e., risk estimates). It also identifies projects that are needed to better characterize the risk associated with exposures to arsenic (i.e., integration of health and exposure data).

This section and the following section will cover only risk assessment research, since more discussion of exposure, health effects, and risk management research will be addressed in Chapters 2, 3 and 4, respectively.

1.4.1. Risk Assessment/Characterization.

The risk assessment/characterization consists of a comprehensive evaluation and integration of the health effects (cancer and noncancer) induced by arsenic; the evaluation of dose-response data, including the development of quantitative risk estimates; and the identification of strengths and uncertainties. This process considers both direct data on arsenic toxicity as well as supporting biological and mechanistic data. The preceding discussion has highlighted a number of issues and research questions that can be addressed to better refine and strengthen risk estimates. Risk assessment methods should address the integration of newer scientific information and data for risk assessment and risk characterization. Agency risk characterization guidance stresses the need for analyses to address central and high-end estimates of individual risk as well as population risks. Better characterization of exposures, including identification of populations with high exposures will contribute to informed decision making for arsenic risks. EPA is also faced with the dilemma of providing guidance to State and local communities on the health risk associated with exposures to arsenic from drinking water while the regulation is in a stage of transition.

Refinement of the quantitative risk assessment is intended to provide a clarification of the dose-response and biological relationship for arsenic induced skin cancers and the development of risk assessment tools for interpreting the dose-response relationship in humans. Data exist on internal cancers from several published studies, in addition a number of epidemiologic studies have been initiated to further investigate the risks for internal cancers. Dose-response assessments for internal cancers are needed. These assessments would aid in defining the magnitude of risks from internal cancers and serve as the basis for comparison to skin cancer risks.

In addition to dose-response assessments, exposure assessments are required to evaluate the relative magnitude of population exposed to arsenic from diet and water. Previous dietary estimates assumed a balanced diet and average nutritional status and did not take into account ethnic, cultural, or economic impacts on food consumption patterns. Improved exposure assessment of background rates will allow for the better risk characterization and comparative risks.

Research Opportunities to Strengthen Risk Assessment:

• Development of risk characterizations to provide support to decision making and assist Regions, States and local communities on health risks associ-

ated with the exposures to arsenic contaminated drinking water (short-term). Significance to risk assessment: Provide guidance to risk managers and regulators on risk levels.

- An assessment and analysis of existing and new data on risks of internal cancers, including consideration of quantitative dose-response models (long-term). Significance to risk assessment: Provide basis for refining risk estimates.

- Development of predictive tools and statistical models for assessing bioavailability, interactions, and dose-response as better mass balance data become available (long-term). Significance to risk assessment: Provide basis for refining dose-response estimates.

- Assessment of exposure levels and incorporation of data into risk estimates for better characterization of actual risks associated with arsenic exposure (long-term). Significance to risk assessment: Improve exposure assessment and risk characterization.

- Assessment of current information on arsenic mode of action (short-term). Significance to risk assessment: Provide a greater understanding of biological mechanisms and factors that may impact the shape of dose-response curve. Significance to risk assessment: Consideration of implications of these factors for risk assessment in human populations, provide insight for dose-response assessment.

- Assessment of noncancer risks and consideration of appropriate models for quantitative estimation of noncancer risks (long-term). Significance to risk assessment: Aid in dose-response assessment.

- Assessment of existing information on arsenic interactions with other metals to predict if response is additive or departures (i.e. synergism, antagonism) from additivity can be estimated (long-term). Significance to risk assessment: Aid in dose-response assessment, mechanism of action and refinement of risk characterization.

1.4.2. Ongoing Activities.

EPA is in the process of reevaluating the risk assessments for arsenic as part of IRIS Pilot Program. This reevaluation will cover both cancer and noncancer risks, will include data not previously reviewed and will include application of proposed revisions to the Agency's Cancer Risk Guidelines. As part of this reassessment, the Agency has conducted a Workshop on biological mechanisms for arsenic-induced carcinogenicity and implications for extrapolating below the observed dose-response range.

1.5. Proposed Risk Assessment Research and Risk Assessment

Risk Assessment Issue 1. Risk assessment and risk characterization for arsenic — short-term efforts

1a. Workshop on Mode of Action for Arsenic

The workshop held May 21-22, 1997, examined current information on the mechanisms by which arsenic induces carcinogenicity and discussed implications for dose-response assessment. The results from this workshop, a joint effort of OW and ORD, can contribute to a further definition of research needs in the area of mechanistic studies and provide input to be addressed in arsenic risk characterization.

High priority; intramural and extramural. Completed.

1b. Synthesis of Data to Support Arsenic Risk Assessment and Risk Characterization

EPA's Health assessment documents for arsenic are based on data available in the late 1980s. The current dose-response estimate for arsenic is based on human data from the Taiwan study. Low-dose risk estimates were developed by applying age-specific prevalence rates for dose and a linear-quadratic dose-response model to estimate lifetime risk of cancer. Since the completion of the EPA assessment, additional studies addressing arsenic risks have become available. Additionally, EPA has received a report from an expert panel addressing arsenic mechanisms and expects to receive a report from the National Research Council on issues in arsenic risk assessment. This effort will synthesize newer information relevant to arsenic risks in a form that will support Agency management decisions for arsenic. Several studies have been published that indicate arsenic exposures induce internal cancers. These findings will be examined and quantitative information on rates of occurrence of internal neoplasms will be evaluated in relationship to the current risk estimate for skin cancer.

Based on information currently available data and assessments (including the IRIS summary and the mechanisms workshop report), ORD will work with OW to develop risk information to assist OW, the Regions, States, and local communities in dealing with arsenic-contaminated drinking water and permitting issues. The focus of this effort will be information to assist in the evaluation of risks from arsenic concentrations in the 2-50 µg/L range of regulatory interest. High priority; intramural and extramural.

1c. Assessment of Exposure Data

This effort will focus on the development of a risk assessment of existing exposure data to investigate background exposures and speciation, and will examine relationships between intake/blood/urine levels. This information will also be integrated with hazard and dose-response information to address integrated risks from arsenic exposures. The goal is to provide a range of risk estimates for various exposed populations and compare relationships for adult and child levels and media, i.e., diet and water. Data from an ongoing EPA cooperative study with Harvard will be analyzed, as well as data from exposure databases such as NHEXAS and NHANES 3. A risk characterization summary will be developed for use in risk characterization for drinking water exposures. This research links with exposure task 5a.
High priority; intramural and extramural.

Risk Assessment Issue 2. Innovative approaches in arsenic risk assessment —Long-term

2a. Evaluation, integration, and modeling of new data on arsenic health effects and mechanisms

The goal of this effort is to integrate future data on arsenic epidemiology and mechanistic research into the hazard and dose-response assessment for arsenic. As appropriate, this effort would include evaluation of the feasibility and development of new risk models. Revised health effects evaluations and decisions regarding model development would build upon additional studies addressing arsenic effects, metabolic rate, tissue dosimetry, and/or arsenic mechanisms. Research directions for human or animal studies are described in the Health Effects chapter. This research is medium priority pending development of new information and therefore will be given a higher priority in out years.
Medium priority; intramural.

2b. Development of Predictive Risk Assessment Models and Tools for Assessing Arsenic Interactions

There are several studies suggesting a strong interrelationship between arsenic and various trace minerals and essential elements. These studies indicate that arsenic interacts with these elements both environmentally and biologically. Interactions with selenium and zinc have shown a reduction in arsenic-induced toxicity, while interactions with lead and cadmium may increase toxicity. The goal of these studies would be synthesize data on interactions and, where feasible, develop predictive models to assess the potential interactions of arsenic with other elements in drinking water. This project would address mechanistic issues regarding arsenic interactions, e.g., additivity of arsenic toxicity for noncancer toxic effects based on the possible interactions. Information can contribute to biologically-based risk assessment by taking into account interactions of arsenic with trace minerals and essential elements. Development of assessment dependent on data feasibility.
Medium priority; intramural and extramural.

Specific projects and products relating to these issues and their status, use and time frame are outlined in Tables 1-1 and 1-2.

2. Exposure to Arsenic Species: Analysis Methods and Human Exposures

2.1. Background

Arsenic in surface and ground water originates from both geological and anthropogenic sources. The geographic distribution of arsenic in surface and ground waters in the United States has been estimated (Frey and Edwards, 1997). Based on a national survey of 140 utilities, representing 36% of the U.S. population, it has been projected that ~15% of the U.S. population is exposed to arsenic in drinking water at levels greater than 2 µg/L (ppb). These estimates drop to 5% and

2% for arsenic concentrations of 5 µg/L and 10 µg/L, respectively (Davis et al., 1994). The reliability of this estimate at 2 µg/L is of some concern given the detection limits of the analytical methods used and the variability associated with analytical measurements near the detection limit. Much higher levels in drinking water (i.e., in excess of 80 µg/L) have been reported in isolated areas in the western United States. These elevated concentrations are commonly, but not exclusively, associated with ground waters (Frey and Edwards, 1997). Arsenic in drinking water is predominately inorganic and is comprised of arsenate (arsenic (V)) and arsenite (arsenic (III)). These inorganic species can interconvert, depending on the oxidative or reductive nature of the water. Inorganic arsenic occurs in drinking water mainly in the form of arsenate, although arsenite has been reported in waters that are anaerobic or very low in dissolved oxygen (ATSDR, 1993). Air levels of arsenic in the United States[5] have a reported range of average site concentrations of 0.01 to 0.45 µg/m^3 (Borum and Abernathy, 1994).

Arsenic is extremely mobile in the aquatic environment. Naturally occurring and anthropogenic arsenic compounds are assimilated into many foods with the highest concentrations found in fish, shellfish, meats, and grains. Arsenic in the environment is metabolized, resulting in a transformation (biological methylation) of some of the arsenic to organic forms (i.e. monomethylarsionic acid (MMA), dimethylarsinic acid (DMA), arsenosugars, arsenobetaine and arsenocholine) that are found in certain foods. This biotransformation can influence the toxicity of the arsenic. For instance, marine fish and shellfish are high in forms of arsenobetaine that are considered to be essentially nontoxic (ATSDR, 1993). Using a "total" arsenic content of foods to evaluate dietary exposure (µg/day) is not an accurate risk indicator because of the toxicity differences of the various arsenic species, which are merely added together in a nonspeciated arsenic exposure assessment. The arsenic species, in at least organic and inorganic fractions, need to be determined to adequately characterize risk.

Arsenic physiologically found in the form of arsenate is first nonenzymatically reduced to arsenite and then undergoes enzymatic methylation to MMA and DMA in the liver (Styblo et al., 1996). Methylated metabolites, arsenate and arsenite are primarily excreted in urine. The concentrations of these metabolites in urine are generally accepted as the most reliable and toxicologically relevant indicator of recent or ongoing arsenic exposure. Arsenic in hair and fingernails is considered a better indicator of past exposure. Blood concentrations of arsenic species are also relevant indicators of recent high-dose arsenic exposure, are less susceptible to contamination during collection, and provide greater likelihood of maintaining the arsenicals in their ingested forms.

Problems in quantifying environmental exposure contribute to uncertainties in the exposure-dose-response chain in human epidemiologic studies and arsenic risk assess-

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[5]Data from the Aerometric Information Retrieval System (AIRS) air monitoring database of the EPA Office of Air Quality Planning and Standards (OAQPS) for the years 1980-91; based on a reporting limit of 0.01 µg/m^3, arsenic was detected at 118 of 257 sampling sites.

Table 1-1. Risk Assessment Research Strategy Matrix for Arsenic

Issue	Task	Product	Use*
RA. Issue 1. Risk assessment and risk characterization of arsenic—Short-term	RA Task 1a. Mode of action workshop High Priority	Refinement of risk estimate for arsenic, revise IRIS summary, provide information for mechanistic studies	Development of MCL-OW, States and local communities, ORD, OSWER
	RA Task 1b. Synthesis of data to support arsenic risk assessment and risk characterization High Priority	Improved risk characterization of arsenic assessment, revised IRIS summary	Support for MCL-OW, OSWER, DOE
	RA Task 1c. Assessment of exposure data High Priority	Determination of existing exposure information for risk assessment	Development of MCL-OW, States and local communities, ORD, OSWER
RA. Issue 2. Innovative approaches in arsenic risk assessment—Long term	RA Task 2a. Evaluation, integration and modeling of new data on arsenic health effects and mechanisms Medium Priority	Assessment of new data, refinement of risk estimates and characterization	Research planning in ORD, Regions, States
	RA Task 2b. Development of predictive risk assessment models for arsenic interactions Medium Priority	Improved risk characterization and revised assessments	States and Regions, DOE, OSWER development of regulations and permits. May impact future MCL

*OW = Office of Water; ORD = Office of Research and Development; OSWER = Office of Solid Waste and Emergency Response; DOE = Department of Energy

Table 1-2. Risk Assessment Task Summary, Current Activities and Proposed Sequence for Studies

Short Study Title	Task[1]		Ongoing	Priority	Time Frame[2]					
	I	E	Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
RA Task 1a. Mode of action workshop— Short-term	I	E	Completed	High	EPA					
RA Task 1b. Synthesis of existing and new data— Short-term	I	E	Y	High	EPA	EPA	EPA			
RA Task 1c. Assessment of exposure data— Long-term	I	E	N	High			EPA	EPA		
RA Task 2a. Evaluation and integration and modeling of new data— Long-term	I	E	N	Medium			EPA	EPA	EPA	
RA Task 2b. Development of predictive models for interaction—Long-term	I	E	N	Medium			EPA	EPA	EPA	

[1]I = Intramural (EPA inhouse research), E = Extramural (EPA sponsorship through grant or coop)
[2]EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort

ment. For example, measuring As species is basic to improved exposure assessment in future epidemiologic studies as well as for exposures studies to be used for the exposure assessment portion of the risk assessment/characterization. This chapter describes key exposure-related issues and research needed to address arsenic exposure and risk assessment. These research issues include estimating species-specific arsenic exposure from environmental media (water, soils, diet) and estimating the bioavailability of arsenic species from various media including biomarkers of exposure.

2.2. What Analytical Methods are Needed for Determining Arsenic in Exposure Assessment Media?

2.2.1. State of the Science.

The word *total* could be a point of confusion in the following sections because *total* in an exposure study often refers to the consideration of all possible exposure routes. In an analysis context, as used below, the word total refers to chemical analysis of the total arsenic content in a sample. When discussing all possible exposure routes, the term "multipathway" will be used. Speciation is another word which can lead to confusion. Speciation is defined as the separation, identification, and quantification of the chemical forms of arsenic. This separation can be as simple as inorganic arsenic from organic arsenic or as complex as complete separation into individual arsenicals. The appropriate degree of speciation is often dependent on the application.

