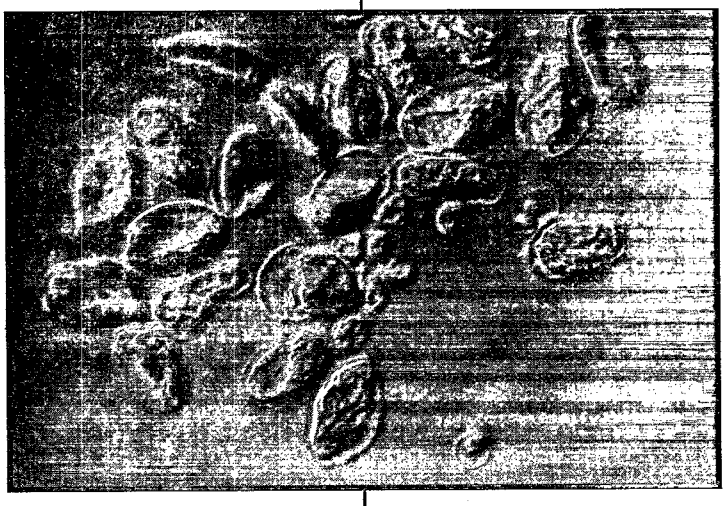
United States
Environmental Protection
Agency

Office of Research
and Development
Washington, DC 20460

EPA 600-R-97-122
December 1997
www.epa.gov

Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water



Cryptosporidium parvum (small) and *Giardia lamblia* (large)

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Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water

Office of Research and Development
Office of Water
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Notice

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Contents

Chapter I
Introduction

Purpose

This document describes the research needed to support EPA's development of drinking water regulations for community systems concerning disinfectants, disinfection by-products (DBPs) and microbial pathogens. It does not specifically address the needs of non-community systems; however, much of the information that will be generated by this research will be relevant to non-community systems as well. While the research needs identified in this plan are extensive, the plan is intended to focus on the key scientific and technical information needed to develop sound regulations. EPA is committed to conducting a substantial research program that will address many of the priority research needs identified in the plan. EPA also hopes to use this plan as a vehicle for discussion with outside groups, including those who participated in the DBP regulatory negotiation, to reach agreement on the components of the plan. EPA anticipates that the plan can then be used to promote coordination and cooperation among the various agencies, private organizations, and universities that are involved in DBP and microbial research. EPA envisions continuing the stakeholder meetings to facilitate coordination of research.

The Problem

For nearly 100 years, public water supplies have been treated with a variety of chemicals targeted at the reduction or elimination of infectious disease risk. But risks remain, as evidenced by the EPA Science Advisory Board's 1990 ranking of pollutants in drinking water as one of the highest health risks meriting EPA's attention. This ranking was based on the exposure of large populations to known and unknown contaminants, including lead, DBPs, and disease-causing microorganisms.

The continued occurrence of waterborne disease outbreaks demonstrates that contamination of drinking water with pathogenic bacteria, viruses, and parasites still poses a serious health risk when treatment is inadequate or when contamination occurs in the distribution system. Thirty-four outbreaks of waterborne disease were reported in 1991-1992, and the causative agent was not identified in most of these outbreaks. A 1993 outbreak of Cryptosporidiosis in Milwaukee, which resulted in an estimated 400,000 cases of acute gastroenteritis, represents the largest documented occurrence of disease associated with contamination of a treated public water supply in the U.S. In addition to these known outbreaks, many others undoubtedly occur each year but are either unrecognized or unreported. Cases not associated with an outbreak (endemic or opportunistic disease) may also be significant, but little is known about the extent to which this is a problem.

To combat waterborne microbial diseases, public water systems disinfect drinking water with chlorine or alternative disinfectants, such as ozone, chloramines, or chlorine dioxide. However, the use of chlorine or other disinfectants, while reducing microbial risks, creates new potential risks, because compounds known as disinfection by-products are formed during the water treatment process. A wide variety of by-products have been identified, a number of which have been shown to cause cancer and other toxic effects in animals under experimental conditions. Additionally, some epidemiology studies have suggested that consumption of chlorinated water may be associated with elevated rates of cancer and adverse reproductive outcomes. In reviewing these data, however, most experts agree that the scientific evidence is inconclusive with regard to the significance of adverse health risks from exposure to disinfected waters.

The challenge in providing safe drinking water today lies in adequately characterizing the risks and then reaching an acceptable balance among competing risks. Increased disinfection can reduce microbial risks but can increase the potential risk from disinfection by-products. The optimal balance will adequately control risks from pathogens, simultaneously control DBPs to acceptable levels, and ensure that costs of water treatment are commensurate with public health benefits. To enable EPA to develop regulations that will achieve this balance, research is needed to obtain a better understanding of the potential health risks and human exposures to pathogens and DBPs. Research is also needed on water treatment processes and other means of reducing these risks.

Regulatory Background

The Safe Drinking Water Act (SDWA) mandates that EPA identify and regulate drinking water contaminants that may have any adverse human health effects and which are known or anticipated to occur in public water

systems. The SDWA also requires the use of filtration and/or disinfection for public water supplies that serve most of the U.S. population. Currently, several regulations attempt to control for DBPs and pathogens in public drinking water supplies:

- *Interim total trihalomethane (TTHM) standard* (promulgated 1979)—This standard is applicable to all community water systems that disinfect and serve at least 10,000 people. Systems must achieve less than 0.10 mg/l of total trihalomethanes as an annual average based on quarterly measurements in the distribution system.

- *Total coliform rule* (promulgated 1989)—This standard is applicable to all public water systems. Systems must demonstrate that the frequency of total coliform presence is below acceptable limits; sampling frequency is based on population served. Small systems that collect fewer than 5 samples per month must conduct periodic sanitary surveys.

- *Surface water treatment rule (SWTR)* (promulgated 1989)—This standard is applicable to all public water systems that use surface water or groundwater under the direct influence of surface water. Systems must achieve at least 3 and 4 log removal and/or inactivation for *Giardia* and viruses, respectively, and if filtration is not part of the treatment process, the system must meet specific criteria for avoiding filtration.

A more comprehensive regulatory strategy is needed to address microbial and DBP contaminants in drinking water. The TTHM standard addresses only one class of by-products. While control of TTHM during the treatment process may also control formation of other by-products, the extent of such a relationship is unknown. Additionally, the TTHM standard applies only to larger systems, so the same protection is not afforded to people served by smaller water systems. While the Total Coliform Rule and SWTR apply to all system sizes, it is not clear that achieving these standards will provide adequate protection from protozoa, such as *Giardia* and *Cryptosporidium*, especially when a system uses a poor quality source water.

In 1992, EPA initiated a negotiated rulemaking to evaluate the need for additional controls for microbial pathogens and disinfection by-products. The negotiators included representatives from state and local health and regulatory agencies, public water systems, elected officials, consumer groups, and environmental groups. The major goal of the Negotiating Committee was to develop an approach that would reduce the level of exposure from disinfectants and DBPs without undermining the control of microbial pathogens. Early in the regulatory negotiation process, participants agreed that large amounts of information necessary to understand how to optimize the use of disinfectants and concurrently minimize microbial and DBPs' risk were unavailable. Because of this lack of data the negotiators agreed that there should be a two-stage DBP rule and Long Term Enhanced Surface Water Treatment Rule (LTESWTR). The Stage 1 DBP rule would be proposed, promulgated and implemented concurrently with the Interim Enhanced Surface Water Treatment Rule (IESWTR) in order to ensure that microbial risk was not increased as the Stage 1 DBP rule is implemented. The Stage 2 DBP rule would follow after additional information on health risk, occurrence, treatment technologies, and analytical methods were developed in order to better understand the tradeoffs between microbial pathogens risk and risks from DBPs. Each rule is described below.

The proposed Stage 1 DBP rule included maximum contaminant levels of 0.08 mg/L for TTHMs, 0.06 mg/L for five haloacetic acids (HAA5), 0.01 mg/L for bromate, and 1.0 mg/L for chlorite along with the best available technologies to control for these DBPs. The proposed Stage 1 DBP rule also included lower MCLs for TTHMs (40 µg/L) and HAA5 (30 µg/L) as a "placeholder" to assure participants favoring further DBP controls that other members would return for Stage 2 DBP negotiations. For the Stage 2 DBP rule, the negotiators agreed that EPA would collect data on the parameters that influence DBP formation and occurrence of DBPs in drinking water through the Information Collection Rule (ICR). Based on this information and new data generated through research, EPA would reevaluate the Stage 2 DBP "placeholder" provisions and repropose, as appropriate, depending on the criteria agreed on in a second regulatory negotiation.

The SDWA was reauthorized in 1996. The 1996 SDWA amendments required EPA to conduct research in several areas including research to better understand the mechanisms by which chemicals cause adverse effects; research on new approaches for studying the adverse effects of contaminant mixtures in drinking water; studies to identify subpopulations that are at greater risk than the general public from exposure to contaminants in drinking water; and pilot waterborne disease occurrence studies in at least five major U.S. communities in collaboration with The Center for Disease Control (CDC). EPA has provided special emphasis in this plan to address these statutory requirements. The amendments also provided an additional $10 million in 1997 for conducting health effects research on drinking water contaminants. Of this $10 million, about $9 million has been targeted toward conducting research for microbial pathogens and DBPs.

The SDWA amendments also established new deadlines for the M/DBP rules. The final Stage 1 DBP rule and the IESWTR must be finalized by November 1998, while the Stage 2 DBP rule must be finalized by May 2002 and the LTESWTR must be finalized by November 2000. The deadlines for promulgation of the Groundwater Disinfection Rule are between August 1999 and May 2002. The ICR was finalized in May 1996, with monitoring starting in July 1997 and ending in December 1998.

Long-term 1 enhanced surface water treatment rule (LT1ESWTR) follows. (Long-term 2 enhanced surface water treatment rule (LT2ESWTR) (final by 5/2002—not a statutory deadline) will be developed to further improve control for pathogens and will be promulgated in conjunction with Stage 2 of the D/DBP rule in order to prevent increased risk for systems complying with the Stage 2 DBP rule.)

- *Information collection rule (ICR)* (proposed 2/94; final 5/96)—Large public systems would be required to collect approximately $130 million of occurrence and treatment information concerning pathogens and DBPs. Information collected under this rule would be used with research to support the development of the interim and long-term enhanced SWTR, and Stage 2 DBP rule.

- *Stage 1 Disinfectant/Disinfection By-Products (D/DBP) rule* (proposed 7/94; final 11/98)—This rule would be applicable to all community water systems that disinfect and is intended to reduce risks from disinfectants and DBPs. Systems would be required to achieve new limits for TTHMs, the sum concentration for five haloacetic acids, bromate, chlorite, chlorine, chlorine dioxide, and chloramines. Systems using conventional treatment (sedimentation and filtration) would also be required to achieve percent reductions of DBP precursors (measured as total organic carbon), depending upon source water quality, prior to disinfection.

- *Interim enhanced surface water treatment rule (IESWTR)* (proposed 7/94; final 11/98)—This rule would be applicable to all public water systems using surface water or groundwater under the direct influence of surface water that serve populations of 10,000 or greater. The purpose of this rule is to enhance protection from pathogens, including *Cryptosporidium*, and to prevent increases in microbial risk while large systems comply with the Stage 1 D/DBP rule. Several regulatory options were proposed, including systems being required to achieve a) proportionally higher levels of pathogen removal depending upon pathogen measurements in the source water, and b) fixed level removal requirements independent of pathogen measurements in the source water.

- *Long-term enhanced surface water treatment rule (LTESWTR)* (final by 11/2000)—This rule, which could include changes to the IESWTR, would extend applicability to surface water systems serving less than 10,000 people. The purpose of this rule is to enhance protection from pathogens, including *Cryptosporidium*, and to prevent increases in microbial risk for systems serving less than 10,000 people, while they comply with the Stage 1 D/DBP rule.

- *Stage 2 DBP rule* (proposed in part 7/94 with the Stage 1 D/DBP rule; final by 5/2002)—This rule would be applicable to all community water systems that disinfect and is intended to further reduce the levels of risk achieved under the Stage 1 rule. Only tentative limits were proposed for TTHMs and the sum concentration for five haloacetic acids.

- *Groundwater disinfection rule (GWDR)* (final between 8/99 and 5/2002)—This rule would be applicable to all public water systems using groundwaters not under the direct influence of surface water. This rule would require all vulnerable systems to disinfect. This rule is intended to enhance protection from pathogens as well as to prevent increases in microbial risk while systems comply with the Stage 1 D/DBP rule.

Figure I-1 depicts the schedule of rules being developed and the concurrent ongoing activities of the ICR and research on microbial pathogens and DBPs.

Drinking Water Treatment—Brief Overview

Figure I-2 shows the conventional treatment process for surface water supplies along with the possible points of disinfection. The disinfectants generally used in the U.S. include chlorine, chloramines, ozone, and chlorine dioxide and various combinations. Chlorine is the most common disinfectant used among water systems. About 80% of large water systems (serving greater than 10,000 people) use chlorine, while almost 100% of smaller systems use chlorine. Chloramines are used by about 20% of the larger systems, while chlorine dioxide is used by about 5% of larger systems, and ozone is used by about 2% of the larger systems (the total does not add to 100% because some systems use combinations of disinfectants).

The formation of DBPs depends primarily on where in the treatment process the disinfectants are added and the source water quality parameters. Generally, the later in the treatment process the disinfectants are added, the fewer DBPs will be formed, all other factors being equal. The most important water quality parameters that influence the formation of DBPs include the nature of the source water, such as the content of precursor materials, water temperature and pH, and conditions under which the disinfectant is used, such as the concentration, contact time, point of addition, and residual maintained.

Policy Questions and Research Goals

In making decisions on appropriate regulatory levels for pathogens and DBPs in drinking water, policy-makers will focus on three major questions:

- What are the health risks caused by exposure to microbial pathogens?

- What are the health risks caused by exposure to DBPs from different treatment processes?

- How can these risks be simultaneously controlled?

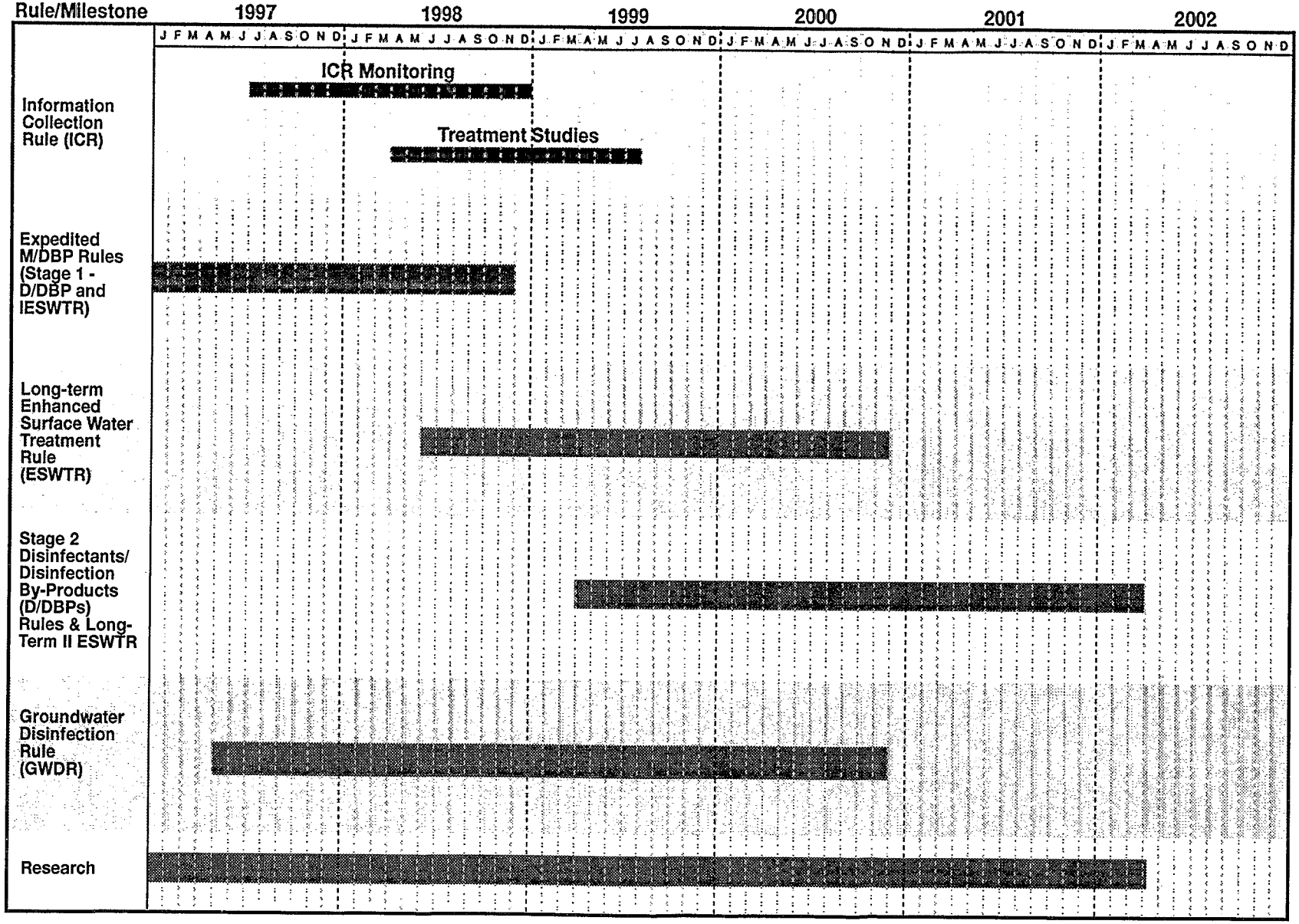

Figure I-1. Schedule for expedited M/DBP rules, long-term M/DBP rules, and GWDR rules and ICR and research.

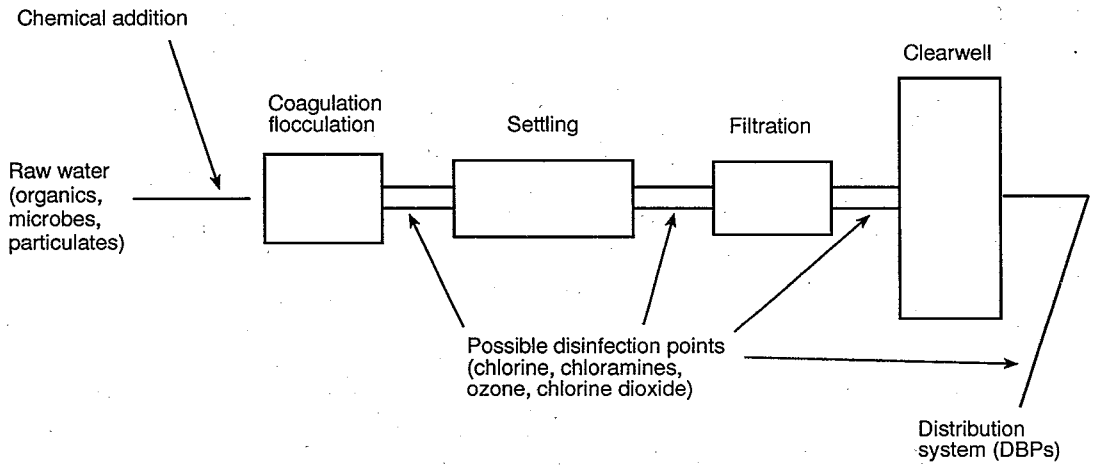

Figure I-2. Conventional treatment (surface supplies).

To provide a specific example, a critical issue will be whether ozonation should be encouraged in place of chlorination. The U.S. has many years of experience with the use of chlorine for disinfection, and most of the research on DBPs has focused on chlorination by-products. Other disinfectants, such as ozone, chloramines, and chlorine dioxide, are less widely used than chlorine and less research has been conducted on their by-products. Recent research indicates that ozone is much more effective in inactivating *Cryptosporidium* than chlorine. This may provide an impetus for many water utilities to switch to ozone as a disinfectant. However, significant uncertainties remain in assessing the health risks resulting from chlorination and use of alternative disinfectants. Before making any major regulatory decisions, policy makers need to know whether the risks from use of alternative disinfectants are greater than, less than, or equal to those from chlorination, and whether pathogens can be adequately controlled with improvements to the chlorination process.

To support the policy-making process, the research goals are

1. To identify the health effects caused by DBPs and microbial pathogens in drinking water.

2. To determine the population distribution of exposure to DBPs and microbial pathogens to which people are exposed.

3. To assess the risks caused by DBPs and microbial pathogens in drinking water.

4. To evaluate the effectiveness of options for reducing risks from DBPs and microbial pathogens.

The first three goals are all part of the risk assessment process—the research proposed in this plan is intended to fill data gaps and reduce the major uncertainties in current estimates of risks from microbial pathogens and DBPs. The fourth goal addresses reducing the risks. Research is needed to fill major gaps in current knowledge about the effectiveness of treatment processes in simultaneously controlling pathogens and DBPs.

The importance of research to support the decision making process for microbes and DBPs in drinking water is further highlighted by the strong research provisions of the 1996 SDWA Amendments. This legislation specifically requires EPA to place a high priority on studies concerning the health effects of *Cryptosporidium* and DBPs, as well as on studies of subpopulations at greater risk of adverse effects from exposure to drinking water contaminants. The Agency is required to conduct research to support the ESWTR, D/DBP rule, and the GWDR, particularly in the areas of cancer and reproductive effects (toxicology and epidemiology studies), and dose-response studies for waterborne pathogens such as *Cryptosporidium* and Norwalk virus.

To ensure the credibility and soundness of EPA's regulatory decision-making, it is imperative that all research is of high technical quality and follows EPA quality assurance guidelines. EPA policy requires peer review for all major scientific and technical studies that support regulatory decisions. EPA expects that all research activities supporting this research plan will undergo appropriate peer review by independent experts.

The following sections provide an overview of research needs for microbial pathogens and DBPs, in the areas of health effects, exposure, risk assessment and risk management. Each section begins with highlights of key scientific issues and then lists research questions and research needs.

Microbial Pathogens—Research Needs

Health Effects Research for Microbial Pathogens

Current knowledge of waterborne pathogens is inadequate for assessing their health risks. While the disease symptoms caused by pathogens are generally known, limited information is available on the doses and conditions that produce effects. For example, EPA has estimated risks from *Cryptosporidium* using the assumptions that ingestion of a single organism can cause an infection and that the probability of infection from one organism can be predicted by extrapolation from higher dose studies. However, there is considerable uncertainty surrounding these assumptions. Additionally, there are uncertainties with regard to infectivity in susceptible subpopulations, the significance of the immune response, and the variation among different strains of *Cryptosporidium* in infectivity and virulence. Research is needed on dose-response relationships, and to evaluate the validity of predicting risks from dose-response curves.

The incidence of waterborne disease in the U.S. is highly uncertain. Further research is needed to determine rates of waterborne illness, and, where elevated rates of illness are identified, to determine whether illness is caused by inadequately treated water or by water quality that has deteriorated in the distribution system.

Research Questions

- What are the waterborne pathogens of public health concern?
- What is the nature and magnitude of disease associated with exposure to these water borne agents?

Research Needs

- Information on the pathobiology of infection and disease for waterborne pathogens, including data on dose-response relationships for various pathogens and different organism strains, pathogen- and host-specific factors involved in infection and disease, and effects on different subpopulations.
- Epidemiology studies to characterize endemic and epidemic illness rates, to assess magnitude of risk, and to provide data for use in verifying risk models.

Exposure Research for Microbial Pathogens

Little information is available on the levels of pathogens that occur in drinking water. Current techniques lack the precision and specificity required to measure low levels of pathogens. Even with improved measurement techniques, it is very difficult to detect very low levels of organisms in tap water. To estimate exposures from tap water, EPA expects to rely on measurements of pathogens in source water, combined with estimates of the removal and inactivation of pathogens by different treatment processes. For systems relying on groundwater, information is needed on the survival and transport of pathogens in the subsurface. Currently, each of these estimation steps has significant uncertainties.

Research Questions

- What methods are needed to adequately measure or estimate occurrence of pathogens in drinking water?
- What are the frequencies of occurrence and densities of pathogens in source water, finished water, and distribution systems, and what is the population distribution of exposures to pathogens?
- What are the factors affecting microbial contamination of groundwater?

Research Needs

- Analytical methods to detect and enumerate protozoa, including methods for protozoa that indicate whether the organism is viable and/or infectious.
- Analytical methods to detect and enumerate viruses in source and finished waters.
- Occurrence information for pathogens in source water and finished waters.
- Assessment of sources of pathogens and the importance of watershed controls.
- Occurrence information for primary and opportunistic pathogens in distribution systems.
- Determination of survival and transport of pathogens in groundwater under different conditions.
- Assessment methods for protecting groundwater sources from pathogens, including methods for determining whether "natural disinfection" is adequate.

Risk Assessment Research for Microbial Pathogens

Assessing the risks of waterborne pathogens depends on adequate effects and exposure information. As indicated above, EPA is likely to rely on estimates of source water pathogen occurrence, and removal and inactivation by treatment and transport through the distribution systems to predict concentrations in tap water. In addition, outbreak data will be assessed to improve our understanding of real time microbial risks especially as it applies to actual source water conditions, treatment techniques, distribution system integrity and health impacts. This information will also be used to improve our comparative risk modeling. These data will be combined

with information on dose-response, including sensitive subpopulations, and water consumption to predict risks.

A comprehensive risk assessment model is needed for assessing the risks from pathogens in drinking water. The currently accepted risk assessment models were developed for assessing chemical risks and do not fully accommodate issues important to the assessment of pathogenic risks, such as microbe/host interactions, sensitive subpopulations and consideration of secondary spread of infection. Dose-response models are needed that can address threshold and non-threshold assumptions within a modified risk assessment paradigm for microbes.

Research Question

- How can the risks posed by pathogens in drinking water be characterized?

Research Needs

- Modification of risk assessment paradigm for microbial disease.
- Development and application of dose-response statistical models and other methods/tools for assessing microbiological disease.
- Methods to characterize risks from mixtures of pathogens, and mixtures of pathogens and DBPs.

Risk Management Research for Microbial Pathogens

Improved methods for analyzing and protecting source waters are needed to help assure that treated water is of acceptable quality. Better data on pathogen removal and inactivation efficiencies of various treatment processes are needed to provide better estimates of risk and to select the treatment processes with the most potential for risk reduction. Research efforts that evaluate treatment effectiveness should simultaneously evaluate control of DBPs (see discussion below). The greatest need is to address the uncertainties surrounding treatment efficiencies for pathogens by focusing research on those organisms that are most resistant to treatment. For example, current data indicate that *Cryptosporidium* is much more resistant to disinfection than most other waterborne pathogens. In surface waters, by focusing on treatment processes that are effective for inactivating *Cryptosporidium*, it is likely that other waterborne pathogens, including those that may be more infectious or have more significant health effects, will also be effectively reduced. However, *Cryptosporidium* analysis is expensive and difficult. Because of the analytical difficulties in measuring *Cryptosporidium* in drinking water, an important need is to identify surrogate parameters for evaluating treatment effectiveness. Potential surrogates include indicator organisms and engineering process control parameters such as particle size counting and disinfection operating conditions. In addition, as the existence and significance of new, potentially dangerous waterborne pathogens are recognized, there is a need to determine the effectiveness of various treatment systems to control these new organisms.

In groundwaters, where protozoa are not expected to occur, it is important to consider viruses when defining adequacy of treatment. Therefore, there is a need to develop information on the effectiveness of alternative treatments for controlling viral contamination in groundwater sources. Currently, EPA uses disinfection data on hepatitis A virus (HAV) for estimating disinfection conditions necessary to inactivate viruses in general. HAV was selected as the target virus because it has been implicated in waterborne disease, it is among the viruses with the most significant adverse health effects, and it is among those most resistant to disinfection. Norwalk virus may be more resistant to disinfection than HAV and therefore may be more suitable than HAV for defining adequacy of disinfection.

While protozoa and viruses might be effectively managed at the treatment plant, bacteria pose a special problem because of their ability to grow in the water distribution system. A number of the bacteria species identified in distribution systems are opportunistic pathogens, which can cause illness in certain population subgroups. Treatment processes at the plant can affect bacterial growth; for example, use of ozone to more effectively control protozoa and viruses may, depending on the organic content of the water, increase nutrient levels in the treated water and thus potentially increase bacterial growth in the distribution system. In addition, there is a need to understand the causes of microbial intrusion into the distribution system and identify effective approaches to prevent this from happening.

Research Questions

- How effective are various treatment processes in removing pathogens?
- How can the quality of treated water be maintained in distribution systems?
- How can source water be protected to ensure that it is consistent with finished water quality of acceptable microbial risk after appropriate treatment?

Research Needs

- Methods to analyze and protect source waters.
- Evaluation of the effectiveness of different treatment processes in controlling pathogens, with a focus on *Cryptosporidium*, including analysis of the effects of treatment on the viability/infectivity of *Cryptosporidium* oocysts that pass through the treatment plant, and on surrogate indicators of treatment effectiveness. Technologies to evaluate include optimization

of conventional treatment, filtration, use of sequential disinfectants, and biological treatment.

- Evaluating the effectiveness of various treatment technologies to control new, potentially waterborne pathogens as their existence and significance is recognized.

- Development and evaluation of technologies appropriate for small systems, which face constraints on cost and operational complexity.

- Evaluating the effectiveness of treatment alternatives to control viral contamination in groundwater sources.

- Identification and characterization of factors which influence microbial growth in distribution systems, and development of strategies to control such growth.

- Understanding the causes of microbial intrusion into the distribution system and developing cost effective approaches for preventing such intrusion.

Disinfection By-Products—Research Needs

Health Effects Research for Disinfection By-Products

In the 20 years since the discovery of chloroform and other trihalomethanes in drinking water, a major research issue has been the evaluation of the adverse health effects of DBPs. However, significant gaps remain in our knowledge of the actual risks to human populations posed by the use of disinfectants, especially from alternative disinfectants such as ozone and chlorine dioxide. A number of epidemiological studies have been conducted, but they have generally been inconclusive. Some studies have shown no association between consumption of chlorinated water and cancer, while others have suggested weak to moderate association with cancers of the colon, rectum and bladder. Epidemiological studies of reproductive effects have been similarly inconclusive. Toxicological studies using laboratory animals have shown that a number of DBPs cause cancer, reproductive toxicity, and other effects, but at concentrations higher than typically are found in drinking water.

Health effects research is needed in three areas. Epidemiological research should be pursued, with a focus on avoiding the inadequacies in previous studies: study design, characterization of exposure, and ascertainment of health effects. Toxicology studies on individual DBPs should be conducted to fill key data gaps and to facilitate extrapolation of animal data to humans. Additionally, toxicology research using complex mixtures of DBPs would be valuable, if the technical difficulties in conducting such mixtures studies can be overcome. For example, epidemiological studies on ozonated water will not be able to evaluate cancer endpoints, because ozone is a recent technology in the U.S. and long-term exposures have not occurred for large numbers of people. EPA will have to rely on individual chemical toxicological studies and mixtures studies to evaluate long-term health effects of ozonation by-products.

Research Questions

- What are the health effects associated with exposure to DBPs?
  - What are the health effects in communities served by disinfected drinking water?
  - What is the toxicity of individual chemical contaminants and of mixtures of DBPs?

Research Needs

- Improved methods for epidemiological research, including better approaches for assessing exposures and health effects.

- Epidemiology research to provide qualitative and quantitative information on the risks of cancer, adverse reproductive outcomes, and possibly other health effects that may be linked to DBP exposures.

- Toxicology studies on newly-identified or poorly-characterized DBPs to provide basic information for traditional hazard identification and dose-response assessment.

- Pharmacokinetic and mechanistic data to facilitate the extrapolation of animal data to humans.

- Animal studies on well-defined and complex mixtures of DBPs to help bridge the gap between epidemiology studies and single-chemical toxicity studies. The goal of these studies would be to assess DBP interactions and to compare the potential toxicity of drinking water preparations that are closer in composition to "real-world" mixtures.

Exposure Research for Disinfection By-Products

DBPs are formed when disinfectants, for example chlorine or ozone, are added to source and drinking water to control microbiological organisms. Chlorine, the most widely used and studied disinfectant, reacts readily with humic substances from decaying animal and vegetable matter (precursors) as well as organic contaminants, i.e., pesticides, and produces a variety of chlorinated products. When bromide ion is present, as it is in most source waters to a greater or lesser degree, brominated and mixed chlorobromo DBPs are also produced. Ozone adds oxygenated species as does chlorine dioxide. Another disinfectant, chloramine, introduces the possibility of nitrogen containing by-products such as cyanogen chloride.

Over 100 different compounds have been detected in drinking water, most of these resulting from the use of chlorine. Less is known about by-products from ozone and chlorine dioxide. For example, it was only recently recognized that ozone disinfection can produce bromate, an ion which may pose significant health risks. The characteristics of the source water, the type of disinfectant used, and how the disinfectant is used are all factors which influence the types and quantities of by-products formed.

Current exposure information is inadequate for conducting a quantitative exposure assessment for the majority of DBPs. Research is needed to better characterize the by-products formed from different treatment processes, especially from alternative disinfectants. Better analytical methods are needed to assess the frequency and magnitude of occurrence of DBPs, particularly for polar, water soluble, and nonvolatile DBPs. Because of limited methods, there is a paucity of exposure data. We do know, however, that the wide range of disinfection methods and background constituents in water supplies will result in a wide range of exposure differences.

Research Questions

- What methods are needed to adequately measure occurrence of DBPs in drinking water?
- What levels of DBPs are people exposed to via their drinking water supplies, and what is the population distribution of exposures?

Research Needs

- Improved methods of analysis for DBPs of concern, including practical methods for chemicals likely to be regulated in the near future, and research methods to aid in the discovery and characterization of DBPs
- Identification of new DBPs, particularly from alternate disinfectants
- Data on exposures to DBPs to develop, improve, and validate exposure models

Risk Assessment Research for Disinfection By-Products

Determining the health risks caused by DBPs is a critical part of the DBP research program—current evidence is inconclusive, and the implications for water treatment expenditures are significant if lower levels of DBPs are required. As indicated above, some epidemiological studies have suggested that elevated rates of cancer may be linked to consumption of chlorinated water. Estimates of excess cancer risk vary from 0 to 10,000 or more cancer cases per year when extrapolated to the U.S. population as a whole. This wide variation in risk estimates results from the application of different methods for estimating risks and different exposure assumptions. Narrowing the broad range in cancer estimates will depend on health effects and exposure research and on advances in risk assessment methodology. In addition to the uncertainties surrounding cancer risk estimates associated with these chlorinated water studies, uncertainties exist for other risks such as reproductive and developmental effects.

