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Report to Congress

EPA Studies on Sensitive Subpopulations and Drinking Water Contaminants

EXECUTIVE SUMMARY

The Safe Drinking Water Act (SDWA) requires the U.S. Environmental Protection Agency (EPA) to establish national drinking water standards that protect the health of the 250 million people who get their water from public water systems. These standards are intended to protect the general public as well as those groups of individuals who may be more sensitive than the general population to the harmful effects of contaminants in drinking water. The high priority assigned to studies of sensitive subpopulations and to the drinking water research program in general reflects the Agency's commitment to ensuring that regulatory decisions on microbiological and chemical contaminants in drinking water have a strong scientific foundation for public health protection.

The 1996 SDWA Amendments (Section 1458(a)) include the following requirements for conducting studies on sensitive subpopulations:

> (1) The Administrator shall conduct a continuing program of studies to identify groups within the general population that may be at greater risk than the general population of adverse health effects from exposure to contaminants in drinking water. The studies shall examine whether and to what degree infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that can be identified and characterized are likely to experience elevated health risks, including risks of cancer, from contaminants in drinking water.
>
> (2) Not later than 4 years after the date of enactment of this subsection, and periodically thereafter as new and significant information becomes available, the Administrator shall report to the Congress on the results of the studies.

This document is the first Report to Congress on the status, results and future directions of studies conducted by the EPA to identify and characterize sensitive subpopulations that may be at greater risk from exposure to drinking water contaminants than the general population. Sensitive subpopulations are defined in this report as groups of individuals who respond biologically at lower levels of exposure to a contaminant in drinking water or who have more serious health consequences than the general population. EPA is conducting a program of studies to identify such groups -- which may include infants, children, pregnant women, the elderly, or individuals with a history of chronic illness -- and to evaluate whether and to what degree they are likely to experience elevated health risks.

The studies conducted or supported by EPA have been guided by the Agency's research plans and strategies, expert workshops on special topics, and consultations with other agencies, research organizations, and the drinking water community. Partnerships with Federal agencies, the water industry, universities and other research entities have been essential to the successful implementation of the Agency's program to address this issue. EPA studies of sensitive subpopulations involve multidisciplinary research and assessments to identify the scope of possible

health outcomes, including cancer, reproductive toxicity, gastrointestinal illness, and other adverse health effects. Approaches being used to address sensitive subpopulation issues include:

- Population-based epidemiology studies to identify potentially harmful contaminants, risk factors and sensitive subpopulations;
- Clinical studies to evaluate the effects of specific contaminants and the host factors that influence the disease process;
- Studies in laboratory animals to provide hazard identification and dose-response data, as well as to elucidate how contaminants cause their effects;
- The development and validation of standardized test methods for the evaluation of contaminants that may be of special concern to certain subpopulations;
- The development of improved methods and data bases to better estimate total exposures to drinking water contaminants from all relevant sources and routes (i.e., oral, dermal and inhalation);
- The compilation of existing data to assist in characterizing specific sensitive subpopulations; and
- The development of improved risk assessment methods that will permit better use of all available information on health effects and exposure.

Important factors that are being investigated include life stage (i.e., fetuses, infants and children, the elderly), gender, genetic traits, health status and exposure. Research has focused on the highest priority waterborne pathogens and chemicals from a public health and regulatory perspective. The parasite *Cryptosporidium*, for example, has been reported to be the cause of over 14 outbreaks in the U.S. since 1985, including one in Milwaukee in 1993 that involved an estimated 400,000 illnesses and over 50 deaths. A large number of these deaths occurred in individuals with weakened immune systems. Data from the laboratory and field suggest that exposure to disinfection by-products (DBPs), which are formed when chlorine and other disinfectants react with naturally occurring materials in the water, may pose a risk of certain types of adverse health effects. The 1996 SDWA Amendments specifically identify these and several other contaminants as high priorities for research and regulatory determinations.

Highlights from the EPA program of studies on sensitive subpopulations are described below:

Waterborne pathogens. The results of an analysis of physiological and exposure-related characteristics of infants and children suggest that these groups may be more sensitive than the general population to waterborne pathogens. This is consistent with data collected on the demographics of foodborne illnesses, but the data from waterborne disease outbreaks in the U.S. are less conclusive. The results of several epidemiology studies and surveys that are currently underway should provide important information on the risks that pathogens in drinking water pose to infants, children, and other age groups. Individuals with pre-existing disease, particularly those with weakened immune systems, are known to be at increased risk following exposure to

opportunistic pathogens such as *Cryptosporidium*. EPA is conducting research in the laboratory and field to further evaluate the impact of host immune status on sensitivity to these agents.

Chemicals. Studies conducted by EPA and others have raised concerns about a potential risk of adverse reproductive outcomes following maternal exposure to DBPs. EPA research has also shown that exposure of laboratory animals to high levels of certain pesticides can cause adverse developmental effects. Current laboratory research on pesticide modes of action, along with epidemiology studies of childhood sensitivity to pesticides, will contribute to a better understanding of the potential risks of these contaminants to subpopulations of special concern. In studies to evaluate the health effects of sulfate, EPA researchers and collaborators found that piglets (as a model for human infants) and previously unexposed adults were not particularly sensitive to the effects of this contaminant in drinking water.