Analytical methodologies which are used for arsenic monitoring under the Safe Drinking Water Act, Clean Water Act, and Resource Conservation and Recovery Act all report "total" arsenic. "Total" arsenic is defined as the solubilized arsenic within the sample after a digestion with hot mineral acids (U.S. EPA, 1971). The digestion oxidizes the matrix (soil, food, biological), solubilizing the available arsenic species without regard to the chemical form or oxidation state of the arsenic. These analytical methodologies, written by EPA (1994a, 1986a), ASTM (1995), SM (1995), NIOSH, and USGS, include guidance on sample preservation, laboratory sample handling, and sample digestion. Atomic spectroscopy is the foundation of these analytical methodologies for determining total arsenic in air, water, soils, foods, and biological fluids. For instance, total arsenic in the FDA's market basket of common foods is determined using an aggressive digestion followed by hydride generation coupled to an atomic absorption spectrometer. These methods provide detection limits as low as 100 ppt (ng/L) by direct analysis using an inductively coupled plasma mass spectrometer (ICP-MS).

Virtually all the data available for arsenic exposure assessment is based on total arsenic determination. Total arsenic concentration is a relatively poor indicator of the risk associated with an arsenic exposure because the chemical form of the arsenic strongly influences its toxicity (ATSDR, 1993). The total arsenic digestion used in EPA, USGS, NIOSH, FDA, ASTM, and SM, methodologies changes the chemical form of the arsenic, resulting in a complete loss of species-based

toxicity information. Therefore, certain aspects of characterization of arsenic exposure require species-specific analytical methodologies capable of providing reliable individual arsenical concentrations.

Speciation-based arsenic analysis partitions the total arsenic into at least inorganic vs. organic fractions prior to detection. The analytical difference between total and speciation-based methodologies is that the speciation-based methods preserve the chemical form and separate the individual arsenic species prior to detection. This analytical difference implies the need to ensure species-specific integrity from sampling to detection. In terms of instrumentation, an interface to chromatographic techniques (liquid chromatography (LC), ion chromatography (IC), capillary electrophoresis (CE)) is required. In this respect, a speciation-based method is analytically very different from a total arsenic determination. To date, these differences have *not* been adequately addressed in the form of arsenic speciation methodology by the EPA, FDA, USGS, NIOSH, ASTM, or SM. In speciation-based analysis, separation schemes (IC, HPLC, CE) have been interfaced to hydride atomic absorption (Gailer and Irgolic, 1994; Hasegawa et al., 1994; Lopez et al., 1993; Haswell et al., 1985); inductively coupled plasma atomic emission spectrometer (ICP-AES) (Alberti et al., 1995; Low et al., 1986; Valez et al., 1995); and inductively coupled plasma mass spectrometer (ICP-MS) (Beauchemin et al., 1989; Hansen et al., 1992; Thomas and Sniatecki, 1995; Story et al., 1992; Hwang et al., 1994; Branch et al., 1994; Larsen et al., 1993a,b; Le et al., 1994a; Magnuson et al., 1996a) for the speciation of arsenic in a variety of matrices. These manuscripts demonstrate a particular aspect of an analytical approach or a unique capability in the area of arsenic speciation. They represent the state-of-the-art in chromatographic technology and innovative detection schemes, but they seldom address all the aspects necessary to formulate an analytical methodology. A complete methodology should address the following questions: 1) What sampling protocol will assure species-specific integrity? 2) How can the matrix be eliminated without the destruction of speciation-based information? 3) What components of a matrix cause spectral and chromatographic interferences?

The peer reviewed literature contains references for the speciation of arsenic in water (Hasegawa et al., 1994; Haswell et al., 1985; Hwang et al., 1994; Thomas et al., 1995; Magnuson et al., 1996a); biologicals (Arbinda et al., 1995; Heitkemper et al., 1989; Larsen et al., 1993b; Low et al., 1986; Story et al., 1992); and foods (Alberti et al., 1995; Beauchemin et al., 1989; Branch et al., 1994; Larsen et al., 1993a; Le et al., 1994a; Lopez et al., 1993; Velez et al., 1995). While these manuscripts represent the technical framework for a method, considerable research will be required before they can be adopted as exposure assessment tools by the Agency. The major analytical challenge will be assuring that the arsenic species within the sample are the same as those detected, i.e., that the extraction, preparation, separation, and detection do not alter the distribution of arsenic species.

The following research issues provide some general direction and time frames for refinement of arsenic speciation methods that are needed in all aspects of arsenic

research. Research should focus on refinement of the existing analytical capability, followed by method validation. The ideal approach would be to develop an extraction and sample preparation scheme that is compatible with a flexible and cost-effective separation and detection scheme. Finally, emphasis in developing a speciation method should be placed on demonstrating the procedure's capability of assuring species-specific integrity from sampling through detection. This preservation procedure must be compatible with the analytical detection scheme and allow for field implementation. The integrity of the species is critical to exposure, epidemiologic, toxicologic, and pharmacokinetic investigation.

Sample Preservation and Preparation: Many liquid samples can be analyzed with little preparation, but the extraction of species-specific information from solid samples is a relatively new area (Alberti et al., 1995; Larsen et al., 1993a; Le et al., 1994a; Valez et al., 1995). Therefore, solids (foods) and tissue-based matrices requiring speciation information are longer term projects (3-5 years), as opposed to the speciation of arsenic in water (Hwang and Jiang, 1994; Hasegawa et al., 1994; Haswell et al., 1985; Thomas and Sniatecki, 1995; Magnuson et al., 1996a) and urine (Larsen et al., 1993b; Low et al., 1986; Story et al., 1992) (1-3 years).

Separation Techniques: The separation system (LC, IC, CE) should provide relatively short analysis times, tolerate diverse matrices, e.g., drinking water and urine, and be compatible with sensitive but conventional detectors. Given the current state of the science in the separation of arsenicals, IC demonstrates a good balance of the above attributes (Arbinda et al., 1996; Martin et al., 1995; Magnuson et al., 1996a). An IC separation for arsenite, arsenate, MMA, and DMA has been demonstrated (Magnuson et al., 1996a) in the literature, making its evaluation a short-term project (1 year). On the other hand, CE has shown some initial capability (Magnuson et al., 1996b), but this approach has sample injection and matrix limitations, which would require considerable research, making it a long-range goal (3 years).

Detection: The cost-effectiveness of speciation will be driven by the capability of the separation scheme to be interfaced to existing instrumentation such as atomic absorption, ICP-AES and ICP-MS. These detector interfaces are similar to those used in total arsenic methods, making their adaptation easier and less research intensive (short-term, 2 years). The applicability of atomic absorption and ICP-AES to the detection of environmentally significant concentrations of arsenic species would be limited without the use of hydride generation to improve sensitivity. Hydride generation affords some freedom in choosing a mobile phase for the chromatographic separation but adds to the instrumental complexity. The use of hydride generation will require an on-line digestion prior to detecting the highly derivatized arsenicals, i.e., arsenobetaine.

2.2.2. Ongoing EPA Research.
The ongoing research in the area of arsenic speciation has focused on utilizing a membrane gas liquid separator with ICP-MS detection. This work has evaluated separation schemes (LC and CE) for the speciation of arsenic in saline matrices. These saline matrices have some of the same analytical difficulties associated with biological matrices (blood and urine), therefore, the initial use of saline matrices represent a logical analytical progression towards biological media. This approach will produce a more sensitive method for exposure measurement purposes.

2.3. What Data are Required to Adequately Assess Arsenic Exposure in Human Populations?

2.3.1. State of the Science.
Arsenic exposure assessment requires evaluation of the relative contribution of (1) *media* (e.g., water, food, dust), (2) *pathways* (e.g., drinking water, diet, hand-to-mouth) and (3) *routes* (e.g., oral, inhalation, dermal) of exposure. For non-occupationally exposed individuals, studies have indicated that uptake of arsenic via dermal exposures from soil and water and inhalation are minor contributors to total exposure; whereas intake from food and water are the most significant environmental arsenic exposure (ATSDR, 1993; Borum and Abernathy, 1994). The major exception to this might be populations in the vicinity of arsenic emitting industrial facilities or areas where soils are contaminated with arsenic. Food is generally estimated to be the major contributor to total arsenic exposure. However, estimates for the contribution of drinking water to total human arsenic exposure vary between 63% and 22%, depending on the assumptions used in the analysis, and could be up to 99% in some areas in the western United States where there is low consumption of fish and shellfish (Borum and Abernathy, 1994). For example, Native American and Alaska Native studies have indicated average seafood consumption rates up to ten times greater than the U.S. EPA average estimate of 6.5 gram/day (CRITFC, 1994; Wolfe and Walker, 1987; George and Bosworth, 1988; Nobmann et al., 1992; Tulalip Tribe, 1996). For these populations, total arsenic derived from seafood and other foods may be important exposure sources in addition to drinking water. Such exposure assessments need to consider species-specific toxicity of the various arsenic forms to accurately assess the risk.

In most epidemiologic studies used for quantitative risk estimation of ingested arsenic, only nonspecialized arsenic intake data are available for drinking water and food. This may not be a serious limitation in situations where drinking water (predominately inorganic arsenic) can be verified to be the major source of arsenic exposure. The degree to which this is a limitation in the United States is difficult to determine because of the lack of a national occurrence database for arsenic in drinking water. However, the contribution of diet to human exposure of arsenic should be considered a potentially important issue for any population because less than half of the water ingested is in the form of drinking water. Drinking water is also ingested as part of foods or beverages (e.g., coffee, tea, juices). Where arsenic levels in public drinking water supplies are relatively low, the contribution of food to total arsenic exposure be-

comes a more important factor. Estimates of total arsenic ingested from foods and beverages often exceed the EPA RfD which is based on inorganic arsenic. The assessment of risk associated with this dietary ingestion will depend on the distribution of arsenicals in various foods and their relative toxicities (i.e., arsenobetaine vs. arsenite). Efforts to estimate arsenic intakes from food compared to drinking water have been limited given the lack of data.

The critical issue for arsenic in foods is whether the form of arsenic is organic or inorganic. Certain organoarsenicals found mainly in seafoods are considered to be virtually nontoxic (arsenobetaine) and others (e.g., methylarsonic acid, DMA) have markedly different toxicologic properties compared to inorganic arsenicals. A recent report from U.S. EPA Region 10 indicates that marine seafood contains predominately arsenobetaine, while inorganic arsenic, MMA, and DMA are found at lower concentrations (U.S. EPA, 1996a). Species-specific data for arsenic (inorganic vs. organic) in food are limited. Inorganic arsenic is found in meats, poultry, dairy products and cereals, whereas the organic forms are predominantly found in fruit, vegetables, marine fish, shellfish, and seaweed (U.S. EPA, 1988; Velez et al., 1996; U.S. EPA, 1996a). Currently systematic, comprehensive studies have not been conducted to evaluate the forms of arsenic in typical U.S. diet(s). Current market basket surveys conducted by FDA analyze only total arsenic (Gunderson, 1995a,b), as have the more comprehensive diet studies reported from other countries (e.g., Dabeka et al., 1993). NHEXAS[6] does a thorough job of evaluating multimedia/multipathway exposures; however, it measures only total arsenic. This will be especially useful in identifying the most significant pathways. Several U.S. EPA Office of Water databases also provide useful arsenic occurrence data for drinking water but are also limited to total arsenic. These databases are the National Inorganic and Radionuclide Survey (NIRS), the National Organic Monitoring Survey (NOMS) and the Federal Reporting Data System (FRDS).

Both EPA and other federal food regulatory agencies must have improved information on toxic forms of arsenic in both specific foods as well as in the foods that comprise the normal daily diets of the U.S. population or its specific high-risk subpopulations. Therefore, analytical methods must be established that perform well for both individual food items (i.e., fish) and for broader food groups and diets that represent total daily ingestion. Species-specific arsenic data on specific foods provides the EPA with an accurate risk assessment tool for supporting its regulatory activities, such as fish advisories, and to identify populations at risk. Species-specific analytical procedures for broader food groups and total daily diets will allow evaluation of information obtained in EPA's measurements programs.

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[6]NHEXAS is the National Human Exposure Assessment Survey being conducted via three consortia in the U.S. in which one of the main goals is to evaluate multipathway, multimedia exposure and relative source contribution by analysis of chemicals of interest in drinking water, tap water, indoor and outdoor air, dust, soil, biological samples and food.

Bioavailability of arsenic species from foods is a related issue. The bioavailability of inorganic arsenic from foods compared to water has not been systematically evaluated, although soluble forms of inorganic arsenic are generally assumed to be highly bioavailable (U.S. EPA, 1984). Overestimation of inorganic arsenic exposure from foods will result in overestimation of risk from arsenic in food. Another related issue is bioavailability of arsenic from soils, which can be an important issue for populations where soils have been contaminated as a consequence of agricultural or industrial activity (Bhumbla and Keefer, 1994). Soil ingestion can be an important risk factor for young children. Soil bioavailability of arsenic can be considerably lower than its bioavailability from water and is impacted by factors such as water solubility of arsenic compounds found in soil (Davis et al., 1996; U.S. EPA, 1996b). The issue of bioavailability from food (and soil depending on the study population) is one that requires formal consideration in any study in which the contribution of food to total exposure is evaluated. This will be discussed in the next section.

2.4. How Can Biomarkers and Bioavailability Data be Effectively Used to Estimate Arsenic Exposure and Uptake?

2.4.1. State of the Science.
Arsenic levels in blood, hair, nails, and urine have all been used as bioindicators of exposure. Blood arsenic is used in poisoning cases as an indicator of acute high level exposure. Poor correlations have been reported between arsenic concentrations in drinking water and blood arsenic levels because arsenic is cleared rapidly from the blood. Arsenic in nails and hair is considered a reliable indicator of exposures that occurred 1 to 10 months earlier, assuming that external contamination of the samples has been eliminated. However, studies that quantitatively correlate past levels of arsenic exposure with arsenic in hair and nails are lacking and are needed for epidemiological studies.

Total urinary arsenic and speciated metabolites in urine are used as indicators of more recent arsenic exposure. It is highly desirable to determine the different arsenic metabolites (arsenite, arsenate, MMA and DMA) in urine, rather than simply using total urinary arsenic. Essentially nontoxic organoarsenicals (e.g., arsenobetaine) found in certain seafoods and excreted in the urine could otherwise lead to overestimation of arsenic exposure when only total urinary arsenic is measured (Klaassen and Eaton, 1993). A major issue that arises with the use of speciated arsenic metabolites in urine is the potential for misinterpretation of data due to the presence of MMA and DMA in urine that is not derived from the metabolism of inorganic arsenic. The issue arises because certain marine fish and shellfish, as well as seaweeds, contain both MMA and DMA, which are excreted in the urine when these foods are consumed (Velez et al., 1996; Le et al., 1994; Buchet et al., 1994, U.S. EPA, 1996a). Various means that have been used to address this issue include: obtaining diet histories from study participants, prohibiting the consump-

tion of certain foods prior to the study, and collecting and analyzing duplicate diet samples. It has also been pointed out that further investigation is needed to identify other arsenic-containing foods in the diet and assess their effect on urinary excretion of arsenicals (Vahter, 1994).

Other than arsenic levels in hair, nails, and blood, there are few biological markers of arsenic exposure. Biomarkers emerging from the research described in Chapter 3 have the potential to improve the sensitivity and specificity of exposure measurements. In addition, biomarkers may make it possible to determine the impacts of various factors such as genotype that could impact human susceptibility to arsenic exposures. One promising biomarker is using blood cell chromosomal mutations as an indicator of arsenic exposure.