The traditional risk assessment process has been focused on the evaluation of risks from exposure to an individual chemical or members of a specific class of chemicals. But exposure to DBPs in drinking water, as is true for many other environmental exposures, is really exposure to a complex mixture of chemicals. Assessment of these compounds or classes of compounds as components of their source water could have a meaningful impact on the understanding of the actual risks resulting from exposures to these various mixtures. The risk assessment should therefore take into account possible interactions between chemicals and evaluate the impact on health risks.

Research Questions

- How can we better characterize the risk posed by exposure to specific DBPs in drinking water?
- How can we characterize the risk posed by exposure to multiple or complex mixtures of DBPs?
- How can the risks from chemicals and microbes be compared?

Research Needs

- For individual chemicals, refinement and application of new models for estimating cancer and noncancer risks, in particular risks associated at exposures typically found in drinking water.
- Improved estimates of risk using epidemiologic data from previous and ongoing studies, incorporating improved estimates of exposure where possible.
- For mixtures of chemicals, application of new methods for assessing risks that include characterization of chemical interactions.
- Assessment of the comparative toxicity of DBPs within classes or families of compounds and also between families.
- For chemicals and microbes, a framework for assessing and comparing risks from different treatment options.
- Better methods for screening and prioritizing potential risks.

Risk Management Research for Disinfection By-Products

Better data are needed on how to control DBPs formed by different treatment processes. Simultaneously, candidate treatment processes must be evaluated for control of microbial pathogens. Treatment options include optimizing conventional treatment; switching to alternate disinfectants, such as ozone; use of granular activated carbon (GAC); or use of membrane technology. The range in treatment costs for the different options is tremendous. EPA has estimated that the increased household costs for systems serving 250,000 people and using conventional treatment would be $5/year (optimized treatment), $10/year (ozone/ chloramination), $60/year (GAC), or $120/year (membrane technology) depending upon which technology might be needed to comply with new DBP standards. For a typical system serving 2,500 people and using conventional treatment the household costs could increase by $10/year (optimized treatment), $60/year (ozone/chloramination), $270/year (GAC or membrane technology) depending upon which technology might be needed. Clearly, research that could lead to improvements in conventional treatment and could demonstrate that acceptable levels of pathogens and DBPs can be achieved will be highly cost-effective.

Current regulations only set a limit for total trihalomethanes, relying on the assumption that practices that control formation of these chemicals will also control other by-products. Research is needed to determine whether this assumption is valid, or whether other surrogate parameters can act as good indicators of DBP control. Depending on the outcome of the health research, other DBPs may become of greater concern.

Research Question

- How effective are various treatment processes in minimizing the formation of DBPs?

Research Needs

- Evaluate processes that prevent DBP formation by reducing precursor compounds in source water.
- Evaluate use of different disinfectants in limiting DBP formation.
- Evaluate promising innovative technologies for small systems to control precursors and DBP formation.

Criteria for Priority Setting

Chapters III and IV of this plan identify research projects intended to meet the research needs described above. The following criteria were used to select the research projects that are included in this plan. All projects included in the plan are generally considered as high priorities for research. However, to provide a sense of relative priority for the projects identified here, priority rankings of High, Medium or Low were developed. The criteria used for ranking are listed in descending order of importance:

- *High risk*—The research is likely to elucidate the concentrations, occurrence, or toxicity/pathogenicity of a contaminant, where preliminary information suggests that it may have a significant impact on public health.
- *High uncertainty*—The research is likely to reduce significant uncertainties associated with current assessments or risk reduction technologies.
- *Regulatory relevance*—The likelihood is high that research will lead to regulatory criteria that reduce the risk to public health in a cost-effective manner.

Additional considerations which were relevant in setting priorities for some projects:

- *Short-term and long-term research needs*—An appropriate balance is achieved between research that addresses specific short-term needs (many objectives must be fulfilled with a 3-5 year time frame to support regulation development) and research that addresses more strategic, long-term needs (e.g., developing new methodologies for more comprehensive assessments of exposure to drinking water contaminants).
- *Linkage to other efforts*—The research is complementary to related research efforts in EPA (e.g., risk assessment methods research), other federal and state agencies, and the private sector.
- *Anticipatory research*—The results of the research will help anticipate future drinking water problems.
- *Wider applicability*—The results of the research may be extended to other drinking water or environmental issues.

Contents of the Following Chapters

Chapter II describes how the proposed research projects presented in Chapters III and IV will be used to support the various drinking water regulations described above. Chapter II briefly describes how the research will assist in estimating national/local costs and benefits of the regulations and how this information can be used by decision makers to balance the risks from microbial pathogens and DBPs.

Chapter III and Chapter IV describe research needed for microbial pathogens and DBPs, respectively. Within Chapters III and IV, specific research projects have been organized into the following categories: Health Effects, Exposure, Risk Assessment, and Risk Management. In some cases, the proposed projects cut across these categories and a coordinated, interdisciplinary approach is required. An example is project HE.M.7,

Characterization of Endemic Disease: Health Effects Associated with Differences in Source Water Quality and Treatment Process, which would include health effects, exposure, and risk management research.

The "State of the Science" sections for each major research question describe past and current research efforts by EPA and others. In the "Research Topics and Priorities" section, projects that are listed are primarily research which is needed but not yet underway. EPA expects to be able to fund a significant portion, but not all, of these projects. EPA's ongoing and completed research has been included in the project listings, as this research should be considered in the debate about relative priorities.

The intent of this research plan is to propose research that will answer the research questions presented generally in Chapter I and more specifically in Chapters III and IV. However, the extent to which some of these questions can be answered may significantly depend on upon the results of the research. The plan attempts to indicate, in general terms, how research directions and priorities may change depending on outcomes of research.

Chapter II. Balancing Microbial and DBP Risks: Integrating Research to Support Rule Development

Chapters III and IV will discuss research needs and projects to address those needs for each of four research topic areas (health effects, exposure, risk assessment, and risk management) as they relate to achieving a better understanding of risks and control of those risks posed by pathogens and DBPs. The purpose of Chapter II is to indicate how research will be used to support the development of the DBP Stage 1 rule, DBP Stage 2 rule, IESWTR, LT1ESWTR, LT2ESWTR, and GWDR.

Overview of Approach to Balancing Microbial and DBP Risks

EPA is attempting to develop regulations that will result in the proper balance between controlling risks from pathogens and DBPs. Figure II-1a shows that in general as the level of disinfection applied to drinking water increases, the risk from exposure to pathogens decreases while the risk from DBPs increases. Clearly, the type of source water treated, technology applied, microorganism removed and disinfectant used, will influence the slope of the risk function. Figure II-1b shows how cost/benefit analysis ideally might be used to minimize social costs associated with the application of technology to minimize exposure to pathogens and DBPs simultaneously. As the level of treatment to lower exposure from both DBPs and pathogens increases, the cost of treatment increases while the potential cost of health damages decreases.

The ability to determine the proper balance between controlling risks from pathogens and DBPs requires enormous amounts of data, some of which will be developed as part of the research described in this document. Since the occurrence of pathogens and DBPs in drinking waters vary greatly, it is very difficult to estimate total national risks or total national risk reductions that might result from different regulatory options. Also, regulatory decisions which lead to minimum social costs at the national level may not be justified if they lead to large adverse changes in social costs at the local level. Recognizing these problems, EPA is developing an approach for estimating national and local costs and benefits (regulatory impact analysis [RIA]) that should support meaningful regulatory decisions. The results from the research described in this plan, the ICR, and supplemental surveys will provide answers to many of the research questions posed in Chapter I and will provide input for estimating the costs and benefits of the various rules and in balancing the risks from pathogens and DBPs.

Integrating Research to Support Rule Development

Following is a discussion, by rule, of key regulatory issues and how the research plan would be used to help resolve these issues. Research projects are listed that are either completed, currently ongoing by EPA, or planned according to the rule they would most significantly support. A key question in the development of the

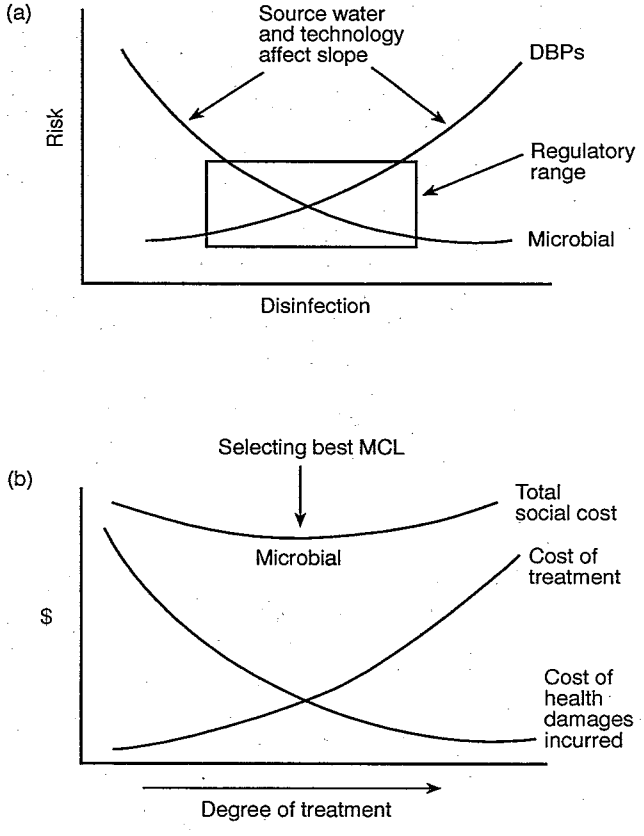

Figure II-1. Risk tradeoff and cost benefit considerations.

drinking water regulations is whether the research will be completed in time to support the development of the various M/DBP rules. Tables II-1, II-2, and II-3 provide the dates by which the research will be completed and the text under each rule provides a discussion on when the research is needed. Before discussing the research projects it is important to first understand how the research will be used in developing regulations.

The overall goal of the SDWA is the establishment of drinking water standards that will protect public health. The SDWA specifies that EPA establish Maximum Contaminant Level Goals (MCLGs) for contaminants at which no known or anticipated adverse effects on the health of persons occur and which allow an adequate margin of safety. MCLGs are nonenforceable health goals based predominately on health effects data and estimates of occurrence/exposure for the contaminant. Establishing MCLGs for a DBP is the first step in deciding that the contaminant poses a human health risk that requires some control. When setting MCLGs for contaminants in drinking water, EPA must also establish a Maximum Contaminant Level (MCL) that is as close to the MCLG as feasible. The SDWA defines feasible as "the use of best available technology, treatment techniques and other means which the Administrator finds, after examination for efficacy under field conditions and not solely under laboratory conditions, are available (taking cost into consideration)." To set an MCL, it has to be both technologically and economically feasible to monitor the contaminant in the drinking water. In cases where monitoring is not feasible, EPA is authorized to develop a treatment technique requirement instead of an MCL. The treatment technique requirement must prevent known or anticipated adverse effects on the health of persons to the extent feasible. Because of the difficulties in monitoring for *Giardia*, viruses, or *Cryptosporidium,* both the 1989 SWTR and the 1994 proposed IESWTR are treatment technique rules. Each rule must also establish compliance monitoring requirements to ensure the contaminant is being accurately characterized.

Under the 1996 amendments to the SDWA, EPA may set an MCL at a level other than the feasible level (as defined in the statute) if the technology or treatment technique would result in an increase in the health risk from other drinking water contaminants. In cases where a treatment technique requirement is set at a level other than the "feasible level," EPA is required to minimize the overall health effects. This provision is relevant to the LT2ESWTR and Stage 2 D/DBP rule, because the control of microbial pathogens may increase the risk to DBPs and the control of DBPs may increase the risk from microbial pathogens. It is therefore important that EPA have adequate knowledge of the extent to which, under given conditions, reduction of one contaminant results in an increase in another. In the case of the LT2ESWTR, this means understanding under what conditions and the extent to which changes in relevant DBPs result from different microbial treatment technique requirements, such as the inactivation of *Cryptosporidium*. Other contaminants or parameters whose levels could be increased by high disinfectant doses under certain conditions include arsenic, lead, and assimilable organic carbon (AOC). AOC provides the nutrients which promote microbial growth in the distribution system, possibly resulting in a series of problems that are not well understood (e.g., growth of opportunistic pathogens and coliform bacteria, rapid disinfection residual decay, and corrosion).

As discussed above, the two primary inputs into the MCLG are health effects data and occurrence/exposure data. Although some data currently exist on the occurrence levels of DBPs and pathogens, the majority of new occurrence data for DBPs will come from the ICR and the majority of new occurrence data for pathogens will come from the ICR, "mini-ICR," and supplemental surveys. When developing MCLs and/or treatment techniques the main inputs include the availability of analytical methods; effectiveness of treatment technologies to control the contaminants; and the cost of these technologies. When designing compliance monitoring strategies the main inputs include the costs of monitoring and the ability of monitoring to accurately characterize the levels of the DBPs at consumers taps.

Surface Water Treatment Rules

The IESWTR was proposed in July 1994. The final IESTWR is required by November 1998. The purpose of the IESWTR is to prevent increases in microbial risk and to enhance control for *Cryptosporidium* while systems serving 10,000 or more people comply with the Stage 1 D/DBP rule. The IESWTR applies to surface water systems serving at least 10,000 people. The Long-Term 1 ESWTR (LT1ESTWR) will apply to surface water systems serving less than 10,000 people and is scheduled to be proposed in September 1999 and promulgated in November 2000. This rule is intended to improve physical removal of *Cryptosporidium* and prevent significant increases in microbial risk for smaller systems while they also comply with the Stage 1 D/DBP rule. The LT2ESWTR will be developed to further improve control for pathogens and will be promulgated in conjunction with the Stage 2 D/DBP rule in order to prevent increased risk for systems complying with the Stage 2 rule.

Participants in the DBP regulatory negotiations were concerned about the extent to which microbial risk might increase if systems were to comply with new DBP standards. RIA modeling analysis indicated that more than one percent of the population in some systems could become infected with *Giardia* if systems were required to meet more stringent DBP standards and comply with the existing SWTR (i.e., providing 3 logs removal whereas 5 logs might be appropriate). While this analysis had significant uncertainties concerning national cyst occurrence and assumptions needed in the risk assessment, the potential increased microbial risks that could result from DBP regulation were significant.

Table II-1. Research to Support the LT2ESWTR

		Expected Completion Date	Priority
A.	**Health Effects Research**		
1.	**Pathobiology of Infection and Disease for Most Important Waterborne Pathogens**		
HE.M.1	Infectious dose of *Cryptosporidium*	1997	H
HE.M.2	Validity of dose-response model for *Crypto* in animals	Proposed	H
HE.M.3	*Cryptosporidium* virulence study using different strains	1998	H
HE.M.4	*Cryptosporidium* infectious dose in normal/immuno-compromised animals	1999	H
HE.M.5	Infectious dose of Norwalk virus	2000	H
HE.M.6	Infectious dose of other priority pathogens	Proposed	M
AWWARF Related Projects			
177	Association between *Cryptosporidium* in finished water & Cryptosporidiosis in population	1997	
354	*Cryptosporidium parvum*: Surrogate human pathogenicity animal model using swine	1999	
2.	**Characterization of Epidemic and Endemic Waterborne Disease**		
HE.M.7	Characterization of endemic disease (with AWWARF)	2000	H
HE.M.8	Immunological assay for assessing exposure in epi studies (with AWWARF)	1998	H
HE.M.9	Investigations of waterborne disease outbreaks	Ongoing	H
HE.M.10	Surveillance tool for waterborne disease outbreaks	Completed	H
AWWARF Related Projects			
168	Prospective epi study of waterborne microbial disease (with EPA)	1997	
268	Fingerprinting techniques for opportunistic pathogens & illness	1998	
B.	**Exposure Research**		
1a.	**Microbial Methods—Protozoa**		
EX.M.1	Immunological techniques for protozoa	1999	H
EX.M.2	Gene probes for detection of viable *Cryptosporidium* oocysts	1998	H
EX.M.3	Cultural method for *Crypto* in environmental samples	Completed	H
EX.M.4	PCR methods for *Giardia* and *Cryptosporidium* (CRADA)	1997	M
EX.M.5	Protozoa methodology protocol development workshop	Completed	H
EX.M.6	Comparison of methods for *Giardial Cryptosporidium* in water	2000	H
EX.M.7	New protozoa agents	1998	H
AWWARF related projects			
160	Vital stain for *Giardia* and *Cryptosporidium*	Completed	
162	UV-VIS spectroscopy for rapid on-line detection of protozoa	1998	
253	Viability method for *Giardia* and *Cryptosporidium*	1998	
259	Improve the IFA method for *Giardia* and *Cryptosporidium*	1998	
283	Detection of *Giardia* & *Cryptosporidium* by flow cytometry	Completed	
351	*Cryptosporidium parvum* viability assay	1998	
358	*Cryptosporidium* and *Giardia* antibody protocol	1998	
364	New approaches for isolation of *Cryptosporidium* and *Giardia*	1998	
366	Assessment of molecular epidemiology of waterborne *Crypto* with respect to origin	1998	
395	Compare study of methods for assessing viability/infectivity of *Crypto* in U.S./U.K.	1999	
1b.	**Microbial Methods—Viruses**		
EX.M.8	Application of PCR technologies and gene probes	1999	M
EX.M.9	Norwalk virus	2000	H
EX.M.10	Methods for emerging viruses	Proposed	H
AWWARF projects			
292	Rapid PCR-based monitoring of entero viruses	1998	
345	Detection and occurrence of caliciviruses in drinking water	1999	
612	Analysis of viruses by gene probe	Completed	
726	Viral and microbial methods for groundwater	1997	
2a.	**Microbial Exposure—Pathogen Occurrence**		
EX.M.11	Intensive eval. of micro. constituents/treatability in surface source waters (mini-ICR with Research Council)	2000	H
EX.M.12	Identification of viruses resistant to disinfection	Proposed	M
2b.	**Microbial Exposure—Watershed Control**		
EX.M.13	Distinguish animal versus human sources	1998	M
AWWARF related projects			
251	Evaluating of sources of pathogens and NOM in watersheds	1998	
2c.	**Microbial Exposure—Opportunistic Pathogens in Distribution System**		
EX.M.14	Occurrence of *Mycobacterium*	1998	H
EX.M.15	Occurrence of heterotrophic bacteria with virulence characteristic	2001	H

(Continued)

Table II-1. (Continued)

		Expected Completion Date	Priority
EX.M.16	PCR method for *Legionella*	1998	L
EX.M.17	Pathogenicity of heterotrophic bacteria in drinking water.	1998	H
EX.M.18	Occurrence of opportunistic pathogens in biofilms	Proposed	M
EX.M.19	Opportunistic pathogens assoc. with (POU)/(POE) filter effluents	Proposed	M
EX.M. 20	Potential pathogenicity of heterotrophic bacteria eluted from point-of -use GAC filters	Proposed	H
EX.M.21	Occurrence of newly emerging pathogens	2000	H
EX.M.22	Exposure as a function of population distribution	1999	H
C.	**Risk Assessment Research**		
1.	**Risks from pathogens**		
RA.M.1	Dev. comprehensive microbio risk assess paradigm for water	2000	H
RA.M.2	Evaluation/application of various dose-response models	1998	H
RA.M.3	Evaluation and application of methods to assess risk associated with exposures to multiple pathogens, routes, and durations	2000	M
AWWARF Related Projects			
801	Microbial risk assessment for drinking water	Completed	
D.	**Risk Management Research**		
1a.	**Pathogen Removal—Optimization of Conventional Treatments**		
RM.M.1	Filtration studies for controlling pathogens	1999	H
RM.M.2	Filtration removal of protozoa and indicators	1998	H
RM.M.3	Optimize conventional treatment for removal of oocysts	1999	H
RM.M.4	Filtration damage viability studies	1999	H
RM.M.5	Evaluate disinfection and optimization in full-scale 1 plants	1997	H
RM.M.28	Evaluation of the effectiveness of conventional treatment processes on removing and inactivating emerging pathogens	Proposed	M
AWWARF Related Projects			
155	Enhanced/optimized coagulation for removal of microbial contaminants	1997	
352	Treatment options for *Giardia*/*Crypto*/ and other contaminants in recycled backwash water	1998	
363	Application of pathogen surrogates measures to improve plant performance	1998	
608	Lime softening processes for *Giardia* and viruses	Completed	
636	Evaluation of roughing filter design variables	Completed	
703	Optimization of filtration for cyst removal	Completed	
834	Balancing multiple water quality objectives	1997	
1b.	**Pathogen Removal—Effectiveness of Different Filtration Processes**		
RM.M.6	Biological treatment for control of oocysts	2000	H
RM.M.7	Filtration techniques other than conventional treatment	2000	M
RM.M.29	Evaluate filtration processes to remove emerging pathogens	Proposed	M
AWWARF Related Projects			
181	Biological particle surrogates for filtration performance eval.	1997	
Particle Counting as Indicator of Treatment Efficacy			
266	Quantitative particle count method development: standardization, sample stability	1998	
291	Particle image velocimetry	1998	
423	Joint project on treatment process selection: particle removal optimization	Completed	
835	Practical guide to on-line particle counting	Completed	
908	National assess. of particle removal by filtration	Completed	
Membrane technology for pathogen removal			
264	Integrated multi-objective membrane systems microbes/DBP precursors	1999	
817	Membrane filtration techniques for microbe removal	Completed	
Microbial effects of biological filtration			
263	Colonization of biologically active filter media with pathogens	1998	
917	Microbial effects of biological filtration (Don Reasoner on PAC)	Completed	
1c.	**Pathogen Removal—Effectiveness of Disinfection for Inactivating Pathogens**		
RM.M.8	Control of Norwalk virus by chlorine and ozone	Proposed	H
RM.M.9	UV disinfection efficiencies for Norwalk virus	Proposed	H
RM.M.10	Inactivation of *Giardia* & *Crypto* by sequential disinfectants	1999	H
RM.M.31	Evaluate disinfection processes to inactivate emerging pathogens	Proposed	M
AWWARF Related Projects			
Disinfection			
262	Booster disinfection for pathogen and DBP control	1998	

(Continued)

Table II-1. (Continued)

		Expected Completion Date	Priority
525	Demo scale eval. of PEROXONE evaluation for disinfection, DBPs	1997	
702	Devt. and validation of rational design methods of disinfection	Completed	
Disinfection of Protozoan Cysts—Inactivation Studies			
151	Cyst and oocyst survival in watersheds and factors affecting inactivation	1997	
273	Synergistic effects of multiple disinfectants (Gene Rice on PAC)	1998	
282	Innovative electrotechnologies for *Crypto* inactivation	1998	
375	Utility *Giardia* and *Crypto* inactivation study—Southern Nevada Water Authority	1998	
731	Ozone disinfection of *Giardia* and *Crypto*	Completed	
906	Effect of various disinfection methods on inactivation of *Crypto*	Completed	
Disinfection Evaluation and Design			
630	Full scale ozone contactor evaluation	Completed	
632	Modeling dissolved ozone in contactors	Completed	
1d.	**Pathogen Removal—Small Systems Technologies**		
RM.M.11	*Cryptosporidium* removal using bag filters	1998	H
RM.M.12	Cost effectiveness of prefiltration for ultrafiltration unit	1999	H
RM.M.13	Development/test innovative technologies for small systems	1999	H
2a.	**Distribution Systems—Indicators for Control of Pathogens in Biofilms and Pipe Sediments**		
RM.M.14	Bacteria interference w/detection of coliforms and E. coli	Proposed	M
AWWARF Related Research			
429	Male-specific coliphages as indicators of viruses & treatment effectiveness	Completed	
2b.	**Distribution Systems—Biofilm Growth and Control of Growth**		
RM.M.15	Kinetic Models for chlorine decay in distribution systems	Completed	H
RM.M.16	Enhancement of EPANET distribution system model	1998	H
RM.M.17	Prelim. studies of biofilm formation rates in pilot-scale distribution systems	1998	M
RM.M.18	Opportunistic pathogens in biofilms	2000	M
RM.M.19	Impact of nutrient removal on growth potential for bacteria	1999	M
RM.M.20	Impact of alternative treatment of biofilm growth	Proposed	M
RM.M.21	Water quality factors in distribution systems	1997	M
AWWARF Related Projects			
Control of Bacteria in Distribution System			
270	Occurrence and control of *Mycobacterium avium* complex	1998	
534	Fatty acid profiling for identification of environmental bacteria in distribution system	Completed	
936	Pathogens in model distribution system biofilms	1997	
Minimization of Regrowth Potential			
183	Factors affecting microbial growth in distribution systems	1997	
704	Factors limiting microbial growth in distribution systems	Completed	
Disinfectant Residual Decay in Distribution System			
261	Guidance manual for installation of booster disinfection	1998	
293	Role of pipe-water interface in DBP formation & disinfection	1997	
294	Travel times & water quality in dead ends	1997	
815	Characterization and modeling of chlorine decay	Completed	
NWRI Related Projects			
Interactions between pipe materials, corrosion inhibitors, biofilm		Completed	
Risk reduction in distribution system by on-line monitoring of pathogen ecology		Completed	
2c.	**Distribution Systems—Effect of Design and Condition on Bacterial Growth**		
RM.M.22	Water quality impacts of dead ends	1998	M
RM.M.23	Mixing in storage facilities	1998	M
RM.M.24	Alternative kinetic models for decay and DBP formation	Proposed	H
RM.M.25	Real-time monitoring systems	1999	M
AWWARF related projects			
154	Biological stability of drinking water in treatment plants and distribution systems	1997	
254	Managing & operating finished water storage facilities	1998	
260	Water quality monitoring of distribution system storage facilities	1998	
729	Biofilm reactor BOC measurement	Completed	
2d.	**Distrib. Systems—Effect of Treatment on Chemical/Biological Stability of Water**		
R.M.M.26	Bacterial growth in distribution systems	Proposed	H
R.M.M.27	Integrated approaches for controlling pathogens	Proposed	M

(Continued)

Table II-1. (Continued)

		Expected Completion Date	Priority
2e.	**Distrib. Systems—Maintaining Distribution System Integrity**		
RM.M.32	Evaluate primary causes of leaks/failures in distribution systems	Proposed	H
RM.M.33	Evaluate devices for determining structural integrity of distribution system	Proposed	H
RM.M.34	Evaluate materials for construction of distribution system	Proposed	H
3a.	**Source Water**		
RM.M.35	Evaluate GIS for defining source water characteristics	Proposed	H
RM.M.36	Evaluate water quality models for routing point and non-point source water discharges	Proposed	H
RM.M.37	Evaluate the impact of sudden increases in source water contamination on drinking water treatment	Proposed	H

In another RIA analysis, potential impacts for different Stage 1 DBP rule options were evaluated assuming that systems would simultaneously have to provide higher levels of treatment for *Giardia* (versus the minimum of 3 logs required for all systems under the SWTR) as a function of higher *Giardia* concentrations in the source water. The goal of such a theoretical *Giardia*-based rule, one of the options proposed in the IESWTR, was for systems to provide adequate treatment to achieve a risk level of less than one infection of *Giardia* per 10,000 people per year. It was assumed that if systems were required to meet such a risk level, they would not incur significant increases in microbial risk while making treatment changes to comply with the Stage 1 DBP rule. The RIA for this *Giardia*-based rule estimated that 400,000 to 500,000 infections of *Giardia* could be avoided per year at a cost of about $400 million per year.

A major shortcoming with the above estimates, in addition to the uncertainties in the assumptions needed for the analysis, was the inability to include impacts for regulating *Cryptosporidium* since occurrence, treatment effectiveness data, and dose-response information was missing. *Cryptosporidium* may be the preferred target organism for defining minimum levels of treatment because it is substantially more resistant to disinfection than *Giardia*. A *Cryptosporidium*-based rule similar to that described for *Giardia* would probably be significantly more costly. Also, such a rule could trigger significant shifts by the industry to greater use of alternative disinfectants such as ozone (since they appear more effective than chlorine for inactivating *Cryptosporidium*), decreasing by-products from chlorine but increasing other by-products.

LT2ESTWR

The majority of the research described in this research plan will be used when designing the LT2ESTWR. The regulatory needs for the LT2ESTWR include 1) a better understanding of the magnitude of the risk from *Cryptosporidium* and other pathogens; 2) a more accurate characterization of the occurrence of *Cryptosporidium* ; 3) an evaluation of the potential for using indicators to determine pathogen occurrence; and 4) the removal and inactivation efficiencies of different treatments and the effects on the distribution system.

EPA is considering at least three different approaches (and combinations of these approaches) to further regulating *Giardia*, *Cryptosporidium*, and viruses (and indirectly regulating other pathogens) in the LT2ESWTR: fixed treatment approach; proportional treatment approach; and watershed-based approach. Each of these approaches has different, but also similar, information requirements. The fixed treatment approach would require all systems to provide at least the same minimum level of treatment (same log reduction of pathogens); the proportional treatment approach would require systems to provide a minimum level of treatment at all times based on pathogen levels in the source water; and the watershed-based approach would require systems to provide a minimum level of treatment at all times based on a combination of factors that indicate the level of the source water's vulnerability to pathogen contamination. Hybrids of these regulatory approaches are also under consideration, e.g., a fixed treatment approach for one pathogen and a proportional level of treatment for another pathogen. Similarly, different regulatory approaches might be considered for different water body types (e.g., one type of requirement might be appropriate for quiescent waters while another type might be appropriate for running waters).

The advantage of the proportional and the watershed-based treatment requirements is that the drinking water treatment required is based on the individual system's source water quality. The treatment would prevent exposure to unacceptable microbial risk and would avoid unnecessary disinfection and associated DBPs. By contrast, the fixed treatment requirement—the one size fits all—could require some systems with high quality source water to provide unnecessary treatment at a high cost to the consumers, while others with highly contaminated source waters might provide inadequate treatment.

In its evaluation of a regulatory option under either of these three structural approaches, EPA plans to use nationwide system-specific data on source water quality and water treatment, as well as research results, to estimate the changes in treatment that would be necessary to meet target microbial risk levels, or conversely to estimate the risks associated with given treatment requirements. In simple terms, the process of relating treatment to microbial risk can be divided into three

steps: step 1) establishing the level of contamination in the source water (the occurrence of the pathogen), either using information on pathogen concentrations or based on pathogen "indicators"; step 2) estimating the reduction in pathogen occurrence due to treatment of known efficacy; and step 3) applying an exposure and dose-response model to the resulting pathogen occurrence to estimate the risk of infection. An additional step in this regulatory process will be to determine the level of DBPs associated with the different treatment requirements. While all of these steps will involve differing degrees of uncertainties, this analytical approach should provide a characterization of relative levels of exposure to microbes (and DBPs) based on source water quality and treatment provided. EPA believes that results of ongoing research studies will contribute to reducing some of the uncertainties in classifying source water pathogen risk, quantifying treatment effectiveness, and measuring health effects due to pathogen exposure.

Table II-1 summarizes research projects completed, ongoing by EPA, or not yet funded that would support the development of the LT2ESWTR. These projects are described more fully in Chapters III and IV. The development of cost/benefits as part of the RIA requires information on the risk estimates of predicted pathogen levels in treated waters, occurrence of pathogens in source waters, and removal and inactivation efficiencies for different technologies.

To develop a better understanding of the magnitude of the risk from *Cryptosporidium* and other pathogens, it will be necessary to develop a better understanding of the dose-response to *Cryptosporidium* and different pathogens and how the risk varies according to strain and immune system response. There are several studies which are evaluating the dose-response to *Cryptosporidium* (HE.M.1-4 and by the American Water Works Association Research Foundation (AWWARF) and CDC). These studies should provide a good understanding of the range of responses to *Cryptosporidium* although the probability of being exposed to one strain versus another is likely to remain uncertain. Several projects are examining the high and low dose-response, immune system effects and clinical symptoms associated with exposure to the caliciviruses, Norwalk virus, and Snow Mountain Agent (HE.M.5). In addition to dose-response studies, epidemiology studies may be useful for verifying whether the risk estimates using traditional risk models are accurate and can provide information to help evaluate appropriate levels of protection (HE.M 7-10). They may also identify the factors relevant to reducing the disease burden from drinking water. AWWARF and CDC are also sponsoring research in these areas. The research described above should be completed in time for the LT2ESTWR.

In order to more accurately characterize the occurrence of *Cryptosporidium* and *Giardia* in raw and finished water, a more precise, accurate, facile, and low cost method is needed for the LT2ESTWR. EPA is conducting a large amount of research to develop a better method for protozoa (EX.M.1-6). AWWARF and CDC are also conducting substantial research to develop a better method for detecting protozoa. EPA believes the prospects are good for a method to be available in time for the proposed LT2ESWTR, that can adequately limit misclassification rates of source water *Cryptosporidium* concentration. There is also research into developing better methods for caliciviruses such as Norwalk (EX.M.8-9), and studies to improve methods are planned for adenoviruses, coxsackiviruses, and hepatitis A (EX.M.8).

The ICR will provide 18 months of data on the occurrence of *Giardia*, *Cryptosporidium*, and viruses from close to 350 different water treatment plants. Other data to be collected include data on turbidity, coliforms, water resource type (river, reservoir/lake) and whether watershed control is practiced. EPA will also conduct supplemental surveys which will complement the ICR data to provide source water microbial occurrence data necessary to support the regulatory impact analysis for different LT2ESWTR options. The "mini-ICR" will also collect pathogen occurrence data (EX.D.11) and will provide a range of data to assess pathogen occurrence variability and develop a better understanding of differences between worst case pathogen levels and other statistical endpoints (e.g., 90th percentile, median). AWWARF and the USDA are conducting several studies on the survival of *Cryptosporidium* in the environment.