Considerable progress has been made in the development of improved methods for evaluating toxicity, assessing exposures, and conducting risk assessments of contaminants and subpopulations of special concern. These new tools will enable Agency scientists to generate critical data and conduct scientifically sound risk assessments in support of the requirements of SDWA and other regulatory statutes.

Future priorities include studies of DBP exposures and adverse reproductive outcomes, risks to infants and children from exposure to waterborne pathogens, and risks to individuals whose health status is compromised. The Agency will continue to support studies that further characterize risks to the elderly and that evaluate the role of genetic factors in environmentally-induced disease. Emphasis will also be placed on the development of improved methods for assessing toxicity, exposure and risk.

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1. INTRODUCTION

Studies to identify and characterize sensitive subpopulations are an important component of the U.S. Environmental Protection Agency's (EPA) drinking water research and assessment program. These studies provide scientific information to support current Safe Drinking Water Act (SDWA) rule making activities (e.g., the Stage 2 Disinfectants/Disinfection By-Product Rule) as well as future regulatory decisions on microbiological and chemical contaminants in drinking water. Sensitive subpopulation research that is conducted in support of other regulatory statutes is also relevant to drinking water issues. For example, both the Food Quality Protection Act of 1996 (FQPA) and 1996 Amendments to SDWA require the development of a screening and testing program to determine whether substances may have adverse effects on the endocrine (i.e., hormonal) system in the body. Collectively, these efforts provide critical information to ensure that public health standards for drinking water (e.g., Maximum Contaminant Levels, or MCLs) protect both the general population and subpopulations of special concern.

Section 1458(a) of the 1996 Amendments to SDWA requires the Administrator to conduct "...a continuing program of studies to identify groups within the general population that may be at greater risk than the general population of adverse health effects from exposure to contaminants in drinking water. The studies shall examine whether and to what degree infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that can be identified and characterized are likely to experience elevated health risks, including risks of cancer, from contaminants in drinking water. Not later than 4 years after August 6, 1996, and periodically thereafter as new and significant information becomes available, the Administrator shall report to the Congress on the results of the studies."

This report summarizes the status, results and future direction of the Agency's studies to identify and characterize sensitive subpopulations that may be at a greater health risk from exposure to drinking water contaminants than the general public. The focus of this report is on studies conducted or supported by EPA's Office of Research and Development and the Office of Water. Relevant sensitive subpopulation studies from other programs within the Agency are also summarized. To fully identify and characterize subpopulations that may be more sensitive than the general population to contaminants in drinking water, the results of EPA studies need to be considered in the context of the larger body of scientific literature on this topic.

Section 2 provides a definition of sensitive subpopulations and an overview of waterborne pathogens and chemicals of special concern. Section 3 describes the risk assessment framework and research approach used by EPA to address sensitive subpopulation issues. The status and results of EPA studies in the areas of health effects, risk assessment and exposure are described in Section 4. Section 5 includes a summary of the report and a discussion of future research directions. References are found in Section 6.

2. BACKGROUND

2.1 Definition of Sensitive Subpopulations

Sensitive subpopulations are defined in this report as groups of individuals who respond biologically at lower levels of exposure to a contaminant in drinking water or who have more serious health consequences than the general population. This definition also includes those individuals who have a greater level of exposure than the general population as a consequence of biological factors that are characteristic of the group to which they belong. As there is no universally accepted definition of the term "sensitive subpopulation," the definition used above is intended only for the purposes of this report.

Sensitive subpopulations may be considered in the context of various intrinsic (e.g., age, gender, genetic traits) or acquired (e.g., pre-existing disease, exposure) characteristics that may modify the risk of illness or disease. Some characteristics of subpopulations may directly influence the underlying processes involved in the response of an individual to a contaminant, such as when a pre-existing medical condition may make an individual less resistant to infection. Other factors, such as socioeconomic status or lifestyle, may have indirect effects. People with low incomes, for example, may not have the same access to health care as those in higher socioeconomic groups. The studies described in this report focus primarily on intrinsic and acquired factors that may directly influence sensitivity.

In some instances, sensitivity factors may be closely linked to each other. For example, the incidence of certain types of chronic disease appears to be related to age or gender. Additionally, people may cycle in and out of being more sensitive than the general population, depending upon their age or health status at a particular point in time. While intrinsic and acquired factors are therefore not entirely independent or fixed for the lifetime of an individual, they provide a useful basis for classifying and studying sensitive subpopulations.

Data on the number and percentage of individuals in some of the major subgroups in the U.S. are shown in Table 1. The data indicate that a significant portion of the population belongs to groups with characteristics that could make them more sensitive than the general population to the effects of environmental contaminants.

Among the many factors that may either directly or indirectly influence sensitivity, those discussed below are considered by EPA to be of greatest relevance for studying sensitive subpopulations exposed to drinking water contaminants.

Table 1. Selected Subpopulations[1] in the United States

Subpopulation	Number of Individuals	Estimated % of Population
Life Stage		
Pregnant women[2]	6,240,000	2.4
Infants and children (<10 years)[3]	38,704,000	14.1
Elderly (65+ years)[3]	34,817,000	12.6
Health Status		
Diabetes (diagnosed and estimated undiagnosed cases)[4]	15,700,000	5.8
Liver impairments[5]	595,000	0.2
Cardiovascular disease[6]	59,700,000	21.7
AIDS[7]	400,500	0.2

[1] Categories of subpopulations are not mutually exclusive.
[2] Ventura *et al.*, 1999.
[3] U.S. Census Bureau, 2000.
[4] CDC, 1998.
[5] EPA, 1998a.
[6] National Heart, Lung, and Blood Institute, 2000.
[7] CDC, 1999.