As indicated above, the amount of each arsenic species absorbed is very important to the overall determination of risk. The bioavailability of each arsenic species found in water and food constituents is an extremely important component of determining the relative source contribution of arsenic exposure from water and diet. The relative source contribution is used to determine an MCLG based on noncancer health effects (U.S. EPA, 1994). Bioavailability studies need to be conducted on each of the arsenic species found in the exposure media of water, soils, and food.

2.5. Proposed Exposure Research

The following exposure issues are not listed based on research priority. They are listed based on the progression within the chapter. The temporal analytical needs of certain tasks have been considered in assigning priority.

Exposure Issue 1. Develop Arsenic Speciation Methodology to Separate Arsenite From Arsenate to Support Water Treatment Decisions in Large and Small Utilities

1a. Evaluate Analytical Techniques for Inorganic Arsenite and Arsenate Speciation in Water

The ability to speciate the valence states of inorganic arsenic may be significant because the treatment processes remove arsenate more efficiently than arsenite, and therefore, it could be beneficial to determine the oxidation state prior to devising a treatment approach for arsenic. However, in normal operation most treatment approaches will tend to convert arsenite to arsenate, and it may not be important to differentiate arsenite from arsenate routinely. This technique will help to establish the best available treatment for drinking waters which are found to contain arsenite. This work could be utilized in the revised arsenic rule in 2000.
(1a High Priority; Short-term)

1b. Evaluate Sample Preservation Techniques for Arsenic Species

The preservation of the individual arsenicals from sampling to detection is a concern in all aspects of the analytical methods. Preservation is not listed as a subtask within other issues but it should be understood that it is of primary concern within all speciation based analysis. This work could be utilized in the revised arsenic rule in 2000.
(1b High Priority; Short-term)

This research will enable measurement of major As species to support decision making to evaluate the best available treatment technology and provide analytical monitoring capability for MCL compliance. Development of analytical methods for water will provide the technological basis for proceeding with development of methods for analysis of more complex matrices.

Exposure Issue 2. Develop Extraction Methods for Inorganic and Organic Arsenicals in Foods to Allow for the Separation and Detection of Individual Arsenic Species in Foods

The primary need is for analytical methods that will allow measurement of the inorganic and organic fractions of arsenic in food. A secondary priority is the ability to distinguish the specific organic forms (e.g., MMA and DMA) that may be of toxicological concern.

2a. Methods for Speciation in Target Food Items (e.g., seafood)

The ability to speciate arsenic in certain foods provides the EPA with an accurate method for supporting its regulatory activities, such as fish advisories. Speciation based methods also are required in research to identify foods and food groups that are associated with the more toxic forms of arsenic so that exposure evaluations accurately reflect the relative importance of foods as compared to other media and exposure pathways.
(High Priority; Short-Term/long-term)

2b. Methods for Speciation in Composite Daily Diet (i.e., duplicate diets)

EPA measurements of human exposure from multiple pathways requires collecting, compositing, and analyzing 24-hour duplicate diet samples for direct comparisons of dietary exposure to other concurrent pathways of exposure. Speciation- based analysis will allow population exposure assessments which accurately quantify the risk associated with diet. The ability to speciate the arsenic in duplicate diet samples will also provide the basis for assessing the bioavailability of ingested arsenic.
(Medium Priority; Long-term)

2c. Impact of Food Preparation on the Distribution of Individual Arsenicals

Develop methodologies to evaluate the effects of preparation and cooking on the distribution of

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arsenicals in ready-to-consume foods. The thermal and chemical environments that the organic and inorganic arsenic species are exposed to during cooking may cause an interconversion of the arsenic species. To date, this interconversion in prepared foods has not been reported in the chemical literature. If this conversion is documented, the priority of this task may require some reconsideration.
(Low Priority; Long-term)

These research areas will address the relative source contribution of arsenic ingestion via diet and improve mass balance data for humans including all ingestion routes. This information could be useful in Effects Issue 3a and Exposure Issue 5, 6 and 8. Research and development of species specific analytical methods must be shared by EPA and other federal food regulatory agencies such as FDA and USDA. EPA research should focus on the analytical procedures that directly support its programs, namely evaluation of dietary intake in ORD total human exposure monitoring programs and risk evaluations for regulatory programs.

Exposure Issue 3. Development of Arsenic Speciation Methodologies in Biological Matrices to Support Exposure Assessment, Bioavailability, and Biomarker Research

3a. Refine and Evaluate an Analytical Approach for the Separation of Arsenite, Arsenate, MMA, DMA and Arsenobetaine in Urine

3b. Refine and Evaluate an Analytical Approach for the Separation of Arsenite, Arsenate, MMA, DMA, and Arsenobetaine in Blood

3c. Refine and Evaluate Analytical Approaches for Speciation of Arsenic to Support Bioavailability Investigations

3d. Refine and Evaluate Analytical Approaches for Speciation of Arsenic in Tissues

The capability of speciating arsenic in biological fluids provides a means of measuring recent exposures to arsenic. This speciated information may indicate the source of the exposure, for instance, high arsenobetaine concentration may indicate a diet high in seafood. The ability to speciate arsenic in all exposure routes provides a unique capability to address the bioavailability (Exposure Issue 8) of the arsenic from the various routes. In addition, this speciation information can be used in identifying a biomarker Exposure Issue 7, Effects Issue 2a) for arsenic.
(3a High Priority; Short-Term, 3b, 3c, 3d, Medium Priority; Long-term)

In pharmacokinetic and mechanistic studies of arsenic, it will be important to be able to distinguish between inorganic arsenic, MMA, and DMA. Ideally, analysis would also differentiate between arsenite and arsenate,

although this may be more difficult to achieve and is therefore a longer term priority. Current toxicological studies are proceeding with the use of radiolabeled arsenic; the eventual availability of non-radio-labeled species-specific methods for biological matrices will be a valuable research tool. These areas have been identified by AWWARF (1995) as high priority projects in arsenic research. The priority assigned above is an indicator of short-term analytical achievability and the use of urine as a primary arsenic exposure indicator.

Exposure Issue 4. Development of Liquid and Solid Species Specific Standard Reference Material for Arsenic in Water, Foods, Urine, and Tissues

4a. Refine and Evaluate a Standard Reference Material for Foods that Provides Species Specific Concentrations of Arsenic

4b. Refine and Evaluate a Standard Reference Material for Biological Tissues that Provides Species Specific Concentrations of Arsenic

4c. Refine and Evaluate a Standard Reference Material for Water, Blood and Urine that Provides Species Specific Concentrations of Arsenic

The development of standard reference materials (SRM) for arsenic that are species specific is an area of research which is fundamental to all speciation based analytical methodology. This research will provide the analytical community the capability of evaluating the developed methodologies accuracy in terms of species specific concentration and provides a means of assuring species specific integrity. This work has an impact on all species specific exposure issues.
(4b Medium Priority; Long-term, 4a, 4c High Priority; Long-term)

This research area will provide the necessary QA/QC materials for speciation based exposure assessment. This research will be conducted primarily by NIST and NRCC. The priority assignments are made based on analytical feasibility and temporal consistency with Exposure Issue 3 and Exposure Issue 2.

Exposure Issue 5. Dietary Exposure Assessment Studies for Populations with High Dietary Intake of Foods Associated with Toxic Species of Arsenic

5a. Dietary Exposure Assessment Studies of Arsenic Species for Typical U.S. Diets and Highly Exposed Subpopulations

High dietary total arsenic exposure can occur because of low levels of arsenic in many foods consumed or because of very high levels in a few foods. The later is usually associated with unique populations whose dietary habits differ from the norm. Studies are needed to evaluate the species of arsenic in the array of foods in the typical U.S. diet and to identify diets containing high levels of the toxic forms of arsenic. The amount and variability of exposure

from food and beverages needs to be quantified for various populations, taking into account demographic characteristics. This could be accomplished by modeling and/or by direct measurement. Neither procedure can be accomplished until analytical methods for speciation of foods are available and a database is created on species-specific arsenic levels in foods. Modeling will utilize species-specific information for food groups and items combined with information on dietary consumption to identify high risk populations. Measurements consistent with market basket collections of the foods consumed by the U.S. populations and specific high risk subpopulations will be used in this modeling. Inclusion of biomarkers in these studies will aid in addressing the species specific adsorption rates of arsenic from ingested food.
(High Priority; Long-term)

This research will address relative source contribution issues with dietary ingestion of arsenic while targeting subpopulations which may have evaluated risk factors associated with dietary ingestion. This information may be helpful in future epidemiology studies and could be used as a relative source contribution estimate for exposure assessment of subpopulations. This is consistent with Exp. Task 4a.

Exposure Issue 6. Development of National Database on Arsenic Occurrence and Concentrations in Water for Use in Epidemiological Studies and Agency Regulatory Activities

> 6a. Development of a National Database on Arsenic Occurrence and Concentrations in Water.

Present databases do not report occurrence and concentrations of arsenic by species in the various media. Also, large amounts of the data on arsenic in drinking water only report arsenic levels that exceed the current MCL of 50 µg/L. As speciation and low-level arsenic detection data continues to be developed in water supplies, there will be a need to assemble this evolving data into a national database on arsenic. This work will act as a refinement of the near-term need to evaluate the currently available databases for use in epidemiological studies and Agency risk assessments/risk characterizations/risk management activities. The research on arsenic occurrence and concentration in water will be primarily conducted by OW with some ORD collaboration.

Future work may be done in soils and diet. This work is of lower immediate priority because it relies on the development and implementation of other research before being feasible.
(High Priority in Water; short-term, Medium Priority in Diet; long-term)
The Office of Water is required to establish a national contaminant occurrence database, which will include arsenic. However, this effort is due to be established by August 1999, which is too late for use in the short-term arsenic proposal. For the proposal, OW is assessing data from many sources for exposure and occurrence projections and regulatory decisions.

Exposure Issue 7. Biomarkers of Exposure in Biological Media

> 7.a. Development of Biomarkers of Exposure in Bio-Media for Use in Epidemiological Studies

The exposure in most drinking water epidemiological studies has been based on the concentration of arsenic in drinking water and food. The analytical measurements used before 1970 to measure arsenic have questionable precision at low concentrations. The use of biomarkers of exposure that would potentially measure the dose and reduce misclassification bias would be desirable in epidemiological studies. Development of these biomarkers tools will improve the precision of the risk estimate.
(High Priority if feasible; long-term)

This exposure issue is related to the analytical development of speciation in Exposure Issue 3a and the QA/QC Exposure Issue 4c. The support of future epidemiology within this exposure issue is related to Effects Issue 2a and 3a.

Exposure Issue 8. Bioavailability of Arsenic

> 8a. Conduct Research to Determine the Bioavailability of All Arsenic Species Found in Water, Soils, and Food Constituents

Arsenic species are only a systemic risk if the ingested arsenic is absorbed from the gastrointestinal tract in a form that is biologically relevant. The question of how much inorganic arsenic vs. organic arsenic found in urine came from the exposure media and how much is a result of biotransformation in the body is also important for assessing exposure risks. Bioavailability studies using newly evolving analytical techniques to speciate arsenic will greatly enhance our ability to assess the relevant risks from each arsenic containing media and allow for more precise estimation of the relative source contribution that arsenic levels in water have to the overall arsenic exposure. The priority of the research is Medium for the near-term because the analytical methods are not available and need to precede this research.
(Medium Priority based on sequencing with other research products; long-term)

Specific projects and products relating to these issues and their status, use and time frame are outlined in Tables 2-1 and 2-2.

3. Health Effects: Hazard Identification and Dose-Response

3.1. Background

This chapter discusses the research questions that address hazard identification and dose- response assessment associated with arsenic exposure. Hazard identification research involves the development and application of methods that demonstrate a qualitative relationship between exposure and effect. Dose-response research then characterizes this relationship to link dose with incidence and severity of effect consider-

ing the mechanism(s) by which arsenic exerts its toxicity. Factors that influence dose-response are also evaluated. This information is then used to develop quantitative models for estimating risk. The arsenicals discussed here include inorganic and organic forms.

3.2. What are the Health Effects Associated with Arsenic Exposure?

Unlike most environmental contaminants, there is a large human database available for inorganic arsenic. The health effects of ingested inorganic arsenic include skin and internal cancers and noncancer-related effects on skin, vascular and gastrointestinal systems, and liver. Inorganic arsenic has also been linked with developmental toxicity. Numerous epidemiologic investigations have consistently reported an association between arsenic exposure in drinking water and cancer. It is interesting to note that this effect has not been demonstrated in arsenic ingestion studies with animals. Having a comparable experimental model system would be useful to better understand the mechanisms of arsenic-induced health effects. While there is a substantial human database for inorganic arsenic, there are a number of uncertainties over the interpretation of these data and their application in risk assessment. Experimental data on the effects of organic forms of arsenic are not as well characterized and thus may be a subject for future research. Limited data in animals indicate that some organic forms of arsenic also produce cancer and noncancer health effects.

3.2.1. State of the Science.
Available information on the health effects of inorganic arsenic and other arsenic species has been discussed in several documents (U.S. EPA, 1988, 1993; ATSDR, 1993).

3.2.1.1. Carcinogenic Effects in Humans — Epidemiological studies conducted in several countries including Taiwan, Mexico, Chile, Hungary, England, Japan, and Argentina have reported an increased incidence of skin cancer in exposed populations (Tseng et al., 1968; Chen et al., 1986; Cebrian et al., 1983; Tsuda et al., 1990; Cuzik et al., 1992). Several of these studies have also reported and analyzed an association between inorganic arsenic ingestion and increased mortality from internal cancers such as liver, bladder, kidney, and lung (Chen et al., 1986; Tsuda et al., 1990; Hopenhayn-Rich et al., 1993; Smith et al., 1992). Studies conducted in the United States have not demonstrated an association between inorganic arsenic in drinking water and skin cancer. The design of the U.S. studies were limited, having insufficient statistical power to detect the effects of concern. The largest epidemiology study is the Taiwan study (Tseng et al., 1968), which also serves as the basis for the current EPA cancer risk assessment (see Chapter 1). In this study, an increased prevalence of skin cancer was observed among approximately 40,000 Taiwanese consuming arsenic contaminated water (up to 1,200 µg/L arsenic) from artesian wells as compared with approximately 7,500 residents from Taiwan and a neigh-

boring island, Matsu, consuming "arsenic free" (0-17 µg/L arsenic) water.

3.2.1.1.1. Ongoing EPA Research. Currently, ORD is conducting a cohort mortality study on approximately 4,000 individuals in Utah. Individuals living in areas with historically high background levels of arsenic will be compared with others living in an area where arsenic concentrations fall within the MCL limit for arsenic. Specific cause of death for cohort members will be compared with deaths for the State of Utah. The cohort was originally ascertained through the historic Mormon Church (Church of Jesus Christ of Latter-day Saints) records. Due to the Mormon lifestyle, risk factors such as smoking, second hand smoke, and alcohol consumption are expected to be minimal. In addition, the use of water rights data, individual well survey and town records have allowed for the development of individual exposure assessments for the cohort members. This U.S. study will evaluate incidences of cancer and noncancer effects and may add to the weight of evidence determination for arsenic and provide insight as to the feasibility of evaluating the incidence of important toxic and carcinogenic endpoints such as cardiovascular effects and internal cancers.