Another important aspect of estimating *Cryptosporidium* occurrence in source water is its variability and the co-occurrence of *Cryptosporidium* with other microorganisms that could possibly serve as indicators. Indicators could be especially important for smaller systems where an approach based on indicators of pathogen occurrence would be ideal because of the cost and the complications associated with pathogen monitoring. To determine which indicators, or combination of indicators, correlate best with pathogen occurrence, EPA will analyze the results of the 18 monthly source water samples collected by systems under the ICR and the results of the related supplemental surveys. In addition, the "mini-ICR" will examine the use of indicators (EX.D.11). The information from the "mini-ICR" should facilitate development of source water pathogen categories based on indicators and watershed characteristics (e.g., the range of pathogen contamination associated with certain fecal coliform distributions in the raw water of a system served by a river source).

From a regulatory standpoint it is important to be able to determine the level of treatment that is achieved by a particular treatment process under different water quality and operating conditions (i.e., performance indicators are needed to establish pathogen removal and inactivation). Typically, performance indicators used in the context of microbial treatment technique requirements are filter effluent turbidity for physical removal and CT values (concentration of disinfectant in mg/L multiplied by the contact time in minutes) for pathogen inactivation. These and other indicators (and combinations thereof) need to be evaluated to determine how they can be

used to demonstrate that the required level of treatment is being achieved. EPA expects that ongoing research on treatment optimization to remove pathogens and on indicators of treatment effectiveness will contribute information to establish the level of physical pathogen removal and to develop regulatory performance criteria and associated monitoring requirements (RM.M.1-7). Regarding regulatory inactivation requirements of pathogens, research on the disinfection of *Cryptosporidium* is a high priority for LT2ESWTR (RM.M 8-10). ICR data may also be used to validate gross assumptions on treatment effectiveness if it is determined that this is possible once the ICR data is received and reviewed. In addition to EPA's research, AWWARF is conducting a considerable amount of research in this area (see related projects). As better design and operating parameters become available, they will be used in an existing water cost model to estimate costs for systems to achieve the removal/inactivation requirements for different regulatory options. Data from these projects would also be used for developing guidelines by which utilities could estimate removal/inactivation efficiencies. The major work in this area should be completed in time for the LT2ESTWR.

There are several projects that will be completed in time for the LT2ESTWR that would help determine the health risk significance from bacterial growth in the distribution system and remedial treatment or operational strategies (EX.M.14-22 and RM.M.14-27). Results from these efforts would determine what amendments to the SWTR and IESWTR or changes to related guidance might be needed to reduce risks from contamination from the distribution system.

D/DBP rules

During the DBP regulatory negotiations participants were concerned with the uncertainty in characterizing risks associated with DBPs from chlorine and alternative disinfectants. RIA modeling indicated that the national baseline incidence of cancer attributed to chlorinated DBPs in drinking water could range from 1 case per year (based on central tendency risk factors from animal toxicology data for TTHMs alone) to over 10,000 cases per year (based on risk factors suggested by a meta-analysis of epidemiology studies by Morris et al). The RIA indicated that under the Stage 1 DBP rule the national cost for avoiding one case of cancer could range from several hundred thousand dollars to several billion dollars per year. Despite these enormous uncertainties, the Negotiating Committee recognized that the existing risks could be large and therefore should be reduced. They reached a consensus that the Stage 1 requirements were of sufficient benefit to be proposed for all system sizes, even though the costs for such a rule were substantial.

While no Stage 2 DBP rule could be agreed to until the benefits of such a rule became more apparent, a possible criterion was proposed, and an RIA was conducted to understand potential cost impacts. It was estimated that if all systems in the U.S. were required to achieve a Stage 2 DBP rule of 40 µg/l for TTHMs and 30 µg/l for HAA5, without restricted use of alternative disinfectants to chlorine (which are less expensive than precursor removal technologies), they would incur annual costs of $1.5 billion per year above those anticipated for Stage 1 ($1 billion per year). If systems were required to use precursor removal technologies such as GAC and membrane technology to meet a 40/30 µg/l Stage 2 rule, they were projected to incur annual costs of several more billions per year than if they could meet such a standard using alternative disinfectants to chlorine. Table II-2 summarizes ongoing, proposed, and completed research projects by EPA and other organizations that will provide valuable inputs to the development of the Stage 1 and Stage 2 DBP rules.

Stage 1 DBP Rule

As discussed previously, EPA must promulgate the Stage 1 DBP rule by November 1998. EPA does not envision making major changes to the 1994 proposal because it was developed through a negotiation process and most of the public comments support the proposal. Research from this Research Plan will be used mainly to support the development of the Stage 2 DBP rule. However, there are several research projects that may have an impact on the Stage 1 DBP rule.

For health effects, a new cancer study for bromate will be available for the final Stage 1 rule (HE.D.7). This may be important because the theoretical 1×10^{-4} cancer risk level for bromate is 0.005 mg/L while the MCL in the proposal was 0.010 mg/L. If the cancer risk from bromate is greater than in the proposal, then there may be concern about the use of ozone as a disinfectant. The Chemical Manufacturers Association has completed a two-generation study on the reproductive and developmental effects of chlorite (HE.D.8). The information from this study will be used to modify, if justified, the MCLG for chlorite and chlorine dioxide. The International Life Science Institute (ILSI) convened an expert panel in 1996 to explore the application of the EPA's 1996 *Proposed Guidelines for Carcinogen Risk Assessment* to the available data on the potential carcinogenicity of chloroform and dichloroacetic acid (RA.D.1). EPA is evaluating the ILSI report and its implications for the MCLGs for chloroform and DCA. Finally, EPA is re-evaluating the available cancer epidemiology data using different meta-analytical techniques to determine the adequacy and accuracy of the previous meta-analysis by Morris et al. (RA.D.5-6). The results from this research may be used in developing better estimates of the potential benefits from the Stage 1 DBP rule.

Additional data on the occurrence of TTHMs and HAA5 has been collected by the American Water Works Association, the American Water Works Systems Company and several states and has been submitted to EPA for consideration. In addition, new occurrence information for chlorite and chlorate have been provided to EPA.

Table II-2. Research to Support the DBP Rules

		Expected Completion Date	Priority
A.	**Health Effects Research**		
1.	**Epidemiology—Development/Application of Improved Tools for Field Research**		
HE.D.1	Improving estimates of residential DBP exposure in epi studies	1997	H
HE.D.2	Improving measures of biologic effect: evaluation of biomarkers	2000	H
HE.D.3	Improving methods for managing health and exposure data	1998	H
2.	**Epidemiology—Feasibility/Full-Scale Studies**		
HE.D.4	Feasibility studies: Cancer (Research Council)	1998	H
HE.D.5	Feasibility studies: Reproductive effect (Research Council)	1998	H
HE.D.6	Full-scale studies; Cancer and reproductive effects		
	–Cancer	Proposed	if feasible H
	–Reproductive effects	Proposed	if feasible H
3.	**Toxicology—Hazard Identification and Dose-Response**		
HE.D.7	Cancer dose-response studies	2000	H
HE.D.8	Reproductive/developmental effects screening studies	2000	H
HE.D.9	Neurotoxicity studies	2000	M
HE.D.10	Immunotoxicity studies	2000	M
AWWARF Related Projects			
738	Dose-response relationship of DCA & TCA-induced proliferation	Completed	
	CMA: Chlorite/Chlorine Dioxide 2 generation reproductive study	1997	
4.	**Toxicology—Pharmacokinetic and Mechanisms of Action**		
HE.D.11	Pharmacokinetic and mechanistic research—cancer	2000	H
HE.D.12	Pharmacokinetic and mechanistic research—reproductive	2000	H
AWWARF Related Projects			
432	Mechanistic basis and relevance of rat kidney tumor formation	Completed	
617	Carcinogenic mechanisms in rat & mouse hepatocytes	1997	
701	Induced hepatic tumors with induction of peroxisomes	1997	
5.	**Toxicology—DBP Mixtures**		
HE.D.13	Mixtures feasibility study	2000	H
HE.D.14	Toxicologic evaluation of drinking water mixtures	Proposed	if feasible H
HE.D.15	Studies of DBP interactions	2000	M
HE.D.16	Mutagenicity screening studies of drinking water mixtures	2001	H
B.	**Exposure Research**		
1a.	**DBP Methods—Stage 1 DBP Rule**		
EX.D.1	Low level bromate measurement	1999	H
EX.D.2	Improved method for haloacetic acids	Completed	H
EX.D.3	Expand quality control for TOC, evaluate new TOC methods	1998	H
EX.D.4	Low level ClO_2 measurement (depends on health data)	Proposed	M
EX.D.5	Real-time monitoring for disinfectant residuals	Proposed	L
EX.D.6	PE studies for DBPs and disinfectants	Ongoing	H
AWWARF Related Projects			
159	Improved methods for isolation and characterization of NOM	1997	
163	Development of improved method for haloacetic acids	1997	
417	Development of fiber optic chemical sensors for monitoring organic compounds (TOC)	Completed	
830	Bromide-ozone interactions (incl. develop analytical technique for total organic bromide)	Completed	
1b.	**DBP Methods—Stage 2 DBP Rule and longer term**		
EX.D.7	Methods for peroxides	2000	M
EX.D.8	Real-time, in-plant monitoring of DBPs	1999	M
EX.D.9	Improved method for aldehydes	1998	M
2a.	**DBP Exposure—DBPs from Different Disinfectant Combinations**		
EX.D.10	Identify new DBPs from alternate disinfectants	2000	H
EX.D.11	Methods for nonvolatile DBPs	2000	H
AWWARF Related Projects			
825	Bromide Survey	Completed	
2b.	**DBP Exposure—Factors that Affect Exposure Levels and Human Exposures**		
EX.D.12	DBP changes in distribution system	Proposed	M
EX.D.13	DBP interactions w/foods and associations w/dietary intake	2000	M

(Continued)

Table II-2. (Continued)

		Expected Completion Date	Priority
EX.D.14	Exposure to DBPs through showering	Proposed	M
EX.D.15	Markers of DBP exposure	Proposed	M
EX.D.16	Models of DBP exposure	2000	H
EX.D.17	Exposure as function of population distribution	Proposed	M
EX.D.18	Tapwater consumption	1997	H
C.	**Risk Assessment Research**		
1.	**Characterizing Risk of Individual DBPs**		
RA.D.1	Cancer risk assessments	2000	H
RA.D.2	Cancer combination study for bromates	1997	H
RA.D.3	Noncancer risk assessments	2000	H
RA.D.4	Risk characterization	2000	H
2.	**Characterizing Risks from Chlorinated Waters**		
RA.D.5	Evaluate newer epidemiologic studies	1998	H
RA.D.6	Assessment of previously conducted studies	1998	H
RA.D.7	Identify ongoing cancer studies	1998	H
3.	**Methods and Models to Characterize Risks from Mixtures**		
RA.D.8	Characterization of interactions for mixtures of DBPs.	1998	M
RA.D.9	Threshold studies for D/DBPs	1998	H
RA.D.10	Use of QSAR model to estimate risk for single cmpnds/classes of compounds within a mixture	1997	H
4.	**Methods and Models to Compare Risks**		
R.A.D.11	Comparative Risk Analysis	2000	H
D.	**Risk Management**		
1.	**Effectiveness of Treatment Processes in Reducing DBP Precursors**		
RM.D.1	Enhanced softening for precursor and pathogen removal	2000	H
RM.D.2	Effects of ozone & biofiltration for control of precursor and pathogens		
a	Control precursor, pathogen and pesticide removal	1998	H
b	Effect of pH on ozonation and enhanced coagulation	2000	H
RM.D.3	Analyze ICR data from GAC, membrane bench and pilot studies	1999	H
RM.D.4	Removal of DBP precursors by GAC and membranes	Completed	H
RM.D.5	Membrane scale-up and fouling	1998	M
AWWARF Related Projects			
DBP Precursor Control—GAC			
816	Removal of DBP precursors by GAC adsorption	1997	
DBP Precursor Control—Coagulation			
531	Humic acid removal using ferric chloride	Completed	
814	Removal of DBP precursors by optimal coag. & and precip. softening	1997	
934	Optimizing ozonation for turbidity & organics removal	Completed	
DBP Precursor Control—Oxidation and Biological Filtration			
252	Optimizing filtration in biological filters	1998	
289	Advanced oxidation and biodegradation processes	1998	
631	Removal of natural organic matter in biofilters	Completed	
712	Design of biological processes for organics control	1997	
DBP Precursor Control—Membrane Technology Issues			
170	Reverse osmosis and nanofiltration for organics removal	1997	
264	Integrated membrane systems to control microbes/ DBP precursors	1999	
601	Ultrafiltration membrane pretreatment and nanofiltration	Completed	
826	Membrane technology for drinking water—joint report	1997	
904	Biofouling in membrane processes	1997	
Other Issues			
271	Improving clearwell design for DBP and CT compliance	1998	
361	Case studies of impacts of treatment changes on biostability on full-scale distrib. systems	1999	
369	Case studies of modifications of treatment practices to meet the new D/DBP regulation	1999	
2.	**Effectiveness of Alternative Disinfectants in Limiting DBP Formation**		
RM.D.6	Ozone by-product formation and control	1999	H
AWWARF Related Projects			
Formation and Control of Ozonation By-Products			
156	Strategies to control bromide and bromate ion		

(Continued)

Table II-2. (Continued)

		Expected Completion Date	Priority
504	Ozone & biological treatment for DBP control and biological stability	Completed	
525	Evaluation of PEROXONE advanced oxidation process	1997	
533	Effect of carbonate/bicarbonate alkalinity on advanced oxidation processes	Completed	
709	Impacts of ozonation on formation of chlorinated DBPs.	1997	
830	Bromide-ozone interaction in water treatment	Completed	
832	Reaction of ozone and hydroxyl radicals with amino acids	Completed	
Formation and Control of Chloramine DBPs			
710	Nitrification occurrence and control in chloraminated water systems	Completed	
803	Factors affecting DBP formation during chloramination	1997	
937	Chloramine decomposition kinetics and degradation products.	1997	
Formation and Control of Chlorine Dioxide-related DBPs			
611	Sources, occurrence, & control of ClO_2 by-product residuals in drinking water	Completed	
833	Minimizing chlorate ion formation in drinking water when hypochlorite used	Completed	
3. Small Systems Technology for Precursor and DBP Control			
RM.D.7	Membranes/advanced oxidation/other technology combinations	1999	H

This new data will be useful when evaluating the potential regulatory impacts of the Stage 1 DBP rule.

Improvements in analytical methods will be completed in time for the Stage 1 DBP rule for bromate (EX.D.1), haloacetic acids (EX.D.2), and TOC (EX.D.3). Research related to improving enhanced coagulation and softening will also be completed in time for the final Stage 1 rule (RM.D.4). Many of these projects will help to better define the precursor removal requirements in the Stage 1 DBP rule. In addition, there are several AWWARF projects that will help to improve the analytical methods and improve DBP precursor removal (see Table II-2).

Stage 2 DBP Rule

The Stage 2 DBP rule is required to be completed by May 2002. In order to meet this deadline, EPA will need to initiate a second regulatory negotiation by late 1999 to complete a proposed rule by late 2000. EPA believes that the majority of research will be completed in time for consideration in the final Stage 2 DBP rule. When developing the Stage 2 DBP rule, there are several critical issues that need to be addressed in order to support the development of different regulatory options including 1) the magnitude of the cancer and noncancer risks (e.g., reproductive risks) from chlorinated waters; 2) the magnitude and relative cancer and noncancer risks (e.g., reproductive risks) from the DBPs formed when using alternative disinfectants (e.g., ozone and chlorine dioxide); 3) the relative risks from brominated species versus the chlorinated species; 4) better methods for DBPs and the collection of additional occurrence data; 5) the evaluation of the effectiveness of GAC and membranes to remove DBP precursors; and 6) the balancing of the risks between pathogens and DBPs.

The magnitude of the health risks from chlorinated waters and from those DBPs formed using different disinfectants is important to understand when trying to determine **"how large is the risk"** or **"should we be concerned."** Understanding the magnitude of the health risks from the use of different disinfectants is critical when evaluating the different regulatory options for the Stage 2 DBP rule and for evaluating the risk-risk tradeoffs between controlling for microbial pathogens and DBPs. For example, using alternative disinfectants may be much more cost effective than using advanced technologies such as membranes or GAC to comply with MCLs for chlorinated DBPs. On the other hand, alternative disinfectants to chlorine create their own DBPs of concern that need to be considered (e.g., bromate with the use of ozone and chlorite with the use of chlorine dioxide). Since ozone and chlorine dioxide are more effective for inactivating *Cryptosporidium* than chlorine it becomes especially important to understand the health risks of DBPs formed using different disinfectants.

Determining the relative risk from alternative disinfectants is important when trying to address **"do the by-products from the use of different disinfectants present more or less of a health risk than the by-products from other disinfectants."** For example, systems may be considering switching to ozone for better control of *Cryptosporidium* and because it forms fewer chlorinated DBPs. The apparent major by-product of ozonation in the presence of bromide is bromate. If bromate presents a greater health risk than chlorinated by-products then the switch to ozone may actually increase the risk from DBPs. However, before these issues can be resolved it is critical that the risks from the by-products formed from alternative disinfectants be evaluated.

Determining the relative risk from brominated species is important when trying to address **"do brominated species pose a greater risk than chlorinated species."** Determining the relative risks between the brominated and chlorinated species is important because there is some evidence that in waters with high bromide concentrations, technologies to remove DBP precursors could increase the concentrations of certain brominated DBPs even though the group concentrations of TTHMs and HAA5 may decrease. This may be of concern if the risks

from the brominated species are shown to present a greater health concern than the chlorinated species.

To determine the magnitude and relative risks from the DBPs formed using different disinfectants, information is needed on the health effects from individual DBPs or mixtures of DBPs along with occurrence/exposure information. In addition, information is needed on whether the risks can most cost effectively be controlled by limiting exposure to individual DBPs and/or surrogate parameters (e.g., TTHMs, total haloacetic acids, total organic halides [TOX], or total organic carbons [TOC]). If the magnitude of national cancer risk attributed to chlorinated DBPs after the Stage 1 rule is determined to be high (e.g., greater than 5,000 cases per year), the costs for implementing a Stage 2 DBP rule, where many systems would be required to use GAC or membrane technology, may be justified. However, if equivalent protection could be provided allowing use of alternative disinfectants, then costs may be much lower.

During the negotiations, concern was also raised as to the significance of reproductive and developmental risks from disinfected waters. This issue is of particular importance from a regulatory perspective. If reproductive or developmental effects are of concern, then standards might be set to prevent the threshold risk level from occurring anywhere in the distribution system because a single excursion above the MCL might induce illness whereas cancer risk is considered to accrue over time. This approach to setting the MCL is unlike the existing TTHM maximum contaminant level (MCL) or newly proposed Stage 1 MCLs for TTHMs and HAA5 (i.e., the sum of concentrations for five haloacetic acids) where compliance is based on an annual average of concentrations measured in the distribution system.

Data from epidemiological and toxicology studies will be used in a weight of evidence approach to better define the magnitude and relative of the risks for chlorinated DBPs (HE.D.1-16 and RA.D.1-11). The epidemiology research will provide direct human information that will reduce uncertainties in the cancer and reproductive risks from chlorinated waters, but uncertainties will remain for the Stage 2 DBP rule (HE.D.1-6 and RA.D.5-7). The majority of cancer epidemiology research will be completed in time for the Stage 2 rule, but the results from newly initiated cancer epidemiology studies would probably not be available in time for consideration for the Stage 2 DBP rule because it takes several years to design and carry out such large studies. The toxicology research will provide substantial new information for evaluating the cancer and reproductive risks from individual chlorinated DBPs and for evaluating the potential for neurotoxicity and immunotoxicity (HE.D.7-12 and RA.D.1-4). Although the majority of this research should be completed in time to be considered for the DBP Stage 2 rule, it is important to note that the information from many of the 2-year cancer bioassays described in Chapter IV will not be available until mid to late 2000. EPA is hopeful that preliminary results will be available that could be used in the regulatory negotiations to provide some direction on the potential health risks from these DBPs. Mixtures research would also provide new information to reduce the uncertainties in the risk estimates for chlorinated waters, but this research is complex and many of the studies, if initiated, may not be available in time for the Stage 2 DBP rule (HE.D.13-16 and RA.D.8-10).

Data from toxicology studies, and to a more limited extent epidemiology studies, will be used to better define the magnitude and relative risks for DBPs formed as a consequence of using alternative disinfectants (HE.D.1-16 and RA.D.1-11). The toxicology research will provide information on the major DBPs formed by the use of chlorine dioxide (chlorite and chlorate), ozone (bromate, glyoxal, formaldehyde), and possible studies on the toxicity of cyanogen chloride (a major by-product from the use of chloramines) (HE.D.7-12). As with the several of the chlorinated DBPs, many of the 2-year cancer bioassays described in Chapter IV will not be available until late 2000. There will be limited information from mixtures research on the potential risks of DBPs from using alternative disinfectants (HE.D.13-16 and RA.D.8-10). Epidemiology studies may provide some information on the potential reproductive risks, but it will be difficult to conduct cancer epidemiology studies for systems using chlorine dioxide and ozone in the U.S. because of the limited historical use and small potential populations exposed.

The EPA/NTP collaborative effort described in HE.D.7-8 will conduct cancer studies, reproductive screening studies, and mechanistic studies for several brominated DBPs (e.g., bromodichloromethane, dibromoacetic acid, dibromoacetonitrile). The reproductive and mechanistic studies should be completed in time for the Stage 2 DBP rule, but results from the cancer studies may not be available until mid to late 2000.

For the Stage 2 DBP rule, there is a need to collect additional DBP occurrence information and DBP precursor information to more accurately estimate the potential risks from DBPs. It will be especially important to collect information on DBPs formed from the use of alternative disinfectants such as ozone and chlorine dioxide. The ICR will be collecting information on four disinfectants, 29 DBPs, five general water quality parameters (pH, alkalinity, calcium hardness, total hardness, and ammonia), and a DBP precursor (bromide) and two surrogates for DBP precursors (TOC, UV-254). Of the 29 DBPs, there will be four THMs, six HAAs (3 others are optional), four acetonitriles, two haloketones, seven aldehydes, chlorate, chlorite, bromate, chloropicrin, chloral hydrate, and cyanogen chloride. The first six months of ICR data should be available by early 1999. In addition to collecting occurrence data for these DBPs, it is also critical to identify new DBPs (EX.D.10) and to develop methods for nonvolatile DBPs (EX.D.11) to ensure the major DBPs have been identified. EPA believes the occurrence data from the ICR will provide the needed information for the critical DBPs for the Stage 2 DBP rule.

Another important area for the Stage 2 DBP rule is the development or improvement of analytical methods for DBPs of greatest concern. As discussed above, there are projects that are attempting to improve the methods for bromate, HAAs, and TOC. In anticipation of the Stage 2 rule, there are research projects to improve the methods for peroxides (EX.D.7) and aldehydes (EX.D.9). Methods for other DBPs that may be considered for the Stage 2 rule were included as part of the ICR and are believed to be adequate for use in the Stage 2 rule (e.g., haloacetonitriles and haloketones). Better methods may need to be developed for MX and cyanogen chloride if they are included in the Stage 2 rule. Methods for use as precursor surrogates (TOC, SUVA, and NOM) or DBP surrogates (TOX and TOBr) need to be developed in case these prove to be good indicators based on information from the ICR. There is research on improving the TOC method (EX.D.3) and to better characterize NOM (AWWARF projects). The method for TOX is considered adequate and there is a project to improve the total organic bromide method (AWWARF).

Another critical area for the Stage 2 rule is to determine the most cost-effective precursor removal technologies and disinfectant application strategies that can be used to reduce the formation of DBPs. Predicting the removal of DBP precursors and DBP formation will be based mostly on data collected from the ICR, but also from treatment research and studies of processes in the distribution system that affect DBP formation (RM.D.1-7; EX.D.16; RM.M.15, 16, 24, 25). In addition to EPA's research, AWWARF is conducting a considerable amount of research in this area (see related projects). As better design and operating parameters become available for defining precursor removal and DBP formation, they will be used for estimating costs for systems to achieve water quality objectives for different regulatory options. EPA believes the majority of the treatment related research will be completed in time for the Stage 2 DBP rule.

All the information cited above will be used to assist EPA in comparing and balancing the risk from DBPs and microbial pathogens. Current comparative risk models for drinking water weigh the outcomes of microbial exposures to that of cancer from selected DBPs. Research needs to be conducted on a variety of models and methods that will allow for the development of a comparative risk assessment model which addresses multiple outcomes (e.g., cancer, developmental, reproductive, neurotoxic effects), their impacts and costs. This research should focus on the risk analysis and risk reduction benefits derived from minimizing exposures that would result in adverse outcomes other than cancer. A comparative risk framework and strategic model has been developed for DBPs and pathogens and is currently being validated and reviewed (RA.D.11). A related project pertinent to pathogen risk assessment (RA.M.2) will provide predictive functions concerning the magnitude of response, severity of effects, and duration of exposure. The two projects are intended to provide a prediction of different health risk endpoints resulting from simultaneous exposure from DBPs and pathogens. EPA intends to use these models as part of its RIA for evaluating different LT2ESWTR/Stage 2 DBP combined regulatory options.

Groundwater Disinfection Rule

The 1996 SDWA amendments require EPA to promulgate drinking water standards for groundwater no sooner than August 1999 and no later than May 2002. EPA plans to propose a groundwater rule in January 1999 and finalize the rule in November 2000 in conjunction with the LT1ESWTR.

Under the negotiated rule-making for DBPs, it was assumed that the GWDR would prevent increases in microbial risk while groundwater systems using disinfection complied with the Stage 1 DBP rule. Ground water systems not required to disinfect would avoid risks from DBPs and not be required to comply with DBP regulations. Also, groundwater systems required to disinfect but serving only transient populations (most non-community systems) would not be subject to DBP standards unless risks from short-term exposure were determined to be of concern.

While some general problems are common to all drinking water systems and can be adequately addressed by research developed for the surface water and DBP rules, a distinct set of conditions and assumptions apply to contamination and treatment of groundwaters that must be considered. Key regulatory issues include 1) whether practical criteria can be determined for when systems can avoid disinfection while still providing a safe water; 2) what level(s) of disinfection to require for systems which are vulnerable to fecal contamination in the source water; and 3) what control measures to require to limit contamination to the distribution system.

Approaches being considered for addressing the above issues include 1) basing regulatory criteria on their ability to ensure that a system is below a desired risk level (e.g., less than a 10^{-4} annual rate of infection from most viruses), taking cost into consideration; 2) requiring disinfection to reduce risks from viruses to the extent that is technically and economically feasible for most systems, while allowing systems that are clearly not vulnerable to fecal contamination to avoid disinfection (e.g., based on occurrence of indicators such as coliforms and/or coliphage, and minimum set-back distances based on hydro geological features); and 3) same as (2) but only requiring systems to disinfect that are clearly vulnerable to fecal contamination (e.g., based on occurrence of coliforms and/or coliphage).

Given the potential occurrence of over 100 enteric viruses in drinking water, the risk-based approach can only practically be pursued by focusing on those viruses which occur most frequently and at the highest levels in drinking waters, are most resistant to ambient stress and treatment, and are clinically most significant. Ideally, EPA would predict a minimum level of treatment or

set-back distance (at a particular site) for virus "A" to ensure that there are less than a fixed rate of infection (e.g., 1 infection per 10,000 people per year) from the viruses "A," "B," "C," and "D," etc. The problems of developing such an approach are numerous including viruses that behave differently in their die-off and transport through the ground; disinfectants with varying degrees of effectiveness for inactivating different viruses; and viruses that occur at different concentrations with variability in source waters and upon infection produce a wide range of different clinical manifestations, ranging from no symptomatic response or mild gastroenteritis to hepatitis and possibly death.

Model development of this approach is further hampered by the wide range of uncertainties for aquifer hydrogeological characteristics and fate and transport properties of the various pathogens and indicator organisms. These difficulties have led to a two-pronged approach for research supporting a GWDR. One prong is to consider the uncertainties and unknowns for the various elements in these models to determine 1) if they can be reduced such that meaningful predictions are fundamentally possible, and 2) if the model predictions can be validated in the field. The other prong is to focus on other approaches to estimating groundwater vulnerability, primarily considering occurrence data and traditional well site selection criteria, such as set-back distances, confining layers, land uses, well depth, etc. These need to be likewise considered for their ability to meaningfully predict vulnerability/non-vulnerability.

The GWDR will affect a fundamentally different class of public water supply systems than the ESWTR. The 10,000 or so surface water systems include a substantial fraction of large community systems with substantial infrastructure and economic resources. The 160,000 groundwater systems are almost exclusively very small non-community and community systems with limited resources and infrastructure. The regulatory realities require that EPA consider simple, feasible assessment, treatment and monitoring approaches.

EPA is considering developing the RIA using three regulatory approaches described above. However, before these approaches can be used, additional information is needed as described below.

Table II-3 summarizes completed, ongoing, and proposed research to help define the significance of the public health problem in groundwater systems. These projects include information on known and estimated disease (outbreaks and endemic disease rates), microbial pathogen and indicator occurrence in source waters and distribution systems, and exposure risks associated with various contamination sources (HE.M.5, 6, 9, and 10; EX.M.8, 10 and 14 -18; RA.M.1-3). This information will indicate the nature and scope of the public health problem and allow for estimates of the baseline risk level from which to base the RIA and develop appropriate regulatory goals. Surveys on disinfection practice by industry will help characterize types and levels of disinfection treatment currently practiced by groundwater systems.

Strategies to determine system vulnerability to microbial contamination and criteria to avoid disinfection have to be developed and field tested. Information on factors affecting and limiting microbial contamination of groundwater will help establish criteria for avoiding disinfection. Such information includes physical and chemical properties governing fate and transport of microbes in the subsurface, site-specific factors such as land use patterns, and hydrogeological properties affecting vulnerability (EX.M.23-26).

UV disinfection research is targeted because it may be the least costly technology for many small systems to adequately treat for viruses, especially non-community systems (i.e., those not having a distribution system), or multiple-well systems (RM.M.9 and RM.M.13). Also, systems using UV disinfection would likely avoid formation of DBPs of any health risk significance.

Approaches for monitoring to ensure public protection from waterborne viruses as well as bacteria may include coliphage and are being investigated (see related projects).

Table II-3. Research to Support the Groundwater Disinfection Rule

	Expected Completion Date	Priority
A. Health Effects Research		
1. Health Research on Waterborne Pathogens		
HE.M.5 Infectious dose of Norwalk virus	2000	H
HE.M.6 Infectious dose of other priority pathogens	Proposed	M
HE.M.9 Investigations of waterborne disease outbreaks	Ongoing	H
HE.M.10 Surveillance tool for waterborne disease outbreaks	Completed	H
AWWARF Related Projects		
268 Fingerprinting techniques for opportunistic pathogens & illness	1998	
B. Exposure Research		
1b. Microbial Methods—Viruses		
EX.M.8 Application of PCR technologies & gene probes to detect viruses in water	1999	M
EX.M.9 Norwalk virus	2000	H
EX.M.10a Methods for emerging viruses	Proposed	H
EX.M.10b PCR-based detection of viruses in water	1997	H
AWWARF Related Projects		
292 Rapid PCR-based monitoring of entero viruses	1998	
429 Male-specific coliphages as indicators of viruses	Completed	
612 Analysis of viruses by gene probe	Completed	
726 Viral and microbial methods for groundwater	1997	
916 PCR technologies for virus detection in groundwater	1997	
2a. Microbial Exposure—Pathogen Occurrence		
EX.M.14 Occurrence of *Mycobacterium*	1998	H
EX.M.15 Occurrence of heterotrophic bacteria with virulence characteristic	2001	H
EX.M.16 PCR method for *Legionella*	Completed	L
EX.M.17 Pathogenicity of heterotrophic bacteria found in drinking water.	1998	H
EX.M.18 Occurrence of opportunistic pathogens in biofilms	Proposed	M
AWWARF Related Projects		
186 Survey viruses in groundwaters	Completed	
3a. Groundwater—Survival and Transport in the Subsurface		
EX.M.23 Virus survival in the subsurface	2000	H
EX.M.24 Virus transport in the subsurface	2000	H
AWWARF Related Projects		
262 Field study of virus and indicator transport in groundwater	1998	
3a. Groundwater—Methods for Protecting Wells and Springs		
EX.M.25 Viral transport and fate models	2000	M
EX.M.26 Vulnerability of groundwater to pathogens	2000	H
EX.M.27 Delineation of natural protection zones	1998	M
EX.M.28 Vulnerability & sensitivity analysis	1998	H
EX.M.29 Occurrence of *Clostridium perfringens*	1997	H
EX.M.30 Aquifer well mapping	Completed	M
EX.M.31 Correlation of water age and microbial viability		H
EX.M.32 Septic tank siting	1999	H
EX.M.33 Virus sampling and phage research	1997	H
C. Risk Assessment Research		
1. Risks from pathogens		
RA.M.1 Devel. compre. micro risk assess paradigm for water	2000	H
RA.M.2 Evaluation/application of various dose-response models	1998	H
RA.M.3 Evaluation and application of methods to assess risk associated with exposures to multiple pathogens, routes, and durations	2000	M
D. Risk Management Research		
RM.M.9 UV disinfection efficiencies for Norwalk viruses	Proposed	H
RM.M.30 Evaluate alternative inactivation processes for controlling viruses	Proposed	H
AWWARF Related Projects		
180 UV inactivation of viruses in natural waters	1997	
353 Inactivation rates of viruses and bacteria in saturated and unsatured subsurface media	1999	
702 Development and validation of rational design methods of disinfection	Completed	
809 By-products of UV treatment of groundwater	Completed	
817 Membrane filtration techniques for microbial removal	Completed	

(Continued)

Table II-3. (Continued)

	Expected Completion Date	Priority
NWRI Projects:		
Deposition mechanisms and long-time scale factors influencing virus transport in porous media	Completed	
Groundwater transport of viruses	Completed	
Field experiment and modeling of vira transport in groundwater	Completed	
Transport and fate of viruses in the vicinity of pumping wells	Completed	

Chapter III. Research for Microbial Pathogens

Background

Waterborne infectious disease outbreaks have been attributed to a variety of pathogenic bacteria, parasites and viruses. *Giardia* has been responsible for about half of the outbreaks of disease where the causative agent was identified. *Cryptosporidium* outbreaks have been reported less frequently, but the number of cases associated with the outbreaks have been much larger. Since 1991, the percent of outbreaks attributable to *Cryptosporidium* has doubled. In 1993–1994 reporting period, about 17% of all reported outbreaks were caused by *Cryptosporidium*. Many outbreaks of acute gastrointestinal illness have not been linked to specific pathogens. Viruses are thought to be the cause of a large portion of the outbreaks where the agent is not identified. Establishing the association between water ingestion and illness is difficult because of our inability to culture many of the viruses. In addition to reported outbreaks where the cause is unidentified, it is likely that many outbreaks occur that are either unrecognized or unreported. Furthermore, if it is determined through further research that endemic microbial disease is a real occurrence (as suggested by studies in Canada), public health concern over waterborne pathogens would increase significantly.