2.1.1 Intrinsic Factors

Life stage. This category includes groups that may be at increased risk because of inherent physiological factors or exposure characteristics that are unique to the particular period of development or age of the individual. These groups include:

- *Fetuses*, who may be at increased risk if exposure of the pregnant woman to a toxic agent occurs during critical developmental stages;
- *Infants and children*, whose defense mechanisms against microbial and chemical contaminants may not be fully developed;
- The *elderly*, who may be less able to mount an effective defense against microbial or chemical contaminants because of a weakened immune system or pre-existing disease.

Gender. Adult females or males may be more sensitive to the effects of certain contaminants because of gender-specific physiological factors or differences in the prevalence of certain types of diseases. For example, men appear to have a greater likelihood of liver impairments, whereas women are more prone to kidney and thyroid disorders. Pregnancy causes

changes in the endocrine system and metabolism, which may in turn influence the body's response to a toxic substance.

Genetic traits. The human body's ability to detoxify and eliminate a chemical agent or mount an effective defense against a microbial pathogen is related, in part, to the genetic make up of the individual. Groups of individuals who share certain genetic characteristics, such as the altered ability of a gene to produce a critical enzyme involved in the metabolism and detoxification of chemical toxicant, may therefore be at greater risk than the general population. As a practical matter, however, genetic influences are complex and still poorly understood. It is unclear to what extent individuals with heightened sensitivities due to genetic factors meet the statutory criterion of "subpopulations that can be identified and characterized."

2.1.2 Acquired Factors

Health status. Groups of individuals with certain pre-existing diseases or clinical conditions may be more sensitive to the effects of chemicals or microbes present in drinking water. For example, people with impairments of the liver, kidney or immune system may be less able to prevent or eliminate the effects of a contaminant due to weakened natural defenses or detoxification mechanisms. Immunocompromised individuals, including organ transplant patients, cancer patients being treated with immunosuppressive drugs, and those whose immune system is weakened by the virus that causes acquired immunodeficiency syndrome (AIDS), are also at increased risk following exposure to certain infectious and chemical agents.

Exposure. Some groups of individuals share certain biological characteristics that result in a greater level of exposure than that experienced by the general populations. For example, although infants consume less water than adults, they may have a higher likelihood of being exposed to toxic levels of a chemical contaminant because their water ingestion rate is three to four times greater when calculated on the basis of volume consumed per kilogram of body weight (EPA, 2000).

2.2 Contaminants of Concern

2.2.1 Waterborne Pathogens

The disinfection of public water supplies has been one of the most successful public health interventions of the 20th century, dramatically reducing the incidence of waterborne disease outbreaks throughout the world. Despite the historic success of modern drinking water treatment techniques, the continued occurrence of waterborne disease outbreaks demonstrates that contamination of drinking water with pathogenic bacteria, viruses, and parasites still poses a potentially serious health risk when treatment is inadequate or when there is contamination in the distribution system. The level of exposure, as well as the characteristics of both the microbe and the host, influence the outcome of infection. The most common health effect that occurs when a susceptible individual is exposed to an infectious dose of a waterborne pathogen from drinking water is an acute form of gastrointestinal disease. Infections are typically mild and transient, but

they may also result in more serious illness or even death in the most extreme cases. Some pathogens may cause longer-term effects, such as heart disease or liver failure.

The pathogenic bacteria most commonly associated with foodborne outbreaks and waterborne outbreaks from public and private water systems are *Escherichia coli, Salmonella, Campylobacter and Shigella* (Gerba *et al.*, 1996). Recently, *E. coli* O157:H7 was implicated as the cause of outbreaks in the U.S. and Canada in which several people died. The most commonly reported cause of waterborne viral gastroenteritis is Norwalk virus. This virus or other members of the calicivirus family are believed to account for a significant portion of the outbreaks for which a causative agent has not been determined. Hepatitis A virus and rotavirus have also been found to cause waterborne disease outbreaks, whereas the extent to which viruses such as coxsackievirus and echovirus may pose a risk following contamination of drinking water is unclear. The protozoan parasites *Giardia lamblia* and *Cryptosporidium parvum* are among the most threatening microbiological contaminants found in drinking water. *Giardia* has been responsible for about half of the outbreaks of disease where the causative agent was identified. *Cryptosporidium* has been responsible for at least 14 outbreaks in the U.S. since 1985, including a 1993 outbreak in Milwaukee which caused an estimated 400,000 illnesses and over 50 deaths. A large number of these deaths occurred in individuals with weakened immune systems.