ORD is also developing a report that will describe the feasibility of conducting epidemiologic studies in the United States that will contribute to an improved quantitative risk assessment of the health effects of arsenic in drinking water. This will include a description of possible study sites, numbers of individuals exposed, levels of exposure, and preliminary power calculations concerning the feasibility to evaluate different health endpoints such as cardiovascular, reproductive, dermatologic and cancer.

Along with these studies, ORD is conducting studies on arsenic urinary metabolic profiles. This project will provide information on baseline data at exposures typically found in the United States. Diet as a source of exposure will be examined along with variability of arsenic metabolic profiles in individuals. It is hoped that the information gained from this study can facilitate the extrapolation of study results from one population to another and allow for standardization of biomarkers for exposure and effect for arsenic that can be used in future epidemiology studies.

Finally, ORD is collaborating with ongoing investigations in other countries such as Chile and India to evaluate the internal carcinogenic, reproductive, and dermatologic effects of arsenic exposure in drinking water. For example in Chile, there are two studies nearing completion.

One is a case control study of lung and bladder cancers examining arsenic exposure in air, water, and food. The second study is an ecologic study of cancer mortality with air and drinking water arsenic exposures. Results from these studies may provide further information on dose-response that can be used in the near term to refine the arsenic risk assessments.

Table 2-1. Exposure Research Strategy Matrix for Arsenic

Issue	Task	Product	Use
EXP. Issue 1. Develop arsenic speciation methodology to separate As(III) from As(V) to support water treatment decisions in large and small utilities.	Exp. Task 1a. Evaluate analytical techniques for Inorganic As(III) and As (V) speciation in water. High Priority, Short-term	As speciation method for drinking water	Treatment evaluation in NRMRL, individual water treatment plant, AWWA
	Exp. Task 1b. Evaluate sample preservation techniques for Arsenic species. High Priority, Short-term	Preservative for asenic speciation methods	Application to all speciation based methods
EXP. Issue 2. Develop extraction methods for inorganic and organic arsenicals to allow for the separation and detection of individual arsenic species in foods.	Exp. Task 2a. Speciation in target food items (i.e. seafood). High Priority, Short-term/ Long-term	As speciation method and improved information on As species for target foods/groups	Exposure assessment by NCEA, NERL, FDA, USDA, OW
	Exp. Task 2b. Speciation in composite daily diet (i.e. duplicate diets). Medium Priority, Short-term/ Long-term	As speciation method to determine inorganic forms in composite samples	Exposure assessment by NCEA, NERL, FDA, USDA
	Exp. Task 2c. Impact of food preparation on the distribution of individual arsenicals. Low Priority, Long-term	Improved information on As speciation for prepared foods	Exposure assessment by NCEA, NERL, FDA, USDA
EXP. Issue 3. Development of arsenic speciation methodologies in biological matrices to support exposure assessment, bioavailability, and biomarker research.	Exp. Task 3a. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA and arsenobetaine in urine. High Priority, Short-term	Analytical method capable of separating inorganic arsenic III from MMA, DMA and arsenobetaine in urine	Support of exposure monitoring and bioavailability studies in NHEERL or NCEA, NIOSH
	Exp. Task 3b. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA and arsenobetaine in blood. Medium Priority, Long-term	Analytical method capable of separating inorganic arsenic III from MMA, DMA and arsenobetaine in blood	Support of exposure monitoring and bioavailability studies in NHEERL or NCEA, NIOSH
	Exp. Task 3c. Refine and evaluate analytical approaches to speciate arsenic to support bioavailability investigations. Medium Priority, Long-term	Speciation method in a variety of sample types foodstuffs, drinking water, biologicals	Analytical support for bioavailability studies
	Exp. Task 3d. Refine and evaluate analytical approaches to speciation in tissues. Medium Priority, Long-term	Speciation method for tissue samples.	Non-radio based analytical support for NHEERL
Exp. Issue 4. Development of liquid and solid species specific standard reference material (SRM) for arsenic in water, foodstuffs, urine, tissues.	Exp. Task 4a. Develop a SRM for foods which provide species specific concentrations of arsenic	SRM to evaluate methods development in food	NERL, Method validation for NCEA exposure assessment, EPA, FDA, USDA, NIST, OW. Method validation in Exp 2&5.

Table 2-1. (cont.)

Issue	Task	Product	Use
	Exp. Task 4b. Develop a SRM for biological tissues which provides species specific concentrations of arsenic Medium Priority, Long-term	SRM to evaluate methods development in tissues	NERL, method validation for NCEA exposure assessment, EPA, NIOSH, NIST. Method validation of Exp. 3
	Exp. Task 4c. Develop a SRM for water, blood and urine which provides species specific concentrations of arsenic High Priority, Long-term	SRM to evaluate methods development in water, blood and urine	NERL, method validation for NCEA exposure assessment, EPA, NIOSH, NIST. Method validation of Exp. 3
EXP. Issue 5. Dietary exposure monitoring studies which address a selected populations exposure to arsenic from a high dietary	Exp. Task 5a. Dietary exposure monitoring studies of arsenic species in the typical U.S. diet and highly exposed sub-populations. High Priority, Long-term	Database on speciated arsenic in typical U.S. foods and for diets of targeted highly exposed populations.	National and regional arsenic diet data for improved EPA risk assessment and risk management decisions. FDA and USDA will also utilize these data. Related to Exp. 2a & 2b
EXP. Issue 6. Development of National Database on arsenic occurrence and concentrations in water, soil and dietary constituents for use in epidemiological studies and Agency regulatory activities.	Exp. Task 6a. Development of a National Database on arsenic occurrence and concentrations in water, soils, and dietary constituents High Priority in water, Short-term/Long-term	National Database on Speciated Low-Level arsenic levels in water, soils and dietary constituents	Arsenic exposure information for epidemiological studies and for Agency risk assessment/risk management activities. Research and results primarily used by OW
EXP. Issue 7. Biomarkers of Exposure in Biological Media	Exp. Task 7a. Development of biomarkers of exposure in biological media for use in epidemiological studies. High Priority (if feasible), Long-term	Standardized biomarkers to assess exposure or arsenic species from various media.	Standardized biomarkers protocols will be used for assessing exposures in epidemiological studies and for improving the precision of the risk assessments
EXP. Issue 8. Bioavailability of Arsenic	Exp. Task 8a. Conduct research to determine the bioavailability of all arsenic species found in water, soils and food constituents. Medium Priority based on sequencing with other research products, Long-term	Empirically derived bioavailability (oral absorption) factors will be determined for each arsenic species from water, soils and various food constituents.	Improvements in the quantitative precision of the arsenic risk assessments and improvements in the determination of the relative source contribution of arsenic in water vs. arsenic in water vs. arsenic in other exposure media.

3.2.1.2. Carcinogenic Effects in Animals — There is limited evidence of inorganic arsenic-induced carcinogenicity in animal studies. Standard experimental animal models do not demonstrate the carcinogenic effects of arsenic seen in humans. However, there are emerging animal models such as transgenic mice that may have utility for arsenic effects research.

There are also limited data concerning the carcinogenic effects of organic arsenic forms in animals. A slight increase in pancreatic tumors was observed in male rats following oral exposure to 4-hydroxy-3-nitrobenzene arsonic acid or roxarsone (NTP, 1989). Male rats that had been initiated with diethylnitrosamine and then exposed to dimethylarsinic acid (DMA) had an increased incidence of basophilic foci (a precancerous lesion) in the liver, suggesting that DMA could be a promoter (Johansen et al., 1984; see also discussion in mechanisms section, below). DMA has also been demonstrated to be a promoter of cancer in multiple organs such as urinary bladder, kidney, liver and thyroid in rats and lung in mice (Yamamoto et al., 1995; Yamanaka et al., 1996). A few studies indicate that organic arsenicals, DMA and roxarsone, may be able to cause mutations and DNA strand breaks (ATSDR, 1993).

3.2.1.2.1. Other Data Related to Carcinogenicity. From studies conducted in animals, it can be concluded that inorganic arsenic induces genetic damage. Experimental evidence suggests that inorganic arsenic does not act to damage DNA directly as a point mutagen, but produces damage at the chromosomal level inducing chromosomal aberrations, micronuclei and sister chromatid exchange in mammalian cells, and neoplastic transformations in Syrian hamster embryo cells (ATSDR, 1993; U.S. EPA, 1993). The

Table 2-2. Exposure Task Summary, Current Activities and Proposed Sequence for Studies

Task - Short Study Title	Task Type[1]		Ongoing	Priority	Time Frame[2]					
	I	E/O	Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
Exp. Task 1a. Evaluate analytical techniques for Inorganic As(III) and As(V) speciation in water	I		Y	High	EPA	EPA				
Exp. Task 1b. Evaluate sample preservation techniques for Arsenic species	I		Y	High	EPA	EPA				
Exp. Task 2a. Speciation in target food items (i.e. seafood)	I	E	Y	High	EPA	EPA	EPA	EPA	X	
Exp. Task 2b. Speciation in composite daily diet (i.e. duplicate diets)		E	Y	Medium		X	X	X	X	
Exp. Task 2c. Impact of food preparation on the distribution of individual arsenicals.	I	E	N	Low		X	X	X	X	
Exp. Task 3a. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA, and Arsenobetaine in urine	I		Y	High	EPA	EPA				
Exp. Task 3b. Refine and evaluate an analytical approach for the separation of As(III), As(V), MMA, DMA and Arsenobetaine in blood	I	E	N	Medium			X	X		
Exp. Task 3c. Refine and evaluate analytical approaches to speciate arsenic to support bioavailability investigations	I	E	N	Medium				X	X	X
Exp. Task 3d. Refine and evaluate analytical approaches to speciate arsenic in tissues	I	E	N	Medium		X	X	X		
Exp. Task 4a. Develop a standard reference material for foods which provide species specific concentrations of arsenic		O	N	High	X	X	X	X		
Exp. Task 4b. Develop a standard reference material for biological tissues which provides species specific concentrations of arsenic		O	N	Medium	X	X	X	X		
Exp. Task 4c. Develop a standard reference material for water, blood and urine which provides species specific concentrations of arsenic		O	N	High	X	X	X	X		

Table 2-2. (cont.)

Task - Short Study Title	Task Type[1]		Ongoing	Priority	Time Frame[2]					
	I	E/O	Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
Exp. Task 5a. Dietary exposure assessment studies of arsenic species for typical U.S. diets and high exposed sub-populations	I	E	N	High				X	X	X
Exp. Task 6a. Development of a National Database on concentrations in water, soils, and dietary constituents	I	E	Y	High/water Medium/ dietary			EPA	EPA	EPA	EPA
Exp. Task 7. Development of Biomarkers of Exposure in biological media for use in epidemiological studies	I	E	Y	High	EPA (pilot)	EPA	EPA			
Exp. Task 8. Conduct research to determine the bioavailability of all arsenic species found in water, soils, and food constituents	I	E	N	Medium			EPA	EPA	EPA	

[1] I = Intramural (EPA inhouse research), E = Extramural (EPA sponsorship through grant or coop), O = other federal, state or private organizations
[2] EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort
X = EPA resources insufficient to address these tasks, need external effort

mechanism(s) for these effects is not known at present. Depending on the mode of action, the dose-response curves could be linear or nonlinear.

3.2.1.2.2. Ongoing EPA Research. Research efforts have been initiated to develop an animal model for testing arsenic-induced carcinogenesis using genetically altered mice. Transgenic p53 knockout mice will be exposed to 4 arsenic species in drinking water: sodium arsenite and sodium arsenate, monomethyl arsonic acid (MMA) and DMA. This limited study will evaluate the animals for the presence of common cancer lesions. Results from this study will be used in the development of an animal model and could allow for a better understanding of mechanism from the determination of the active form for arsenic carcinogenesis. Other studies on carcinogenesis focus on the actions of arsenicals in multistage carcinogenesis, an evaluation of arsenic as a tumor promoter, interactions between arsenic and genetic material (DNA methylation) and the mechanistic aspects associated with variations in susceptibility within the human population.

3.2.1.3. Noncarcinogenic Effects in Humans — Exposure to inorganic arsenic may result in adverse effects other than cancer in humans. Dermal changes including variations in skin pigments, thickening of skin (e.g., hyperkeratosis) and ulcerations, peripheral neuro-

toxicity (e.g., tingling and loss of feeling in arms and legs) and auditory nerve damage, peripheral vascular and cardiac effects, goiter, gastrointestinal and liver effects, developmental toxicity, and diabetes have been observed. These effects are seen at various levels in the range of exposures reported in the epidemiology studies (U.S. EPA, 1993; ATSDR, 1993).I

n humans, acute oral poisoning with inorganic arsenic leads to gastrointestinal irritation accompanied by difficulty in swallowing, thirst, abnormally low blood pressure, and convulsions (Gorby, 1994). Both acute and chronic exposures to inorganic arsenic result in capillary damage to target tissues which exacerbates the damage observed in these tissues (Clarkson, 1991). Signs of chronic exposure to arsenic in drinking water are dermal changes such as variations in skin pigments, hyperkeratoses, and ulcerations. Blackfoot disease, a peripheral vascular disease leading to peripheral tissue necrosis, has been observed in humans consuming arsenic contaminated drinking water in Taiwan (Tseng et al., 1968) and India (Bagla and Kaiser, 1996). Human studies have reported peripheral and central neurologic effects after exposure to inorganic arsenic (Morton and Dunnette, 1994). Enlargement of the liver was noted in populations in India. Ischemic heart disease and diabe-

tes were observed in Taiwanese where Blackfoot disease is endemic.

Some human studies have reported an association between arsenic exposure and adverse reproductive outcomes and developmental impacts (Rogers, 1996). The types of effects noted in occupationally exposed humans include spontaneous abortion, congenital malformations and low birth weight. Exposure to inorganic arsenic was associated with decreased maternal blood glutathione levels indicative of maternal oxidative stress.

When considering the range of noncancer effects associated with inorganic arsenic exposure, hyperkeratosis observed in the Taiwanese population (Tseng et al., 1968) is considered the most sensitive endpoint of toxicity and serves as the basis for EPA's current noncancer risk assessment.

     3.2.1.4. Noncarcinogenic Effects in Animals — Signs of acute inorganic arsenic poisoning in animals include vomiting and diarrhea, weakness, trembling, tachycardia and collapse (U.S. EPA, 1993). Like humans, target organs appear to include liver, kidney, and the developing organism.

In animal studies, arsenite and arsenate have greater potency as developmental toxins than the methylated, organic forms (Willhite, 1981). Types of malformations observed include exencephaly, encephalocele, cleft palate and lip, and malformations of the eye and ear, skeleton, kidney and urogenital system as observed in hamsters, mice, rats and rabbits (Rogers, 1996). *In vivo* studies in animal models indicate that these teratogenic effects are not secondary to maternal toxicity (Golub, 1994). There is some evidence to support a variety of different mechanisms, similar to those associated with carcinogenicity, including alteration of DNA methylation, inactivation of methyltransferases, modulation of protein phosphorylation and production of reactive oxygen species. Significantly, the dose-response relationships for arsenite and arsenate are very different, and recent evidence suggests that the mechanisms responsible for induction of malformations of these two inorganic arsenicals may be different (Tabacova et al., 1996).