The sources of pathogenic microbes in drinking water associated with disease are usually related to fecal matter from warm-blooded animals and humans. Humans are the main source of pathogens, but animals are frequently implicated as in the outbreaks caused by *Giardia* and *Cryptosporidium*. Another source of potential pathogens is the water distribution system and its associated storage facilities. Breaks in the integrity of the distribution system can allow the introduction of pathogens. In addition, many bacteria can grow and persist in the distribution system, and some of them (e.g., *Mycobacteria* and *Aeromonas*) can cause infections and disease under certain conditions. The conditions are not well defined, but they can include a host whose natural defense barriers have been compromised, an organism that has the ability to take advantage of the opportunity presented by a compromised host, and an environment that is conducive to the growth of the pathogen.

This chapter describes proposed research for microbial pathogens in the areas of health effects, exposure, risk assessment, and risk management. The major research questions in each area are summarized in Table III-1. For each question, the state of the science, research needs, and proposed research projects are described.

Health Effects Research

1. **What are the major pathogens of public health concern?**

2. **What is the nature and magnitude of disease associated with exposure to these waterborne agents?**

State of the Science

The continued occurrence of waterborne disease outbreaks in the U.S. and questions in the scientific community about the adequacy of conventional water treatment in preventing endemic waterborne disease highlight the need for research to evaluate the impact of water quality and type of treatment process on the occurrence of waterborne disease. A critical public health issue relates to the need to identify and characterize pathogens that may pose increased risks of infection

Table III-1. Major Research Questions for Microbial Pathogens

Health Effects
1. What are the major pathogens of public health concern?
2. What is the nature and magnitude of disease associated with exposure to these waterborne agents?
Exposure
1. What methods are needed to adequately measure or estimate occurrence of pathogens in drinking water?
2. What are the frequencies of occurrence and densities of pathogens in source water, finished water, and distribution systems, and what is the population distribution of exposures to pathogens?
3. What are the factors affecting microbial contamination of groundwater?
Risk Assessment
1. How can the risks posed by pathogens in drinking water be characterized?
Risk Management
1. How effective are various treatment processes in removing pathogens?
2. How can the quality of treated water be maintained in distribution systems?
3. How can source water be protected to ensure that it is consistent with finished water quality of acceptable microbial risk after appropriate treatment?

and disease in the general population, as well as in susceptible populations such as the immuno-compromised, elderly, or infants.

As discussed earlier, a variety of pathogenic bacteria, viruses and parasites are still considered to pose serious public health risks when treatment is inadequate. In general, the health risks associated with exposure to these agents in drinking water are poorly characterized. The known source water contaminants of greatest concern include the protozoan parasites *Cryptosporidium* and *Giardia*, and the enteric viruses hepatitis A and Norwalk virus. "Emerging" pathogens about which relatively little is known but which could be important public health concerns under certain conditions include *Microsporidium*, *Cyclosporidium*, hepatitis E, and *Helicobacter pylori*. Opportunistic or conditional organisms are those that must be amplified in the environment and then come into contact with a host that is susceptible to disease. Examples of these types of organisms are *Legionella* and *Mycobacterium*. Research is needed to characterize the magnitude of the risk caused by these organisms in susceptible populations and to more carefully describe the risk factors for susceptibility.

Characterizing microbial health risks requires knowledge of a number of important pathogen- and host-specific factors. Reliable information on the infectious dose of these agents is necessary for quantitative risk assessments, yet such data are either limited or unavailable for most important waterborne pathogens. A need also exists to better characterize the virulence of these agents, the range of responses to infection, and the influence of host factors (e.g., immune status) on the course of infection and disease. Understanding the virulence characteristics of pathogenic and opportunistic microorganisms is important for estimating the likelihood that infections will lead to disease in healthy and compromised individuals. Humans exposed to pathogens may in some cases be asymptomatic or may experience mild to severe effects. Although gastrointestinal symptoms are most commonly observed, other disease symptoms or states (e.g., cardiovascular, respiratory, liver, and central nervous system effects) may also be induced by certain pathogens. Finally, secondary spread of disease is an important but poorly quantified factor that should be investigated.

Cryptosporidium is known to cause an acute, self-limiting disease in immunocompetent persons. Infections in immuno-compromised individuals generally cause a more chronic, severe disease for which no safe and effective form of treatment is available. Additional health research on *Cryptosporidium* is needed to permit a more comprehensive characterization of the important pathogen- and host-specific factors described above. Some data on the infectious dose of *Giardia* are available, and additional research on this protozoan is considered to be a lower priority than *Cryptosporidium* at the present time since *Cryptosporidium* appears to be more resistant to disinfection. Very little is known about the pathogenicity of the enteric viruses, which are believed to be responsible for a significant portion of the outbreaks for which the causative agent was not identified. A continuing investigation of the infectious dose of Norwalk virus should provide important information to help characterize the risk posed by this agent. Important data gaps exist for hepatitis A virus, but research in humans is problematic because of its highly pathogenic nature. As current studies resolve critical issues for priority pathogens such as *Cryptosporidium* and Norwalk virus, efforts will shift to emerging pathogens. Clearly, the list of known and emerging pathogens for which major data gaps exist is extensive and growing, and prioritization of these agents for further study will be an ongoing effort as new information on exposure and health concerns becomes available.

Epidemiology studies of both endemic waterborne disease and epidemic events (i.e., outbreaks) can be highly useful in characterizing the magnitude of microbial risks, identifying etiologic agents, characterizing the health effects associated with a variety of different pre- and post-treatment contamination problems, evaluating differences in susceptibilities of different populations to pathogens, and validating risk models. These studies can also help to identify important research needs in the areas of health effects, exposure, risk assessment, and engineering. Exposure research on known opportunistic and "emerging" waterborne pathogens should be linked with health research in the laboratory and field to permit a determination of the public health importance of finding these agents in water supplies. Better surveillance tools are needed to enable public health officials and scientists detect and respond more quickly when waterborne disease is first identified in a community.

The existing epidemiologic data base is inadequate for determining the nature and magnitude of endemic and epidemic waterborne disease in the U.S. A limited number of follow-up studies of the most significant outbreaks have been conducted. The results of two recent studies of endemic waterborne disease in Canada indicated that there was an excess risk of gastrointestinal illness of 15% to 35% in the study groups that consume water treated by conventional techniques. As described below, the EPA has initiated epidemiology studies to further address the issue in U.S. populations, and additional studies are being planned through a collaborative effort between EPA and the Center for Disease Control (CDC). The EPA and CDC are also working together to develop a biannual report on waterborne disease outbreaks. Finally, the EPA is developing improved estimates of annual incidence of endemic waterborne disease in the U.S., using more recent pathogen occurrence data and improving estimates of exposure and health effects.

Research Topics and Priorities

a. Pathobiology of infection and disease for the most important waterborne pathogens

Research on the pathobiology of infection and disease includes studies to describe dose-response relationships, characterize pathogen virulence and the range of outcomes of infection, and evaluate the impact of host immune status on infection and disease. Two approaches for obtaining this information include highly controlled clinical studies in humans and laboratory research in animals. Epidemiology studies, which are described in section (b), are also very effective tools for characterizing infections and the factors that influence disease outcomes.

Nearly all of the health effects research on microbial pathogens was assigned a high priority because it addresses high risk, high uncertainty issues of considerable regulatory importance. The 1996 SDWA Amendments specifically require EPA to conduct the types of research described below, including dose-response studies on pathogens such as *Cryptosporidium* and Norwalk virus, and studies of the factors that influence these relationships in susceptible populations. If individuals exhibit significant immune response to *Cryptosporidium* (project HE.M.1), if the current high-to-low dose extrapolation of risk is not appropriate (project HE.M.2), or if oocyst strain infectivity (project HE.M.3) in immunocompetent individuals varies significantly, then these factors would greatly affect the overall risk assessment. From a cost-benefit perspective, research that better defines the dose-response curve and its significant associated uncertainties for the most important waterborne pathogens is a high priority, because of the high and possibly exponentially increasing costs of treating water to decrease the concentration of viable cysts to lower and lower levels. Over-predicting the risk could have dramatic cost implications as well as cause utilities to change to alternate disinfectants such as ozone. Project HE.M.4 was ranked high because it addresses the critical risk assessment issue of variations in susceptibility to *Cryptosporidium*, and it could affect the EPA/CDC guidance to severely immuno-compromised persons. The Norwalk infectious dose study (project HE.M.5) is also a high priority because of its potential impact on the risk assessment for groundwater systems. As laboratory techniques to identify and characterize pathogenic or toxigenic microorganisms improve, and as current research activities resolve critical uncertainties for *Cryptosporidium* and Norwalk virus, priorities for research on other pathogens such as those considered in project HE.M.6 would increase from medium to high.

HE.M.1—Infectious dose of *Cryptosporidium* Infectious dose study in groups of immunocompetent volunteers with and without preexisting antibodies to this protozoan, with rechallenge of the latter group of volunteers one year after initial exposure.

Priority: High

HE.M.2—Validity of the dose-response model for *Cryptosporidium* using low challenge doses in test animals Dose-response study in mice to evaluate the suitability of the low dose extrapolation approach used in the existing model.

Priority: High

HE.M.3—*Cryptosporidium* virulence study using different strains Identify, collect, and propagate in calves four isolates of *C. parvum* from geographically diverse sites, identify molecular or biochemical markers of virulence, and ultimately establish dose-responses in humans for two of the new isolates.

Priority: High

HE.M.4—*Cryptosporidium* infectious dose in normal and immuno-compromised animals Determine and compare the infectious dose of oocysts in immunocompetent and immunocompromised juvenile and adult guinea pigs.

Priority: High

HE.M.5—Infectious dose of Norwalk virus Second phase of an EPA-funded infectious dose study in humans to further characterize the dose-response and the influence of host-specific factors (such as immune status) on infection and disease. The first phase will be complete in 1997, and the second phase will end in 2000.

Priority: High

HE.M.6—Infectious dose of other priority pathogens (to be determined) Studies of pathogens such as rotavirus, opportunistic bacteria, or emerging pathogens, to be prioritized upon further consideration of needs.

Priority: Medium

b. Characterization of epidemic and endemic waterborne disease

Research described in this section includes community-based epidemiology studies to characterize endemic as well as epidemic waterborne infectious diseases. A major area of interest is the microbial health risks associated with the use of different drinking water treatment techniques (particularly filtration vs. no filtration). An important aspect of this research is to develop better tools to assess exposure to waterborne pathogens in epidemiology or surveillance studies, and to facilitate early detection of outbreaks when they occur. The projects described below, like those identified above, are considered high priority because they fulfill the top three criteria of addressing high risk, high uncertainty issues that have significant regulatory impact. These efforts will lead to a better understanding of the magnitude of endemic and epidemic waterborne disease, and of the factors that contribute to their occurrence. Better

sensitivity in epidemiological studies will allow for improved validation of dose-response predictions from existing/newly developed dose-response curves. The projects listed below are considered a high priority because they are expected to narrow the uncertainty in risk estimates for *Cryptosporidium* and for other priority pathogens as well. Furthermore, the 1996 SDWA Amendments require EPA and CDC to jointly conduct waterborne disease occurrence studies for at least five major U.S. communities or public water systems, and to develop a national estimate of waterborne disease occurrence.

HE.M.7—Characterization of endemic disease: Health effects associated with differences in source water quality and treatment process This includes epidemiologic research to evaluate the impact of different treatment strategies on reducing endemic waterborne disease. This effort should be linked to exposure research involving the identification of new pathogens and the development of field detection techniques, as well as to risk management and assessment research activities. This research should also provide opportunities for studying subpopulations that may be highly susceptible to waterborne infectious disease. Both surface and groundwater sources of varying water quality should be considered for study. In an ongoing, phased effort, potential study sites in several communities have been identified where treatment changes are planned, and the health status of selected communities before and after these changes will be determined. The EPA/CDC waterborne disease occurrence studies required by the 1996 SDWA Amendments have also been initiated in 1997. To the extent possible, these studies will include efforts to identify the etiology of waterborne illnesses that are reported.

Priority: High

HE.M.8—Immunological assays for assessing exposure in epidemiology studies Development or improvement of immunological tools to determine the presence of antibodies to important waterborne pathogens, and application of these tools in community-based studies. This research explores the possibility that serological tools may be useful tools for assessing exposure to important waterborne pathogens. An ongoing phased study is evaluating the use of serosurveys as a tool for assessing exposure to *Cryptosporidium*. After completing the feasibility phase to more fully evaluate the usefulness of this technique, full-scale studies in several cities may be conducted. Concurrent with this effort is a study to evaluate the ability of the ELISA technique to measure *Cryptosporidium* antibodies in human sera.

Priority: High

HE.M.9—Investigations of waterborne disease outbreaks Rapid deployment of EPA scientists with appropriate expertise in health, exposure and control technology to conduct epidemiologic investigations of outbreaks as they occur. This would greatly enhance the opportunity to characterize the microorganism(s) responsible for the outbreak, the host factors that influence infection and disease (including the identification of susceptible subpopulations), and the status of the treatment process prior to and during the outbreak. This would be a joint initiative with the CDC, and would involve appropriate state and local agency personnel.

Priority: High

HE.M.10—Surveillance tools for waterborne disease outbreaks Development of tools or mechanisms of surveillance to improve the recognition and subsequent investigation of waterborne disease in communities. An ongoing study is evaluating the feasibility of using anti-diarrheal drug sales as a surveillance tool for waterborne disease outbreaks.

Priority: High

Exposure Research

1. **What methods are needed to adequately measure or estimate occurrence of pathogens in drinking water?**

State of the Science

Methods for measuring some of the important pathogens associated with waterborne infectious disease are either nonexistent or not effective because they are too inaccurate and imprecise. In either case, these shortcomings have produced great uncertainty with respect to exposure assessments, which has hindered the establishment of sound regulations for drinking water quality and led to the use of many assumptions in characterizing risks associated with drinking water.

Giardia and *Cryptosporidium* usually occur in very low densities in source water and finished drinking water. This characteristic necessitates sampling large volumes of water, sometimes up to 1000 liters, through a filter. This and subsequent steps in the currently available method may contribute to its inaccurate and imprecise nature. A major issue is that only a small fraction of the total sample volume collected can be feasibly analyzed; low-percent recoveries and poor precision are difficult to avoid. The current procedures are being evaluated and improved by EPA scientists and other researchers. New methodology, such as the gene probe polymerase chain reaction method, is being developed and will become available for evaluation at some time in the future.

Some methodology is available for measuring waterborne viral pathogens such as the enteric viruses,

rotavirus, and hepatitis A virus. In the case of the latter two viruses, the methods for their detection and quantification are time-consuming and non-facile. Norwalk virus has been associated with many waterborne outbreaks as shown by seroepidemiology. This virus, however, cannot yet be grown in tissue culture. This lack of a suitable method for detecting and measuring this viral pathogen has limited the conduct of exposure assessments and meaningful effects assessments.

Some of the newly emerging pathogens associated with water cannot be efficiently measured in water samples because suitable methods are not available. Two examples of pathogenic protozoa for which monitoring methods do not exist are *Cyclospora* and *Microsporidia*. Methods for these parasites should be developed and evaluated in anticipation of the future need to measure these pathogens. Similarly, the waterborne pathogen *Mycobacterium avium* cannot be easily measured because the available methods have been developed for testing clinical samples. The same can be said for *Helicobacter pylori*, another potential waterborne pathogen that has been associated with cases of gastric ulcers and stomach cancer in humans.

Pathogens may be present in tap water due to inadequate disinfection or may enter faulty distribution systems post treatment. Due to the acute nature of most microbial diseases, real-time continuous monitoring techniques are needed to detect the possible presence of pathogens in distribution systems and to provide timely advice to water consumers.

Research Topics and Priorities

a. Methods for detecting and enumerating *Cryptosporidium*, and *Giardia* (including identifying the viability potential) in source and finished drinking water, and methods for other emerging protozoa

Cryptosporidium is emphasized because of the great attention placed on the organism due to recent outbreaks and its resistance to inactivation by chlorine. This protozoan may become the focal organism for drinking water regulations. Research that is expected to result in improved methods for detecting *Cryptosporidium* or in a method for detecting viable oocysts has generally been assigned a high priority. These projects are expected to improve EPA's ability to estimate occurrence and exposure. Project EX.M.4 was assigned as medium priority because this methodology will not provide means of determining viability or infectivity of cysts or oocysts.

EX.M.1—Immunological techniques for protozoa Conduct research to examine and improve immunological techniques for detecting *Cryptosporidium*, and other pathogenic protozoa. Practical, improved technology will enhance the isolation, identification, and quantification of pathogenic protozoa.

Priority: High

EX.M.2—Gene probes for detection of viable *Cryptosporidium* oocysts Develop probes to mRNA and other nucleic acids, and examine their potential as viability markers for pathogenic protozoan cysts and oocysts.

Priority: High

EX.M.3—Cultural method for *Cryptosporidium* in environmental samples Develop a cultural method for detecting *Cryptosporidium* in environmental water samples. The objective is to develop and evaluate a tissue culture assay for oocysts.

Priority: High

EX.M.4—PCR methods for *Giardia* and *Cryptosporidium* Develop polymerase chain reaction (PCR) methods for *Giardia* and *Cryptosporidium* in environmental samples. Methods will be investigated for recovering protozoa nucleic acids directly from water samples.

Priority: Medium

EX.M.5—Protozoa methodology protocol development workshop (Ongoing) This workshop will produce protocols for developing and evaluating a new method; for comparing methods; and for determining the equivalency of procedures, reagents, and materials within a method. It also will develop recommendations on sample volume for raw waters to be included in a comparison survey.

Priority: High

EX.M.6—Comparison of methods for *Giardia* and *Cryptosporidium* in water Comparison of the best available methods for detecting and quantifying cysts and oocysts through multi-lab evaluation using water samples from multiple sites, using criteria developed in project EX.M.5.

Priority: High

EX.M.7—New protozoa agents Develop methods to identify new potential protozoan pathogens in drinking water such as *Cyclospora* or *Microsporidia*. The objective of this research is to develop procedures, either *in vitro* or *in vivo*, for producing stocks of these potential pathogens. Methods for detection and identification will be developed and evaluated using the stock organisms.

Priority: High

b. Methods for detecting and enumerating viruses in source and finished drinking waters

Molecular biology techniques have allowed for the detection of viruses in water samples but they cannot

indicate whether a virus is or is not infectious. To determine infectivity, the virus needs to be grown in tissue culture. Accurate exposure assessments will not be possible until these research needs are met.

Improving methods for detection and infectivity assessment of Norwalk virus (EX.M.9) was considered a high priority because it may be used as a target virus for treatment and/or risk assessment, especially for groundwater systems (see Chapter II, section on groundwater disinfection rule). Methods for virus identification which do not indicate infectivity are generally of medium priority (EX.M.8). Project EX.M.10 is a high priority because this data will help determine if viruses other than HAV or Norwalk may be more appropriate for defining disinfection conditions necessary to protect from viruses in ground and surface water supplies.

EX.M.8—Application of PCR technologies and gene probes for virus detection in water (Ongoing) Conduct studies to evaluate the application of the polymerase chain reaction and gene probes for virus detection in water. The viruses being studied are enteric adenovirus, Coxsackie virus, hepatitis A viruses, and rotavirus.

Priority: Medium

EX.M.9—Norwalk virus Develop a cultural method for Norwalk and Norwalk-like viruses. The objective of this study will be to identify cell culture lines that will replicate Norwalk virus RNA. Develop PCR/gene probe methods for the *in situ* detection of the replicated particles.

Priority: High

EX.M.10—Methods for emerging viruses Develop methods for identification and quantification of emerging viruses.

Priority: High

2. **What are the frequencies of occurrence and densities of pathogens in source water, finished water, and distribution system water, and what is the population distribution of exposures to pathogens? What are the sources of pathogens in source waters and finished drinking water? For example, livestock, wildlife, wastewater management, distribution systems, etc.**

State of the Science

The occurrence and densities of waterborne pathogens in source waters, finished drinking water, and distribution systems are not well known. *Giardia* cysts and *Cryptosporidium* oocysts have been detected in source waters and also in drinking water samples. In one study, fewer than 20% of the drinking water samples contained *Cryptosporidium* oocysts, whereas more than 50% of the surface and spring water samples contained *Cryptosporidium* oocysts. *Giardia* cysts were not found in drinking water samples, but they were detected in surface water samples, including pristine river water samples. In another study, 78% of watersheds were positive for *Giardia* on multiple occasions, while 86% of the sites were multiply-positive for *Cryptosporidium*. All of these studies of the occurrence of protozoa in source and drinking waters have limitations. Surveys of protozoan cysts and oocysts are few in number and, therefore, difficult to translate to the national level. The results of the protozoan surveys, although accomplished with state-of-the-art methodology, still leave much uncertainty because the method used lacks sensitivity and the detection of cysts and oocysts does not indicate their viability or whether or not they are infectious.

Another major issue is the extent to which watershed control can limit pathogen concentrations in source waters. While several surveys have indicated lower *Giardia* and *Cryptosporidium* levels in source waters of systems with protected watersheds, the effectiveness of watershed management practices on reducing pathogen levels is not well defined. However, it is clear that various sources of watershed contamination will play a significant role in risk management decisions. EPA recently awarded a grant that will focus on detecting fecal contamination and its sources in water and watersheds. AWWARF is also sponsoring two projects in this area; one project is examining the survival of *Cryptosporidium* and *Giardia* exposed to different environmental conditions including water temperature, cyst/oocyst stage, and physical stress on the viability and susceptibility to disinfection. Another study will evaluate the effects of watershed management practices on pathogen levels in source waters.

There is also insufficient information about viruses in surface and groundwaters. Recent studies indicated that 20% to 25% of all groundwaters were contaminated by enteric viruses detected by cultural methods and gene probe methods. Gene probe methods detect important viruses such as hepatitis A virus, rotavirus and Norwalk virus, but they cannot determine if the viruses are infectious and, therefore, whether they pose a definite risk to exposed individuals. This again points to the need to develop tissue culture methods for the more important viruses so that this significant information gap can be filled.

Although we have a relatively good understanding of the linkages between pathogens in drinking water and illness in water consumers, there are still many questions to be answered, such as where do pathogens occur, how many are there and where did they come from. Some of the questions have been answered for selected pathogens. Some studies have been conducted to determine the occurrence in nature of *Giardia* and *Cryptosporidium* , but they have been limited in scope. National surveys have not been conducted and these are critically needed if the extent of the potential risk from these organisms is to be defined. Such studies are in the planning stages. Under the Information Collection Rule, EPA intends to require that source waters and

finished waters at water utilities all over the U.S. be surveyed to determine the occurrence of *Giardia, Cryptosporidium*, enteric viruses, and indicators. This information is sorely needed for developing the Enhanced Surface Water Treatment Rule. However, since the ICR will not include intensive monitoring during storm events, optimal regulatory monitoring strategies to define treatment needs under maximum stress situations will not be apparent unless additional survey work is conducted. Also, as discussed above, the lack of effective methods for enumerating pathogens and for indicating whether pathogens are viable or infectious will compromise the risk assessment process.

Research should be considered for pathogens, especially emerging pathogens, where there is evidence that they have the potential to become a significant waterborne problem. The pathogenic protozoa *Cyclospora* and *Microsporidia* fall into this category. These microorganisms are transmitted by the fecal-oral route and cause severe gastrointestinal illness; there is some evidence that they may be waterborne. Anticipatory research should be initiated to determine how frequently they occur and at what levels in source waters and drinking water. In the event that they become a significant problem, exposure assessment information will be available to risk assessors and managers. Research should also be conducted to determine the extent and densities of emerging bacterial pathogens, such as *Mycobacteria* and aeromonads, in drinking water. These microorganisms are known to be transmitted via the waterborne route and studies have shown the linkage between water and illness in water consumers. Since the presence of the organisms is not identified by common measures of drinking water quality, there is no information available on their occurrence and levels.

Just as the virulence, survival, and infectious dose characteristics in microbial pathogens can vary and affect their ability to cause waterborne disease, there are many characteristics of exposed individuals and human populations that vary and influence the course of infection and disease. Areas of uncertainty include the proportion of the exposed population at highest risk (such as the immuno-compromised, the aged, and very young); how much water is consumed (boiled vs. non-boiled water, tap vs. bottled water); the extent and effect of protective immunity; and the significance of other exposures, e.g., foods that carry the same microbial pathogens as those found in water. Characterizing the nature of exposed populations and their behavioral patterns will provide valuable information for the risk assessment process.

Research Topics and Priorities

a. Surveys to determine pathogen occurrence in source and finished waters

Research in this area will help in determining optimum survey strategies, sampling frequencies, and statistical parameters for adequately representing or determining pathogen occurrence in source waters. Watershed characteristics (e.g., land/water use, population densities, and hydrology) and temporal storm events are important variables that need to be considered together when collecting, analyzing and interpreting microbial survey data. In addition, the research will provide information on whether indicators can be used for estimating source water pathogen occurrence (ground or surface) or the absence of pathogens in finished waters (ground or surface). Finally, pathogen occurrence data can be used to evaluate predictions of aquifer vulnerability.

Project EX.M.11 is considered a high priority because it will supplement ICR information by providing data on short-term variations in the microbiological quality of raw and treated water due to storm runoff and pollution events. Such events and the problems associated with treating rapidly deteriorating water quality are considered critical risk factors in the occurrence of waterborne disease outbreaks and spikes in endemic illness (not detected as an outbreak). Data from this project will clarify the range of pathogen occurrence, potential indicators, and appropriate targets for defining minimum treatment under the ESWTR, e.g., whether risk reduction levels could be set based on the 90th percentile level of oocysts detected based on some minimum frequency of monitoring, e.g., monthly sampling for 18 months. Where year-round target treatment levels are set, i.e., based on source water measurements and with a monitoring scheme which is intended to prevent big spikes in endemic levels, has enormous cost/benefit implications. This study would also validate treatment effectiveness at full-scale treatment plants by targeting water systems with high source water pathogen loadings. Project EX.M.12 is a medium priority unless new evidence indicates that emerging viruses are more resistant to disinfection than HAV or Norwalk.

EX.M.11—Intensive evaluation of microbiological constituents and treatability in surface source waters Develop data on short-term fluctuations in pathogen occurrence related to meteorological and pollution events. These data are needed to evaluate the effectiveness of treatment and control measures. Validate alternative and prototype methods for indicators and pathogens. Include microbiological parameters and methods as in the ICR, but possibly use more effective analytical techniques, should they become available.

Priority: High

EX.M.12—Identification of viruses resistant to disinfection As new virus methods become available, evaluate new viruses for their potential occurrence in drinking waters and their resistance to disinfection. Studies should examine which viruses are most likely to occur in fecally contaminated source waters receiving different levels of disinfection.

Priority: Medium

b. Importance of watershed control (including point source, non-point source, and septic tank controls) for source water pathogen occurrence

Often it is difficult to determine the origin of non-point-source fecal contamination in surface water source and therefore difficult to prioritize watershed control measures. Project EX.M.13 will provide an additional tool for water utilities to assess whether non-point-source fecal contamination is of animal or human origin.

EX.M.13—Distinguish animal versus human sources Distinguish animal from human sources of pollution using gene probe methodology based on phylogenetic differences between human and non-human *E. coli* or *Bacteroides* or immunoassays for human related chemicals such as caffeine. These probes will be used to identify sources of pollution.

Priority: High

c. Occurrence of and exposure to primary and opportunistic pathogens in distribution systems

Project EX.M.14 is a high priority because *Mycobacterium* is relatively more resistant to disinfection than most other bacteria, and because a published study showed an association between hospital-acquired infections and this organism in drinking water. Projects EX.M.15 and EX.M.17 were assigned as high priority because they are expected to provide information which, in conjunction with the results of other ongoing studies, will establish whether heterotrophic bacteria in the distribution system pose a risk to immunocompetent individuals. Project EX.M.21 is also a high priority, as it is anticipatory in nature and will address potential pathogens that could affect both immunocompetent and immuno-compromised individuals. Depending on the outcome of this research (i.e., finding of opportunistic pathogens in the distribution system) the medium or low priority of the other projects on opportunistic bacteria in this section and in the distribution system risk management section would be reassessed.

EX.M.14—Occurrence of *Mycobacterium* Determine the occurrence of ***Mycobacterium avium*** (MAC) in potable water distribution systems and compare MAC water isolates to MAC strains isolated from clinical specimens obtained from immuno-compromised patients.

Priority: High

EX.M.15—Occurrence of heterotrophic bacteria with virulence characteristics Determine the frequency of occurrence of heterotrophic bacteria isolated from drinking water that demonstrate virulence characteristics.

Priority: High

EX.M.16—PCR method for *Legionella* Develop a method for detecting *Legionella* in water using the polymerase chain reaction (PCR) procedure. Also determine whether *Legionella* growing inside amoebae in potable water can be detected by PCR.

Priority: Low

EX.M.17—Pathogenicity of heterotrophic bacteria found in drinking water

Conduct surveys to identify heterotrophic opportunistic bacteria associated with drinking water and granular activated charcoal (GAC) filter effluents. Identify potential pathogens using compromised animals. Establish a data base for distribution systems on a regional and national scale.

Priority: High

EX.M.18—Occurrence of opportunistic pathogens in biofilms Examine the occurrence of specific opportunistic pathogens in biofilms associated with treated drinking water distribution systems and how they are affected by various factors. Organisms of special concern are *Aeromonas*, *Pseudomonas*, and non-tuberculosis *Mycobacteria*.

Priority: Medium

EX.M.19—Opportunistic pathogens associated with point-of-use (POU) and point-of-entry (POE) filter effluents Determine the potential for colonization and growth of opportunistic pathogens in POU/POE water treatment devices and microbial purifiers under actual use conditions.

Priority: Medium

EX.M.20—Potential pathogenicity of heterotrophic bacteria eluted from point-of-use GAC filters Initial finding indicate that some opportunistic pathogens can grow on GAC filters. Research is needed to determine the potential for heterotrophic bacteria from GAC POU filters to cause illness in compromised animal models. Data would be used in developing human risk estimates.

Priority: Medium

EX.M.21—Occurrence of newly emerging pathogens Conduct a national survey to determine the occurrence of newly emerging and potential pathogens in potable water distribution systems. Pathogens and opportunistic pathogens of special interest are *Aeromonas*, *Pseudomonas*, and *Helicobacter*.

Priority: High

EX.M.22—Exposure as a function of population distribution Conduct a series of studies to identify exposure as a function of age, other

individual susceptibility factors such as protective immunity, behavioral patterns and environmental factors that affect water consumption.

Priority: High

3. What are the factors affecting microbial contamination of groundwater?

State of the Science

Groundwater is the source of drinking water for about 1/3 of the U.S. population. There are approximately 180,000 community and non-community public water systems utilizing groundwater . About half of the groundwater community systems disinfect, but a majority of the non-community systems do not. The drinking water quality of systems that do not treat for pathogens is dependent on having source waters at the wellhead that do not contain pathogens in sufficient numbers to cause health problems, and on monitoring for indicator organisms to warn of any microbial contamination.

The actual occurrence of pathogens in drinking water originating from groundwater is uncertain. Preliminary results of the groundwater survey being carried out by AWWARF indicate that greater than 20% of the well waters sampled contain viruses. These results are surprisingly similar to the percentage of systems in which viruses were detected in an earlier survey of vulnerable groundwater systems by EPA and AWWARF. Many state laboratories report that greater than 40% of the private well waters tested contain coliform bacteria. Records of waterborne disease outbreaks show that the primary cause of waterborne disease outbreaks have included groundwater that had not been disinfected. This is particularly significant since it is estimated that these records may underestimate the actual number of outbreaks by an order of magnitude.

Although the disease agent in most groundwater-related outbreaks was unknown, the majority of outbreaks were believed to be caused by viruses. The primary viruses known to be agents of waterborne disease are enteric viruses such as polio, Coxsackie, echo, hepatitis A and E, rotavirus, Norwalk, and Norwalk-like. The bacteria primarily responsible for waterborne outbreaks are *Salmonella*, *Shigella*, enteropathogenic *Escherichia coli*, and *Vibrio cholera*. The protozoa, *Giardia* and *Cryptosporidium*, are also potential groundwater contaminants although their presence would likely be due to poor well location or construction.

The sources of pathogens in groundwater include surface waters, septic tanks, cesspools, leaking sewer lines, municipal land treatment systems, animal feeding operations, sludge disposal areas and municipal landfills. Since pathogens must be transported by percolating water from these sources through the unsaturated zones and then by regional or gradient flow through the saturated zones to a well or spring, most control measures are based on placing sources far enough away from springs or wells that any pathogens will either be physically removed, die or be inactivated before they reach a place of withdrawal. The extent of removal and die off is dependent on numerous factors (not all of which have been identified) pertaining to the characteristics of the pathogens, the nature of the soils and aquifer materials and the distance and time required for the pathogens to be transported from a source to a well. As a general rule, viruses are presumed be transported further in the subsurface than either bacteria or protozoa due to their much smaller size.

Methods in use or proposed for determining whether a well or spring is in danger from a potential source of contamination range from using arbitrary setback distances to some type of vulnerability assessment method to predict the relative vulnerability of a water well or spring to contamination by pathogens. A variety of methods have been proposed for doing groundwater vulnerability assessments including a) methods that give numerical ratings to the physical factors (such as soil types, geology, and depth to groundwater) that affect groundwater vulnerability to contamination by pathogens, and b) mathematical models. Additionally, decision trees that combine several methods in an ordered manner may be the most effective way to make this determination.