Drinking Water Contaminants and Health Effects of Concern

Pathogens
- Bacteria (e.g., *Mycobacterium avium complex*, *E. coli* O157:H7)
- Viruses (e.g., Norwalk virus)
- Parasites (e.g., *Cryptosporidium, Giardia lamblia*)

Chemicals
- Disinfection by-products (e.g., trihalomethanes)
- Arsenic
- Sulfate
- Pesticides
- Other inorganic and organic contaminants

Health Effects
- Gastrointestinal illness
- Cancer
- Adverse reproductive outcomes
- Immune system effects
- Neurotoxicity

"Opportunistic" pathogens are microorganisms that normally do not pose a serious risk to healthy individuals but are more likely to cause disease (often severe) in individuals with weakened immune systems. *Cryptosporidium* and microsporidia are opportunistic protozoans that can cause life threatening illnesses in immunocompromised individuals. Opportunistic bacterial pathogens of concern include *Mycobacterium avium, Legionella* species and *Pseudomonas aeruginosa.* These microorganisms are able to grow and persist as biofilms on pipes in the distribution system.

2.2.2 Chemicals

A wide variety of naturally occurring and man-made chemicals may contaminate drinking water. These substances vary considerably in terms of the types and severity of effects that they elicit in both the general population and in groups that may be more sensitive. The extent to which a substance may be harmful is a function of exposure, the chemical and physical properties of the agent, and the inherent sensitivity of the host. At sufficiently high levels of exposure, chemicals may affect different organ systems and may cause a range of effects (e.g., irritation, liver disease, adverse reproductive outcomes, cancer). For some chemicals, the parent compound is responsible for the toxic effect, and the biochemical process called biotransformation (involving metabolism) is required to detoxify the substance. In other cases, the biotransformation process itself is responsible for the production of the toxic form of the contaminant.

A considerable amount of information exists on the special sensitivities of certain subgroups, particularly infants and children, to the drinking water contaminants lead, nitrate/nitrite and fluoride. Prenatal and postnatal exposures to lead have been shown to increase the risk of neurodevelopmental damage in infants and children. Nitrate and nitrite are known to pose a risk to infants whose immature enzyme systems cannot adequately protect hemoglobin, the oxygen carrying pigment in the red blood cells, from oxidation. The oxidized form of hemoglobin, called methemoglobin, does not carry oxygen effectively and can be life threatening without immediate medical attention. Fluoride can cause discoloration of the tooth enamel in children if exposure occurs during the period of tooth formation. EPA has developed National Primary Drinking Water Standards (MCLs) for lead and nitrate/nitrite that protect infants and children from harmful levels of these contaminants in drinking water. A secondary standard has been established for fluoride to protect children from discoloration of tooth enamel.

In the 1970s, scientists determined that a number of biologically active chemical substances, referred to as disinfection by-products (DBPs), are formed when chlorine and other chemical oxidants used to treat drinking water react with naturally occurring materials in the water. It is now known that disinfected water may contain hundreds of different DBPs, including trihalomethanes, haloacetic acids, haloacetonitriles, and a number of other types of chlorinated and/or brominated compounds. Some DBPs have been found to cause adverse health effects in laboratory animals exposed to high concentrations of these compounds. Epidemiology and toxicology studies have raised concerns over potential risks of cancer and, more recently, adverse reproductive effects.

Arsenic has been found to cause different types of cancer and noncancer effects in populations from various locations throughout the world. As noted by the National Research Council in their recent report on arsenic in drinking water (NRC, 1999), a variation in susceptibility to arsenic-induced effects may exist between population groups and individuals. The extent to which genetic background, gender and diet may influence sensitivity to this source water contaminant is unclear. Laboratory animal research on certain pesticides (e.g., chlorpyrifos) has suggested that the fetus and young animals may not have the same capacity as adults to detoxify and eliminate these substances from the body. Chemicals known as endocrine disruptors

affect the natural hormones in the body that are responsible for the maintenance of normal body function and the regulation of developmental processes. Small disturbances in endocrine function, especially during certain stages of the life cycle (e.g., development, pregnancy and lactation) can lead to profound and lasting changes.

3. OVERVIEW OF RESEARCH PROGRAM

3.1 Risk Assessment Framework

The process of risk assessment, as described by the National Academy of Sciences (NAS) in 1983, provides the framework used by EPA to identify key issues, information gaps and research needs for sensitive subpopulations (NRC, 1983). The NAS risk assessment paradigm, which was developed primarily for the assessment of chemical risks, has four main steps: hazard identification, dose-response assessment, exposure assessment and risk characterization. Although there are some features of microbiological risk assessment that make it distinct from the assessment of chemical risks (e.g., pathogen viability, infectivity and secondary spread), the NAS framework may be used as a guide for both types of contaminants. This Report to Congress focuses primarily on the first three steps of the risk assessment process. Health effects studies cover the first two steps (hazard identification and dose-response assessments), whereas exposure studies cover the third step. The Agency will conduct formal risk characterizations (step four) as part of the regulatory development process for specific contaminants of concern.

3.2 Identification and Prioritization of Research Needs

Studies conducted by EPA to address sensitive subpopulation issues have been guided by the Agency's research plans and strategies (EPA, 1997; 1998b; 1998c; 1999b), expert workshops on special topics (e.g., EPA, 1993; 1998d), and consultations with other Federal agencies and research organizations. In addition, a special series of meetings on sensitive subpopulations was held with drinking water stakeholders as part of the SDWA 25th Anniversary Futures Forum activities. Participants in these meetings emphasized the need for better information to characterize sensitive subpopulations, the contaminants that pose special risks, and the exposure levels at which the effects may occur.