Limited toxicity data on organic forms of arsenic suggest that irritation of the gastrointestinal tract, mild effect on liver, tubular damage to kidneys and some neurological effects may result following oral exposure in animal studies. The limited nature of these data make it difficult to quantitatively compare these effects with those resulting from inorganic arsenic exposure (ATSDR, 1993).

     3.2.1.4.1. Ongoing EPA Research. ORD is conducting several developmental toxicity studies that evaluate the effects of metals, such as zinc and selenium, and antioxidants on the prevention of arsenic-induced malformations and the mechanisms related to arsenic-induced malformations. This line of research addresses questions related to mechanism(s) of action and modifiers of susceptibility that could impact the assessment of risk for potentially sensitive members of

the population. Further, these data may provide dose-response information for effects other than cancer. In addition, the Utah study, discussed above, will examine noncarcinogenic endpoints.

3.3. What are the Characteristics of Dose-Response for Various Toxic Endpoints?

3.3.1. State of the Science.

The risk assessment process relies on scientific data characterizing the effects of contaminants on human health, and models that extrapolate existing data to estimate internal dose and effects where data are lacking. Physiologically based pharmacokinetic (PBPK) modeling links environmental exposures with target tissue dose and provides a basis for extrapolation among chemical classes. Development of biologically based dose-response (BBDR) models integrate information on toxicant distribution and mechanisms by which a chemical may cause an adverse effect to relate exposure with effects. The arsenical doses associated with the effects described above are summarized in ATSDR (1993) and U.S. EPA (1993).

     3.3.1.1. Pharmacokinetic and Biologically-Based Models — The shape of the dose-response curve for arsenic-induced cancer and noncancer effects relating the range of observation to the range of extrapolation is a source of uncertainty in arsenic risk assessment. This uncertainty influences both selection of a dose-response model and high to low dose extrapolation. There are several factors that can influence dose-response, including metabolism, tissue dosimetry, mechanism of action, and other factors that may modify toxicity and individual susceptibility. Arsenic undergoes a complex cycle of reduction and oxidative methylation in humans and other species. This cycling contributes to the mechanism for arsenic-induced toxicity and perhaps its carcinogenic effect. Development of PBPK models using experimental animal data and/or metabolic data from observational human studies can provide insight into the kinetics of substances through a quantitative, biologically based description between exposure and target tissue dose of the active chemical species. Human data usually include exposure and excretion information. Therefore, use of animal models would compliment the human data to provide further information concerning exposure and target tissue dose. This is particularly important because there are multiple target tissues (e.g., skin, lung, liver, bladder, kidney), and the target tissue dose of arsenate, arsenite and their methylated metabolites is a balance between competing processes of reduction, methylation, binding, and excretion. Additional advantages of these models include the evaluation of different exposure scenarios on cumulative tissue dose and body burden, helping to prioritize areas for further study, providing a link with other models that may be developed (e.g., BBDR) to assess toxicological effects, and studying the impacts of a variety of host factors on toxicity in humans.

Establishing a model(s) may assist in the evaluation of the dose-response relationship for arsenic-induced health effects. When appropriate human data are not available, there may be potential to utilize animal models or other laboratory models to understand dose-response relationships for arsenic induced health effects. For some adverse effects, studies in animal models can provide evidence to confirm the effects associated with arsenic exposure in human epidemiologic studies, and thus also provide a basis for mechanistic research.

Research with laboratory model systems can also facilitate the dose-response evaluation of noncancer effects such as developmental toxicity described above or in the area of vascular effects. For example, recent *in vitro* work with cultured human vascular endothelial cells suggests that the arsenic-induced cardiovascular effects could arise from toxicant induced injury to vessel walls (Chen et al., 1990; Chang et al., 1991). Development of animal models to study dose dependency and mechanistic aspects of these and other noncancer effects would complement epidemiological evaluations for noncancer effects and subsequent dose-response evaluations.

Further discussion on the role of mechanism and modifiers of susceptibility in dose-response is given below.

3.3.1.2. Ongoing EPA Research — Current ORD research efforts focus on improving our understanding of arsenic metabolism, factors that may influence arsenic metabolism, arsenic effects on cellular enzymes (e.g., heme oxygenase, arsenic methylation and research that will support the development of a PBPK model for humans and animals. Metabolism work is important in the development of biomarkers of exposure for use in epidemiologic studies. Current efforts are evaluating the utility of arsenic metabolic profiles as markers of exposure for human epidemiologic and PBPK studies.

Research on PBPK model development of arsenic is underway using the mouse as the animal model. The rat has been excluded from the studies because of the unique accumulation of arsenic in red blood cells. The rabbit has been suggested as a model for PBPK model development relevant to humans based on somewhat similar urinary metabolic profiles. However, the utility of the rabbit as a model has not been adequately evaluated. The mouse was selected since mice methylate arsenic and excretes inorganic and organic forms in urine. The physiologic parameters for mice for PBPK models are well known, and thus enables an easier "scale up" of the model to humans. Arsenic tissue dosimetry studies currently being conducted with the mouse can be used in conjunction with BBDR model development for biomarkers of exposure or effect.

Mechanistic research combined with information from metabolism studies and studies evaluating the modifica-

tion of toxicity and susceptibility can eventually be used in the development of a BBDR model. This information can improve risk estimation for arsenic induced toxicity and carcinogenicity by improving our understanding of "dose" and its relationship to effect.

3.4. What are the Mechanisms Associated with Arsenic Carcinogenicity and Toxicity?

3.4.1. State of the Science.
Mechanistic research conducted to refine arsenic risk assessment encompasses the range of events from exposure to target tissue dose associated with adverse health effects and can impact all phases of risk assessment, particularly dose-response. A major challenge in this area is the limitation in sensitivity and specificity of current analytical techniques used to measure arsenicals in tissues, body fluids and other media (see Chapter 2). This has had a major impact on pharmacokinetic and toxicological mechanistic studies because it is difficult with current methodologies to extract and distinguish between arsenite and arsenate and their metabolites in biological and environmental samples. This is important because different forms of arsenic exhibit differences in disposition and toxicity, and they act by different mechanisms at the biochemical level.

It has long been known that arsenate is reduced to arsenite and subsequently methylated to form MMA and DMA in humans and experimental animals. The methylated metabolites of arsenic are also the predominant forms excreted in the urine of most species. Historically, the operative assumption has been that arsenite is the active or carcinogenic form of arsenic and that methylation is simply or solely a mechanism of detoxification and excretion. The basis for this assumption is that the methylated forms of arsenic are far less acutely toxic than either arsenite or arsenate (ATSDR, 1993). Recently, an alternative interpretation has been proposed. Brown and Kitchin (1997) suggest that DMA may be an arsenic metabolite of importance in carcinogenesis, and thus methylation of arsenic to DMA may be a toxification pathway.

Until lately, there were no studies that had directly tested the assumption of methylation as a simple detoxification mechanism. However, DMA has recently been shown to increase the enzyme activity of a rat kidney enzyme, ornithine decarboxylase (ODC) (Yamamoto et al., 1995), which has been shown as a biological indicator of cell proliferation and promoter activity (Brown and Kitchin, 1996). As mentioned previously, DMA has also been demonstrated to be a promoter of cancer in multiple organs such as bladder, kidney, liver, and thyroid in rats, and lungs in mice (Yamamato et al., 1995; Yamanaka et al., 1996). In addition, arsenite has been shown to produce a dose-dependent increase in rat liver ODC activity (Brown and Kitchin, 1996). It has been postulated, therefore, that arsenic may act as a promoter rather than an initiator of carcinogenesis and affect

some but not all elements of multistage carcinogenesis (Brown and Kitchin, 1996). There are insufficient data on the shape of the dose-response curve for other promoters (Kitchin et al., 1994). Epidemiological evidence that arsenic acts at a later stage in the development of cancer, as noted with increasing risk of lung cancer mortality with increasing age of initial exposure, independent of time after exposure ceased (Brown and Chu, 1983), provides some support to the hypothesis that arsenic may act as a promoter of carcinogenesis. Further studies are needed to clarify the mechanism of arsenic carcinogenesis and the dose-response of arsenical promotion. These studies may provide insight on the nature of the dose-response relationship for arsenic carcinogenicity and the role of methylation as a toxification/detoxification mechanism.

The mechanism for arsenical carcinogenesis may be related to arsenic biotransformation. Arsenic is methylated by an arsenic methyltransferase utilizing S-adenosylmethionine (SAM) as the methyl donor. Arsenic may perturb the utilization of methyl donor groups needed for normal DNA methylation by interacting with the substrate, SAM, or the methyltransferases. Depending on the conditions, this perturbation could result in hypo- or hypermethylation of DNA. High doses of arsenic were thought to compete for the methyl donor pool during detoxification, leading to hypomethylation (Mass, 1992). Since arsenic interacts with methyltransferases, it may inhibit or enhance other methyltransferases that could lead to hypermethylation. Mass and Wang (1997) found that exposure to arsenite and to a lesser extent, arsenate, but not DMA, produced significant hypermethylation of cytosine residues in the 5' promoter region of the p53 tumor suppressor gene in human lung adenocarcinoma cells. They postulated that this hypermethylation could result in suppression of the expression of tumor suppression genes and lead to cancer. An effect of arsenic on p53 or some other tumor suppressor gene by alteration of DNA methylation provides a heritable mechanism whereby arsenic appears to act as a nongenotoxic agent. Yet inhibition of tumor suppressor gene function (or even enhancement of oncogene expression) is known to lead to genetic instability. This would endow arsenic with properties of both a genotoxic and nongenotoxic agent; it would also provide a mechanism whereby arsenic can act as an initiator and/or promoter/progressor.

Additional considerations for arsenic methylation include saturation of this enzyme process in humans and the effects of preexisting disease on the capacity for humans to methylate arsenic. Saturation of arsenic methylation has been suggested as a hypothesis for low dose nonlinearity (U.S. EPA, 1988; Petito and Beck, 1991; Carlson-Lynch et al., 1994). There is uncertainty, however, regarding the dose at which saturation might occur. Other researchers have concluded that the data do not support a nonlinear mechanism for methylation (Hopenhayn-Rich et al., 1993; Smith et al., 1995).

In an evaluation of Taiwanese populations, Hsueh et al. (1995) identified chronic liver disease as a risk factor that increases the development of skin cancer. In a separate study comparing healthy individuals to those with liver disease, it was noted that preexisting disease did not change the cumulative excretion of arsenic in urine but did alter the ratio of the MMA and DMA metabolites (Buchet et al., 1984; Geubel et al., 1988). Studies in animals suggest that liver disease may reduce the availability of the methyl donor group, SAM, necessary for arsenic methylation.

3.4.2. Ongoing EPA Research.
One focus for mechanistic research on arsenic carcinogenicity and toxicity at EPA focuses on arsenic methylation and the enzymes involved in that process. This includes the interaction between arsenic and DNA methylation which could explain whether arsenic suppresses expression of certain genes from their function. Questions on whether arsenic acts as a carcinogenic promoter are also being addressed. The two hypotheses that DMA is an active metabolite of arsenic in the carcinogenic process and that free radicals may contribute to arsenic carcinogenesis may contribute to arsenic carcinogenesis are being evaluated. With respect to noncancer effects, the mechanism by which arsenic perturbs the cell cycle and induces cell death is being investigated in animal embryos. Information from these studies will reduce the uncertainty in selection of dose-response models for cancer and developmental effects. Mechanistic information will also be of use in the development of a BBDR model relating tissue dose with response.

3.5. What are the Modifiers of Human Susceptibility?

3.5.1. State of the Science.
Susceptibility is influenced by the magnitude and species of exposure and by the characteristics of the exposed organism. These modifiers can range from environmental factors to those that are characteristic to the organism. Environmental factors include diet or concurrent exposure to other toxicants. Diet and other environmental factors can affect arsenic methylation. Methylation of arsenic requires the availability of a methyl group donor (SAM). A low protein diet or diet deficient in the amino acid methionine can result in decreased availability of SAM. (However, a low fat diet is also considered to lower the risk for developing some forms of cancer.) Further, diets low in cysteine, choline, folate, and vitamin B12 can minimize the methyl groups available for transmethylation (Montgomery et al., 1990). In addition, it has been shown that selenium, a related metal, inhibits the methylation of arsenic in vitro (Styblo et al., 1996). The role of diet and environmental factors in arsenic methylation can be studied in animals where these factors can be manipulated. Such studies would be useful in the design of human epidemiological studies to determine the influence of dietary and nutritional factors on the capacity for arsenic methylation. Environmental

factors that influence either exposure to arsenic or the effects of arsenic need to be identified for incorporation into the design of epidemiologic studies.

Characteristic modifiers include variation in susceptibility within the human population reflective of genotypic differences, age of the individual exposed (e.g., children, elderly), pregnancy, gender differences, and whether the individual is predisposed to susceptibility due to co-occurrence with another disease. Evaluation of arsenic metabolites excreted in urine from chronically exposed individuals suggest that there may be differences in the pattern and extent of arsenic methylation among the human population (Vahter et al., 1995b). Such differences could reflect genetic polymorphisms for the enzymes involved in arsenic methylation. Polymorphisms for enzymes that catalyze other methylation processes have been observed (Weinshilboum, 1989). Its also been observed that some nonhuman primates and the guinea pig have limited or no methylation capacity (Vahter and Marafante, 1985; Vahter et al., 1995a; Healy et al., 1997).

In addition to the above potential modifiers, there is evidence suggesting that arsenic is an essential trace element for goats, chickens, minipigs, and rats (NRC, 1989). However, no comparable data are available for humans, and demonstration of arsenic essentiality in humans is hampered by the lack of a postulated mechanism. The possibility of arsenic as an essential element could affect the interpretation of arsenic risk at low-doses.

3.5.2. Ongoing EPA Research.
Current research is being conducted by EPA to evaluate the impact of micronutrient status on arsenic metabolism and toxicity. In addition, studies are being completed on the preventive effects of zinc, selenium and antioxidants on arsenic induced malformations in rodent embryos. Results from these studies may be used in the evaluation of dose-response relationships for arsenic induced toxicity and carcinogenicity.

3.6. *Proposed Health Effects Research*

Proposed research topics and current activities are summarized in Tables 3-1 and 3-2. Figure 3-1 diagrams the relationship between exposure and effects research and the types of studies needed.

Effects Issue 1. What are the Health Effects and Dose-response Associated with Arsenic Exposure?

Future epidemiological studies should be designed to improve exposure analysis, provide information on arsenic speciation, reduce confounding factors and bias, and utilize biomarkers if possible. Use of biomarkers can help reduce uncertainty in the interpretation of epidemiological studies. Biomarkers may be developed as indicators of exposure, effect, or susceptibility. Chapter 2 discussed development of biomarkers of exposure. This chapter focuses on biomarkers of effect and susceptibility. In a long-term research plan, biomarkers identified from mechanistic research in experimental model systems can be used to help design future

epidemiology studies to improve the sensitivity and specificity of exposure measurements (see also Chapter 2), provide insight into the shape of the low-level dose-response curve, and indicate the potential for a biological effect in humans. In addition, biomarkers may make it possible to determine the effect of various factors such as genotype that could impact human susceptibility to arsenic exposures.