Arbitrary setback distances are very difficult to defend scientifically but are the easiest to implement from a regulatory standpoint. The use of vulnerability indexes or avoidance criteria to assess the vulnerability of groundwater to pathogens has great potential for screening purposes, but the use of vulnerability assessment methods in general has been questioned by the scientific community if such methods are going to be used for making site-specific decisions. The use of such methods will probably require extensive evaluation and testing before they are accepted as regulatory tools. Efforts are being initiated by EPA to develop avoidance criteria for the Groundwater Disinfection Rule (GWDR).

The use of predictive computer models for making regulatory decisions regarding disinfection of groundwater has had difficulty in gaining regulatory acceptance although significant advances have been made in the development of mathematical models to predict the transport and survival of pathogens in the subsurface. A key element of these models is the inactivation rate chosen for the pathogens (viruses). Survival times for many of the primary pathogens of concern in the subsurface and in groundwater are unknown. Existing information about a few pathogens suggests that the die off of bacterial pathogens is much faster than viruses, and that survival times longer than one year for viruses would be unlikely. However, data on inactivation rates for pathogens under the various subsurface conditions are limited and contradictory. A critical need is to better determine these inactivation rates in the unsaturated and saturated soils and aquifers. Limited additional work in this area has recently been funded by AWWARF, but a more extensive effort is needed.

The major hindrance in obtaining final acceptance for any vulnerability assessment tool is the extensive field testing needed to confirm the tool's protective capability for making site-specific decisions. Extensive field validation is extremely difficult, time-consuming and expensive and the number of field tests that can be performed is limited by a lack of available resources.

The majority of groundwater-based public water supplies (at least 140,000) are very small, non-community systems with extremely limited resources. For these systems, virus fate and transport models will not be appropriate for predicting vulnerability. Vulnerability assessments might best be made through a sanitary survey and wellhead protection approaches. Therefore, general hydrogeological and land use criteria must be considered and tested for their utility in predicting vulnerability. A high priority exists for developing practical cost-effective approaches. The approach eventually chosen is likely to be a decision tree that combines elements of several methods in a structured prioritized manner.

On July 10–11, 1996, the EPA's Office of Groundwater and Drinking Water conducted a Workshop on Predicting Microbial Contamination of Groundwater Systems. Workshop participants identified the following indicators as potentially useful for predicting fecal contamination of groundwater: *E. Coli,* Enterococci, *Clostridium perfringens,* and Coliphages (somatic and male-specific). The following research on indicators of fecal contamination of groundwater was identified at the workshop: Determining how the survival and occurrence of *Clostridium perfringens* correlates with the occurrence of pathogens in contaminated groundwaters; delineating the range of hosts for somatic coliphages to determine whether they have enough specificity as an indicator of fecal contamination; and measuring the occurrence of male-specific coliphages in small populations to determine whether they have enough sensitivity to use for small systems (< 100 people). Where appropriate to do so, the projects described below incorporate the recommendations of the workshop.

Research Topics and Priorities

a. Survival and transport of pathogens in the subsurface

Determination of the survival times of pathogens, especially viruses, in both the saturated and unsaturated subsurface is the major research need for any method for determining whether groundwater does or does not have to be disinfected. Information on virus inactivation times in the subsurface for many major viral pathogens is nearly nonexistent. Survival data must be in a form that can be incorporated into decision-support systems for determining whether groundwater should not be disinfected. Information on the factors determining the extent of transport of pathogens in different hydrogeologic settings, especially where preferential flow paths exist and in the unsaturated zone, is also a major need if transport models are going to be used.

Project EX.M.23 is considered high priority because it addresses an area of high risk: the concentration and occurrence of a major group of contaminants – viruses. It also is an area in which currently there is a high degree of uncertainty. For similar reasons, project EX.M.24 is also a high priority. The assessment of viral behavior in the subsurface requires knowledge of both their fate and transport, which are intimately linked. Furthermore, once viral die-off rates are determined, the data can be applied to many models for estimating setback distances. Project EX.M.26 is considered high priority because this approach has the most promise for developing practical criteria that can be implemented, even if such criteria may apply only to a limited number of hydrogeological situations. Currently, there is a high degree of uncertainty in assessing the vulnerability of groundwater to contaminants. Projects EX.M.29 and EX.M.33 are considered high priority because participants from the Workshop on Predicting Microbial Contamination of Groundwater Systems considered this research as critical for supporting the Groundwater Disinfection Rule. The other projects are considered medium priority because the feasibility of success in generating criteria that can be practically implemented is very uncertain, and research in this area is already underway.

EX.M.23—Virus survival in the subsurface
Inactivation times for the viral pathogens of regulatory concern are not known for most soil types and conditions. This work would determine inactivation times of viral pathogens in several groundwaters and soils under both unsaturated and saturated conditions. The project will focus on the role of subsurface ecology, including both geochemical and biological factors such as predation, as a determinant of subsurface virus survival. Initial work will use bacteriophages as surrogates for human enteric viruses. Controlled laboratory experiments with human enteric viruses will be used to confirm that the mechanisms that control bacteriophage survival also control enteric virus survival.

Priority: High

EX.M.24—Virus transport in the subsurface
Methods are needed for predicting the transport time between wells and springs and sources of pathogens. This research would evaluate the factors which govern the transport of viral pathogens in both the unsaturated and saturated zones of the subsurface. Subsequently, methods would be developed for incorporating this information into either predictive models or decision-support systems for determining whether groundwater should not be disinfected.

Priority: High

b. Methods for protecting wells and springs from pathogens

Scientifically defensible methods for determining setbacks between sources and wells or springs are needed to aid decision makers in determining whether groundwater achieves "natural disinfection" or if chemical disinfection is required. Additional evaluation/testing of proposed mathematical models such as CANVAS is needed to address scientific or regulatory concerns. Methods to assess the vulnerability of groundwater to pathogens by the development of vulnerability indexes should be critically evaluated and tested. Both vulnerability rating systems/models may require additional field tests.

EX.M.25—Viral transport and fate models Critical evaluation of the use of mathematical viral fate and transport models for making decisions on whether drinking water from groundwater sources should or should not be disinfected. Emphasis will be placed on the feasibility and reliability of existing models. Available information and data will be used when possible.

Priority: Medium

EX.M.26—Vulnerability of groundwater to pathogens Critical evaluation, emphasizing feasibility and reliability, of methods being developed to assess the vulnerability of groundwater to pathogens by the development of vulnerability assessment systems. Available information and data will be used when possible.

Priority: High

EX.M.27—Delineation of natural protection zones Examine and test an alternative method to conventional contaminant transport models and vulnerability assessment methods for delineating a protective zone around a well or spring. The method will integrate the analytical element method for delineation of time-of-travel capture zones with information on survival and transport of pathogens. The capture zone concept will be tested with data developed under the New England virus study.

Priority: Medium

EX.M.28—Groundwater vulnerability and sensitivity assessment methods This research examines the range of physical, biological, institutional and operational factors that could be used to determine these vulnerabilities, including (but not limited to) hydrogeological factors, land uses and groundwater/wellhead protection program determinations. The ultimate product is to be a pragmatic, field-tested assessment methodology that, given generally available information, can estimate vulnerability to microbial contamination in small-to-medium groundwater systems. It may result in separate approaches for larger and smaller systems, based on economic feasibility. Initial work has been to develop appropriate criteria. Subsequent work will be to field validate the criteria against carefully described vulnerable and non-vulnerable systems.

Priority: High

EX.M.29—Occurrence of *Clostridium perfringens* in the subsurface *C. perfringens* will be collected from over 100 groundwater sites as part of a larger virus survey.

Priority: High

EX.M.30a—National aquifer and well map A random selection of drinking water systems using groundwater was mapped onto USGS aquifer maps on a state-by-state basis. Community, non-community and transient systems were mapped separately based on their zip codes. (Completed 1995)

Priority: Medium

EX.M.30b—Sensitivity mapping A random selection of drinking water systems using groundwater was mapped onto USGS aquifer maps on a state-by-state basis. Community, non-community and transient systems were mapped separately based on their zip codes. (Completed 1995)

Priority: Medium

EX.M.31—Correlation of water age and microbial viability This work would investigate the relationship between water age and the presence of human enteric viruses.

Priority: High

EX.M.32—New York City Watershed Protection Septic Siting Study. The septic system types to be investigated include continuous use functioning systems, weekend use systems, seasonal use systems and newly installed systems, both residential and commercial. Study sites will be representative of varying hydrological, chemical, physical and design parameters. A minimum of three sites will be selected for the Phase 1 investigation, which includes site selection, installation of five monitoring wells at each site and baseline data collection. Phase II will include spiking studies using phage, bacterial or other tracers.

Priority: High

EX.M.33—Phase 2 Virus Sampling and Phage Research for the Santa Ana River Water Quality and Health Study (includes Virus Testing of Groundwater for GWDR and Santa Ana River Water Quality and Health Study) Samples of groundwater and river water will be taken monthly for virus cell culture and PCR

analysis. Bacteriophage and coliform samples will also be taken. Phage will be evaluated as indicator organisms for enteric viruses. All production and monitoring wells sampled in the first project year were negative for enteric viruses.

Priority: High

Risk Assessment Research

1. How can the risks posed by pathogens in drinking water be characterized?

State of the Science

The Agency has not established a formal methodology to assess the risk for microbial contaminants as it has for chemicals. In 1991, a joint EPA/AWWARF conference evaluating drinking water and health in the year 2000 proposed the application of the National Academy of Science risk paradigm for microbial contaminants. However, as discussed previously microbial risk assessment is relatively new and the issues that need to be addressed are more complex than those currently used for defining chemical risks. The 1996 Safe Drinking Water Act Amendments (SDWAA) contains provisions that focus on the need to ensure that adequate health protection is conferred to the most sensitive subpopulations, especially children, in all future drinking water regulations, taking into consideration, cost and benefit of disease prevention or control. Pathogen interactions may pose overwhelming health risks to some groups of individuals such as infants, young children, the malnourished, the elderly or immuno-compromised individuals. Under the FY 97 SDWAA initiative additional resources have been identified for the expansion of research efforts relating to pathogen risk assessment. The focus of risk assessment studies has been on infectivity and determinations of the smallest pathogenic dose (numbers of infectious microorganisms) able to produce an infection in healthy individuals. Studies are needed in selected subpopulations to determine host susceptibilities (lack of or reduced capacity of host resistance and defense mechanisms) and relationship to pathogen entry and establishment of infection or other forms of parasitism (e.g., transient carrier state, colonization, pathogenic interaction). Studies are needed to relate pathogen virulence and host resistance so that risk assessments can be made about carrier states, colonization, infection, disease course and outcome (e.g., clinically asymptomatic persons, disease state, full recovery, chronic debilitate recovery, mortality). Increased efforts will include research to assess and quantify effects of immunity of exposed individual and population; evaluation and quantification of the disease process including secondary spread, magnitude and severity of effects, in addition to infection and the effects of multiple exposures and routes of exposure.

Previously, a risk assessment model was developed for *Giardia* contamination in drinking water by Rose, et al., 1991, in which dose-response data from human volunteer studies were modeled using a Poisson distribution. Actual dose-response curves were developed using a low-dose extrapolation model and a maximum likelihood estimate. Based on various input variables, such as number of organisms and mean response rate, the risk of infection and the risks of disease were estimated, including risk from exposure to a single organism. Log order reductions of cysts from source water needed to achieve an acceptable risk level (e.g., less than one infection per 10,000 people per year) can be calculated using this approach. However, as noted before, there are many variables that need to be taken into account for pathogen risk assessment that are not currently being addressed in this approach, such as age, severity of response, or host immunity. Although, similar models typically have been used in the quantitation of chemical carcinogens, risks associated with pathogenic exposures may be biologically more compatible with other approaches for evaluating dose-response relationships for pathogens. Therefore, model validation research will be expanded to include a comprehensive evaluation of several statistical models. Of particular concern are the risks posed to children and other potentially susceptible populations. Research efforts have been expanded to address issues relating to quantitatively and qualitatively measuring and characterizing risks to these populations. These approaches will allow for the development of risk estimates following acute or chronic exposures and address issues such as sensitivity, multiple endpoints and severity. The evaluation of these additional approaches for pathogenic assessment are needed, therefore, to augment current dose-response models for quantifying risks.

Research Topics and Priorities

a. Modification of risk assessment paradigm for characterizing microbial risks

RA.M.1—Development of a comprehensive microbiology risk assessment model for water (Ongoing) This project is a high priority because EPA needs a suitable and comprehensive microbiological risk assessment model for water (drinking, recreational, shellfish, wastewater, reuse) in order to establish or modify drinking water and water quality standards for pathogens or their indicators. This project will identify the proper elements and processes needed to perform microbial risk assessment. Existing paradigms such as the National Academy of Sciences chemical risk assessment approach and the ecological risk assessment approach will be used as the starting point and these will be modified and amended for microbial risk assessment. The selected approach will be validated with case studies.

Priority: High

b. Accuracy of dose-response models in predicting waterborne disease

The goal of this effort will be to develop both qualitative and quantitative microbiological exposure response models, validate/ confirm input assumptions and characterize the uncertainties surrounding those assumptions. Unlike previous studies, dose-response data will be analyzed and evaluated using various statistical approaches such as using a logistic regression model similar to that developed to characterize the risks from non-cancer effects. These projects are high priority because models will address issues relating to the magnitude of response and accounts for severity of effects and duration of exposures. These studies will enhance current efforts and allow for better comparisons of effects other than infection, such as respiratory disease, diabetes and immune deficiency. Of particular concern are the risks posed to children and other potentially susceptible populations. Research efforts have been expanded to address issues relating to quantitatively and qualitatively measuring and characterizing risks to these populations.

RA.M.2—Evaluation/application of various dose-response relationship models for quantitating pathogenic risks

2a. Evaluation of various dose-response relationship models

Conduct extensive literature search to evaluate all available data relating to adverse effects and dose-response for *Giardia* and *Cryptosporidium* and other pathogens of concern. Research will then be conducted in two phases. Initial efforts focus on the development and evaluation of statistical approaches used to characterize the dose-response relationship for humans exposed to waterborne pathogens. Phase 2 will include the analysis of dose-response data from existing studies comparing the various statistical approaches including logistic regression. Model application and severity of effects categorization will be tested using data for bacteria, protozoans and viruses. As appropriate, quantitative estimates will be developed for establishing risk levels for specific pathogens. This research will provide relevant information on the virulence of risks associated with a specific pathogen and individuals or populations at risk and support development of regulatory guidelines/ criteria.

Priority: High

2b. Virulence factors and host susceptibility: impact of waterborne pathogens on human subpopulations

Under the FY 97 SDWAA initiative, additional resources have been identified for the expansion of research efforts relating to pathogen risk assessment. Increased efforts will include research to assess and quantify effects of immunity of the exposed individual and population; evaluation and quantification of the disease process including secondary spread, magnitude and severity of effects in addition to infection, and the effects of multiple exposures and routes of exposures.

c. Characterization of risks posed by exposure to multiple or complex mixtures of pathogens

Similar to chemical exposures in drinking water, microbial exposures occur in conjunction with chemical or other pathogenic exposures by multiple routes. While much has been done in the development of models for estimating risks for chemical mixtures, very little information is available regarding the risks associated with mixed or multiple pathogenic exposures. The overall impact of microbial-environmental interactions, microbial-chemical interactions, and microbial-microbial interactions to changes in emergent populations on water quality has not been thoroughly evaluated. Source waters containing acids, organochemicals, or heavy metals can damage or kill biological waste treatment microbial colonies and again may enhance growth of disinfectant resistant pathogens. Such microorganisms may be able to metabolize water disinfectants to reduce their effectiveness. Microorganisms also can metabolize other chemical contaminants to potentially toxic compounds, as well as produce toxic compounds effective in pathogenic interactions (enterotoxins, lysins, and hemolysins to enhance invasiveness and tissue destruction). Assessment risks of waterborne toxins from algal blooms or bacterial overgrowth can be predicted based on knowledge of the organisms present in ground or surface waters and in the distribution system, survival and growth enhancing mechanisms of nutrient abundance, and waste runoff. The potential for co-infection between enteric viruses and bacteria to enhance adverse health effects will be explored. For most pathogenic agents, exposure is expected to be extremely low or zero within the system. The greatest potential for mixed or multiple contaminant exposure occurs with bacteria due to their capability for regrowth and biofilm development within the distribution system. Interactions between microorganisms during mixed infections have yet to be investigated, (e.g., interactions, such as the reported ability of Coxsackie virus to increase host susceptibility to Shigella). Chemical, environmental, and microbial interactions could contribute to low-level human and animal population exposures, e.g., liver tumor, promoter toxins (microcystin-LR). Microcystin-LR produced by cyanobacteria during water blooms may contribute to liver tumor promotion in the exposed populations. Endemic disease of unknown etiology could be the result of human exposure to low levels of waterborne microbial toxins. Research is needed to address the impacts of multiple exposures of pathogens or mixed exposures (i.e., chemical and microbial exposure) on immune response and effects levels. Development of a preliminary assessment of the existing available information and framing of the scope and magnitude of this issue is also needed.

RA.M.3—Evaluation and application of issues and methods to assess risk associated

with exposures to multiple pathogens, routes, disease course and outcomes and duration

3a Feasibility assessment on interactions Conduct a preliminary assessment and frame issues related to mixed exposures of pathogens in drinking water. This preliminary assessment would include an evaluation of existing data relating to mixtures and potential interactions, and identify issues needed to be address and research needs. Future research projects will be developed and prioritized based on the research issues and needs identified in the preliminary assessment of mixtures.

Priority: Medium

3b Research would also be conducted to test the application of dose-response models/approaches for identifying and estimating risks for multiple pathogens. The emphasis of this effort will be to address bacterial agents where the greatest potential for mixed exposures may occur. A dose-response plane would be developed using individual dose-response curves from various pathogens or chemicals and pathogens. Validation studies would be conducted using an appropriate animal for pathogenic response and multiple exposures scenarios. Study design would include sequential chemical and pathogenic exposures as well as continuous exposures at subthreshold doses. This research is low priority because of the lack of general methods for assessing mixtures and the need to develop single pathogen health and exposure data.

Priority: Low

Risk Management Research

Disinfectants are used by virtually all surface water systems in the U.S. and by an unknown percentage of systems that rely on groundwater. Chlorine has been the most widely used and most cost-effective disinfectant. Disinfection is most efficient when it is applied as part of the multiple barrier concept; that is, use of the best available water source, protection of that source from contamination, and use of water treatment to remove and inactivate pathogens. Recently there has been growing recognition that water quality can deteriorate dramatically during distribution. Therefore, another part of the barrier to infectious disease is a properly designed and operated distribution system. Each component of our research is designed to evaluate the effectiveness of one of more of these barriers and will collectively provide information on the combined effectiveness of these barriers.

While disinfection is an integral part of water treatment, filtration may be necessary to reduce pathogen levels and make disinfection more reliable by removing turbidity and other interfering constituents. For example, in the U. S. the waterborne disease outbreak rate for communities using surface sources without filtration is eightfold greater than communities with filtered water systems. Properly designed and operated water treatment systems that include filtration and disinfection can greatly reduce the risk of waterborne disease. There is a need, however, to find the proper balance between controlling risks from microbial pathogens and disinfection by-products.

This section deals primarily with the treatment and distribution system research needed to support regulation development for control of microbial pathogens. This research must be conducted as an integrated program with the research described for controlling disinfection by-products (see Chapter IV). Separate studies not discussed in this section but which are complementary to this research deal with development of cost/benefit methodology, which can be utilized to make effective risk management decisions.

1. How effective are various treatment processes in removing/inactivating pathogens?

State of the Science

The primary processes for removing pathogens from drinking water are water treatment filtration systems and disinfection. For filtration systems the specific sequence and type of unit processes to be used are dependent on source water quality. Optimized treatment trains will lead to a low probability of pathogens entering the distribution system. Breakdowns, such as in equipment or lapses in operational control, can lead to significant problems.

The disinfection process is the final treatment barrier for minimizing pathogen transmission. In some cases, disinfection may be the only treatment barrier (e.g., a disinfected groundwater supply). In either case, the disinfection process must also be optimized to aid in removing pathogens. Water plants must remove as much particulate material (e.g., clays, microbes, etc.) as possible in order to increase the effectiveness of disinfection.

EPA and others have been conducting research on pathogen removal and inactivation of microorganisms for many years, although the types of pathogens studied and associated removal processes evaluated have varied over this period. However, improvements in treatment technology, pathogen detection and an increased understanding of waterborne disease etiology have increased the need for research in this area. More sophisticated monitoring requirements have led to rethinking of which treatment processes should be used and how these processes should be operated. Most current research on pathogen removal has focused and will continue to focus on *Cryptosporidium* oocyst removal and inactivation because it is an excellent surrogate for treatment efficiency. However, new pathogens such as *Microsporidia* and *Cyclospora cayetanensis* are appear-

ing on the horizon and may pose even greater challenges in the future. Therefore, as we make progress in answering important questions regarding the treatment of *Cryptosporidium*, future efforts will move toward addressing the treatability of other waterborne pathogens as their existence and significance is recognized. The pathogens of greatest concern in groundwater sources (especially the enteric viruses) are different from those occurring in surface sources and information on treatment alternatives that are effective against viruses are needed to identify appropriate treatment where needed.

EPA and the American Water Works Association Research Foundation (AWWARF) are conducting the majority of the treatment research in the U.S.. EPA has conducted filtration studies with both conventional and alternative filtration processes for removal of pathogens. Information gathered from those studies has led to implementation of the Surface Water Treatment Rule and has provided guidance to many water utilities. AWWARF is currently funding research intended to develop design and operational criteria for the optimization of various treatment processes to remove protozoan cysts, specifically *Giardia* and *Cryptosporidium*. Parallel studies are being conducted to determine if a relationship exists between cyst removal and the removal of cyst-sized particles. AWWARF plans to conduct studies at utility-owned pilot- and full- sized facilities. Research is being conducted to assess particle-size analysis as a means of optimizing filtration and the impact of sequential disinfection on the survival of *Cryptosporidium* oocysts. This information will be used in workshops and guidance documents to assist drinking water utilities to more effectively operate drinking water treatment plants. Surveys of water utility performance and studies in detection methods have been funded by AWWARF and are currently ongoing. Montgomery Watson is conducting a disinfection study of approximately 20 utilities; the study should define disinfection conditions necessary for *Cryptosporidium* inactivation using multiple sequential disinfectants. The American Water Works Association (AWWA) through its Water Industry Technical Action Fund (WITAF), the Water Research Center in the UK, and many others are also studying pathogen removal/inactivation processes. AWWARF has recently initiated studies to begin evaluating the effectiveness of conventional and innovative treatment processes for removing and inactivating selected emerging waterborne pathogens.

EPA is conducting research on the use of slow sand filters for removing oocysts, and conducting comparative jar tests for evaluating removal rates of preserved versus unpreserved oocysts. Pilot conventional and direct filtration systems are being spiked with fresh oocysts to determine optimal removal conditions. The removal of particles by conventional and enhanced filtration is being studied. Total particle counts, particle counts in the oocyst size range and indigenous bacterial spores are being studied as possible surrogates for oocysts. There is evidence that oocysts may be damaged through treatment and therefore susceptible to disinfection. It has also been observed that 3-5 micron-sized oocysts may be able to fold or squeeze through 3-micron membranes under pressure. In addition, a series of studies is being conducted that evaluate the effectiveness of biological treatment plus final disinfection on the removal of oocysts, spores, and DBP precursors. Several small-system technologies such as diatomaceous earth and membrane package plants are being evaluated. EPA is also conducting studies on cyst viability and on treatment effectiveness under varying conditions, e.g., storm events with high turbidity and high pathogen loadings.

There are a number of questions to be answered with regard to the removal/inactivation of pathogens from drinking water. The Milwaukee experience reinforces the need to find answers to these questions which include a more complete understanding of the optimization of filtration for removing pathogens, the role of disinfection, and the types of technology that might be useful for small utilities.

Results from research to date indicate that there is much to be learned regarding the conditions that lead to optimal operation of drinking water treatment plants for the removal of oocysts and other pathogens. For example, it has become apparent that oocysts have physical properties that make them both difficult to remove and very resistant to disinfection. Research has shown that the organism is flexible and that it can penetrate porous media. In contrast, it is also sticky so that it adheres to unit process walls and piping making removal difficult to calculate. It has a surface charge that is different from particles normally found in water, so that standard coagulation procedures may not adequately remove oocysts during conventional treatment (coagulation, settling, filtration and disinfection). Results from EPA studies have shown that preserved oocysts which are normally used in treatment research and are most convenient for spiking studies do not behave in the same way as natural oocysts. Therefore, more studies on treatment effectiveness need to be conducted using natural oocysts. Because oocysts are pathogens and cannot be spiked into operational treatment plants, there is need for the development of surrogates which are nonpathogens but behave in the same manner as oocysts. Small systems present a special problem because the technologies used must be easy to operate and have low maintenance requirements. However, as has been discussed, removal of oocysts requires careful attention to operational detail. This was one of the major lessons learned from Milwaukee.

Bench-scale, pilot plant and field-scale studies will be required to address these research issues. Initially, technology evaluations will be conducted at bench and pilot scale. This will be followed by field studies (RM.M.5) of the most promising technologies which will evaluate their ability to control both pathogens and DBPs. In general, these field studies will be conducted at sites where these technologies are being utilized by certain utilities such that evaluations of the important operating parameters can be conducted and results can be com-

pared with full-scale operations. New techniques for monitoring treatment plant effluents and for process control will also be investigated. Improved electronic measuring techniques could allow for real-time measurement of treated water quality. All future projects will incorporate multiple pathogen removal, surrogate analysis and DBP reduction efforts as part of the research protocol.

Research Topics and Priorities

a. Optimization of conventional treatment processes to remove pathogens

All of the projects listed below except RM.M.28 are considered high priority and were selected for consideration because they address the major scientific unknowns: removal of oocysts via conventional treatment, development of surrogates for oocyst removal, and viability of oocysts through multiple treatment steps. Results of these studies will provide information necessary for setting feasible risk based treatment levels. They also provide the data to develop practical performance monitoring procedures using surrogates and to determine whether compliance is achieved for meeting level of treatment requirements. Projects 2, 3 and 4 expand on current promising research efforts by EPA. RM.M.28 is considered medium priority at this time until the existence and significance of specific emerging pathogens is better defined.

RM.M.1—Filtration studies for controlling pathogens (Ongoing) Bench-scale and pilot-scale studies have been conducted to evaluate pathogen removal mechanisms. Current studies are attempting to find surrogates for pathogens or surrogates for treatment evaluation. Particle counting, zeta potential, microbial counting and other techniques are used to determine removal of pathogens. Criteria for measuring damage to oocysts are also being developed.

Priority: High

RM.M.2—Filtration removal of protozoa and indicators Conduct pilot-scale studies to assess conventional water treatment and direct filtration for removal of protozoans and indicators.

Priority: High

RM.M.3—Optimize conventional treatment for removal of oocysts Conduct bench studies to evaluate and demonstrate that, if treatment (coagulation/ settling) is optimized for turbidity/spore/ particulate reduction, coincidental removal of oocysts occurs. Determine if there are some coagulants that are selective for removing oocysts.

Priority: High

RM.M.4—Filtration damage viability studies Conduct bench and pilot studies to assess the capacity of oocysts to remain viable through various types of treatment. Conduct disinfection studies to determine if oocysts that are damaged by passing through treatment are more easily inactivated than undamaged oocysts.

Priority: High

RM.M.5—Evaluate disinfection and optimization in field-scale treatment plants Conduct field-scale studies of pathogen and DBP control at existing water treatment plants. Use oocysts, spores, particle and turbidity analysis as part of the evaluation process. (This is a component of Project EX.M.11)

Priority: High

RM.M.28—Evaluation of the effectiveness of conventional treatment processes on removing and inactivating emerging pathogens As the existence and significance of new, emerging pathogens are identified by NERL and NHEERL researchers, NRMRL will initiate research on the effectiveness of conventional treatment to remove and inactivate these pathogens.

Priority: Medium

b. Effectiveness of different filtration processes in removing pathogens

The research described in these projects represent variations of conventional treatment. Biological treatment is rated "high" because it has the potential for controlling DBPs and pathogens simultaneously. Task RM.M.7 is rated "medium" because the technologies are expected to have similar results for *Cryptosporidium* as for *Giardia*, on which a number of studies have already been conducted. RM.M.29 is considered medium priority at this time until the existence and significance of specific emerging pathogens is better defined.

RM.M.6—Biological treatment for control of oocysts

Conduct studies on the effectiveness of biological treatment for control of oocysts while simultaneously controlling disinfection by-products.

Priority: High

RM.M.7—Filtration techniques other than conventional treatment Examine other filtration techniques such as diatomaceous earth filtration and slow sand filtration to determine how *Cryptosporidium* removals compare with those of *Giardia* (already determined from previous studies).

Priority: Medium

RM.M.29—Evaluation of different filtration processes on removing emerging pathogens As the existence and significance of new, emerging pathogens are identified by NERL and NHEERL researchers, NRMRL will initiate research on the effectiveness of innovative filtration processes to remove these pathogens.

Priority: Medium

(See also project RM.M.14 below)

c. Effectiveness of disinfection processes in inactivating pathogens

Research is needed on the disinfection effectiveness of various disinfectants for viruses and protozoa. For example, some research suggests that reductions in viable *Cryptosporidium* oocysts are achieved after sequential disinfection using different disinfectants (i.e. chlorine/chloramine, ozone/chloramine). EPA uses disinfection data on hepatitis A virus (HAV) for estimating conditions necessary to inactivate viruses because of its relatively high resistance to disinfection. Norwalk virus, which has also caused waterborne disease outbreaks, may be more resistant to disinfection than HAV and therefore may be more suitable than HAV for defining adequacy of disinfection.

Establishing whether Norwalk virus is more resistant to disinfection than HAV is particularly important for groundwater systems. However, it is also relevant for surface water systems which use physical means for removal of protozoa and must provide a minimum disinfectant dose to assure adequate virus removal/ inactivation. Because of its potential to reduce health risk, project RM.M.8 was assigned a high priority. A Norwalk virus project on UV inactivation was also assigned a high priority because of its potential usefulness for disinfecting groundwater. (Norwalk virus was not included in the AWWARF UV virus inactivation study.) In addition, systems using groundwaters will need information on other treatment alternatives that are effective against viruses, as this is an important consideration of deciding on groundwater disinfection methods. Therefore, RM.M.30 is a high priority project. RM.M.31 is considered medium priority at this time until the existence and significance of specific emerging pathogens is better defined.

Project RM.M.10 on sequential disinfection treatment, which will expand on AWWARF's and Montgomery Watson's research, was assigned a high priority because it is expected to develop criteria for more efficient and cost-effective disinfection strategies. This additional research is needed to develop a generic model concept by which utilities with different operating conditions could estimate inactivation efficiencies.

RM.M.8—Control of Norwalk virus by chlorine and ozone

Compare kinetics of Norwalk virus inactivation to that of poliovirus 1 and MS-2 coliphage, and determine the extent of removal by pretreatment and filtration and the extent of inactivation with chlorine or ozone.

Priority: High

RM.M.9—UV disinfection efficiencies for Norwalk viruses

Evaluate efficiency of ultraviolet light for inactivation of Norwalk virus, and determine UV intensity and exposure time to achieve 1,2,3 and 4 $\log_{10}$ inactivation.

Priority: High

RM.M.10—Inactivation of *Giardia* and *Cryptosporidium* by sequential disinfectants Define the treatment conditions (concentration, contact time, temperature) needed to inactivate *Giardia* and *Cryptosporidium* with different sequential disinfectants.

Priority: High

RM.M.30—Evaluation of alternative inactivation processes for controlling viruses Evaluate other innovative advanced oxidation processes and removal systems such as ultrafiltration membranes, mixed oxidant generators, TiO_2 and UV and combinations of these processes for removing and inactivating viruses. This project is closely related to RM.D.7.

Priority: High

RM.M.31—Evaluation of different disinfection processes in inactivating emerging pathogens As the existence and significance of new, emerging pathogens are identified by NERL and NHEERL researchers, NRMRL will initiate research on the effectiveness of innovative disinfection processes to inactivate these pathogens.

Priority: Medium

Other projects that also address this topic:

RM.M.3—Optimize conventional treatment for removal of oocysts

RM.M.5—Evaluate disinfection and optimization in full-scale treatment plants

RM.D.2—Effects of ozone and biofiltration for control of precursors, pathogens and for pesticide removal

RM.D.7—Membranes/advanced oxidation and other technology combinations

d. Appropriateness and costs of technologies for small systems

Any changes in regulations requiring small systems to upgrade treatment for *Giardia* or *Cryptosporidium* would be a major challenge because of their limited financial resources for acquiring and operating drinking water treatment plants. In addition, most utilities have difficulty in finding and retaining qualified operators. In setting any new regulatory criteria for small systems, EPA needs information on the effectiveness, costs and feasibility of appropriate treatment technologies. Therefore, research projects to develop and demonstrate small-scale, cost-effective treatment technologies which are easily installed and automated, and which do not require highly skilled operators are a high priority. Developing cost curves will be an important element of all small-system technology projects.

RM.M.11—*Cryptosporidium* removal using bag filters Identify vessel, bag, and basket design characteristics for optimal removal and treatment train requirements relative to variable raw water characteristics. Operational factors relative to cost and performance should also be considered.

Priority: High

RM.M.12—Cost-effectiveness of prefiltration for ultrafiltration unit Determine range of raw water characteristics relative to various pre-treatment technologies used to increase membrane life, reduce maintenance costs, and enhance DBP precursor removal. This is cross-referenced with RM.M.17, RM.M.18, and RM.M.20.

Priority: High

RM.M.13—Development/testing of innovative technologies for small systems Conduct studies on new synthetic resins, pulsed UV, electron beam irradiation, high-pressure distillation, non-porous hollow fiber membranes, and cartridge filtration. In addition, conduct verification testing of package drinking water systems for use by small communities. This work should be coordinated with RM.M.4, RM.M.10, RM.M.30 and RM.D.7.