EPA has placed considerable emphasis on research to address sensitive subpopulation issues for waterborne pathogens and chemicals on the current drinking water regulatory agenda (e.g., *Cryptosporidium*, DBPs). Studies are increasingly focusing on pathogens and chemicals that may be candidates for future regulations, including those on the EPA's Contaminant Candidate List[1] (EPA, 1998e).

3.3 Research Approach

[1]The EPA was required by SDWA to establish a list of contaminants, called the Contaminant Candidate List (CCL), to aid in priority setting for the Agency's drinking water program. The CCL contains 60 microbiological and chemical contaminants that are currently not subject to any proposed or promulgated national primary drinking water regulation, are known or anticipated to occur in public water systems, and may require regulation under SDWA.

Studies of sensitive subpopulations typically involve multidisciplinary research and assessments to identify a range of possible health outcomes, including cancer, reproductive toxicity, gastrointestinal illness, and other adverse health effects. EPA is using several approaches to address sensitive subpopulation issues: 1) population-based epidemiology studies to identify potentially harmful contaminants, risk factors and sensitive subpopulations; 2) clinical studies to evaluate the effects of specific contaminants and the host factors that influence the disease process; 3) studies in laboratory animals to provide hazard identification and dose-response data, as well as to elucidate how contaminants cause their effects; 4) the development and validation of standardized test methods for the evaluation of contaminants that may be of special concern to certain subpopulations; and 5) the development of improved methods and data bases to better estimate total exposures to drinking water contaminants from all relevant sources and routes (i.e., oral, dermal and inhalation). EPA is also compiling existing data to assist in characterizing specific sensitive subpopulations, and is developing improved risk assessment methods that will permit better use of all available information on health effects and exposure.

To address the broad scope of sensitive subpopulation research issues, EPA has established partnerships to leverage resources and capabilities with various Federal and state agencies, universities, the water industry and other public or private research entities. Collaborations have been established with the Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) and National Institute of Environmental Health Sciences (NIEHS) to address several high priority epidemiology and toxicology research needs. For example, EPA, CDC and NIEHS established eight Centers of Excellence in Children's Environmental Health and Disease Prevention Research. The Centers are conducting basic and applied research in combination with community-based prevention efforts. EPA and the American Water Works Association Research Foundation (AWWARF) are co-funding several important drinking water research studies under the auspices of the Microbial/Disinfection By-Products Research Council[2]. The Agency's extramural grants program supports research on waterborne pathogens, chemicals in drinking water and endocrine disruptors in universities and non-profit research organizations throughout the country. In addition, EPA has worked on endocrine disruptor testing and research issues in close collaboration with international organizations and advisory groups, particularly the Organization of Economic Cooperation (OECD) and Development and the Endocrine Disruptor Screening and Technical Advisory Committee (EDSTAC).

[2]The Microbial/Disinfection By-Product Research Council was established in 1995 by the EPA and AWWARF for the purpose of making funding decisions on cooperative research. The Council is composed of three EPA representatives, three members of the AWWARF Board of Trustees, and three representatives of the Disinfectant/Disinfection By-Product Rule Regulatory Negotiation group.

4. EPA STUDIES ON SENSITIVE SUBPOPULATIONS

Studies conducted or supported by EPA to identify and characterize sensitive subpopulations can be described in the context of the various intrinsic and acquired factors described in Sections 2.1.1 and 2.1.2. While many of the studies are still in progress, those that have been completed are providing important insights to improve risk assessments and guide future research activities. A description of EPA research and assessments on sensitive subpopulations is found below.

Factors Considered in Studies of Sensitive Subpopulations

Life stage
- Fetuses
- Infants and children
- Elderly

Gender

Genetic traits

Health status
- Pre-existing diseases
- Immune system deficiencies

Exposure

4.1 Life Stages

4.1.1 Fetuses

Disinfection by-products. One of the most important investigations to draw attention to the issue of DBPs and adverse reproductive outcomes was a prospective epidemiology study, funded in part by EPA, of 5,144 pregnant women in California (Waller *et al.*, 1998). The authors of this study reported an association between exposure to high levels of trihalomethanes and the incidence of miscarriage. The potential for DBPs to cause adverse reproductive outcomes was also examined in an EPA-funded study in Colorado, in which the authors reported an association between high trihalomethane levels and low birth weight (Gallagher *et al.*, 1998). These studies and a small number of other published reports have provided some clues suggesting that fetuses could be sensitive to DBP-induced toxic effects. However, the uncertainties in the epidemiologic data, particularly with respect to the exposure assessment, preclude a more definitive conclusion about the possible association between DBPs and adverse reproductive outcomes.

EPA is supporting several studies to address the need for additional information on this issue, including: 1) a reanalysis of the California spontaneous abortion study using improved exposure data; 2) an ongoing prospective pregnancy study in California to which information on DBP levels from selected drinking water utilities is being added; 3) a major new spontaneous abortion study in North Carolina, Virginia and Texas, co-funded with AWWARF; and 4) birth defects studies that are being conducted in conjunction with CDC's Centers for Birth Defects Research and Prevention in locations throughout the country. Efforts to improve the exposure assessment component of epidemiology studies are discussed in Section 4.5 of this Report.