Based on current information, biomarkers such as hyperkeratoses and chromosomal alterations in human blood cells are technically feasible and have potential for success. Additional biomarkers may include but are not limited to DNA methylation (see mechanism section, below) and micronuclei in exfoliated bladder cells.

1a. Conduct Feasibility Study on Important Health Endpoints Resulting from Arsenic Exposure

This research will determine the feasibility of conducting an epidemiologic study in the United States or other appropriate populations focusing on important health endpoints. Research in this area would be used to determine if the conduct of an epidemiology study in the United States or other location would reduce the uncertainty in the existing risk assessment. Further research, for example, on the incidence of internal cancers, reproductive, dermatologic, neurologic and vascular effects may provide the data that can contribute to the evaluation of dose-response relationships at low arsenic doses and quantify the corresponding risks. This research has been initiated; results are expected in the near term.
(High priority; intramural and extramural tasks)

1b. Directed Epidemiologic Research on the Health Effects Associated with Arsenic Exposures

(i) To address uncertainties associated with the current risk assessments for arsenic, this research would build upon ongoing studies of appropriate study design to evaluate the human health effects of arsenic at low doses and determine the dose-response relationship for important health effects attributed to arsenic exposure. This research would expand the scope of ongoing studies in China, Chile, and India, for example, in order to estimate the level of exposure to individuals and follow these individuals over a period of time. Since this research builds on existing studies, it could be completed in the near term.
(High Priority, intramural and extramural)

ii) Pending the outcome of the feasibility study (1a), a new long-term epidemiologic study would be initiated. This study would be developed in areas where exposures could be well defined and would support the development of a dose-response curve. These studies are long-term in design and would be resource intensive. This research might be developed through or in collaboration with other groups such as the National Institutes of Health or the World Health Organization on study design and data analysis.
(High Priority, if feasible; intramural and extramural task)

Table 3-1. Effects Research Strategy Matrix for Arsenic

Issue	Task	Product	Use
EFF. Issue 1. What are the health effects and dose-response associated with arsenic exposure?	1a. Determine feasibility study on important health endpoints for carcinogenic effects for epidemiologic studies. High Priority, Short-term	Determination if epidemiologic study with improved design is feasible.	Determine health endpoint and dose-response for use in full scale epidemiologic study.
	1b. Directed epidemiologic research on arsenic health effects utilizing ongoing studies of following outcome of feasibility study High Priority, if feasible	Epidemiology studies that determines relationship (linear or nonlinear) between arsenic exposure and effect	Basis for improved risk assessment and derivation of MCL.
	1c. Research on important health endpoints in animals. Medium Priority	Results from animal studies on developmental, reproductive, cardiovascular, neuro- and other endpoints of arsenic toxicity.	Determine appropriate endpoint for future study design and serve as basis for risk assessment.
EFF. Issue 2. What are the dose-response relationships at low doses?	2a. Develop biomarkers of effect and susceptibility High Priority, Short-term	Biomarkers to assess biologic effect and susceptibility	Standardize protocol for assessing effects and utilize tools for improving the precision of the risk assessment. Relates to Exposure Task 7
	2b. Research to support refinement of a PBPK model High Priority, Long-term	Relevant species-specific parameters for development of PBPK model.	Incorporation into PBPK model (RA task 1a).
	2c. Develop laboratory model systems to assess mechanism of arsenic induced carcinogenicity and toxicity. Medium Priority, Long-term	Animal model utilizing transgenic mice or other appropriate organism or model system.	Understand cause and effect relationship between arsenic exposure and effect.
	2d. Determine mechanisms by which arsenic exerts its carcinogenic and noncarcinogenic effects. High Priority, Long-term	Results from in vitro and in vivo studies on mechanisms of arsenic-induced carcinogenicity and toxicity	Reduce uncertainty in low-dose extrapolation in arsenic risk assessment.
EFF. Issue 3. What are the modifiers of susceptibility?	3a. Factors that affect human susceptibility High Priority, Long-term	Refined PBPK and BBDR models	Necessary component of PBPK and BBDR models, and improve understanding of human susceptibility.

1c. Research on Important Health Endpoints in Animals

This research would complement epidemiologic investigations concerning the health effects and dose-response analysis of arsenic exposures. This research would include evaluations on developmental, reproductive, cardiovascular, neuro- and other endpoints. Use of animal models may enable this question to be answered more easily or practically than human studies. Research in these areas should combine *in vitro* and *in vivo* techniques in animals to determine dose-response to further characterize the toxicity of various arsenic species and help target endpoints for study in epidemiologic studies. (Medium priority; intramural and extramural task)

Effects Issue 2: What are the Dose-Responses Relationships at Low Doses?

Research in this section includes those studies that can be used to support the assessment of health endpoints for characterizing risks.

2a. Develop Biomarkers of Effect

Use of biomarkers can help reduce uncertainty in the interpretation of epidemiologic studies and provide insights into the shape of the dose-response curve, and mechanism of action. Biomarkers such as hyperkeratoses may provide insight into such factors such as human variability and early markers of effect. These studies would further develop biomarkers like the cellular genetic markers or DNA methylation or micronuclei from exfoliated bladder cells to be used as measures of biologic effect and susceptibility. This research would develop and evaluate additional biomarkers of effect for use in epidemiologic studies. Development of this tool could facilitate the development of a human biologically

Table 3-2. Risk Assessment Task Summary, Current Activities and Proposed Sequence for Studies

Task - Short Study Title	Task[1] I	Task[1] E	Ongoing Y/N	Priority	Time Frame[2] FY97	FY98	FY99	FY00	FY01	FY02
Short-term RESEARCH										
Task 1a. Feasibility study on important health endpoint (Utah cohort; feasibility study)	I	E	Y	High	EPA	EPA	EPA			
Task 1b. Directed epidemiology study (i) - ongoing study collaboration (Chile, China, India), EPA grant-India	I	E	Y	High	EPA	EPA	EPA	EPA		
Task 2a. Develop biomarkers of effect (Urinary Metabolic Profile)	I		Y	High	EPA	EPA				
Task 2c. Develop laboratory model systems for arsenic mechanistic evaluation - p53 deficient mice	I		Y	Medium	EPA	EPA	EPA			
Task 3a. Impact of micronutrient status on arsenic metabolism and toxicity	I		Y	High	EPA	EPA	EPA			
Task 3a. Prevention of arsenic induced malformations by antioxidants, selenium and zinc	I		Completed	Medium	EPA					
Long-term RESEARCH										
Task 1b. Directed epidemiology study (ii) - long-term development	I	E	N	High if feasible				X	X	X
Task 1c. Research on important health endpoints in animals.	I	E	N	Medium		X	X	X	X	X
—Tumor studies in p53 mice AWWARF/ACWA		E	Y	Medium		X	X	X	X	
Task 2b. Refinement of PBPK model	I		Y	Medium	EPA	EPA	EPA	EPA	EPA	EPA
—Biomethylation and disposition of arsenic	I		Y		EPA	EPA	EPA	EPA		
—Determine toxicodynamics of arsenic in mice	I	E	Y			X	X	X	X	
Task 2d. Arsenic mechanism - Arsenicals, oxidoreductases, and cellular redox status	I		Y	Medium	EPA	EPA	EPA	EPA		
—Arsenic mechanism (free radicals)	I		Y		EPA	EPA	EPA	EPA	EPA	
—Arsenic mechanism (Enzymology of arsenic methylation)	I		Y		EPA	EPA	EPA	EPA		
—Arsenic mechanism (Action of arsenicals in multistage carcinogenesis)	I		Y		EPA	EPA	EPA	EPA		
— As-GSH interactions and skin cancer, EPA grant		E	Y	High		X	X	X	X	

Table 3-2. (cont.)

Task - Short Study Title	Task¹ I	E	Ongoing Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
—Arsenic mechanism (Mechanistic basis of alteration of DNA methylation by arsenic)	I		Y		EPA	EPA	EPA	EPA		
—Arsenic mechanism Identification of human arsenic methyltransferase gene)	I	E	N			X	X	X	X	X
—Arsenic mechanism (Arsenic perturbation of cell cycle and induction of cell death in embryos)	I		Y		EPA	EPA	EPA	EPA		
Task 3a. Impact of macronutrient status on arsenic metabolism and toxicity	I	E	N	High		X	X	X	X	X
—Genetic biomarkers of methylation in humans	I	E	N	High		X	X	X	X	X
—GSH reductase and cellular redox, EPA grant		E	Y	High		X	X	X	X	

¹I = Intramural (EPA inhouse research), E = Extramural (EPA sponsorship through grant or coop)
²EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort
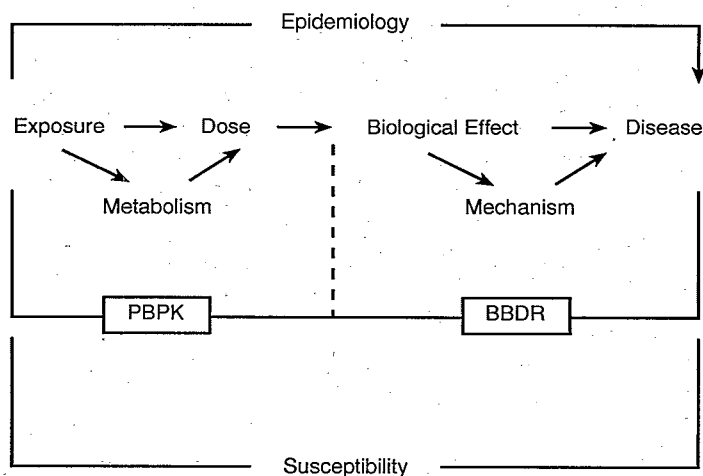X = EPA resources insufficient to address these tasks, need external effort

Figure 3-1.

based dose-response model and improve our understanding of dose-response relationships for estimating risk. (High priority; intramural task)

2b. Research for Development of a PBPK Model

Refinement of a PBPK model (and the studies necessary for model development) for arsenicals would provide a better understanding of the metabolism and relevant tar-

get tissues subject to arsenic toxicity. Included in this area are human and animal in vivo and in vitro studies that would characterize arsenic metabolism in humans and improve mass balance data on typical human metabolism of arsenic at various doses, by different routes of exposure and with different chemical forms. Development of a PBPK model provides information relating exposure with target tissue does, thereby reducing uncertainty in the arsenic risk assessment for cancer and noncancer effects. This long-term research would identify appropriate biomarkers that could improve the uncertainty associated with exposure assessment in epidemiologic studies.
(High priority; intramural and extramural task)

2c. Develop Laboratory Model Systems to Understand Mechanisms of Arsenic Toxicity and Carcinogenicity

This research would encompass the development of laboratory model systems such as an animal model utilizing transgenic mice or other appropriate organisms or in vitro systems to better understand arsenic mechanism of action. Mechanistic research is long-term in nature. In order to understand how arsenic causes cancer or other toxic effects, it may be useful to develop a model system to potentially generate hypotheses concerning the molecular mechanism of carcinogenesis and toxicity in humans. Understanding the mecha-

nism can often be used to identify biomarkers that would be useful for developing dose-response relationships, for detecting human populations sensitive to arsenic. A better understanding of the mechanism of action for arsenic induced carcinogenicity and toxicity can lead to the future development of a biologically based dose-response model for arsenic. Pilot studies have been initiated to determine the feasibility of developing a model system. Pending results, the overall priority of this research area may be reconsidered. (Medium priority; intramural and extramural task)

2d. Determine Mechanisms by Which Arsenic Causes Cancer and Noncancer Effects

This long-term research effort will utilize *in vitro* and *in vivo* techniques to evaluate mechanisms for cancer and noncancer effects induced by arsenicals. Mechanistic research further refines the link between exposure and effect. Areas for investigation include: enzymology of arsenic methylation; action of arsenicals in multistage carcinogenesis or as tumor promoters; free radical involvement in carcinogenesis, mechanistic basis of alteration of DNA methylation by arsenic; identification of the human arsenic methyltransferase gene; effects on methyl dependent recombination repair, and investigation of noncarcinogenic mechanisms of action. The results from these studies may provide insights regarding the mode of action for arsenic and assist in the low-dose evaluation in arsenic risk assessment through the incorporation of biological data in the assessment model.(High priority; intramural and extramural task)

Effects Issue 3: What are the Modifiers of Susceptibility?

3a. Factors that Affect Human Susceptibility

Variation is known to exist in human exposure response to environmental toxicants and may be due to such factors as age, lifestyle, genetic background, sex and ethnicity. This area of research would involve studies evaluating genetic polymorphisms, differences in metabolism and other aspects associated with factors affecting human susceptibility to disease. The objective of this research would be to evaluate the variation in arsenic metabolism as reflected in variations in urinary metabolites or other biomarkers of exposure. In addition, this research area would compare biomarkers of arsenic metabolism in individuals exposed to varying levels of arsenic with differences that include nutritional status, age, sex and genetic variations. This research may involve epidemiologic studies, clinical or animal studies and is long-term in nature.
(High priority; intramural and extramural task)

Specific projects and products relating to these issues and their status, use and time frame are outlined in Tables 3-1 and 3-2.

4. Risk Management Research for Arsenic in Water

4.1. Background

When EPA establishes an MCL, the Agency must define best available technology (BAT) for large public water systems and identify affordable technologies for small systems. Therefore, treatment options capable of removing arsenic from drinking water supplies must be identified and tested. The goal of this part of the Plan is to assure that the desired final drinking water arsenic concentration be technically achievable, and the control technology(ies) reliable and cost effective, while not significantly increasing residual management problems. At this time, considerable uncertainty exists on whether known arsenic control technologies will function effectively if lower arsenic levels are promulgated. Additional data are needed to determine the effectiveness of arsenic treatment and control. In the pursuit of an achievable arsenic MCL, EPA is mindful that arsenic removal technologies must not adversely impact the treatment of other water quality parameters, but need to build on those technologies wherever possible.

Arsenic exists in water supplies as several chemical species usually encompassing two oxidation states (arsenic III and arsenic V), with arsenic (V) being more easily removed. The common soluble species of arsenic (V) are forms of arsenic acid: H_3AsO_4, $H_2AsO_4^{-1}$, $HAsO_4^{-2}$ and AsO_4^{-3}. The common soluble species of arsenic (III) are: H_3AsO_3 and $H_2AsO_3^{-1}$. In the pH range of 5 to 9, equilibrium data indicate that the predominant arsenic (V) species will be $H_2AsO_4^-$ and arsenic (III) species will be H_3AsO_3. In addition to soluble arsenic species, there is increasing evidence (Chen et al., 1994) that particulate arsenic is a common constituent in the water supplies. A recent arsenic survey (Edwards et al., 1997) of domestic water systems showed significant levels of particulate arsenic, averaging 17% of the total. A third component for drinking water arsenic could be organically bound, but levels reported on this component were rarely greater than 1 μg/L (Anderson and Bruland, 1991). For this analysis only soluble inorganic arsenic and particulate arsenic will be considered as the species requiring control.