Priority: High

2. How can the quality of treated water be maintained in distribution systems?

State of the Science

While much waterborne disease is associated with contaminated water sources and inadequate water treatment, protection of water quality during distribution to the customer is often neglected. Continuous, adequate water pressure and residual level of disinfectant are important, especially in areas lacking adequate sewerage and sewage disposal facilities. Sewage and contaminated surface or groundwater can enter the water system through cross-connections and broken or leaky water pipes in older and poorly maintained water distribution systems. In the U.S., 24% of the waterborne outbreaks reported in community water systems over the past decade were caused by contamination entering the water distribution system, i.e., not originating from poorly treated water. To lower the risks of waterborne disease, contamination of water distribution systems must also be prevented.

Maintenance of a disinfectant residual is required to provide an additional barrier of protection from pathogens that might penetrate the water distribution system; however, the effectiveness of this residual to protect against significant contamination through a cross-connection or infiltration is uncertain. The real value of maintaining a disinfectant residual in the distribution system is to help identify the occurrence of such contamination by monitoring for the loss of the residual. Although the behavior of some constituents in the distribution system, namely chlorine, has been well studied, the fate of others is less known. These include alternative disinfectants (such as chloramines), biologically assimilable organic carbon, particulate material (including microorganisms), and genotoxicity. Better characterization of water quality problems is needed particularly at dead-end branches where stagnant flow conditions prevail.

The survival and growth of bacteria, such as *Legionella, Mycobacterium*, and *Aeromonas*, under limited nutrient conditions of water distribution systems, is also of concern because of potential risks that may be associated with inhalation, ingestion, or dermal exposure. The maintenance of a disinfectant residual is not always effective in preventing the survival and growth of bacteria within a distribution system, and defining criteria for biologically stable drinking water is important to prevent potential risks of infection from these or other microorganisms. Research has shown that *Legionella* proliferation can be controlled in potable water by interfering with the *Legionella*-protozoan receptor site interaction.

Distribution systems represent the final link in the chain between raw source water, treatment facilities and the consumer. However they are generally designed and operated to satisfy hydraulic reliability objectives—providing adequate water quantity and pressure for fire flow, and domestic, commercial and industrial demands—rather than to maintain water quality. This frequently results in large service mains, dead-end branches, and large storage facilities which keep water in the system for long periods of time, leading to degradation of water quality.

Individual distribution systems contain hundreds and even thousands of miles of pipe. As water flows through this pipe and sits in storage reservoirs, reactions can take place between constituents within the water itself and with materials along the wall of the pipe and reservoir. The distribution system is thus a giant chemical

reactor, with residence times far in excess of those seen within a treatment plant.

The complex, looped nature of the piping network, in some systems, the presence of multiple sources of water feeding the system, the fill-and-draw operation of storage facilities and variable water usage rates at different locations and times of the day create very complex flow patterns. These patterns often defy any intuitive sense of where water is traveling at any given point in time. Such flow patterns, combined with time spent in storage, contribute to residence times that can exceed several days. The result, as verified by field surveys, is that water which left a treatment plant with a very uniform level of quality, can exhibit a highly variable pattern of water age and quality in both time and space throughout a distribution system. Some of the negative impacts of time spent by water in a distribution system include loss of disinfectant residual, growth of disinfection by-products, growth of biofilm colonies along pipe walls, and the protection and subsequent release of nuisance and pathogenic organisms from the biofilm over time.

External contamination of water flowing in the distribution system is an ever-present threat to public health and has been shown to be the most frequent cause of waterborne disease outbreaks. There is growing evidence that endemic and epidemic waterborne disease is associated with breaks in the integrity of distribution lines, cross-connections and other breaches of distribution system integrity. Research is needed to improve the design, construction, rehabilitation, operation, and maintenance of distribution system integrity. As pipe ages and corrodes it exerts a higher chlorine demand and provides more environmental niches for biofilm protection and proliferation. Many water distribution systems in this country are approaching 100 years old. An estimated 26% of distribution system pipe is unlined cast iron and steel and is in poor condition. At current replacement rates for distribution system components, a utility will replace a pipe every 200 years.

The volume available in storage facilities is often several times that of the pipes in the distribution system. The degree to which water is well mixed within these facilities is largely unknown, as is the possible impacts of discharging extremely old water from unmixed zones under conditions of high demand. Guidelines on how to design and operate storage facilities to promote better mixing are needed.

Most medium- and large-scale utilities employ sophisticated data acquisition systems for monitoring and controlling the hydraulic performance of their distribution systems. The methods and benefits of extending these systems to include water quality parameters should be studied. There is currently no consensus in the water industry on the relative effectiveness of pipe cleaning versus pipe repair or replacement for enhancing water quality. The same can be said for identifying effective institutional programs for implementing cross-connection and backflow prevention programs.

For the past decade or more, extensive field studies have been conducted characterizing the chemical changes occurring in drinking water in distribution systems and identifying biofilm growth along pipe walls. EPA has developed a sophisticated computer model (EPANET) that tracks the fate of chemical species in complex pipe networks and is currently used by utilities and engineers throughout the world. EPA has also developed methods for determining organic carbon available to support biofilm growth and has developed guidebooks for controlling such growth in distribution systems.

Microorganisms are known to colonize the walls of pipe in the form of thin biofilms. The negative impacts of such biogrowth, particularly with regard to harboring and breeding pathogens, requires more study. Research is also needed to determine the proper combination of nutrient reduction and disinfectant level to control biofilm growth under site-specific conditions.

The AWWA Research Foundation has supported studies examining the kinetics of chlorine consumption in distribution systems and the factors limiting microbial growth. The National Water Research Institute is funding research to understand the microbial interactions within biofilms. French researchers at N.A.N.C.I.E. have been operating a full-scale distribution system simulator for several years. They have quantified the effects of pipe material, biological seed concentration and disinfectant choice on biofilm formation. Researchers at Lyonnaise des Eau have studied the factors contributing to chlorine demand from the pipe wall and have developed a chlorine microsensor that can be placed at the pipe wall. At least one water authority in the UK is experimenting with on-line sensing of water quality conditions within distribution systems and is developing a biofilm monitor.

Research studies indicate the need for more accurate kinetic models that can simulate the loss of chlorine, the formation of disinfection by-products and the growth of microorganisms in distribution systems. Research is also needed to identify the factors that affect the growth of biofilms and the survival of opportunistic pathogens in distribution systems. There is also strong evidence of the interactions between treatment and regrowth of bacteria in the distribution system. These studies indicate the need to conduct research on the potential for modifying treatment to control the formation of biofilm and the survival of pathogens.

Research Topics and Priorities

Priorities were assigned on the following basis: Due to the growing evidence that endemic and epidemic waterborne disease is associated with breaks in the integrity of distribution lines, cross-connections and other breaches of the distribution system integrity, all projects

addressing the cause of microbial intrusion into the distribution system and corrective actions are rated high priority. Until it has been established that heterotrophic bacteria pose a health risk and that present disinfection practices may be inadequate to prevent an unacceptable risk, projects proposed which are related to microbial quality are assigned a medium priority. The only other distribution system projects in this section of the plan which were considered a high priority are those which will provide information for disinfection by-product risk assessment modeling, i.e. the kinetic models for chlorine decay, DBP formation and the enhancement of the EPANET model.

a. Use of coliforms (or other surrogates) to indicate adequate control of primary and opportunistic pathogens in biofilms and pipe sediments

Coliforms are used to determine the sanitary quality of drinking water. If opportunistic pathogens are found to pose significant risks, additional research in this area will be needed to assess the use of coliforms as surrogates.

RM.M.14—Bacteria interference with detection of coliforms and *E. coli* The presence of high densities of bacteria is known to interfere with assays for total coliforms, the current basis for regulating the microbial quality of drinking water. Research is needed on issues such as interference with the presence-absence approach to coliform monitoring.
Priority: Medium

b. Water quality factors affecting biofilm growth and the effectiveness of disinfectant residuals in controlling growth

RM.M.15—*Kinetic Models for chlorine decay in distribution systems Using laboratory and field studies, alternative kinetic models for chlorine decay in distribution systems are being evaluated. Reactions of chlorine at the pipe wall can be very important in some systems and can be correlated to hydraulic roughness coefficients. This work is being performed in association with AWWARF, Montgomery Watson, and Lyonnaise de Eau.

Priority: Completed

RM.M.16—Enhancement to the EPANET distribution system water quality model (Ongoing) A new version of EPANET, a program that models water quality fate and transport in distribution systems, is being developed. It incorporates new kinetic models for chlorine decay and THM formation, variable geometry storage tanks with incomplete mixing, and more flexible operational rules for specifying system operation.

Priority: High

RM.M.17—Preliminary studies of biofilm formation rates in pilot-scale distribution systems (Ongoing) Study of the factors affecting the rate of biofilm growth on pipe walls using a pilot-scale distribution system is beginning. The pilot system consists of multiple recirculating loops of 6" pipe with removable biofilm coupons inserted in the wall. Initial experiments will compare biofilm growth rates under different chlorine levels. This will expand to compare rates under alternative disinfectants and nutrient control strategies.

Priority: Medium

RM.M.18—Opportunistic pathogens in biofilms Identify the prevalence of opportunistic pathogen growth in biofilms and develop mitigation measures.

Priority: Medium

RM.M.19—Impact of nutrient removal on growth potential for bacteria Pilot studies are being conducted on removal of nutrients from treated drinking water. Pilot-scale pipe loop studies will be conducted to evaluate growth potential for bacteria in distribution systems.

Priority: Medium

RM.M.20—Impact of alternative treatment on biofilm growth Assess the potential of alternative treatment systems to promote biofilm growth in the distribution system, using a pilot-scale distribution system.

Priority: Medium

RM.M.21—Water quality factors in distribution systems (Ongoing) Studies are underway to investigate the importance of biofilm development and microbial interactions on the beneficial and detrimental processes in drinking water distribution systems. One aspect of this research addresses the interactions between pipe materials, corrosion inhibitors, disinfectants, organics, and distribution biofilms. A second effort addresses on-line monitoring of pathogen ecology for quantitative evaluation of mitigation procedures.

Priority: Medium

See also RM.M.26—Bacterial growth in distribution systems

c. Effect of design and condition of the distribution system on bacterial growth

Additional characterization studies are needed to identify points in the distribution system that are particularly vulnerable to degradation of water quality. The first candidates for study are dead-end locations, for which there is a dearth of long-term data. Studies have shown

that up to 25% of drinking water consumers drink their water from dead-end sections of the distribution system. Additional knowledge is needed on the role that storage facilities play in influencing water quality changes. The long detention times in such facilities can reduce disinfectant residual but might also reduce the nutrients that promote biofilm growth. Further study is needed on how to design a tank to promote uniform mixing within it. Guidelines on size and location of influent and effluent lines to accomplish this goal are needed.

Computer modeling needs to be enhanced to accommodate the effect that mixtures of treated source waters have on kinetic coefficients that model the decay of chlorine or growth of by-products. More fundamental kinetic models of by-product formation need to be developed that take into account the concurrent loss of disinfectant and production of multiple species of by-products. The same can be said for modeling the complex chemistry of chloramines when used as a disinfectant.

Improved information management can help shift the emphasis in distribution system operation towards a better blend of public health and hydraulic reliability objectives. Advances in remote sensing and data acquisition technologies applied to the specific needs of the water utility industry can make system operators more aware of current water quality conditions within their system and help them make short-term decisions to improve its quality (e.g., disinfectant doses, tank fill/release rates, and pump control strategies).

RM.M.22—Water quality impacts of dead ends Examine the water quality impacts of dead ends. Conduct continuous, long-term monitoring of water quality conditions such as coliform, chlorine residuals and corrosion by-products at dead-end branches and loops of a distribution system.

Priority: Medium

RM.M.23—Mixing in storage facilities Study mixing in storage facilities, including the factors affecting mixing and residence times in distribution system storage facilities. Develop guidelines for maintaining well-mixed conditions.

Priority: Medium

RM.M.24—Alternative kinetic models for decay and DBP formation Develop multi-component kinetic models for disinfectant residual decay and formation of selected DBPs in distribution systems.

Priority: High

RM.M.25—Real-time monitoring systems Study real-time data acquisition and control. Demonstrate monitoring of water quality variables in real-time and use to modify distribution system operation to maintain good water quality.

Priority: Medium

Other projects which also address this topic:

RM.M.30 Opportunistic pathogens in biofilms

d. Effect of filtration/disinfection treatment processes on chemical and biological stability of water in distribution systems

Future research will continue to emphasize the role that biofilm development along pipe walls plays in posing risks to public health. Both a better biological and chemical engineering understanding of the structure and growth dynamics of biofilms are needed in order to develop effective control programs, some of which may involve treatment decisions at the water treatment plant. In particular, the degree to which treatment technologies minimize nutrient availability in the treated water will affect subsequent growth of bacteria in the distribution system.

RM.M.26—Bacterial growth in distribution systems Quantify the factors affecting the growth of biofilm on pipes, and identify effective control strategies.

Priority: High

RM.M.27—Integrated approaches for controlling pathogens Characterize the interactions among treatments on the microbial quality of water in distribution systems. Interactions of concern include effects of corrosion control, loss of residual disinfectants and GAC for DBP control on microbial quality.

Priority: Medium

e. Maintaining distribution system integrity

Microbial pathogens and other contaminants can enter the distribution system in many ways including: piping failure, construction activities, repair and maintenance operations, back pressure, sewage cross-connections, poor system design, and poor operational practices. As we move toward the 21st century, greater attention will have to be given to design, operation and maintenance of distribution systems to ensure water quality as well as hydraulic reliability. This will include consideration of advanced materials of construction as well as installation of sensors for real-time monitoring of important distribution system quality indicators such as disinfectant residuals, water pressure, flow direction, microbial densities, total organic halides, and other quality parameters.

RM.M.32—Evaluate the primary causes of leaks and failures in water distribution systems There is increasing concern over the potential deterioration of drinking water distribution system components and evidence exists that, especially in the largest urban areas in the U.S.,

this deterioration is well underway. Recent boil-water orders and MCL violations in New York City and Washington D.C. support this concern. This task will support a coordinated effort with organizations such as the American Water Works Association Research Foundation, the American Public Works Association, the Civil Engineering Research Foundation, the Water Environment Federation Research Foundation, the Cross Connection Control Association, and the Association of State Drinking Water Administrators to determine the primary causes of leaks in distribution systems.

Priority: High

RM.M.33—Evaluate state-of-the-art devices for determining the structural integrity of water distribution systems Research will be conducted on state-of-the-art technology that can be used to establish the structural integrity and reliability of drinking water distribution system components. For example, sensors that can be used to provide acoustic leak detection capability or that can be imbedded into system components to predict component failure and to establish structural integrity will be investigated. Remote monitoring techniques and telemetry will be investigated to measure real-time water quality in distribution systems and indicate integrity and reliability of distribution system components.

Priority: High

RM.M.34—Evaluate materials for constructing distribution system components Many materials in common use in drinking water distribution systems are subject to corrosion and failure under stress. These failures can range from leaks to catastrophic failure. This task will examine the potential for the use of new construction material that can resist the common mechanisms of failure in pipelines. For example, stainless steel is now being evaluated for use in drinking water systems in Japan. Stainless steel is resistant to corrosion, is flexible and has a long structural life.

Priority: High

3. How can source water be protected to ensure that it is consistent with finished water quality of acceptable microbial risk after appropriate treatment?

State of the Science

Passage of the 1996 Amendments of the Safe Drinking Water Act has focused the attention of water utility mangers and public health and regulatory officials on source water protection and its role in protecting public water supplies. There is growing awareness that water treatment and /or disinfection may not always be adequate to ensure the provision of potable and safe water to the consumer. The cryptosporidiosis outbreak in Milwaukee, Wisconsin, has raised the possibility that even water suppliers which meet all of the Surface Water Treatment Rule (SWTR) requirements are vulnerable. In the Milwaukee case more then 400,000 illnesses and as many as 100 deaths were associated with the outbreak. The cause of the outbreak was attributed to a combination of poor treatment operations and a sudden increase in source water turbidity resulting from a wet weather flow event. This and other similar but less dramatic waterborne outbreaks have spurred an interest in assessing the occurrence of protozoan cysts in source and treated water. This research activity is closely related to ongoing research being conducted under NRMRL's Wet Weather Flow (WWF) Program. The WWF Program is examining techniques for characterizing WWF events, and for development of Best Management Practices for controlling the impact of WWF events on water quality in receiving streams. For example these studies will characterize the factors that influence the overland flow of pathogens such as *Cryptosporidium*, and evaluate the effectiveness of end-of-the-pipe control technologies and on-site waste water treatment technologies. This project will also utilize results from projects currently being funded by the AWWARF and WERF.

Research Topics and Priorities

a. The impact of source water protection on the performance of drinking water treatment systems

Areas of potentially productive risk management research are as follows: development and calibration of Geographic Information System (GIS) techniques for describing source water characteristics; development, application and calibration of new and existing water quality models (BASINS); and defining the factors that influence the performance of conventional treatment when concentration of contaminants in source water increases rapidly. Given the current emphasis on source water protection in the 1996 Amendments to the Safe Drinking Water Act, all of these activities are categorized as high-priority research.

Task RM.M.35—Evaluate Geographic Information Systems (GIS) techniques for defining source water characteristics GIS techniques have become widely used for integrating and displaying land use data for watersheds and river basins. This tool is very effective for visually displaying and integrating various types of data bases that can lend insight into the factors that influence watershed functions. For example, GIS have been used in the Ohio River Basin to show the relative location of water supply intakes, dams and waste water and industrial discharges on the Ohio River using EPA's REACH file as an integrator. However, little has been done with integrating GIS and functional models to predict the behavior of the

watershed and its impact on water quality. For example GIS, soil moisture vegetative cover and atmospheric models can be used to predict the types and severity of wet weather flow events that may be expected to take place in a given type of watershed. This information can be used to understand and characterize the effects of point and non-point source run off on groundwater surface water interactions and on surface and groundwater quality. There are many existing data bases available through agencies such as the Corps of Engineers, the USGS and the USEPA that can be utilized to provide basic data input for this type of analysis. This task will evaluate existing data bases and models that can be integrated with GIS to provide information that could be used to define the characteristics of watersheds and show how these characteristics influence water quality in rivers, streams and the subsurface.

Priority: High

Task RM.M.36—Evaluate water quality models for routing point and non-point source water discharges Water quality models can be used to provide the linkage between wet weather flow events and water quality in drinking water sources. The USEPA, the COE, along with other government agencies, academia and the private sector have invested a great many resources in developing and distributing hydraulic and water quality models for use in river basins and watersheds. This task will examine and evaluate these models and make recommendation as to which are most appropriate for use in specific types of circumstances. Issues related to field calibration, types of input data required, and ease of use will be investigated. This project will also address the relationship between best management practices as evaluated in our Wet Weather Flow program and their impact on protecting source waters for drinking water purposes.

Priority: High

Task RM.M.37—Evaluate the impact of sudden increases in source water contaminant concentration on drinking water treatment There is increasing evidence that drinking water unit processes are vulnerable to sudden increases in contaminant concentration in raw water. The Milwaukee cryptosporidiosis outbreak was in part due to the effect of a wet weather flow event that resulted in sudden and unexpected increases in turbidity in the source water. This wet weather flow event in combination with poor treatment operations resulted in the largest recorded waterborne disease out break in the history of the U.S. There is other, although less dramatic, information that sudden changes in contaminant concentration will degrade the effluent quality of treated water. This task will investigate the design and operating variables that influence water treatment systems. Research will be conducted to define the conditions that cause water treatment systems to fail under the influence of rapidly increasing raw water contaminant concentrations.

Priority: High

Table III-2. Research Priorities for Health Effects of Microbial Pathogens

Research Topics	
a. Pathobiology of infection and disease for the most important waterborne pathogens	
HE.M.1—Infectious dose of *Cryptosporidium*	High
HE.M.2—Validity of d-r model for *Cryptosporidium*	High
HE.M.3—*Cryptosporidium* virulence study	High
HE.M.4—*Cryptosporidium* infectious dose/immunity	High
HE.M.5—Infectious dose of Norwalk virus	High
HE.M.6—Infectious dose of other pathogens	Medium
b. Characterization of epidemic and endemic waterborne disease	
HE.M.7—Characterization of endemic disease	High
HE.M.8—Immunological assays for use in epidemiology studies	High
HE.M.9—Investigation of waterborne outbreaks	High
HE.M.10—Surveillance tools for outbreaks	High

Table III-3. Research Priorities for Exposure to Microbial Pathogens

Research Topics	Proposed Projects	Priorities
Microbial Methods		
a. Methods for detecting and enumerating *Cryptosporidium* and *Giardia* (including identifying the viability potential) in source and finished drinking water, and methods for other emerging protozoa	EX.M.1—Immunological techniques for protozoa	High
	EX.M.2—Gene probes for detection of viable *Cryptosporidium* oocysts	High
	EX.M.3—Cultural method for *Cryptosporidium* in environmental samples	High
	EX.M.4—PCR methods for *Giardia* and *Cryptosporidium*	Medium
	EX.M.5—Protozoa methodology protocol development workshop	High
	EX.M.6—Comparison of methods for *Giardia* and *Cryptosporidium* in water	High
	EX.M.7—New protozoa agents	High
b. Methods for detecting and enumerating viruses in source and finished drinking waters	EX.M.8—Application of PCR technologies and gene probes for virus detection in water	Medium
	EX.M.9—Norwalk virus	High
	EX.M.10—Methods for emerging viruses	High
Microbial Exposure		
a. Surveys to determine pathogen occurrence in source and finished waters	EX.M.11—Intensive evaluation of microbiological constituents and treatability in surface source waters	High
	EX.M.12—Identification of viruses resistant to disinfection	Medium
b. Importance of watershed control (including point source, non-point source, and septic tank controls) for source water pathogen occurrence	EX.M.13—Distinguish animal versus human sources	High
	EX.M.14—Occurrence of *Mycobacterium*	High
	EX.M.15—Occurrence of heterotrophic bacteria with virulence characteristics	High
c. Occurrence of and exposure to primary and opportunistic pathogens in distribution systems	EX.M.16—PCR method for *Legionella*	Low
	EX.M.17—Pathogenicity of heterotrophic bacteria found in drinking water	High
	EX.M.18—Occurrence of opportunistic pathogens in biofilms	Medium
	EX.M.19—Opportunistic pathogens associated with point-of-use (POU) and point-of-entry (POE) filter effluents	Medium
	EX.M.20—Potential pathogenicity of heterotrophic bacteria from POU filters	Medium
	EX.M.21—Occurrence of newly emerging pathogens	High
	EX.M.22—Exposure as a function of population distribution	High
Microbes in Groundwater		
a. Survival and transport of pathogens in the subsurface	EX.M.23—Virus survival in the subsurface	High
	EX.M.24—Virus transport in the subsurface	High
b. Methods for protecting wells and springs from pathogens	EX.M.25—Viral transport and fate models	Medium
	EX.M.26—Vulnerability of groundwater to pathogens	High
	EX.M.27—Delineation of natural protection zones	Medium
	EX.M.28—Vulnerability & sensitivity analysis	High
	EX.M.29—Occurrence of *Clostridium perfringens*	High
	EX.M.30—Aquifer well mapping	Medium
	EX.M.31—Correlation of water age and microbial viability	High
	EX.M.32—Septic Tank Siting	High
	EX.M.33—Virus sampling and phage research	High

Table III-4. Research Priorities Risk Assessment for Microbial Pathogens

Research Topics	Proposed Research	Priority
a. Modifications of risk assessment paradigm for characterizing microbial risks	RA.M.1—Development of a comprehensive microbiology risk assessment model for water	High
b. Accuracy of dose response models in predicting waterborne disease	RA.M.2—Evaluation/application of various dose-response relationship models	High
c. Characterization of risks posed by exposure to multiple or complex mixtures of pathogens	RA.M.3—Evaluation and application of issues and methods to assess risk associated with exposures to multiple pathogens, routes, disease course and outcomes, and durations	Medium

Table III-5. Research Priorities for Risk Management of Microbial Pathogens

Research Topics	Proposed Research	Priority
Pathogen Removal		
a. Optimization of conventional treatment processes to remove pathogens	RM.M.1—Filtration studies for controlling pathogens	High
	RM.M.2—Filtration removal of protozoa and indicators	High
	RM.M.3—Optimize conventional treatment for removal of oocysts	High
	RM.M.4—Filtration damage viability studies	High
	RM.M.5—Evaluate disinfection in field-scale treatment plants	High
	RM.M.28—Evaluation of the effectiveness of conventional treatment processes on removing and emerging pathogens	Medium
b. Effectiveness of different filtration processes in removing pathogens	RM.M.6—Biological treatment for control of oocysts	High
	RM.M.7—Filtration techniques other than conventional inactivating treatment	Medium
	RM.M.29—Evaluation of different filtration processes on removing emerging pathogens	Medium
c. Effectiveness of disinfection processes in inactivating pathogens	RM.M.8—Control of Norwalk virus by chlorine and ozone	High
	RM.M.9—UV disinfection efficiencies for Norwalk viruses	High
	RM.M.10—Inactivation of *Giardia* and *Cryptosporidium* by sequential disinfectants	High
	RM.M.30—Evaluation of alternative inactivation processes for controlling viruses	High
	RM.M.31—Evaluation of different disinfection processes in inactivating emerging pathogens	Medium
d. Appropriateness and costs of technologies for small systems	RM.M.11 *Cryptosporidium* removal using bag filters	High
	RM.M.12—Cost-effectiveness of prefiltration for ultrafiltration unit	High
	RM.M.13—Development/testing of innovative technologies for small systems	High
Distribution systems		
a. Use of coliforms (or other surrogates) to indicate adequate control of primary and opportunistic pathogens in biofilms and pipe sediments	RM.M.14—Bacteria interference with detection of coliforms and *E. coli*	Medium
b. Water quality factors affecting biofilm growth and the effectiveness of disinfectant residuals in controlling growth	RM.M.15—Kinetic Models for chlorine decay in distribution systems	Completed
	RM.M.16—Enhancement to the EPANET distribution water quality model	High
	RM.M.17—Preliminary studies of biofilm formation rates in pilot-scale distribution systems	Medium
	RM.M.18—Opportunistic pathogens in biofilm	Medium
	RM.M.19—Impact of nutrient removal on growth potential for bacteria	Medium
	RM.M.20—Impact of alternative treatment on biofilm growth	Medium
	RM.M.21—Water quality factors in distribution systems	Medium
c. Effect of design and condition of the distribution system on bacterial growth	RM.M.22—Water quality impacts of dead ends	Medium
	RM.M.23—Mixing in storage facilities	Medium
	RM.M.24—Alternative kinetic models for decay and DBP formation	High
	RM.M.25—Real-time monitoring systems	Medium
d. Effect of filtration/disinfection treatment processes on chemical and biological stability of water in distribution systems	RM.M.26—Bacterial growth in distribution systems	High
	RM.M.27—Integrated approaches for controlling pathogens	Medium
e. Maintaining Distribution System Integrity	RM.M.32—Evaluate the primary causes of leaks and failures in water distribution systems	High
	RM.M.33—Evaluate state-of-the-art devices for determining the structural integrity of water distribution systems	High
	RM.M.34—Evaluate materials for construction distribution system components	High

(Continued)

Table III-5. (Continued)

Research Topics	Proposed Research	Priority
Source water		
a. The impact of source water protection on the performance of drinking water treatment systems	RM.M.35—Evaluate GIS techniques for defining source water characteristics	High
	RM.M.36—Evaluate water quality models for routing point and non-point source water discharges	High
	RM.M.37—Evaluate the impact of sudden increases in source water contaminant concentration on drinking water treatment	High

Chapter IV. Research for Disinfection By-Products

Background

Public health concern over the disinfection process was first raised over 20 years ago with the identification of chloroform and other trihalomethanes (THMs) in chlorinated drinking water. Since that time, over 100 chemical by-products of the disinfection process have been found in treated drinking water. Based on several studies, the most prevalent chlorination by-products by weight are the total THMs (TTHMs), followed by the haloacetic acids (HAAs), chloral hydrate, haloacetonitriles, haloketones, and chloropicrin. Between 20% and 60% of the halogenated material resulting from chlorination are accounted for by these compound classes. The concentrations of the chlorination by-products depend on several factors, with the total organic carbon (TOC) level (a surrogate for the amount of precursor material) in the water being the most important. In addition, the concentrations of chlorinated by-products are generally higher in surface waters than ground waters because the level of TOC is higher in surface waters.

The concentrations of the TTHMs and HAAs likely comprise more than 50%, on a weight basis, of the halogenated by-products that have been identified in drinking water. Based on the model used in the proposed Stage 1 DBP rule to predict occurrence of TTHMs and HAAs in systems serving greater than 10,000 people and using surface water, the median concentration of TTHMs nationally is 45 μg/l with a 95th percentile of 104 μg/l (the proposed Stage 1 Maximum Contaminant Level (MCL) for TTHMs is 80 μg/l). Of the THMs, chloroform generally occurs in the highest concentrations, but the brominated and bromochloro- compounds are found in the highest concentrations in high bromide waters. For HAAs, the model predicted that the median concentration for the sum of five of the HAAs nationally is 27 μg/l with a 95th percentile of 86 μg/l (the proposed Stage 1 MCL for the HAAs is 60 μg/l). Of the HAAs, dichloroacetic and trichloroacetic acid generally have the highest concentrations, but the brominated and bromochloroacetic acids occur in the highest concentrations in high bromide waters. The other chlorination by-products generally occur at levels less than 10 μg/l.

Chloramines react to form chlorine-containing by-products, but generally at significantly lower levels than does chlorine. When free chlorine is present during the application process, the level of chlorine-containing by-products increases. Chloramination also produces nitrogen-containing by-products, such as cyanogen chloride and organochloramines. Cyanogen chloride generally occurs at concentrations < 5 μg/l (Stage 1 does not propose an MCL for cyanogen chloride).

The disinfectant chlorine dioxide does not react to form significant levels of chlorine-containing organic by-products, but chlorine dioxide has been found to produce the inorganic by-products, chlorate and chlorite. Limited data suggest that chlorite and chlorate are expected in concentrations between 0.5 to 1.5 mg/L and 0.1 to 0.5 mg/L, respectively (the proposed Stage 1 MCL for chlorite is 1.0 mg/L; an MCL is not proposed for chlorate).

Relative to chlorination, considerably less is known about by-products of ozonation. The most prevalent ozone by-products are aldehydes, ketones, carboxylic acids, ketoacids, and hydrogen peroxide. Bromate, bromoform, and dibromoacetic acid are formed in high bromide waters. The available health and exposure data for these by-products suggest that bromate is of greatest concern. The nationwide distribution of bromate occurrence in surface waters using ozone for pre disinfection has been roughly estimated as a median of 1 to 2 μg/l and a 90th to 95th percentile in the range of 5 to 20 μg/l (the proposed Stage 1 MCL for bromate is 10 μg/l).

This chapter describes proposed research for DBPs in the areas of health effects, exposure, risk assessment and risk management. The major research questions in each area are summarized in Table IV-1. For each question, the state of the science, research needs and proposed research projects are described.

Health Effects Research

1. What are the health effects associated with exposure to DBPs?

Information on the health effects of DBPs from both epidemiology and toxicology studies is currently inadequate for conducting comparative assessments of the potential cancer and noncancer risks posed by the use of chlorine, chloramine, ozone, chlorine dioxide, or combinations of these disinfectants. The anticipated increased use of alternatives to chlorine in the future underscores the need to assign a high priority to research that will permit a better characterization of the risks that may be

Table IV-1. Major Research Questions for Disinfection By-Products

Health Effects

1. What are the health effects associated with exposure to DBPs?
   - 1.1 What are the health effects in communities served by disinfected drinking water?
   - 1.2 What is the toxicity of individual chemical contaminants and of mixtures of DBPs?

Exposure

1. What methods are needed for measuring occurrence of DBPs in drinking water?
2. What levels of DBPs are people actually exposed to via their drinking water supplies, and what is the population distribution of exposures?

Risk Assessment

1. How can we characterize the risk posed by exposure to specific and multiple or complex mixtures of DBPs in drinking water?
2. How can the risks from chemicals and microbes be compared?

Risk Management

1. How effective are various treatment processes in minimizing the formation of DBPs?

associated with exposure to the by-products of these alternatives. The toxic effects of many DBPs, particularly those associated with the use of disinfectants other than chlorine, are unknown or poorly characterized. Beyond the need for basic toxicologic data, an improved understanding of the chemical, physical and biological processes involved in the toxic response is critical for evaluating the human risk associated with exposure to these contaminants. Improved estimates of exposure and health must be utilized in future epidemiology studies so that the public health risks to communities served by disinfected drinking water may be characterized with a reasonable degree of confidence.

The criteria listed in Chapter I were used to select and prioritize research projects. As an iterative research plan, priorities are likely to change as the results of ongoing research and information about emerging problems become available. This is a particularly important issue with respect to the planning of health research to assess the risk associated with exposure to DBPs. The current research plan emphasizes the need for feasibility studies to determine if full-scale epidemiology studies are likely to provide better estimates of cancer and reproductive risks than those derived from previous studies. In the event that full-scale studies are not conducted, risk assessors will place a greater reliance on the use of animal toxicity data for individual DBPs. This will necessitate an enhanced program to improve the scientific basis for extrapolating animal toxicity data to humans. Under this scenario, research on toxic mechanisms and pharmacokinetics will receive considerably more emphasis. Priorities for health research on individual DBPs will also be influenced by the ability of mixtures research to address the overarching question of drinking water health risks from consumption of disinfected water.

The 1996 SDWA Amendments assign a high priority to the types of research activities described below, emphasizing the need for toxicology and epidemiology research to evaluate the cancer and reproductive risks that may be associated with exposure to DBPs resulting from different disinfectants. The Amendments also place a priority on research to understand the mechanisms by which DBPs cause their effects (cancer and noncancer), the risks posed by complex mixtures of contaminants, and the factors that influence effects in the general population and in susceptible groups.

1.1 What are the health effects in communities served by disinfected drinking water?

State of the Science

The identification of potentially carcinogenic DBPs such as chloroform in drinking water two decades ago prompted a number of epidemiology studies to evaluate cancer risks in communities served by chlorinated drinking water supplies. These studies have primarily involved comparisons of populations consuming chlorinated surface water or unchlorinated ground water. Some investigations have shown no associations between consumption of chlorinated water and cancer, while others have suggested weak to moderate associations with cancers of the colon, rectum and bladder (collectively, up to 10,000 cases annually). In general, the risk estimates derived from these studies are highly uncertain due to problems with study design, characterization of exposures and ascertainment of health effects. Recent studies in Iowa and Canada have provided additional weight-of-evidence for the association between exposure to chlorinated by-products and the risk of cancer. Epidemiology studies to investigate the possible association between DBP exposures and adverse reproductive outcomes have similarly not provided conclusive evidence of causality, but they have been useful for generating hypotheses and identifying research needs. The high priority given to epidemiology research in this plan is responsive to the need to address these important public health concerns.