To further explore the relationship between DBP exposures and adverse reproductive outcomes, EPA has developed an extensive extramural and in-house toxicology research program. A key feature of the extramural effort is a collaborative research project with the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences. NTP conducts screening studies in rodents using a standardized protocol to evaluate the effects of

DBPs on both male and female reproductive systems, as well as on fetal development. Studies have been conducted on a number of individual DBPs, and an evaluation of a mixture of four haloacetic acids is now underway. Sodium bromate and bromochloroacetic acid have been shown to exhibit selective reproductive toxicity at high experimental exposure doses (NTP, 1996; 1998). Additional studies are being conducted to follow up on these results in more detail.

EPA scientists are currently conducting animal studies on the potential for two DBPs, dibromoacetic acid and bromochloroacetic acid, to delay puberty and alter male reproductive competence in the offspring. Other ongoing studies are evaluating the effects of exposure to mixtures of DBPs on reproductive outcomes. A multigeneration study has been initiated to evaluate the potential effects of a priority DBP (bromochloroacetic acid) following long-term, low dose exposure throughout the life cycle of the experimental animal.

In 1998, EPA published a report that evaluated the available data for each of the disinfectants and DBPs, for which Maximum Residual Disinfectant Level Goals (MRDLGs) and Maximum Contaminant Level Goals (MCLGs), respectively, were developed in support of the final Stage 1 D/DBP Rule (EPA, 1998f). These nonenforceable health goals are set at exposure levels for which no known or anticipated adverse health effects occur, including an adequate margin of safety. On the basis of this analysis, EPA concluded that the MRDLGs and MCLGs for all the D/DBPs in the Stage 1 Rule were protective of fetuses, infants and children.

Arsenic. EPA scientists and collaborators are studying sensitive subpopulation issues for arsenic in regions of the world where the drinking water is highly contaminated. A study in Chile evaluated the potential association between exposure to arsenic in drinking water and the risk of mortality to the fetus and newborn infants (Hopenhayn-Rich *et al.*, 2000). While the results were suggestive of a possible association at high exposure levels, the data are still insufficient to allow firm conclusions. A second Chilean study is examining the possible association of low level exposure to arsenic with low birth weight, prematurity, and indicators of maternal health. A study to evaluate the health effects of arsenic has also been initiated by EPA researchers and collaborators in Inner Mongolia. A variety of health endpoints, including adverse reproductive outcomes, will be examined in an area with a wide range of arsenic concentrations in the drinking water supply.

Pesticides/endocrine disruptors. Under the EPA's research programs on pesticides and endocrine disruptors, a wide range of studies are being conducted to provide insights into risks that these chemicals pose to the developing fetus and to other life stages. EPA researchers have demonstrated that selected organophosphate, triazine and dithiocarbamate pesticides can cause adverse effects on the development of animals when exposure to high experimental doses occurs during critical periods of development (Cooper *et al.*, 1999). Current research on the mode of action of some of these agents is being conducted to help evaluate the extent to which these effects may be relevant to humans at the lower exposure concentrations that may occur in drinking water.

In support of both Food Quality Protection Act (FQPA) and SDWA, significant progress has been made in the development of standardized and validated methods for testing of chemicals that may have estrogenic or other endocrine effects in humans. Research has focused on the development of mammalian, non-mammalian and *in vitro* (i.e., cell culture) screening assays. The assays will be used to help identify chemicals that will require further testing, to provide information on the mechanisms by which they may cause their effects, and to help understand the stages of the life cycle that may be most susceptible to toxic insult with these substances. Some of these screening assays have reached the pre-validation stage. EPA estimates that all of the assays under development will be validated by 2003.

4.1.2 Infants and Children

Waterborne pathogens. To evaluate the factors that may result in a greater sensitivity of infants and children following exposure to waterborne pathogens, EPA is conducting a review of data on various physiological and exposure-related characteristics of these groups that can influence infection and disease outcome. The immaturity of the child's organ systems, particularly the immune system and gastrointestinal tract, is a factor that can increase the likelihood of infection and the severity of the illness. Inherent exposure-related physiological factors (e.g., a higher water ingestion per unit body weight compared to adults) may also contribute to a greater risk.

The issue of whether children are more likely than adults to experience waterborne gastrointestinal illness is being examined as part of a series of studies being conducted or supported by the Agency in different parts of the U.S. Researchers are evaluating the health status of families in three communities before and after the local water utilities upgrade their treatment systems. The results of the first of these "community intervention" studies will be available in FY2001. As part of the EPA/CDC program of waterborne disease occurrence studies (required by the 1996 SDWA Amendments), researchers from the University of California at Berkeley are conducting a large epidemiology study in a Midwestern community that may provide additional information on the extent to which children and other demographic groups are more sensitive to waterborne infectious disease. Beginning in 1998, EPA supported the addition of a water component to the CDC's Foodborne Diseases Active Surveillance Network (FoodNet). This multi-state gastrointestinal illness surveillance program is collecting information on the risks to children and other demographic groups from exposure to microbiological contaminants in food, drinking water and recreational water.