A number of control technologies can remove arsenic: coagulation/filtration (CF), lime softening (LS), activated alumina (AA), ion exchange (IE), reverse osmosis (RO), nanofiltration (NF) and electrodialysis reversal (EDR). Iron removal processes, such as manganese greensand adsorption, have also been found to remove arsenic. All of these technologies have been applied to water supplies containing arsenic and demonstrated to work. A new, lower MCL, however, would push the required performance of some of these technologies beyond reported levels opening up areas of uncertainty in performance, reliability and impact on other treatment operations.

Historically, the level of treatment chosen for arsenic has been closely correlated to the MCL of 50 µg/L. Improvements in analytical techniques plus the statutory requirements in the SDWA of 1996 may establish a substantially lower limit. If the MCL for arsenic is lowered, a parallel evaluation of available treatment technology capability must also be carried out to document required performance and/or identify areas where additional research is necessary.

4.2. State of the Science for Arsenic Control

4.2.1. How Effective are Available Technologies for Meeting a Lower Arsenic MCL?

As discussed above, there are numerous treatment technologies that can be brought to bear on removing arsenic from drinking water. The AWWARF Research Needs Report (1995) and Malcolm Pirnie's Report on Treatment and Occurrence of Arsenic in Potable Water Supplies (1993) indicate that little is known about the performance of these processes for treatment of arsenic concentrations in the less than 50 µg/L range. The key risk management issues are

(1) what are the performance limitations on treatment technologies that could be applied for arsenic control, (2) how does this treatment impact small systems, and (3) what impact is there on the management of process residuals?

Table 4-1 shows the performance of eight arsenic control technologies, which have the capability of meeting the current MCL. Table 4-1 also projects the level of performance that may be required of these technologies if the MCL is lowered. In some instances, control technologies have performed efficiently and approached a concentration that might be expected under a more stringent MCL, but in the overwhelming number of cases the required performance was not documented, particularly at the field scale level and for a sustained period of time. Performance data gaps exist and the proposed research under this Plan would address those gaps by collaborating with existing studies, conducting independent performance studies, and initiating basic research on arsenic's interactions with chemicals/additions.

AWWARF is presently conducting arsenic treatment removal efficiency research for lime softening and coagulation/filtration. Although most of this research is bench scale, some full scale performance data will be collected that will reduce some of the uncertainty associated with arsenic control (Edwards, 1994; McNeill and Edwards, 1997; Hering et al., 1996). Because arsenic-containing ground water and surface water varies in composition, it would be prudent for EPA to investigate additional water quality parameters before casting final judgement on lime softening and coagulation/filtration. Adsorptive media (ion exchange resin and activated alumina) and membranes are also being studied, but using a fairly high natural organic material raw water

(Total Organic Carbon ≈ 3 mg/L) which is not representative of most ground waters. Since ground water systems are the most likely candidates for the adsorptive technologies like activated alumina, research would be required to determine key performance and cost factors for a source water with lower total organic carbon (TOC). The proposed research in this Plan would build on, augment, and validate the arsenic control data available, generate additional treatment information and advance the understanding of the control technologies (BAT) necessary to achieve a new arsenic standard for drinking water.

The regulation of arsenic by a more stringent MCL may impact other treatment operations. Because significantly higher removals can be achieved with As V than As III, a preoxidation step in the selected treatment process may be frequently necessary, to optimize removal efficiency. In some cases a specific oxidation step in the treatment process will need to be added to optimize removal efficiency, but in others only optimization of existing unit processes like softening or filtration may be sufficient to improve arsenic control. Although oxidation of As III to As V is not difficult with commonly used oxidants, the oxidation kinetics of the available oxidants has not been well characterized to provide adequate information to design reliable facilities. The kinetics for the oxidation of arsenic by the various oxidants needs to be more adequately characterized. Furthermore, short or long-term storage and aeration, while not as effective as chemical oxidants, may be adequate in some situations and preferable because of confounding problems associated with chemical oxidants. While researching the performance aspects of arsenic control, this research effort will also look at the entire water treatment system and make recommendations on leveraging existing options for arsenic control.

4.2.2. Are There Cost Effective Technologies for Small Systems?

Small water supply systems (<10,000 customers) pose special problems for regulation and a change in the arsenic MCL could cause significant operational/compliance problems for these systems. Table 4-1 illustrates the arsenic removal gap that exists between current control technologies and the projected future need. In some cases the optimization of the control technique may be technically insufficient or too costly for a small system to implement. In addition, potential changes in residual disposal regulations triggered by a lower arsenic MCL could add substantial costs to the total costs of arsenic treatment. In situations where technology or economics fail for small systems, alternative compliance approaches must be developed, such as point-of-use treatment.

4.2.3. How Can the Residuals be Effectively Managed?

While the treatment of source water for arsenic removal has been widely documented, efficiency, reliability and cost effectiveness are topics slated for additional research. The im-

Table 4-1[1]. Arsenic Control Technology Performance (100 µg/L Influent)

Technology	Performance[2] Currently Required, %	Reported Treatment Performance, %	Projected[3] Performance Needed, %
1. Coagulation Filtration	50	90 to 99	98
2. Lime Softening	50	40 to 99	98
3. Activated Alumina	50	43 to 94	98
4. Ion Exchange	50	75 to 96	98
5. Reverse Osmosis	50	96 to 99	98
6. Nanofiltration	50	95 to 98	98
7. Electrodialysis Reversal	50	Not reported	98
8. Iron Removal Processes	50	95 to 98	98

[1]Adopted from Malcolm Pirnie, 1993
[2]Based on current MCL of 50µg/L
[3]Based on treatment requirements significantly less than 50µg/L

proved treatment efficiency will produce a residue with elevated arsenic concentrations, which might affect disposal options and cost of residual management. Currently residuals subjected to the toxicity characteristic leaching procedure (TCLP) are characteristically a hazardous waste due to arsenic if the TCLP extract contains 5 mg/L or more of arsenic. The TCLP procedure defines a TCLP hazardous waste as producing an extract containing greater than 100x the referenced MCLs of specified chemicals. Lowering the MCL for drinking water might initiate a new regulatory requirement under the Resource Conservation and Recovery Act (RCRA) in which case the TCLP arsenic trigger value will also be lowered. Thus, the strengthening of the arsenic drinking water MCL could have a multiple regulatory impacts on a utility and contribute to unfavorable economics for various arsenic removal technologies. All of the research projects initiated under this plan will require residuals management to be an evaluation factor. Identification, characterization, and minimization of the volume of arsenic containing sludges and other types of residuals and the degree of arsenic mobility will be a research topic. If recycling is not a technical option, the minimization of the volume of arsenic containing sludges and degree of arsenic mobility will be a research topic.

4.2.4. Ongoing EPA Research. EPA sponsored research has been recently completed on the evaluation of ion exchange and coagulation-microfiltration technologies for removal of arsenic from ground water. Laboratory and pilot plant studies have shown that ion exchange treatment with brine regeneration reuse (over 20 cycles) can effectively reduce arsenic V to less than 2 µg/L and significantly reduce the quantity of brine residual for disposal. A coagulation (iron coagulant)-microfiltration process was also successfully piloted to reduce arsenic V to less than 2 µg/L. Both of these

technologies will have full scale demonstration conducted by the utility that co-sponsored part of the pilot studies with in the next 2 years.

4.3. Risk Management Research

The reliable control of arsenic at levels below 50 µg/L by currently available treatment technologies has not been completely demonstrated. In addition to the overall performance problem there are special technical and economic concerns raised by application of arsenic control to small drinking water systems. Thirdly, additional arsenic removal from drinking water may result in an enriched residual and possibly generating a new regulated waste stream.

Risk Management Issue 1 (RM 1). How Effective are Available Technologies for Meeting a Lower Arsenic MCL?

RM 1a. Laboratory and Field Testing on Different Arsenic Control Technologies

A reduction in the MCL for arsenic in the near future is going to require that control technology be capable of meeting the technical requirements of the revised limit. Currently, there are at least eight different types of control technology applicable to arsenic control and a significant amount of laboratory and pilot plant work on the performance/reliability has been completed and shown to achieve levels below the current MCL. The main focus of the research has been on the CF and LS methods for surface waters with high levels of TOC and on IE and AA methods for ground waters. Short-term research conducted in RM 1a. will verify the sustained performance of full scale proven arsenic control technologies to achieve 10 µg/L or less of arsenic in treated waters. Long-term research will involve studies to optimize and improve efficiency of proven control technolo-

gies to consistently achieve levels lower than 10 µg/L of arsenic. Lab and pilot plant research will also be carried out under RM 1a. to investigate the impact of TOC and other water quality parameters on the performance and capability of the technologies. To help define the specific research needs and gaps, a workshop will be conducted with leading experts in the field of arsenic research technology. This state of the science workshop will review past work and provide guidance for new research. The SDWA Amendments of 1996 call for promulgation of a new arsenic MCL and this research directly supports that requirement by determining the availability of reliable control technologies. High Priority for activated alumina, ion exchange, conventional coagulation/filtration, lime softening and iron removal processes. Medium Priority for Reverse Osmosis, Nanofiltration, and Electrodialysis Reversal

Risk Management Issue 2 (RM 2). Are There Cost Effective Technologies Available for Small Systems?

RM 2a. Cost Evaluations for Laboratory and Field Testing of Arsenic Control Technologies

Small drinking water treatment and distribution systems pose several additional challenges to regulators. The economic impact of a lower MCL for arsenic could be significant. As part of the technical evaluation for the various arsenic treatment technologies studied in RM 1a., the economics of each system will also be evaluated using existing OW cost equations and models and other available costs information. Applicability of the control technologies to point of use (POU) considerations will also be part of the technical/economic evaluation.
Medium Priority

Risk Management Issue 3 (RM 3). How can Residuals From Arsenic Control be Managed Most Effectively?

RM 3a. Arsenic Control Residual Management

A reduced MCL for arsenic will result in the production of more arsenic enriched residual material. The disposal of this material will likely be impacted by a lower arsenic TCLP value and trigger regulation under RCRA. Residuals associated with RM 1a. and other arsenic removal projects will be evaluated for quantity and arsenic content and mobility with emphasis being on reducing the environmental impact of its disposal. Short-term research will characterize the residuals produced by all arsenic control technologies and identify acceptable disposal options considering existing and potentially modified residual disposal regulations. Long-term research will involve studies to optimize treatment to reduce the quantity of residuals for disposal and to develop meth-

ods to reduce cost of disposal assuming more stringent residual disposal regulations will occur. Residuals are important from a total arsenic management standpoint, and have not received sufficient attention in past studies. High Priority

Specific projects and products relating to these issues and their status, use and time frame are outlined in Tables 4-2 and 4-3.

5. Cross Linking and Summary of Arsenic Research

The preceding chapters have presented research options and priorities for arsenic. Each chapter focused on a particular aspect of the standard risk assessment/risk management paradigm and associated research needs. Accordingly, the chapters did not always provide a global perspective on the total plan.

A series of tables were developed for this chapter in order to assist the reader in forming a comprehensive picture of the arsenic research plan. Tables dealing with research initiatives on the following topics are included:

- Analytical Methods

- Exposure Assessment

- Metabolism/ Biomarkers/PBPK Model Development

- Health Effects and Dose-response

  - Cancer endpoints
  - Noncancer endpoints

- Mechanisms of Action

- Human Susceptibility Characteristics

- Potable Water Treatment Modalities

The tables integrate the various components of the research plan; they illustrate the importance of specific research opportunities, interaction of components of the plan and limitations on what can reasonably be accomplished in a limited time span. Each table highlights the contributions of the proposed activity to the arsenic risk assessment, presents a priority for the activity and targets a time frame for its accomplishment. The projected responsibility for ORD is also delineated.

Table 4-2. Exposure Research Strategy Matrix for Arsenic

Issue	Task	Product	Use
RM Issue 1 How effective are the available arsenic treatment technologies for meeting a lower MCL	RM Task 1a. Conduct laboratory and field tests on arsenic control technologies including As III oxidation. High Priority (CF, LS, AA, IE, Fe/MnP) Medium Priority (NF, RO, ER)	Series of reports describing the technical performance of the different arsenic control technologies	Will be use in the rule making process to demonstrate the capabilities and performance of arsenic control technologies to Achieve revised MCL
RM Issue 2 What are the technical and economic considerations of arsenic control for small systems	RM Task 2a. Complete cost evaluations for arsenic control technologies in RM 1a. Medium Priority	Report describing the economic considerations associated with the operation of each treatment technology studies in RM 1a.	Will be used to determine any adverse economic considerations that will arise from small systems complying with the revised MCL for arsenic
RM Issue 3 How can arsenic enhanced residuals be effectively managed	RM Task 3a. Conduct studies on the arsenic characteristics of the residual material generated by testing in RM 1a. High Priority	Reports on the quantity and the composition of arsenic containing residuals and disposal options for each treatment technology considering existing and more stringent residual disposal regulations	Used to determine the recycle/disposal options for the residual material generated by the technologies tested in RM 1a and to determine total costs of arsenic treatment for large and small systems
	RM Task 3b. Conduct studies to modify treatment methods to reduce quantity of residuals and to develop residual disposal methods to reduce costs under more stringent regulations	Report on treatment modifications to reduce residuals and more cost-effective disposal methods	Will be used to provide guidance to utilities on residual disposal options and residual costs

Table 4-3. Risk Management Task Summary, Current Activities and Proposed Sequence for Studies

Task - Short Study Title	Task[1]		Ongoing	Priority	Time Frame[2]					
	I	E/O	Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
RM Task 1a. Bench field	I	E	Y	High for CF, LS, AA, IE and Fe/MnP Medium for NF, RO and ER	EPA	EPA	EPA			
RM Task 2a. Technical and economic considerations of arsenic control for small systems		E	N	Medium		EPA	EPA			
RM Task 3a. effective management of arsenic enhanced residues		E	N	High	EPA	EPA	EPA	EPA		
RM Task 3b. Treatment modification to reduce arsenic residuals		E	N	Medium				EPA	EPA	EPA

[1] I = Intramural (EPA inhouse research), E = Extramural (EPA sponsorship through grant or co-op)
[2] EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyong EPA's planned effort.
NOTE: RM Tasks 2a. and 3a. are to be carried out as subtasks under the technology performance research in RM Task 1a.