Obtaining reliable estimates of exposure in cancer studies has been particularly problematic due to the need to reconstruct historical exposures that may span several decades back in time. Additionally, most epidemiology studies to date have relied upon either TTHMs or chloroform as surrogates for exposure to the complex mixture of DBPs in water. Recent studies have demonstrated that THMs as a class or individually may not adequately predict exposure to other types of DBPs. It is now recognized that the relative concentrations of the individual THMs in a given water supply, and their relative toxicities in animal tests, vary considerably. Furthermore, other types of by-products may be of greater concern from a health perspective. For example, recent toxicologic data suggest that of all the DBPs for which data exist, dibromoacetic acid is perhaps the most potent male reproductive toxicant in rodents. Levels of this DBP and other toxicologically important brominated by-

products, including bromodichloromethane (primarily a chlorination by-product) and bromate (an ozonation by-product), are greater in communities where bromide concentrations in the source water are high. These concerns highlight the importance of selecting the appropriate marker(s) of DBP toxicity to use in both cancer and reproductive outcome epidemiology studies.

Health data in cancer epidemiology studies have commonly been obtained from cancer mortality rates, death certificates, or interviews. The variable quality of information obtained by these measures and the potential problems in associating exposures to cases are important uncertainties that need to be addressed in future cancer studies. With respect to adverse reproductive effects, the few existing studies have focused on a limited range of health outcomes (fetal development and selected congenital malformations). To comprehensively address this issue, studies need to include an examination of measures of fecundity and fertility in both males and females. Future epidemiology studies to address these health issues clearly need improved assessments of exposure and health effects, enhanced coordination with animal toxicology research to ensure emphasis on the most appropriate endpoints and markers of exposure, and greater emphasis on interdisciplinary approaches in the field.

EPA has used a three-step strategy to define the critical issues in human health research for both cancer and reproductive endpoints: 1) sponsor expert panel workshops to discuss the available data, determine if additional epidemiology research can improve the state of the science, and if so, obtain guidance on research approaches and priorities; 2) conduct methods development and feasibility studies, with consideration of the recommendations of the expert panel; and 3) conduct full-scale studies, depending upon the outcome of the feasibility studies.

EPA has conducted expert panel workshops (step #1) for both cancer and reproductive endpoints. The cancer workshop panel recommended conducting feasibility studies to identify geographic locations with adequate exposure data and appropriate cohorts for study (including the possibility of using existing cohorts that are being studied for other potential exposures). Several possible designs for full-scale studies (i.e., cohort, case-control, and case-control nested within a cohort) were suggested. The panel recommended research on biomarkers of exposure, effect, and susceptibility, and strongly encouraged research to improve exposure assessment for epidemiologic studies. The recommendations of the cancer workshop panel with respect to assessment activities are discussed in the Risk Assessment section of this chapter.

In 1993, EPA and the International Life Sciences Institute (ILSI) convened an expert panel to review the published epidemiologic and experimental data on reproductive and developmental effects, and to develop a strategy for related short-term and long-term research. The panel concluded that the current available data on the effects of chlorination by-products provide an inadequate basis for identifying DBPs as a reproductive or developmental hazard. Recommendations were made for refining studies using existing data bases, strengthening studies designed to collect new data, improving exposure assessments, investigating selected health endpoints, and developing a stronger link between animal research and epidemiology studies (e.g., laboratory development and field testing of biomarkers). EPA subsequently conducted a one-day workshop in March of 1995 to review ongoing laboratory and field research on reproductive and developmental effects of DBPs. Participants discussed directions for future research in this area, and reiterated several of the general conclusions of the 1993 workshop. In July of 1997, EPA convened an expert panel to review the existing reproductive epidemiology data base and to develop recommendations for future research.

Current Epidemiology Studies Current DBP epidemiology research in the U.S. is focused primarily on evaluations of the of the possible associations between exposure to by-products and the risks of adverse reproductive outcomes. Two epidemiology studies of adverse reproductive outcomes are being conducted in New Jersey. One is using improved methods for estimating exposures to test the findings of earlier studies in that state in which neural tube defects were associated with elevated levels of THMs, nitrates, and solvents. The second is a cross-sectional study of public drinking water contamination and birth outcomes in various counties in New Jersey, using ambient levels of THMs and selected solvents as markers of exposure. The State of California is evaluating possible associations between individual or TTHMs in residential drinking water and adverse pregnancy outcomes, including spontaneous abortion, low birth weight, preterm delivery and intrauterine growth retardation. Finally, a pilot study using a geographic information system and water quality modeling is evaluating the relationship between birth weight and exposure to DBPs. This EPA-funded project is listed below under the section "Development/application of improved tools for field research." The results of all of these studies should be available in 1997.

Research Topics and Priorities

The following research addresses many of the recommendations of the participants in the cancer and reproductive effects workshops, as described in the State of the Science section above. These projects are all highly ranked because they address potential risks of greatest concern for DBPs in drinking water (cancer and adverse reproductive outcomes), and if successful, they will significantly reduce uncertainties in the current risk assessments and will lead to more scientifically sound, cost-effective regulations

a. Development/application of improved tools for field research

This research addresses important weaknesses in drinking water epidemiology studies through the development and application of better approaches for assessing exposure and health effects. Methodologic research should be conducted concurrently with the feasibility studies described below, and the improved methods should be integrated into the design of full-scale studies as they become available.

HE.D.1—Improving estimates of residential DBP exposures in epidemiology studies This includes research described in the Exposure section that has a direct application to epidemiology studies. Projects EX.D.14 through 16 are particularly relevant to epidemiology research and also provide information that can be used in assessing risks.

Priority: Variable (see Exposure section)

HE.D.2—Improving measures of biologic effect: Field evaluation of biomarkers Field evaluation of morphological, biochemical, and/or molecular alterations that may result from exposure to DBPs. An initial focus on possible biochemical indicators of male reproductive toxicity is supported by recent progress in this area in the laboratory. The development of biomarkers for cancer may provide some important insights into mechanisms of action. However, the priority of this line of research for supporting epidemiology studies will depend upon the priority given to new full-scale epidemiology studies in the future. [See project EX.D. 15 in the Exposure section on biomarkers of DBP exposure]

Priority: High

HE.D.3—Improving methods for managing health and exposure data This ongoing project is evaluating the use of a geographic information system (GIS) and water quality modeling in a study of the potential impacts of chlorination and chloramination on reproductive health of populations in Colorado. GIS, which is a data management and visualization tool that has been developed for use in other contexts, is assisting in study design, sample selection, and analysis of data. If effective, this approach could be applied in future full-scale studies.

Priority: High

b. Feasibility/full-scale studies

Plans for future epidemiologic research will be influenced by current assessments of existing data (see Assessment section below), the outcome of epidemiology studies now underway, and ongoing efforts to improve epidemiologic methods. The availability of suitable health and exposure data, as well as the amount of resources available, will be key determinants in the number, types and locations of studies that will be conducted. Some elements of study design may be similar for both cancer and reproductive outcomes, such as identifying areas with water quality parameters of interest (e.g., pH, bromide concentration).

Cancer epidemiology studies in communities served by water treated with disinfectants other than chlorine or chloramine will not be possible due to the unavailability of adequate historical exposure data. Assessments of potential cancer risks associated with exposure to the by-products of alternative disinfectants will therefore need to rely upon data from toxicity studies of individual DBPs and mixtures of DBPs (see toxicology section below). Epidemiology studies of adverse reproductive outcomes for the various treatment options may be possible since these studies are not constrained by the need for such long-term exposure data.

The general goal of the feasibility studies is to demonstrate that an acceptable epidemiologic test of the possible association between DBP exposures and cancer or noncancer risk can be conducted. More specifically, the studies must provide reasonable assurances that: 1) the subjects' exposures to DBPs can be accurately assessed at least over the latent or critical period of the development of the adverse effects of concern; 2) study sites exhibit water quality parameters (e.g., bromide levels, pH) and treatment processes of greatest interest; 3) the study population exhibits enough variation in DBP exposure to allow a dose-response function to be established; 4) suitable measures or markers of exposure and effect will be used; 5) the test for DBP effect will not be unduly confounded by factors such as differences in demographic characteristics, unmeasured exposure to environmental contaminants other than DBPs, and residential mobility; and 6) the study will have sufficient statistical power across a reasonable range of sample sizes and odds ratios.

HE.D.4—Feasibility studies: Cancer To be conducted in communities served by chlorinated and chloraminated water supplies, with a focus on cancer of the bladder, colon, rectum, and other possible cancer sites. Reassessment of the existing cancer epidemiology data (see Assessment Section below) is an essential prerequisite to determining whether new studies should be carried out.

Priority: High

HE.D.5—Feasibility studies: Reproductive effects To be conducted in communities served by chlorinated, chloraminated, and possibly ozonated water supplies. Studies may focus on at least one of the following endpoints: human fertility and fecundity (male and female), growth retardation, and common malformations. The few available DBP reproductive epidemiology

studies have been reviewed in several expert workshops convened by EPA (described above). The research recommendations that have been developed from these workshops should be considered in the conduct of future feasibility studies.

Priority: High

HE.D.6—Full-scale studies: Cancer and reproductive effects Dependent upon the findings of Projects 4 and 5 above. May include new studies and/or collaboration with planned, recently completed or ongoing case-control studies.

Priority: Dependent upon outcome of feasibility studies. (If feasible, high)

1.2 What is the toxicity of the highest priority chemical contaminants and mixtures of DBPs?

State of the Science

The toxicologic literature on individual DBPs has grown considerably over the last 20 years, particularly for the by-products of chlorination. Basic toxicologic information is available on many of the THMs, HAAs, aldehydes, and miscellaneous organic and inorganic contaminants found in treated drinking water. A number of these by-products have been shown to cause cancer, reproductive effects, and various target organ toxicities in experimental animals, though most commonly at exposure levels that are from one to several orders of magnitude higher than the ambient concentrations to which people are exposed.

The DBPs that have been studied experimentally represent only a fraction of the by-products that may be present in treated drinking water. Consequently, there are many uncertainties in assessing risks based on such limited data. While the ambient concentrations (typically in the µg/L range) of many of the known DBPs are likely to be greater than the levels of most of the other by-products in the complex mixture, there may be poorly characterized or as yet unidentified by-products that are of concern from a health perspective. For example, the highly mutagenic by-product MX and related halogenated hydroxyfuranones may be of public health importance even though they are present in relatively low concentrations in treated drinking water. The toxicity of many of the brominated, mixed bromochloro, and inorganic by-products has been inadequately studied. This includes DBPs such as the brominated THMs and MX-related compounds (formed with chlorination and chloramination), bromate and the brominated acids (from ozonation and chlorination), cyanogen chloride (from chloramination), and chlorate (from chlorine dioxide). In addition, nearly all of the available toxicologic data on DBPs pertain to individual compounds. There is little information on the toxicity of complex mixtures of DBPs, or on the toxicologic interactions that may occur between the individual DBPs in a mixture.

Perhaps the most critical underlying issue for toxicologic research on DBPs is the need to better understand the predictive relationship between toxicologic endpoints and human disease (i.e., animal-to-human extrapolation). The metabolism of DBPs, and the mechanisms by which they cause their effects in animals, directly influence the shape of the dose-response curve at low doses; this has important implications for estimating the risks posed by DBPs to humans.

Whereas the epidemiology data suggest possible associations between DBPs and bladder or colo-rectal cancer, the experimental carcinogenicity data indicate that the liver and kidney are the most common target organs for the THMs and HAAs. The main exceptions are the rare intestinal tumors in animals exposed to bromodichloromethane and bromoform (which corresponds to the epidemiology data), and tumors of the thyroid and peritoneal mesothelioma in bromate-treated animals. The mutagenicity of DBPs varies within and between classes, with the brominated by-products generally more mutagenic than those that are chlorinated. Basic cancer dose-response information is inadequate for a number of potentially important by-products, including chlorate, cyanogen chloride, MX, and several of the brominated acetic acids. In addition, more detailed biologic information is needed to further characterize the carcinogenicity of dichloroacetic acid, bromodichloromethane, and bromate, which appear to be the most important by-products from a risk perspective based on a consideration of their estimated cancer potencies and ambient exposure levels.

Several DBPs have been shown to cause reproductive and developmental toxicity in laboratory animals, although an examination of the existing data base suggests that the studies have not been performed in a completely systematic manner. In general, more data are available on the effects of DBPs on the development of the embryo and fetus than on other parts of the reproductive process. Recent data from relatively low dose studies of the brominated acids suggest the need for more detailed investigations of some of these by-products. Screening-level data are needed for a number of halomethanes, haloacids, halonitriles, ketones and inorganics (particularly bromate).

The neurotoxicity and immunotoxicity of DBPs in general have not been well characterized. There are few indications in the literature that these endpoints should be of concern at ambient exposure levels. Nevertheless, a limited screening effort to evaluate selected DBPs for these endpoints in a systematic manner is needed to ensure that this assessment is correct. Preliminary results from studies in rats have shown that relatively low doses of dichloroacetic acid (similar to the lowest doses at which other noncancer effects have been observed experimentally) can cause reversible neurotoxicity after exposure periods of three months. These findings suggest that additional research to characterize the potential neurotoxicity of dichloroacetic acid and related haloacids is warranted.

A number of studies have been conducted to address questions concerning the toxicity of "real world" mixtures of DBPs. These studies, which used either concentrates of drinking water or humic acid preparations treated with various disinfectants, were largely negative or inconclusive, and had a number of technical limitations. In addition, a few studies have evaluated mixtures of drinking water contaminants such as pesticides and other organics, but research on defined mixtures of DBPs is lacking. Little is known about the possible toxicologic interactions of individual DBPs in a mixture, i.e., whether their toxicity is additive, as is the current default assumption, or if their toxicity is either more or less than additive. To address the many issues relating to toxicology, sample preparation, chemical analysis and assessment, an integrated, cross-disciplinary research effort is necessary.

With respect to the disinfectants themselves, the toxicologic data base on chlorine, chloramine, and chlorine dioxide is considered variable, although there is generally little health concern over exposure to the levels of disinfectant residuals commonly found in finished drinking water. Additional data are needed, however, to better characterize the potential immunotoxicity of these disinfectants.

EPA is currently conducting hazard identification and dose-response research on a number of DBPs across a variety of toxic endpoints. Chronic cancer bioassays have recently been completed or are near completion for di- and trichloroacetic acid, bromodichloromethane, chloral hydrate, and bromate. The current focus of mechanistic and pharmacokinetic studies is on dichloroacetic acid, bromodichloromethane, and bromate. Research is being conducted at EPA on the male reproductive toxicity and the embryotoxicity of selected HAAs and THMs. EPA is also evaluating the neurotoxicity of dichloroacetic acid. These by-products were selected for more detailed studies because they appear to be of greatest concern from a risk perspective.

The following listing of research activities outside of EPA is incomplete, but is nevertheless intended to provide some useful information on other important ongoing research. In collaboration with EPA, the National Toxicology Program (NTP) has a screening program to evaluate the reproductive, developmental, and immunotoxic effects of selected DBPs. The NTP also plans to conduct mechanistic research using short-term models (e.g., transgenic animals) to evaluate selected DBPs, and will initiate chronic bioassays on several high priority DBPs, including bromodichloromethane, chlorate, dibromoacetic acid, dibromoacetonitrile and MX. Mechanistic research on the carcinogenicity of chloroform is being conducted by the Chemical Industry Institute of Toxicology. The Chemical Manufacturers Association is conducting a two-generation rat reproductive study on chlorite. Research in Finland recently completed a study that demonstrated the carcinogenicity of MX in a chronic cancer bioassay. A cancer bioassay on dibromochloroacetic acid was recently initiated in Japan.

Research Topics and Priorities

Toxicologic research described in this chapter can be grouped into three distinct categories: a) hazard identification and dose-response studies to fill data gaps for newly identified or priority contaminants; b) developing more detailed toxicologic information for the most important substances, particularly in the areas of pharmacokinetics and mechanism(s) of action to facilitate extrapolation of data to humans; and c) evaluating the toxicity of simple and complex mixtures of DBPs. The preferred research approach involves initial screening-level studies of DBPs to fill data gaps, followed by more detailed research if additional data are needed for quantitative risk assessment. Toxicology studies of individual DBPs and possibly drinking water mixtures will be particularly important for evaluating the relative cancer risks that may be associated with disinfection strategies other than chlorination and chloramination, since historical exposures to the by-products of the alternative treatments are too short to evaluate such risks in epidemiology studies.

The data obtained over the next five years from DBP screening studies and from the more focused mechanistic studies on selected priority by-products will greatly enhance the assessment of risks that may be associated with exposure to individual by-products of chlorination and alternative disinfectants. These studies will also provide insights into the relative risks of different treatments. It is clear, however, that laboratory studies of DBP mixtures and/or field studies of human populations represent more relevant approaches for comparing the risks of the various treatment processes (technical constraints and data limitations notwithstanding).

a. Hazard identification and dose-response

For many newly identified and some known drinking water contaminants, basic information is needed to describe their potential toxicity for a variety of endpoints, including cancer, reproductive and developmental toxicity, and neurotoxicity. An important component of research to address data gaps, potentially applicable to one or more of the listed toxicity endpoints and closely aligned with data generation efforts, is the development of structure-activity relationships (SAR). When sufficient data on related DBPs exist, SAR models can be derived and used to provide preliminary estimates of toxicity of untested DBPs, prioritize newly identified chemicals for testing, and in some cases, generate insight into molecular mechanisms of toxicity.

Experimental research to fill data gaps for hazard identification and dose-response assessment purposes is described below. The cancer dose-response studies and the reproductive/developmental effects screening studies are high priorities because they will help identify those DBPs with the highest risk, provide dose-response information that can be used in conducting better risk assessments, and provide better information to more

accurately estimate costs and benefits of the rules. The neurotoxicity and immunotoxicity studies are medium priorities because of the lack of published studies demonstrating that these endpoints are of great concern.

HE.D.7—Cancer dose-response studies Two-year exposure studies in laboratory animals to evaluate the potential carcinogenicity of DBPs, using study designs that will provide better information for use in Agency risk assessments. Selection of an appropriate range of doses that will permit an evaluation of the dose-response in the low-dose range (to the extent possible experimentally) will be a key consideration in the study design. These studies also address selected pharmacokinetic and mechanistic questions that will provide data for use in more biologically based risk assessments (see Projects HE.D.11 and 12). As mentioned above, the NTP is planning to initiate chronic exposure studies on several high priority DBPs in 1997 and 1998.

Priority: High

HE.D.8—Reproductive/developmental effects screening studies Evaluation of the reproductive and developmental toxicity of priority DBPs in standardized screening tests, and conducting specialized developmental toxicity studies on selected DBPs and disinfectants (e.g., two-generation studies, research to identify alterations in pregnancy maintenance and ovarian function). Current priorities in an ongoing EPA/NTP collaborative screening program include bromate, chlorodibromomethane, bromodichloromethane, bromoacetonitrile, dibromoacetonitrile, and bromochloroacetic acid.

Priority: High

HE.D.9—Neurotoxicity studies Characterization of the neurotoxicity of priority DBPs, with an initial focus on dichloroacetic acid and related HAAs.

Priority: Medium

HE.D.10—Immunotoxicity studies Evaluation of the potential immunotoxic effects of selected high priority DBPs and disinfectants in laboratory animals using a tiered approach that includes several measurements of immune function. This research will be conducted in a coordinated effort with NTP.

Priority: Medium

b. Pharmacokinetics and mechanisms of action

Research on pharmacokinetics (i.e., distribution, metabolism and elimination) and mechanisms of action is necessary to interpret the biological significance of an effect and to provide a sound scientific basis for assessing risk. By describing metabolism, tissue dosimetry and tissue response, physiologically based pharmacokinetic (PBPK) models and biologically based dose-response (BBDR) models permit a more accurate prediction of the shape of the dose-response curve for humans exposed to a particular contaminant. This research also includes the development of a structure/ activity framework for assessing the toxicity and mechanisms of action of related DBPs, and provides insights on the development of biomarkers of effect and exposure. Due to the resource demands and longer time frame for this type of research, only the highest priority individual DBPs and classes of DBPs are selected for study. As mentioned above, dichloroacetic acid, bromodichloromethane, and bromate are considered to be three of the most important DBPs for which this type of detailed information is desirable with respect to cancer. Current data suggest that more detailed studies of the reproductive and developmental toxicity of certain THMs and HAAs are warranted. These projects are considered to be high priority because they address major uncertainties in the risk assessment process, and focus on the toxic endpoints of greatest concern. This research is also responsive to the research requirements of the 1996 SDWA Amendments, which direct the Agency to conduct research to improve the biological basis for drinking water risk assessments.

HE.D.11—Pharmacokinetic and mechanistic research to improve cancer risk assessment for priority DBPs This includes research in two interrelated areas: 1) Studies to evaluate the pharmacokinetics and toxicity of selected DBPs to obtain better estimates of metabolism and relevant target tissue dosimetry; 2) Mechanistic studies to evaluate the physiological, biochemical and molecular changes that accompany the carcinogenic response. These efforts will provide data to support more biologically based risk assessments for a small number of the highest priority DBPs, and will in some cases lead to the development and subsequent validation of physiologically based pharmacokinetic (PBPK) models and/or biologically based dose-response (BBDR) models. Pharmacokinetic and toxicity research at EPA is currently focused on selected THMs and HAAs, with a primary emphasis on the development and validation of PBPK model for bromodichloromethane. Mechanistic research is currently being conducted on dichloroacetic acid and bromate. These by-products were selected for study because the results of screening studies, combined with estimates of exposure, indicated that they could be of greatest importance from a risk assessment perspective. This research is linked with the dose-response studies described in HE.D.7.

Priority: High

HE.D.12—Pharmacokinetic and mechanistic research to improve assessments of repro-

ductive toxicity and developmental effects for priority DBPs Research to further characterize the potential reproductive and developmental toxicity of priority DBPs. Ongoing research is focused on the THMs and HAAs, using a variety of *in vitro* and *in vivo* techniques. Contaminants are selected for these more detailed investigations on the basis of results of earlier screening-level studies described in HE.D.8.

Priority: High

c. DBP mixtures

As an integral part of a multi-disciplinary effort on drinking water mixtures, toxicology research can provide the data needed to characterize the relative toxicity of complex mixture preparations and to evaluate the interactions between key components of the mixture. Important issues in complex mixtures research include the need to determine the appropriate study design and to overcome technical problems relating to sample preparation and chemical analysis. The first two mixtures projects described below represent a phased approach in which a feasibility study is conducted before attempting full-scale studies to evaluate the relative toxicity of complex mixture drinking water samples. The feasibility study, as well as the mutagenicity screening study, are considered high priority because they address a potentially high-risk, high-uncertainty issue, and they could lead to further research that will provide information on the relative risks of different disinfected waters. The DBP interactions study can provide useful insights into the assumptions currently used in assessing risks for mixtures. It is ranked medium because it is a less-direct approach to assessing the relative risks of complex drinking water samples.

HE.D.13—Mixtures feasibility study Assessment of the feasibility of studying drinking water mixtures, and development of a research strategy. This involves the use of workshop(s), special consultations and pilot studies, and must be linked to similar feasibility assessments in related areas (e.g., exposure/chemistry).

Priority: High

HE.D.14—Toxicologic evaluation of drinking water mixtures Toxicologic testing and development of new methods as needed to evaluate the relative toxicity of drinking water samples that vary by disinfection technique and selected water quality parameters. This also includes research to identify the individual components or classes of DBPs that contribute most to the overall toxicity of the mixture.

Priority: Depends upon outcome of Project 13 (High if feasible)

HE.D.15—Mutagenicity screening studies of drinking water mixtures Use of *in vitro* assays to evaluate the relative mutagenicity of complex mixtures of DBPs in concentrated extracts of drinking water treated with different disinfectants (ongoing).

Priority: High

HE.D.16—Studies of DBP interactions Research to evaluate DBP interactions in well-defined mixtures, with an initial focus on the major classes of DBPs (e.g., THMs and HAAs). This is linked to mixtures assessment activities in Section D, Risk Assessment, below.

Priority: Medium

Exposure Research

Approximately 100 different DBPs have been identified in treated drinking water. For a relatively small number of DBPs, perhaps 10-15, occurrence data are reasonably well established in terms of concentration ranges typical of source waters and some treatment processes. Major gaps still exist in our knowledge about what DBPs are formed from different treatment processes, particularly processes that use alternate disinfectants, such as ozone. Research in this area is hampered by lack of analytical methods. Uncertainties also exist regarding actual exposures to DBPs.

1. What methods are adequate for the analysis of DBPs?

State of the Science

Analytical methods for specific DBPs are either research methods, often the methods used in the discovery process, or practical methods required for regulatory compliance monitoring or large-scale exposure surveys. Research methods are usually unacceptable for regulatory use or even large-scale exposure surveys because they are usually too poorly tested and documented, relatively complex and costly, and often infested with unexpected problems. Regulatory methods are desired that are simple, relatively cheap, free of problems, accurate, precise, multi-laboratory tested, and have method detection limits (MDLs) no greater than 20% of the proposed MCL. The requirement of an MDL no greater than 20% of the MCL is highly desirable because this level is sufficient to ensure that normal measurement variability does not produce an out-of-compliance measurement when the utility is in compliance.

Very good practical methods of analysis are available for a few of the DBPs, e.g., chloroform, bromodichloromethane, chlorodibromomethane, and bromoform (the trihalomethanes, THMs). These successful practical methods rely on the use of high resolution gas chromatography (GC) and GC/mass spectrometry, the development of which had an enormous impact on our ability to discover, identify, and measure thermally stable, readily extracted, and reasonably volatile organic compounds in drinking water. Thermally stable volatile com-

pounds are capable of passing into the gas phase without chemical decomposition or other chemical changes.

Methods for other by-products are useable, but further improvement is highly desirable. For example, the analytical methods currently used for the haloacetic acids, which are currently proposed for regulation, are not simple. These methods require a very skilled laboratory technician and are relatively costly compared to the methods used for the THMs.

A major and very significant analytical limitation exists for the measurement of polar, water soluble (difficult to extract), and nonvolatile organic and inorganic substances in source and treated drinking water. The lack of research methods for these type of compounds has impeded the capability to identify and conduct exposure studies for additional by-products, especially those from alternate disinfectants or from combinations of disinfectants. A major need is the development of new extraction techniques and instrumentation for the identification and measurement of polar, water soluble, nonvolatile substances in drinking water.

From the exposure point of view, another need is for real-time methods to continuously monitor finished and source water for DBPs and precursors. Real-time monitoring would provide information on the temporal variations in the concentrations of DBPs which is needed to determine the true level of exposure by the consumer. As a by-product of this development, treatment plants could use these technologies to provide on-line, in-the-plant process monitoring and feedback control of DBP formation by adjusting process parameters as a function of current conditions. Current AWWARF-sponsored research on real-time monitoring methods addresses TOX and TOC, but not disinfectant residuals or by-products.

Smaller treatment plants generally need to rely on commercial laboratories for the analysis of DBPs due to the relatively expensive equipment requiring highly trained personnel (e.g., high resolution GC/MS). Development of alternative simpler "kit-like" methods for specific DBPs would be less expensive, easier to use and may provide better consistency and quality control in reporting.

Research Topics and Priorities

a. Additional methods or method improvements needed to implement the Stage 1 DBP rule

The improvement of the methods for bromate and haloacetic acids are considered high priority because they would help in the implementation of the Stage 1 DBP rule. In addition, the potential health risks posed by these chemicals at potentially low levels requires better analytical methods to ensure the best possible occurrence data are available when estimating risks. The evaluation of the TOC method is a high priority because of the importance of TOC in the generation of DBPs and the regulatory requirement to measure TOC in the enhanced coagulation requirements. The development of a more sensitive chlorine dioxide method is a medium priority because, as discussed in the project description, the need for a more sensitive method is dependent on the outcome of the CMA two-generation rat study (described in the Health Effects section, above). The real-time monitoring for disinfectant residuals is a low priority because compliance with the proposed criteria (MCLs for TTHMs and HAAs) is based on an annual average of concentrations measured in the distribution system. However, if reproductive/developmental effects are of a concern, then standards may be established to prevent the threshold level from occurring anywhere in the distribution system. In this case, real-time monitoring may become more important. The performance evaluation (PE) studies for DBPs are a high priority because it is critical that there are sufficient and qualified laboratories for performing analytical work required by the ICR and Stage 1 DBP rule.

EX.D.1—Low level bromate (BrO_3^-) measurement The need for a practical analytical method for bromate has been established by the current proposal to set an MCL of 0.01 mg/L. The current standard analytical method for bromate has a serious interference from chloride at this concentration and the method is not sufficiently sensitive to measure bromate reliably at the proposed MCL. A recently developed ASTM method has the potential to reduce the method detection limit (MDL) of bromate ion from 0.02 mg/L to at least 0.002 mg/L which is 20% of the proposed maximum contaminant level (MCL) of 0.01 mg/L. To be practical, this new method must be validated by multi-laboratory testing. Lower detection limits are desired for possible use in the Stage 2 DBP rule.

Priority: High

EX.D.2—Improved method for haloacetic acids A recently developed method for the determination of haloacetic acids reduces some of the concerns about method deficiencies in extraction, derivatization, and lab safety and it expands the method to include all nine possible bromo-, chloro-, and mixed bromochloroacetic acids. This new method must be validated by multi-laboratory testing. The long-term need is to develop a simpler method that has increased sensitivity. Even more capabilities may be needed for the Stage 2 rule.

Priority: High

EX.D.3—Expand quality control for TOC, evaluate new TOC methods
The currently proposed DBP rule specifies total organic carbon (TOC) as a required test method. Several different technical approaches are available and the only documented method has quality control deficiencies. This project is needed to

evaluate the published methods and instrumentation for TOC to determine whether they can achieve the required MDLs and precision. A documented method with full analytical quality control directions will be produced. To be practical, this new method must be validated by multi-laboratory testing.

Priority: High

EX.D.4—Low-level ClO_2 measurement A more sensitive laboratory method for chlorine dioxide will be needed if an ongoing CMA study on the reproductive effects of chlorite shows risk below 0.8 mg/L. The existing method has a detection limit deficiency.

Priority: Medium (until risk is clear; could be elevated to high priority)

EX.D.5—Real-time monitoring for disinfectant residuals Develop performance criteria for real-time, on-line, in-the-plant continuous monitoring technologies for disinfectant residuals to provide in-plant feedback control of their concentrations. This is needed for the proposed disinfection rule.

Priority: Low (except if developmental or reproductive risks become evident, could be elevated to high priority)

EX.D.6—PE studies for DBPs and disinfectants A requirement of the proposed rules is that laboratories participate in performance evaluation studies to meet the laboratory certification requirements of the rules. Some additional research will be required to develop procedures for preparing, stabilizing, and distributing DBP PE samples and statistically analyzing the results of the PE studies. Conduct performance evaluation studies of methods for disinfectants and DBPs.

Priority: High

b. Methods needed for Stage 2 DBP rule and the longer-term

The method for peroxides is a medium priority because peroxides are relatively unstable and decompose to form other substances. In addition, peroxides will be addressed in the Stage 2 DBP rule and therefore there is not an immediate need to develop improved methods. The real-time, in-plant monitoring of DBPs is a medium priority for the same reasons discussed above for monitoring of residuals. The improved method for aldehydes is a medium priority because of the uncertainties with the results of the ICR and because this information is not needed for the Stage 1 DBP rule. The priorities of the projects below may change, or additional projects may be required, depending on the ICR data, project findings under the exposure research described in the next section, health effects, and risk assessment information.

EX.D.7—Methods for peroxides Peroxides are believed to be formed in water treated with ozone. Exposure issues are uncertain and cannot be answered until research indicates whether these substances are produced in quantities that would be a concern. Develop research methods for the determination of peroxides that may form in water treated with ozone.

Priority: Medium (5 yrs, $100K for multi-laboratory validation)

EX.D.8—Real-time, in-plant monitoring of DBPs Develop real-time, on-line, in-the- plant or field continuous monitoring technologies for disinfection by-products to provide data on temporal variations in the concentrations of DBPs for exposure studies and in-plant feedback control of their formation.

Priority: Medium

EX.D.9—Improved method for aldehydes Aldehydes are formed in water treated with ozone. A major issue is the reaction of formaldehyde with chloramine (added to provide a disinfectant residual) to form cyanogen chloride. The method for aldehydes being proposed for the Information Collection Rule (ICR) is a research method which may not be a practical method for regulatory compliance monitoring. Develop an improved method for aldehydes that form in water treated with ozone.

Priority: Medium

2. What levels of DBPs are people exposed to via their drinking water supplies, and what is the population distribution of exposures?

State of the Science

The types and concentrations of by-products that are formed by different disinfectants are not fully known. A number of factors other than the disinfectant itself are known to influence the formation and type of DBPs, for example, variation in the amount of organic material in the source water, pH and water temperature (see Risk Management section of this chapter). Because the data base is incomplete, not all disinfection scenarios have been thoroughly studied, and there are few analytical methods for polar, water soluble and nonvolatile DBPs, this major question cannot be answered at this time.

The complexity of the exposure question is illustrated by a number of additional questions. When tap water is used to dilute frozen juices, make ice cubes, take showers, take baths, or make coffee, are consumers exposed to the same DBPs that are found at the treatment plant or to different substances? Since 40%-60% of the drinking water ingested by humans is associated with dietary intake, what effect does food processing and preparation have on DBPs? What happens to the DBPs found at

the treatment plant when the water is stored for long periods in reservoirs or tanks? What happens to these substances when the water is piped long distances, trapped for long times in dead-end pipes, or blended with water from different sources that has been treated differently? Presently we cannot fully answer any of these questions.

Although the drinking water regulations were intended to protect the consumer, except for THMs, very little is known about changes in DBPs and other substances that occur in the distribution system and the actual exposure by people to DBPs. The ICR will provide extensive DBP occurrence data within treatment plants and distribution systems, but mainly for chlorinated DBPs. This data will be used for developing and testing models for predicting DBP occurrence at consumer taps. In addition, several long-term research projects are needed to address these questions.