To determine the influence of age and other demographic parameters on sensitivity to microbial diseases and mortality, EPA conducted an analysis of data from FoodNet (prior to the inclusion of the water component) and from waterborne disease outbreaks that were reported through 1994 (EPA, 1998g). Information from FoodNet indicated that there have been many more cases of foodborne illnesses in infants and children than in other age groups. The waterborne disease outbreak data generally did not reflect a greater sensitivity of infants and children. These results should be interpreted with caution due to the incomplete nature of the

information examined and the possible influence of biases in reporting data for certain age groups (e.g., there may be a greater frequency of reporting cases in the very young and elderly by adult caregivers).

Chemicals. Several assessment-related activities are being conducted by the Agency to better characterize the risks to children following exposure to chemicals in drinking water. EPA will soon publish the results of a workshop in which experts reviewed information on critical "windows" of exposure during which time the developing organism (fetus, newborn, child and adolescent) may be particularly sensitive to the effects of selected chemicals. Other EPA projects that are underway include an assessment of the potential risk of childhood cancers associated with exposure to chemicals in drinking water, and an analysis of the potential relationship between early-life exposures and lifetime cancer risks. In addition to these efforts, EPA is evaluating innovative statistical approaches (i.e., Benchmark Dose and Categorical Regression) to determine their applicability in assessments of the dose-response in children for two drinking water contaminants, chloral hydrate and nitrate/nitrite.

In response to concerns about the potential sensitivity of infants to sulfate-induced diarrhea, the EPA supported a study using neonatal piglets as a model to evaluate the effects of inorganic sulfate in drinking water on bowel function in human infants (Gomez *et al.*, 1995). The results of this study did not indicate that infants may be particularly sensitive to sulfate, as the presence of sulfate in drinking water at levels of up to 1200 mg/L (as sodium sulfate) produced minimal or no adverse health effects. A similar absence of effects was observed in EPA-sponsored studies with adult volunteers who had no previous exposure to sulfates in drinking water (Heizer *et al.*, 1997). The results suggest that transient populations may not have a greater sensitivity to sulfate as had been previously suggested (EPA, 1999a).

EPA is supporting an epidemiology study of childhood sensitivity to pesticides in which several routes of exposure (i.e., ingestion, dermal and inhalation) to persistent organic compounds are being evaluated. In another study conducted as part of the National Health and Nutrition Examination Survey (NHANES), EPA is supporting data collection and analysis of serum or urine levels of several organochlorine, organophosphate and pyrethroid pesticides, as well as selected polychlorinated biphenyls (PCBs). Samples are being taken from approximately 1,000 children and young adults between 6 to 19 years of age, of which a subset will be assessed for deficits in thyroid function.

Finally, the Border XXI Program is a cooperative binational effort between several Federal agencies of the U.S. and Mexico to help ensure human and environmental health along the U.S.-Mexico border. As part of this program, EPA is conducting multimedia studies to characterize exposures of children to various pesticides and metals. The data will provide a basis to validate age-dependent exposure models that incorporate activity patterns, water consumption, diet and nutritional status.

4.1.3 The Elderly

As people age, sensitivity may change due to alterations in the way the body responds to a contaminant. Altered biochemical processes (e.g., metabolism) that are responsible for the detoxification or activation of a toxic agent may impact sensitivity to a chemical contaminant. A less active immune system or an increased likelihood of pre-existing disease may be risk factors for disease caused by waterborne pathogens. To obtain information on pre-existing diseases that are most common in the elderly, EPA collected data from several national surveys on the prevalence of chronic disease in the U.S. The surveys indicated that osteoporosis, cardiovascular disease, diabetes and hypertension are more prevalent in individuals over 65 years of age than in the remainder of the population (EPA, 1998a).

EPA's waterborne disease occurrence studies are examining the extent to which the elderly and other subgroups may be more susceptible than the general population following exposure to waterborne pathogens. With regard to chemical exposures, EPA researchers are developing a special animal model that can be used in studies to evaluate if older rodents may be at greater risk than other age groups from exposure to chemical contaminants. Results obtained to date indicate that the model may be a good tool for studying age-related toxic effects on the liver.

4.2 Gender

Adult males and females show distinct differences in the incidence of certain chronic disorders, the presence of which may reduce the ability of the affected individual to mount an effective defense against subsequent exposure to a waterborne pathogen or toxic chemical. Females appear to be more prone to anemia, osteoporosis, kidney problems and thyroid disorders, while males have a higher reported incidence of liver disease (EPA, 1998a).

EPA research has shown that exposure of adult female rodents to certain pesticides (e.g., atrazine) can cause changes in the regulation of reproductive function (Cooper *et al.*, 2000). To determine if similar results can be observed for DBPs, Agency researchers are examining if DBP exposures can impact hormonal cycles in nonpregnant female rodents. An EPA-funded study at Colorado State University is following up on findings by EPA scientists that sperm production in rodents exposed to high concentrations of selected DBPs may be adversely affected. These new studies are being conducted in rabbits, which have a longer period of reproductive development than that of rodents.

EPA studies with the haloacetic acid family of DBPs have demonstrated that certain brominated by-products can cause decreases in the sperm quality of male rodents following exposure to high experimental doses (Linder *et al.*, 1995). Studies are now underway to determine if these effects can be observed at lower exposure levels. In the course of these investigations, EPA researchers made an important scientific finding that could lead to the development of a sensitive biological marker, or biomarker, of male fertility (Klinefelter *et al.*,

1997). The specific protein on the sperm membrane (SP22) that is correlated with sperm fertility may serve as an invaluable tool for determining if low level exposures to DBPs are associated with adverse male reproductive effects. Furthermore, this biomarker could have public health implications that extend well beyond the original drinking water context for the research.