Table 5-1. Research Priorities for Arsenic: Exposure Research - Methods

Research Issue	Research Opportunities*	Contribution to Risk Assessment	Issues/Limitations/Links
Refinement of Analytical Methods. The species specific toxicity of arsenic requires the utilization of speciation because ased analysis to accurately quantify the risk associate with primary exposure route (i.e. drinking water and dietary ingestion of arsenic) Methods are required to extract, separate and quantify arsenic compounds in a wide variety of biological and dietary samples to support this risk assessment. To date, validated analytical methods, similar to those used in compliance monitoring not exist.	Speciaton based methodologies are needed in biological samples (i.e. urine and blood) and dietary ingestion samples (i.e. duplicate diet and targeted food items). The separation of the valence states of inorganic arsenic may be a consideration in treatment related issues. Biological Samples: The separation of inorganic arsenic (As(III) and As(V)), MMA, DMA and arsenobetaine is important in pharmacokinetic, mechanistic, biomarkers and bioavailability studies. The analytical methodologies must address sensitivity issues in urine and blood while providing species specific integrity. Biological tissue will require unique extraction procedures prior to analysis. Dietary Samples: A reliable extraction and speciation analysis procedure for inorganic and organic arsenicals is required to address the relative source contribution of arsenic dietary ingestion. The primary concern will be the separation of inorganic from organic arsenic with specific applications requiring a more complete speciated analysis. Tasks: EXP 1a - 4c	Speciation based analytical methods are needed to accurately quantify the risk with exposure routes which contain both organic and inorganic arsenic. The relative source contribution of diet to arsenic exposure needs to reflect a speciation based analysis. Analytical methods development can support a range of pharmacolinetic, mechanistic, biomarker and bioavailability studies to obtain a better understanding of the biological processing of arsenic.	Methods for the analysis of arsenic in drinking water were identified as a high priority of treatment removal efficiency considerations. Analytical techniques which aid in the assessment of relative source contribution of dietary ingestion, aid in treatment evaluation, identify biomarkers, aid in pharmacokinetic and mechanistic studies require a speciation based methodology which is applicable to diverse and complex matrices.

Significance for Risk Assessment/Priority

Dietary arsenic exposure in the U.S. is a component of understanding cumulative arsenic risks from drinking water and food. Pharmacokinetic and mechanistic work to better understand the physiological processing of arsenic and its toxicological activities require speciation based analytical data in biological matrices.
Priority: High

Time Frame/ORD Role

Near- to mid-term (1-5 years) for methods. development. Research should be coordinated with other organizations such as FDA, USDA and CDC, NIST.

*Under research opportunities, task numbers reference proposed research in the Risk Assessment (RA), Exposure (EXP), Health Effects (EFF) and Risk Management (RM) chapters.

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Table 5-2. Research Priorities for Arsenic: Exposure Research - Background Exposures

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Background Levels of Arsenic Exposure in the U.S. Population Aside from drinking water, the diet is the primary source of exposure to arsenic for the general U.S. population. Intake and bioavailability of arsenic requires additional research.	Duplication diet sampling (collection of total dietary samples for individuals in study groups) and market basket sampling (collection of representative food product samples from retail markets) are both useful approaches. Data on contributions of individual foods and/or food groups to arsenic intake is important. The bioavailability of arsenic species may be influenced by complex food matrices. Human bioavailability data are needed for determining uptake of dietary arsenic. Tasks: RA 1c; EXP 2a,b, 4a, 5a, 6a, 8a	Better knowledge of dietary inorganic arsenic exposure would provide perspective on the relationship between arsenic and arsenic from drinking water. This information will be useful for risk characterization, as low-dose risk estimates should be considered in context of arsenic exposure. For example, cumulative inorganic arsenic exposure will need to be considered in margin of exposure comparisons. There is substantial information on total arsenic in the U.S. diet and limited information on inorganic arsenic.	Methods development will be needed for measuring inorganic arsenic in the diet. Relevent methods for assessing bioavailability need definition. Mass balance studies of arsenic absorption, distribution and excretion will support bioavailability determinations. Also provide data for assessing benefits, determining margin of exposure (MOE) and relative source contribution.

Significance for Risk Assessment/Priority

This research will support refinement (verification or change) of current estimates of inorganic arsenic intake in the diet. It will provide improved data for the relative source contribution in the risk assessment.
Priority: High

Time Frame/ORD Role

Short to mid term (2-5 years) Data could be collected relatively rapidly if sufficient resources and analytical methods are available. Need to work with FDA and USDA.

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Table 5-3. Research Priorities for Arsenic: Linking Exposure and Effects Research

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Metabolism, PBPK Models and Biomarkers of Exposure and Effect	Data on absorption distribution metabolism and excretion are needed to quantify the concentration and species of arsenic present at target issues. Opportunities exist to conduct studies in populations that have significant environmental exposure. Mass balance data from humans will be needed for PBPK model development. Biomarkers of exposure will help correlated exposure data with observed health effects. Urine and blood arsenic have been identified as useful biomarkers of recent exposure. Hair and nail arsenic reflect longer term exposures. Other endpoints such as methylation of DNA have been suggested as biomarkers of both exposure and effect but require quantification and validation. Excretory products will help elucidate metabolic processing and pathway saturation. Tasks: RA 1b, 2a; EXP 7a, 8a; EFF 2a, 2b.	Researchers hypothesize that saturation of arsenic metabolism may affect the dose-response relationship although available data suggest that metabolic processes are substantially similar over a broad dose range. Analytical and logistical issues complicate the quantification of arsenic exposure from multiple sources. If a simple biomarker could be correlated to total exposure it would be of great value in risk assessment.	Mass balance studies will address bioavailability of arsenic from the diet. Analytical data are needed to speciate and quantify human environmental exposures and tissue exposures. Blood and urine are very limiting as biomarkers because they only reflect recent exposures, demand frequent sample collection and are labor intensive. Information on other biomarkers with longer half lives will contribute to an understanding of mechanism of action and pharmacokinetics.

Significance for Risk Assessment/Priority

		Time Frame/ORD Role	
Validated, practical biomarkers of long-term arsenic exposure would contribute to exposures assessment and epidemiological research. Absorption, distribution, metabolism and excretion data are required of PBPK modeling. Will help answer question regarding saturation of arsenic metabolism. Provide data for pharmacokinetics modeling Priority: High if feasible		Medium for data collection and interpretation; longer term for model development and verification. Appropriate for ORD sponsorship.	

Table 5-4. Research Priorities for Arsenic: Effects Research - Cancer Endpoints

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Determine Cancer Endpoints and Dose-Response Associated with Arsenic Exposure	A number of health effects in humans and animals are attributed to arsenic in drinking water. Research in Chile, India, and Taiwan are evaluating arsenic induced internal cancers. Data from these ongoing studies can be used to determine dose-response at low doses. In the long-term, a feasibility study in the U.S. is underway to determine the potential for a full scale study of cancer and important noncancer health endpoints. Studies in animals may facilitate an evaluation of other endpoints and compliment human studies. Tasks: RA 2a; EFF 1a, 1b, 1c.	Internal cancers induced by arsenic are probably the health endpoint of concern. Dose-response models for these endpoints would be considered as the basis for arsenic risk assessments and regulatory decision making.	Strengthening exposure data in ongoing studies and future epidemiologic studies is needed. This will require close collaboration and cooperation with the principal investigators. Utilization of biomarkers may facilitate exposure and effects analyses.

Significance for Risk Assessment/Priority

Provides information on health endpoints and dose-response at low doses of arsenic exposure. This area is a source of uncertainty in the current arsenic risk assessments. Results from ongoing studies are expected in the near term and could be used to refine existing risk assessments for arsenic.
Priority: High if feasible

Time Frame/ORD Role

Applying data from ongoing studies in a dose-response analysis could be completed in the short-term (1-3 years). This research could be completed by EPA. The feasibility study and full scale study is an area of long-term research that will require collaboration with non-EPa organizations with results not expected for more than 5 years.

Table 5-4b. Research Priorities for Arsenic: Health Effects

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Noncancer Effects Limited data indicate that health effects other than cancer may present significant health concerns for arsenic. Vascular damage has been noted in diverse studies and is a potentially important issue for the U.S. population because of the high background rate of cardiovascular disease. Neurological effects from arsenic have been noted in a drinking water study with a U.S. population. Dermatological abnormalities (hyperkeratosis and other effects) have been extensively documented to result from arsenic exposure. These effects form the basis for EPA's current RfD for arsenic, but dose-response data are lacking. Potential development effects from arsenic have also been identified.	Generate epidemiological data on arsenic's noncancer health effects. Dose-response data on noncancer effects would be particularly valuable in supporting arsenic risk conclusions. There is a significant opportunity to conduct dose-response studies of hyperkeratosis in suitable human populations. Hyperkeratosis occurs more frequently than skin tumors in persons exposed to arsenic, allowing generation of response data at lower exposure levels. Animal toxicity studies can provide insight into the hazard and dose-response for noncancer toxic effects, such as vascular, neurological, and developmental effects, provided that the animal models are relevant to humans. Tasks: RA 1b, 2b; EFF 1a, 1b, 1c.	Data to evaluate risks from noncancer effects of arsenic exposure are limited. Additional data on the occurrence of these effects, preferably including data on dose-response or the occurrence of effects at lower dose levels, can fill a significant data gap. Hyperkeratosis is strongly indicated as a precursor of skin tumors; refinement of the dose-response for this endpoint may enable it to be used as a surrogate in consideration of the skin cancer dose-response. In addition, risks from cardiovascular, neurological and developmental effects are not well characterized.	Priority should be placed on seeking opportunities for add-ons to ongoing epidemiological studies. Cooperative efforts can support improved dose-response information and occurrence data for noncancer endpoints. The feasibility of conducting significant new epidemiological studies in relevant U.S. or international populations should be assessed, with attention to ability to generate adequate exposure and effects measures. A longer term priority is new epidemiological studies. Where animal research is undertaken, similarities and differences in animal and human response need to be integrated in the design and interpretation of studies to insure relevance.

Significance for Risk Assessment/Priority			Time Frame/ORD Role
Data on the noncancer health effects of arsenic may have important impact on the overall health risks from arsenic. Documentation of a risk of hyperkeratosis at doses below those associated with cancer may provide significant support for the weight of evidence cancer risk assessment. Priority: High			Limited add-ons to existing studies may be completed on a short-term basis, while substantial new epidemiological studies are probably long-term in nature. It is appropriate to expend ORD's limited resources in support of studies of limited scale. EPA needs to seek cooperative relationships with other agencies to support substantial new studies.

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Table 5-5. Research Priorities for Arsenic: Mechanisms of Toxicity

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Mechanisms of Toxicity	Current research suggests a number of promising approaches that may aid in understanding arsenic toxicity. There is potential for studies with a wide range of experimental systems (biochemical, cell cycle, tissue culture, whole animal). These studies will look at a range of endpoints that may relate to arsenic toxicity (DNA damage, DNA methylation, initiation/promotion experiments/ oncogene studies, enzyme systems, enzyme kinetics, etc.) Tasks: RA 2a, 2b; EFF 2c, 2d.	Provides insight into mechanisms that may influence to arsenic carcinogenesis and toxicity.	Multiple mechanisms for arsenic toxicity may be present. Tools to relate mechanistic risk to human risk need to be developed. Appropriate studies will relate mechanistic information to observed human toxicity. Work should be linked to studies of human susceptibility.

Significance for Risk Assessment/Priority

Potential for elucidating mode of action for arsenic.
Could assist in the evaluaiton of low dose risks and
susceptibility factors.
Priority: High

Time Frame/ORD Role

Long-term
ORD laboratories will contribute to specific
studies. ORD can fund related academic
research.

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Table 5-6. Research Priorities for Arsenic: Modifiers of Susceptibility

Research Issue	Research Opportunities	Contribution to Risk Assessment	Issues/Limitations/Links
Modifiers of Human Susceptibility	Factors affecting human susceptibility include environmental and characteristic modifiers. Examples include diet or concurrent exposure to other toxins, genetic differences, age, gender, and preexisting disease. Epidemiologic or human clinical studies can provide insight on the influence of these factors on the incidence of effect in arsenic-exposed populations. In vitro or animal studies may also be conducted when human testing is not feasible or practical. Research on susceptibility factors can also provide insights on mechanisms for human toxicity. Tasks: EFF 3a.	Identification of factors influencing human susceptibility to arsenic toxicity. This research may: 1) improve our understanding of human variability and sensitivity to the action of toxic agents, 2) identify potentially sensitive populations such as children, disease or nutritionally compromised individuals, 3) provide insight into mechanisms of action, and 4) help in the design of future epidemiology and toxicology studies.	This research requires measurable environmental or human characteristics that may relate to arsenic toxicity. A variety of susceptibility factors can be proposed. Research efforts will need to determine practical human endpoints or environmental conditions, consider costs and scientific merits. Where possible, research could be linked with ongoing studies. Close collaboration with principle investigators would be needed.

Significance for Risk Assessment/Priority

Potential for identification of sensitive subgroups with high susceptibility to arsenic toxicity. Presence or absence of susceptibility factors may have implications for risk management decisions. Potential for direct insight into mechanisms of action for arsenic toxicity which could aid in evaluation of low dose risks.
Priority: High

Time Frame/ORD Role

Research could be completed in a 3-5 yr time frame through use of clinical and in vitro techniques and through application of data from ongoing studies. Additional research would be needed to evaluate effects of susceptibility factors on arsenic dose-could be completed by EPA and possibly with collaboration with non-EPA organizations.

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Table 5-7. Research Priorities for Arsenic: Risk Management Research

Research Issue	Research Opportunities	Contribution to Risk Management	Issues/Limitations/Links
Cost-Effective Treatment Techniques for Removing Arsenic from Drinking Water The reliable control of arsenic at levels below 50 μg/L by currently available treatment technologies has not been adequately demonstrated. In addition, there are special technical and economic concerns associated with application of arsenic control to small drinking water systems.	Important research issues include: 1) Laboratory and field testing of different arsenic control technologies. Seven applicable arsenic control technology types need to be evaluated for performance and reliability. 2) Evaluating the cost effectiveness of the arsenic control technologies for small drinking water systems. 3) Determining effective management controls for residuals produced from arsenic control technologies. Tasks: RM 1a, 2a, 3a, 3b; Exp 1a.	This work will determine the feasibility of any new proposed arsenic MCL by determining BAT and the costs associated with arsenic controls, both in large and small drinking water systems.	Analytical methodology refinements in arsenic speciation will be needed for optimal determinations of control treatment technologies and for determination of risks from residuals using TCLP tests.

Significance for Risk Assessment/Risk Management and Priority

	Time Frame/ORD Role
Provides critical information for EPA's determination of arsenic control BAT and the feasibility for reducing ing water supplies, especially in small systems. Priority: High (RM 1a, 3a,b), Medium (RM 2a)	Short- to mid-term (1-4 years) for determining cost effective control technologies and BAT feasibility. ORD will work closely with OW and outside entities, such as AWWARF, in conducting this research and determing feasibility.

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Table 5-8. Summary of Tasks and Priority

Task		Short-Term	Long-Term	Priority
RA	1a	X		High
	1b	X		High
	1c	X		High
	2a		X	Medium
	2b		X	Medium
Exp	1a	X		High
	1b	X		High
	2a	X		High
	2b	X	X	High (short-term) Medium (long-term)
	2c		X	Low
	3a	X		High
	3b		X	Medium
	3c		X	Medium
	3d		X	Medium
	4a		X	High
	4b		X	Medium
	4c		X	Medium
	5a		X	High
	6a	X	X	High (water) Medium (diet)
	7a		X	High
	8a		X	Medium
Eff	1a	X		High
	1b		X	High
	1c		X	Medium
	2a	X		High
	2b		X	Medium
	2c		X	Medium
	2d		X	High
	3a		X	High (long-term) Medium (short-term)
RM	1a	X		High
	2a	X		Medium
	3a	X		Medium
	3b		X	Medium

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