Research Topics and Priorities

a. Characterize types and concentrations of DBPs formed from different disinfectants and combinations

Research is needed to better characterize the types and concentrations of DBPs that are formed with chlorine as a function of water quality and disinfectant conditions. Similarly, research must address the types and concentrations of DBPs formed with ozone plus chlorine and chloramines as residual disinfectants, with chloramine alone, and chlorine dioxide alone, as a function of water quality and disinfectant conditions. The identification of new DBPs from alternate disinfectants is a high priority because the information from this project in conjunction with toxicity data can provide estimates of the risks from alternate disinfectants and thus help answer questions relating to the magnitude of the risks from alternative disinfectants. The methods for nonvolatile DBPs are a high priority because without these methods it will be impossible to accurately determine the occurrence of nonvolatile DBPs and thus estimate the risk from these chemicals.

EX.D.10—Identify new disinfection by-products from alternate disinfectants Identify previously unidentified organic DBPs in drinking water treated with alternative (nontraditional) disinfectants and determine the effects of operating conditions on DBP formation. This knowledge will allow more complete exposure assessments and risk assessments and will not be limited to the examination of XAD resin extracts, but will explore alternative extraction schemes.

Priority: High

EX.D.11—Methods for nonvolatile DBPs Develop extraction methods and advanced instrumentation to characterize the nonvolatile and difficult to extract organic and inorganic DBPs. This knowledge will allow the development of more practical analytical methods for both the regulatory program and permit more complete exposure assessments and risk assessments.

Priority: High

b. Evaluate factors that affect exposure levels, and assess human exposures to DBPs

All the projects, except the modeling of DBP exposure, are a medium priority because the data generated from these projects, while important, are not absolutely needed for completing the Stage 1 or 2 DBP rule (the majority of information on exposure will come from the ICR). The modeling of DBP exposure is a high priority because this information can be used in reducing the uncertainty in risk assessments and in providing more accurate estimates of the costs and benefits of the various rules.

EX.D.12—DBP changes in distribution systems Characterize the changes that occur in the distribution system including reservoirs, tanks, dead-end pipes, or in water blended with product from different sources that has been treated differently. Include the characterization of DBPs in all exposure field studies that collect drinking water samples. This work should be coordinated with distribution system studies in the Risk Management section. The results will allow more complete exposure assessments and risk assessments.

Priority: Medium

EX.D.13—DBP interactions with foods and associations with dietary intake Determine what effects disinfectants and DBPs have when they interact with other foods, e.g., frozen juices, coffee, etc. Determine what other substances are formed that impact human exposure and contribute to the risk assessment. Determine the influence of food preparation factors such as temperature and storage on the degradation of DBPs.

Priority: Medium

EX.D.14—Exposure to DBPs through showering and other household tapwater uses Determine human exposure to volatile DBPs through inhalation and dermal exposure during hot showers and hot tub baths. Expand limited existing data on trihalomethanes to the potentially more significant haloacetic acids, haloacetonitriles, haloketones, aldehydes, etc. Existing data on human activity patterns and existing household exposure models should be used. These exposure data are needed to complete the risk assessment.

Priority: Medium

EX.D.15—Markers of DBP exposure Discover the underlying biochemical reactions related to exposure by people to DBPs and use these as biochemical markers of human exposure. Do DBPs react with DNA or proteins and can markers of this exposure be found? This information could be critical to long-term risk assessment.

Priority: Medium

EX.D.16—Models of DBP exposure Develop models of human exposure to disinfectants and DBPs and validate these models with actual exposure data. The goal of this model development is to allow the calculation of actual human exposure to a variety of DBPs given knowledge of precursors in the source water, the treatment technology, consumption patterns, and the model being developed for the decay of disinfection residuals in the distribution system (see Risk Management section, project 3). Various models will be developed using surveys and ICR data.

Priority: High

EX.D.17—Exposure as a function of population distribution Conduct a series of studies to identify exposure as a function of age, behavioral patterns and environmental factors that affect water consumption. These studies should be done in conjunction with project EX.M.22.

Priority: Medium

EX.D.18—Tap water consumption and chemical contaminants The results will consist of two sets of tables. One set of tables will provide tap water intake in terms of milliliters/person/day and the other will be in terms of milliliters/kilogram bw/day. The tables will provide estimates of the mean with intervals, as well as estimates of the median with 90th, 95th and 99th percentiles. In addition, the tables will provide the sample size and estimated population for each distribution. Graphics for selected distributions will also be included. Further, tap water intake will be analyzed based on economic status and age; race and age; residential status and age; and geographic region and age. The four geographic regions include: the Northeast, South, Midwest and West.

Priority: High

Risk Assessment Research

Critical to establishing a regulatory strategy for drinking water is identifying those contaminants which pose the greatest risk to human health and, consequently, what treatments can be used to reduce these risks and at what cost? To characterize the magnitude and severity of adverse health effects associated with exposures to DBPs it is necessary to use the methods and tools of risk assessment. The central role of the risk assessment is to evaluate the scientific data, and to provide risk managers with qualitative and quantitative estimates of risks posed by specific waterborne agents. With this information different risk reduction options can be developed. Through the development and application of consistent methods and tools for integrating and interpreting the scientific data, risk assessment studies can provide the framework for comparing chemical and microbiological risks. Ideally such comparisons would be made on information taken from studies involving exposure to mixtures of DBPs and microbes actually present in the source and drinking water of various treatment and distribution systems. However, this is often not possible because of the lack of information on these whole mixtures, or alternative approaches for assessing multiple exposures and effects.

Congressional interest has recently focused on risk based decision making, with emphasis on better risk characterizations and on reducing uncertainties in risk assessment. The risk characterization should incorporate more realistic exposure scenarios, identify populations at high risk especially children, provide where feasible quantitative analyses of uncertainty and sensitivity analyses, and include estimates of risks from exposures to chemical mixtures. Risk characterization and comparison of DBPs and microbes, the final product of the risk assessment, will also provide perspective on assumptions and areas of uncertainty in the risk and exposure assessments.

1. How can we characterize the risk posed by exposure to specific and multiple or complex mixtures of DBPs in drinking water?

State of the Science

Current approaches for characterizing the risks associated with exposures to D/DBPS in drinking water contain many assumptions and uncertainties. Many of these problems relate to deficiencies in the underlying scientific data bases for individual contaminants and mixtures and the methods and models used in risk assessment. As mentioned before, much of the uncertainty in conducting risk assessments arises from not knowing what DBPs are formed and from a lack of toxicity data including inadequate human data, insufficient understanding of the mechanisms of toxicity, extrapolation of animal data to human and lack of interactions data for mixtures. Because of this lack of information, risk estimates for DBPs are only possible for a limited number of individual contaminants, and only qualitatively for disinfected waters from epidemiology studies. Consequently, EPA has developed a phased approach for characterizing the risks posed by exposure to DBPs. First, single chemical assessments will be conducted using improved methods for both qualitative and quantitative assessments of human risks associated with exposures to drinking water. Particular emphasis will be given to addressing risks

to children, pregnant women and elderly. In addition, EPA will evaluate previously conducted epidemiology studies to provide better estimates of actual risks based on existing information, and to assist in designing future epidemiology studies, if warranted. In the second phase, assessment efforts will use the information on dose and toxicity for single chemicals to predict risk associated with definable mixtures of agents, and to develop methods to assess risk based on generalizations across classes of DBPs.

Much scientific progress has been made in the development of alternate models for estimating noncancer risks levels for single chemicals. Traditionally, EPA risk assessments have been based on the most sensitive endpoint and data set unless it could be demonstrated that this endpoint was not relevant to human toxicity. Alternate approaches to analyzing data are being investigated to calculate risk estimates that use more of the available data and result in a risk assessment in which there is greater confidence both statistically and biologically. Because these approaches use more of the available data, they provide risk estimates that are closer to the actual risk. Because the methods incorporate varying endpoints and severity, some expression of the risk of adverse health effects from chemical exposures in excess of the MCLG can be developed. Depending on the nature of the data available, estimates using these models can provide incidence rates for any of the effects occurring in an exposed population. However, these models have been developed and tested using empirical data sets only and applied to a few well-studied pesticides. The application of these models for developing drinking water standards has not been tested nor compared with estimates developed using current approaches.

Additionally, EPA is revising the cancer risk assessment guidelines to place greater emphasis on route of exposure and mode of action when assessing the carcinogenicity of chemicals. The revisions will also recommend chemical-specific determinations of whether the dose response is linear or nonlinear, thus providing for a different quantitative approach than the no-threshold linearized multistage model.

As mentioned in the health effects research, EPA conducted a workshop on scientific considerations for conducting epidemiologic studies for cancer and exposure to chemical by products of drinking water disinfectants. The participants concluded that current studies are insufficient to conclude that the reported associations are causal or provide an accurate estimate of the magnitude of human risk. In addition to the recommendations discussed previously, the workshop participants suggested reanalysis of previously conducted interview-based case control studies using improved exposure estimates and analytical methods to determine the validity of these risks and to address confounding factors and bias not adequately excluded in previous reports such as Morris, et al. Reassessment of existing data will also assist in the design of feasibility studies for cancer and reproductive/developmental effects and determination if full-scale studies are warranted by addressing systematic errors and biases of previous studies.

In addition to applying improving risk assessment methods for individual DBPs, advancements are being made in risk assessment methods for mixtures. Typical human exposures to DBPs are from low doses of multiple chemicals from multiple routes and can be either continuous, episodic, chronic, subchronic or acute exposures. However, most of the available laboratory toxicity data provide information on single chemicals or binary pairs rather than on the mixture as a whole. Additionally, animal laboratory studies on whole mixtures have been hampered by the difficulty of developing representative concentrates of DBP mixtures. Therefore, established drinking water standards are based on risk assessments for individual chemicals and epidemiologic data. The Agency has not yet characterized risks from interactions among pollutants and their consequent effects on human health. The movement toward complete risk characterizations incorporates a need to realistically describe exposure scenarios at various drinking water facilities and thus to include the risks from exposures to chemical mixtures.

However, for any mixture of concern, data are generally insufficient to characterize the risks: not all components of the mixture will be known, the proportions of the known components will be uncertain, interaction effects data on combinations of the components will be sparse, and epidemiologic data on human health effects will be rare. Currently, EPA is developing drinking water feasibility studies that will provide better methods for identifying and quantifying mixtures components, improve sample preparation and study design for animal testing, and improve the analytical tools needed to use human data.

Despite these limitations, significant advances have been made in theoretical development and application of risk assessment methods for characterizing the risks from complex mixtures. These methods use data from single chemical components or similar mixtures to generalize across classes of chemicals or mixtures. If studies cannot be designed to adequately address the issues described above, then the application of these methods along with improved exposure data and health information on simple mixtures can be used as alternative methods for estimating risks from more complex mixtures.

In addition to specific drinking water projects, EPA is conducting research in other problem areas to develop scientifically valid approaches for implementing PBPK models and sensitivity analysis in mixtures risk assessments. This research is aimed at identifying those parameters which most influence the dose response for a chemical or mixture. Research is also being conducted that will test approaches for assessing risks for complex mixtures using both observational data on the mixture itself from existing human studies and data on individual

components of the mixture. These methods may have application to drinking water mixtures once validated.

The Agency has recently released a risk characterization policy that addresses the need for more informative and consistent approaches for communication of Agency risk assessments to decisions makers and the public. The risk characterization provides an evaluation of the assumptions, uncertainties, and selection of studies and models used in the risk assessment. Development of a risk characterization will be required for every Agency risk assessment.

Research Topics and Priorities

a. Characterizing risks of individual DBPs

In order to characterize the risks associated with exposure to disinfectants and disinfectant by-products, quantitative risk assessment models that have been developed for dose-response modeling need to be applied to both existing human data and animal laboratory data. Estimates developed by improved methods need to be compared against existing values in order to address uncertainties and assumptions. These projects are high priority because they will be used to establish MCLGs, provide information needed for characterization of risks for each chemical, and provide information for conducting cost and benefit analysis.

RA.D.1—Cancer risk assessments (Ongoing) Reanalyze cancer risk assessments for D/DBPs including chloroform, bromodichloromethane, dibromochloromethane and bromoform, di- and trichloroacetic acid, chloral hydrate and bromate using the revised Agency cancer risk assessment guidelines and improved dose-response modeling where appropriate. Reassessments of cancer dose-response data and risk characterizations have been completed for DCA and chloroform applying the new cancer guidelines. A workshop was conducted by ILSI to discuss these case studies and an independent expert peer review panel is evaluating case studies.

Priority: High

RA.D.2—Cancer combination study for bromates Case study examining the validity of combining bromate data sets prior to modeling and calculating a pooled slope factor. Also includes the modification of risk assessment software to support computer program for use in developing other DBP cancer estimates. Several papers have been published in peer reviewed journals. In addition this method has been presented in the proposed cancer guidelines and as such has undergone extensive peer review and public comment as an alternative statistical approach for assessing dose-response data. Case study for bromate has been completed and a journal publication is being developed.

Priority: High

RA.D.3—Noncancer risk assessments (Ongoing) Prepare full risk assessment for disinfectants and DBPs, including di- and trichloroacetic acid, bromo and dibromochloroacetic acid, four THMs, chlorine, chlorine dioxide, chloramine, chlorite and chloral hydrate. Incorporate benchmark and categorical regression analyses. A benchmark for TCA has been completed and presented at the Society of Toxicology meetings in March 1997. A journal article is in preparation. Additional assessments will be conducted on high priority Stage 1 and Stage 2 DBPs as newer data become available. In addition preliminary assessments will be conducted on newly identified DBPs to identify data gaps and research needs.

Priority: High

RA.D.4—Risk characterization Develop risk characterizations for selected disinfectants and DBPs which implement the revised Agency policy. Risk assessments for chlorine, chloramine, chlorine dioxide and chlorite, THMs, HAAs and chloral hydrate, and bromate have been developed; however, the uncertainties and assumptions associated with those risk estimates have not been fully characterized. Include the development of a risk characterization model for estimating variance in uncertainty factors applied to cancer and noncancer estimates; particular emphasis will be given to identifying and characterizing risks to children and higher-risk subpopulations. This will be particularly useful in comparing cancer estimates (i.e. upper-bound vs maximum likelihood estimates). In preparation for the final promulgation of Stage I DBP Rule a risk characterization is being developed for chlorine and chloramine as well as several other DBPs.

Priority: High

b. Characterizing risks from chlorinated waters

Although many of the epidemiologic studies have methodologic problems or systemic biases that limit the interpretation of results, the application of consistent statistical tools and improved methods and data on exposure to chlorinated water or DBPs will provide greater understanding of the reported risks. Reassessment of existing data will address confounding factors identified in earlier studies and assist in the design of feasibility studies for cancer and reproductive/developmental effects and determination if full-scale studies are warranted. These studies are high priorities because they are aimed at reducing uncertainties in cancer and reproductive assessments and providing more realistic

estimate of actual risks as well as a common methodology for evaluating risks associated with chlorinated water. In addition, where possible quantitative estimates will be used for comparative risk analyses with risks from pathogens.

RA.D.5—Evaluate newer epidemiologic studies (Ongoing) Four new studies evaluating the possible association between drinking water and adverse health outcomes have been conducted since the publication of the meta-analysis of chlorinated drinking water studies. A review of these studies and data using methods/approaches applied to earlier studies is being conducted to assess their impact on previous findings. The results of this analysis will be included in the meta-analytical report currently being developed and included in the peer review workshop.

Priority: High

RA.D.6—Assessment of previously conducted studies (Ongoing) The objective of this effort is to develop and apply consistent statistical tools and improved methods for analyzing existing epidemiologic studies and data. Primary focus is to address confounding factors and biases identified in earlier studies and to assist in the design of future human studies. Reanalysis of a previous meta-analytical report is being conducted using several different meta-analytical parameters not previously applied. To date, previously published epidemiologic studies of total and various site-specific cancers, including bladder and rectal cancers, have been reviewed and re-evaluated as to their suitability for providing a valid summary estimate of relative risks. A comprehensive re-evaluation of the application of meta-analytical techniques to these data has been completed. A combination peer review/public participation workshop will be conducted to evaluate the technical merit of this report and implications for future epidemiologic studies and assessments in this area. The workshop will be conducted in the Fall of FY 97.

Priority: High

RA.D.7—Identify ongoing cancer studies (Ongoing) Identify cohort studies of dietary and case control studies of cancer risks recently planned or compiled or being conducted in areas with water exposures of interest. This information will assist in determining the need for future studies, targeting geographic areas for future studies and study design.

Priority: High

c. Methods and models to characterize risks from mixtures

Scientific advances in the development of innovative risk assessment tools in the area of study design, statistical methodology and computers models have been developed to estimate health risks from exposures to chemical mixtures.

For any mixture of concern, it is not possible to test all combinations of the components; therefore, risk assessors need methods that can be used to generalize risk estimates from the data that do exist. With this goal in mind, several feasibility studies have been designed to test their application to drinking water. Included in this research are models that characterize interactions of chemicals (i.e., synergism, additivity, or antagonism). These studies will provide estimates based on realistic exposure scenarios i.e., multiple chemicals, multiple routes. Another expected result from these studies will be the development of experimental design methods for assessing risks of multiple chemicals; currently, much of this research cannot be conducted using laboratory studies because of the large number of test animals needed.

These methodologies, if successfully developed, would have enormous impact on the evaluation of risk from exposure to multiple chemicals at drinking water treatment facilities and for source water quality studies. These studies are high priorities because they can provide better methods for quantifying the risks from mixtures, reduce the uncertainty in the current risk estimates for mixtures, and provide a framework for estimating relative risks associated with drinking water.

RA.D.8—Characterization of interactions for mixtures of DBPs Develop procedures and conduct studies to extract, evaluate and summarize interaction data from a number of studies and combine the results across studies and endpoints to define the type of interaction i.e., additivity, synergism or antagonism. This research involves the combining of risk estimates for mixtures of DBPs. It involves both biological and statistical evaluations of mixture data. Issues include, but are not limited to, similarity of mechanism of action across DBPs, incorporation of interaction data into risk estimates, appropriateness of combining data, and the analysis of variability and uncertainty of risk estimates.

Priority: High

RA.D.9—Threshold studies for D/DBPs Research is being conducted to build a dose-

response plane using experimental data from a mixture of trichloromethane, bromodichloromethane, dibromochloromethane and trichloromethane under the assumption of additivity for the single components. For any given point on this plane, the threshold for an adverse effect can be estimated for the mixture. Health effects data for the mixture are being developed by EPA and will be used to determine if the whole mixture response is greater or less than the additive, and also to test study design. Effort includes development of computer algorithms, testing of epidemiologic data and the development of an optimal study design for laboratory studies of mixtures. Goals include the detection of interaction effects, establishment of thresholds for the mixtures tested, comparison of chlorination with ozonation DBP mixtures relative toxicity by testing proportions of THMs reflecting actual treatment formation. Work is being conducted in two animal system models thereby allowing for the investigation into interspecies scaling factors.

Priority: High

RA.D.10—Use of QSAR model to estimate risk for single components and classes of compounds within a mixture Estimate an adverse effect level for DBPs with limited or no health effects data using QSAR. EPA data on mixtures of DBPs formed following various treatment trains such as chlorination plus chloramination could be used to estimate Lowest Observed Adverse Effect Levels (LOAELs) or genotoxic potential for single components and whole mixtures. Compare predicted estimates to measured values to confirm the accuracy and precision of the model. Primary focus for this effort is to evaluate and apply a system that can be used in conjunction with other short-term tests for estimating effects and relative risk levels. Additionally, efforts are being directed to employing this model in prioritizing and selecting newly identified DBPs of potential concern. Research is focused mainly on Stage 2 and future DBP assessment efforts. Currently, thirty DBPs are being evaluated.

Priority: High

d. Methods and models to compare risks

Comparative risk assessment is a relatively new initiative in risk assessment that has not been well defined. The result is a variety of definitions, approaches and applications. For drinking water, the focus is to develop a comparative risk model to measure and compare the known and potential health risks that might result from exposure to multiple stressors transmitted from the same drinking water source. For example, acceptably treated drinking water serves as a source of chemical (DBPs), biological (microbial), and physical (distribution system characteristics) stressors. Exposure to these stressors may result in a variety of adverse health outcomes including acute and chronic gastrointestinal illness, cancer, liver toxicity, and reproductive and developmental disorders. Despite scientific advances in identifying and quantifying the risks associated with any individual stressor, an appropriate methodology has not been developed that would allow us to assess these different risks in a similar way in order that they can be compared in a meaningful way. In addition, there is a paucity of data on the nature and magnitude of risk from these stressors.

RA.D.11—Comparative risk analysis Current comparative risks models for drinking water weigh the outcomes of microbial exposures to that of cancer from selected DBPs. Research needs to be conducted on a variety of models and methods that will allow for the development of a comparative risk assessment model which addresses multiple outcomes (e.g., cancer, developmental, reproductive, neurotoxic effects), their impacts and costs. This research should focus on the risk analysis and risk reduction benefits derived from minimizing exposures that would result in adverse outcomes other than cancer. Data will be developed for use in the regulatory modeling effort described in Chapter III. A comparative risk framework and strategic model has been developed for DBPs and is currently being validated and reviewed. SAB formal review of this approach is scheduled for the Spring of FY 98.

Priority: High

Risk Management Research

How effective are various treatment processes in minimizing and controlling the formation of DBPs?

State of the Science

Naturally occurring materials, such as humic and fulvic acids and bromide, which are present in many surface water sources react with chemical disinfectants to produce disinfection by-products. Factors affecting the formation of disinfection by-products include the nature of the source water and content of precursor materials, the water temperature and pH, and conditions under which the disinfectant is used, such as the concentration, contact time, point of addition, and the residual maintained. Control strategies must consider these factors because they affect both the formation of specific by-products and other potential risks. For example, raising the water pH to control lead corrosion may decrease the formation of haloacetic acids, but it increases trihalomethane formation and results in a species of chlorine that is a less effective disinfectant.

Several options are available for the control of disinfection by-products: 1) removal of precursor material before disinfection, 2) changes in the disinfection process or

use of a disinfectant that will minimize the formation of selected by-products, 3) removal of disinfection by-products after they are formed. The various treatment technologies are very similar with regard to their overall effect on disinfection by-product formation. Disinfection by-products tend to increase in time so that moving the point-of-disinfection to the end of the water treatment process is an inexpensive modification that can reduce the formation of by-products without substantially increasing microbial risks, provided an adequate disinfection contact time is maintained. Appropriate coagulation and clarification can effectively remove precursors, and this treatment can be adjusted for the enhanced removal of natural organic matter, thereby minimizing by-product formation potential.

Numerous studies have been conducted on DBP formation and control. Early bench-scale studies conducted by EPA, AWWARF and others examined the factors affecting the formation of trihalomethanes (THMs), the kinetics of the reaction, and means of assessing precursor, i.e., THM formation potential. Numerous field-scale studies were conducted examining modifications to the practice of chlorination, alternatives to chlorine (chloramine, chlorine dioxide and ozone), and removal of precursor, principally by granular activated carbon (GAC). More recent research conducted by AWWARF and EPA has included haloacetic acids (HAAs), total organic halide (TOX), chloral hydrate (CH), haloacetonitriles (HANs) and other DBPs as targets for removal. Isotherms and kinetic studies are being conducted to provide inputs to GAC models and improved GAC models were developed. Numerous pilot- and full-scale GAC studies are being conducted in the field, including on-site reactivation of spent GAC. Other means of precursor control are currently being studied, including membranes, enhanced coagulation and, more recently, biological filtration. The ICR will collect bench- and pilot-scale data characterizing GAC and membrane performance on high TOC waters throughout the U.S.

Results from the research to date indicate that enhanced softening may be effective in removing Total Organic Carbon (TOC) which is a measure of the precursor material for disinfection by-products. Studies have also shown that biological filtration may be an effective tool for removing both precursors and protozoa simultaneously. It was also learned that control of pH in biological and conventional treatment can minimize the formation of the five haloacetic acids to be regulated. Membranes have shown promise for removing precursors and pathogens simultaneously and may be especially useful in small-system applications. Although biological treatment using ozone is effective for removing precursors and controlling protozoans, it has by-products of its own that must be evaluated.

Critical questions that must be answered are as follows: To what extent can surrogates be used to indicate effectiveness of treatment, e.g., TOX, TOC; and, what operational concerns pertain to the different technologies? The projects selected for research in this section are intended to define the variables that influence the formation of DBPs. These projects also address concerns of the simultaneous reduction of risks from microbial and chemical contaminants.

Bench- and pilot-plant studies will initially be conducted to assess different technologies and approaches. This will be followed by field studies (see RM.M.5) to evaluate the more promising technologies. In general, these field studies will be conducted at sites where these technologies are being utilized by certain utilities, such that we can conduct parametric evaluations of the important operating parameters and make comparisons with full-scale operations.

Research Topics and Priorities

a. Effectiveness of different treatment processes in reducing DBP precursors (as a function of water quality and system size)

Research is needed on the effects of enhanced coagulation and enhanced softening on the operation of filtration processes. Recent EPA studies indicated the pH of filter operation was critical to aluminum solubility and filter run time, and that membrane materials are fouled by different types of organic substances. For utilities facing control of both precursors and pesticides, assessment of their control by oxidative and biological processes is needed. The causes and prevention of membrane fouling, and the reliability of scaling up from bench-scale membrane studies need to be evaluated.

Projects that develop treatment and operational criteria for technologies for DBP precursor removal and also assess their efficacy to reduce microbial or chemical contaminants were all considered a high priority. The membrane scale-up and fouling research was assigned a medium priority because results from a related AWWARF study and data provided by utilities as the result of their ICR membrane studies may prove adequate.

RM.D.1—Enhanced softening for precursor and pathogen removal Assess TOC removal by lime softening. Study filter operations associated with enhanced softening. Assess filter run time, particulate and pathogen control, and corrosion implications downstream of enhanced softening.

Priority: High

RM.D.2—Effects of ozonation and biofiltration for control of precursor, pathogens and for pesticide removal

a.—Control of precursor, pathogen and pesticide removal Evaluate ozonation and biofiltration for control of precursors and pathogens. Assess oxidation and biodegradation of precur-

sor materials. Include control of pesticides by ozonation and biodegradation.

Priority: High

b.—Effect of pH on ozonation and enhanced coagulation Evaluate the effect of pH on ozonation and enhanced coagulation. Recent EPA studies indicated levels near the proposed Stage 2 MCLs for TTHM and HAAs could be met with these processes. It has been found that low pH enhances coagulation and minimizes bromate formation. High pH promotes oxidation by hydroxyl radicals. Study variations in pH since pH affects aluminum solubility and filter run time.

Priority: High

RM.D.3—Analyze ICR data from GAC, membrane bench and pilot studies Analyze data collected from ICR activities involving bench and pilot studies using GAC and membrane technology. Cost and performance data will be developed from this project.

Priority: High

RM.D.4—Removal of DBP precursors by GAC and membranes ICR bench and pilot studies will provide performance and cost data for different water quality conditions.

a—Evaluation of membrane reliability Evaluate membrane reliability for multiple contaminant removal using bench and pilot studies. Conduct a pilot study at a full-scale water plant to evaluate nanofiltration.

Priority: Completed

b—Evaluation of GAC Evaluate GAC for multiple contaminant removal at bench and pilot scale.

Priority: Completed

RM.D.5—Membrane scale-up and fouling Conduct bench- and pilot-scale membranes studies in parallel to assess the appropriateness of bench-scale membranes to predict larger-scale performance. Examine techniques to limit membrane fouling.

Priority: Medium

b. Effectiveness of using different disinfectants in limiting DBP formation

Research is needed on the use of biological treatment for the control of ozone DBPs, and the control of Assimilable Organic Carbon (AOC) and Biologically Degradable Organic Carbon (BDOC). AOC and BDOC are measures of microbial nutrients that could promote distribution system regrowth. Questions to be answered include: to what extent can chlorite/chlorate by-products of ClO_2 be removed or formation limited; to what extent can bromate formation be limited while using ozone; and, for which water qualities are combinations of ozone/chloramines appropriate for primary residual disinfections without increasing bacterial growth? Because ozone promotes regrowth of organisms in distribution systems, nutrient control is very important. Improving the understanding of how, and the extent to which, ozonation by-products and AOC formation can be controlled is considered a high priority for assessing the risks and the benefits associated with the use of ozone.

RM.D.6—Ozone by-product formation and control

Evaluate technologies for control of AOC and BDOC. Examine factors affecting formation of ozone DBPs, AOC and BDOC by ozonation and control by biofiltration. Assess bromate formation. This project relates to RM.M.14 and RM.M.26.

Priority: High

c. Small systems technologies for precursor and DBP control

Small systems pose a special problem because of the economic limitations on most small communities. Developing inexpensive, low-maintenance technologies to control disinfection by-products is considered a high priority.

RM.D.7—Membranes/advanced oxidation and other technology combinations Preliminary results indicate that a combination of ultrafiltration membranes with advanced oxidation processes results in reduction of organics, lower DBP formation, and less mutagenicity than typical treatment trains with post-chlorination. Conduct additional investigations of these approaches individually and in combination for oxidation processes as UV, UV irradiated TiO_2, iodinated resins, hydrogen peroxide, and on-site mixed oxidant generators.

Priority: High

Table IV-2. Research Priorities for Health Effects for Disinfection By-Products

Research Topics	Proposed Projects	Priorities
DBP Epidemiology		
a. Development/application of improved tools for field research	HE.D.1—Improving estimates of residential DBP exposures in epidemiology studies	*
	HE.D. 2—Improving measures of biologic effect: Field evaluation of biomarkers	High
	HE.D.3—Improving methods for managing health and exposure data	High
b. Feasibility/full-scale studies	HE.D.4—Feasibility studies: Cancer	High
	HE.D.5—Feasibility studies: Repro effects	High
	HE.D.6—Full-scale studies: Cancer and repro	**
DBP Toxicology		
a. Hazard identification and dose-response	HE.D.7—Cancer dose-response studies	High
	HE.D.8—Repro/developmental effects screening studies	High
	HE.D.9—Neurotoxicity studies	Medium
	HE.D.10—Immunotoxicity studies	Medium
b. Pharmacokinetics and mechanisms of action	HE.D.11—Pharmacokinetic and mechanistic research—cancer	High
	HE.D.12—Pharmacokinetic and mechanistic research—reproductive effects	High
c. DBP mixtures	HE.D.13—Mixtures feasibility study	High
	HE.D.14—Toxicologic evaluation of mixtures	**
	HE.D.15—Mutagenicity screening studies of mixtures	High
	HE.D.16—DBP interactions	Medium

* See projects under part 2.b. of DBP Exposure section.
** Priority depends upon outcome of feasibility studies.

Table IV-3. Research Priorities for Exposure to DBPs

Research Topics	Proposed Projects	Priorities
DBP Methods		
a. Additional methods or method improvements needed to implement the Stage 1 DBP rule	EX.D.1—Low-level bromate measurement	High
	EX.D.2—Improve method for haloacetic acids	High
	EX.D.3—Expand quality control for TOC, evaluate new TOC methods	High
	EX.D.4—Low-level ClO_2 measurement	Medium
	EX.D.5—Real-time monitoring for disinfectant residuals	Low
	EX.D.6—PE studies for DBPs and disinfectants	High
b. Methods needed for Stage 2 DBP rule and the longer term	EX.D.7—Methods for peroxides	Medium
	EX.D.8—Real-time, in-plant monitoring of DBPs	Medium
	EX.D.9—Improved method for aldehydes	Medium
DBP Exposure		
a. Characterize types and concentrations of DBPs formed from different disinfectants and combinations	EX.D.10—Identify new disinfection by-products from alternate disinfectants	High
	EX.D.11—Methods for nonvolatile DBPs	High
b. Evaluate factors that affect exposure levels, and assess human exposures to DBPs	EX.D.12—DBP changes in distribution systems	Medium
	EX.D.13—DBP interactions with foods	Medium
	EX.D.14—Exposure to DBPs through showering	Medium
	EX.D.15—Markers of DBP exposure	Medium
	EX.D.16—Models of DBP exposure	High
	EX.D.17—Exposure as a function of population distribution	Medium
	EX.D.18—Tap water consumption	High

Table IV-4. Research Priorities for Risk Assessment for DBPs

Research Topics	Proposed Projects	Priorities
a. Characterizing risks of individual DBPs	RA.D.1—Cancer risk assessments	High
	RA.D.2—Cancer combination study for bromates	High
	RA.D.3—Noncancer risk assessments	High
	RA.D.4—Risk characterization	High
b. Characterizing risks from chlorinated waters	RA.D.5—Evaluate newer epidemiologic studies	High
	RA.D.6—Assessment of previously conducted studies	High
	RA.D.7—Identify ongoing cancer studies	High
c. Methods and models to characterize risks of DBP mixtures	RA.D.8—Characterization of interactions for mixtures of DBPs	High
	RA.D.9—Threshold studies for D/DBPs	High
	RA.D.10—Use of QSAR model to estimate risk for single components and classes of compounds within a mixture	High
d. Methods and models to compare risks	RA.D.11—Comparative risk analysis	High

Table IV-5. Research Priorities for Risk Management of DBPs

Research Topics	Proposed Research	Priorities
a. Effectiveness of different treatment processes in reducing DBP precursors (as a function of water quality and system size)	RM.D.1—Enhanced softening for precursor and pathogen removal	High
	RM.D.2—Effects of ozonation and biofiltration for control of precursor, pathogens, and for pesticide removal	
	a. Control of precursor, pathogen, pesticide removal	High
	b. Effect of pH on ozonation and enhanced coagulation	High
	RM.D.3—Analyze ICR data from GAC, membrane bench and pilot studies	High
	RM.D.4—Removal of DBP precursors by GAC and membranes	Completed
	RM.D.5—Membrane scale-up and fouling	Medium
b. Effectiveness of using different disinfectants in limiting DBP formation	RM.D.6—Ozone by-product formation and control	High
c. Small systems technologies for precursor and DBP control	RM.D.7—Membranes/advanced oxidation & other technology combinations	High

☆U.S. GOVERNMENT PRINTING OFFICE: 1998 -650-001/80182