4.3 Genetic Traits

With the tremendous growth over the past decade in research related to the Human Genome Project, interest and knowledge regarding the genetic underpinnings of disease and susceptibility have greatly increased. As described below, EPA scientists have begun evaluating and applying new tools to study sensitive subpopulation issues for both waterborne pathogens and chemical contaminants in drinking water. The genetic influences on sensitivity to environmental contaminants are complex and only beginning to be understood. As a practical matter, it is therefore not clear to what extent such factors can be used to define groups that meet the statutory criterion of "subpopulations that can be identified and characterized."

Waterborne pathogens. Sensitivity to infection and disease caused by pathogenic bacteria, viruses or parasites is based in part on host susceptibility or resistance factors that may be under genetic control. Changes in sensitivity may be due to alterations in genes that are involved in the body's immune defense system or that code for certain receptors on the surface of host cells that are attacked by the infectious agent. Genetically induced changes in patients with an unrelated disease may predispose these patients to infections by waterborne pathogens.

The presence of these genes provides an opportunity to identify biomarkers of susceptibility. As described in a report that will soon be finalized by EPA, a review of the literature was conducted to identify potential biomarkers of susceptibility in animals and/or humans for ten waterborne pathogens: *Mycobacterium* species, *Helicobacter pylori*, *Pseudomonas* species, *Legionella* species, coxsackievirus, adenovirus, hepatitis A, *Entamoeba histolytica*, *Cryptosporidium*, and *Toxoplasma gondii*. Due to the highly complex nature of this issue, additional studies are necessary to determine the extent to which these biomarkers are useful in identifying subpopulations that may be more sensitive to infection with waterborne pathogens.

Chemicals. Metabolism, which is mediated by enzymes that are under genetic control, is known to play an important role in the toxicity of chemicals. Individuals with either a lower capacity to detoxify chemicals or a greater capacity to activate chemicals, due to variability in the quantity or activity of metabolic enzymes, may be at greater risk of cancer or other adverse health effects. EPA is conducting an analysis of genetic and other factors that may play a role in the metabolic detoxification or activation of chemical contaminants. This project involves an evaluation of data on the impact of age, gender, ethnicity, diet, common pharmaceuticals and behavioral characteristics (smoking, alcohol ingestion) for two important enzyme systems, the cytochrome P-450 isoforms and the glutathione-*S*-transferases. Related to this effort is a research project to determine the extent of human interindividual variability (adults and children) in the

expression of cytochrome P-450 isoforms in samples of human liver cells derived from organ donors. The ultimate goal is to develop a tool for identifying subpopulations that may be more sensitive because of inherent differences in the ability to metabolize chemical toxicants.

EPA investigators are conducting animal studies on one aspect of how genetic make-up may predispose some individuals to DBP-induced cancer. Specifically, efforts are being directed toward determining whether individuals whose blood cells express different forms or amounts of glutathione-*S*-transferases vary in sensitivity to the genotoxic effects of selected DBPs. This type of study could have broad applicability, since the glutathione-*S*-transferase family of enzymes comprises a fundamental detoxification mechanism for several classes of toxic substances.

EPA researchers are also using a rat model of hereditary kidney cancer to evaluate the influence of genetic predisposition on the risk posed by exposure to DBPs. The objectives are to determine whether this genetically-altered strain of rat is more sensitive to the effects of exposure to trihalomethanes, and if the resulting tumors share critical features of cancers that may be linked with human exposure to DBPs.

This line of investigation is being extended to other chemical contaminants. The metabolism of arsenic by enzymes under genetic control is believed to be an important determinant of its toxicity and carcinogenicity. Some data from the published literature suggest that the pattern and extent of arsenic metabolism may differ among individuals. Results of a study conducted by EPA researchers in an arsenic-exposed population in Utah showed no differences in the amounts of the various forms of arsenic found in the urine of adults and children (Calderon *et al.*, 1999), suggesting that arsenic may be metabolized in a similar manner in both of these subgroups. The data are being further analyzed to develop gender-related metabolic profiles. Related research in rodents includes efforts to develop an animal model for investigating genetically determined variations in the metabolism of arsenic, and studies to evaluate the influence of dietary constituents (e.g., folate and selenium) on this process.

Along with the increased interest in the genetic foundation of disease has come tremendous innovation in the tools for investigating gene expression. Two complementary techniques that are rapidly becoming essential for such research are DNA microarrays and genetic engineering. Microarrays are glass slides or nylon filters onto which are spotted thousands of genes (DNA). When complementary DNA obtained from a tissue sample is overlaid onto the spotted template, it binds to the arrayed genes and can be detected through the use of fluorescent probes or a radioactive label. In such a manner, investigators are able to rapidly screen how toxicants can influence the expression of thousands of genes at a time. Over the past year, EPA investigators have been collaborating with Federal, academic, and industry researchers to develop methods for applying this powerful technology to elucidate the genetic mechanisms of action of environmental toxicants, including DBPs. Once affected genes are identified, investigators can use genetic engineering techniques to further study how specific genetic abnormalities alter the risk posed by exposure to drinking water contaminants.

4.4 Health Status

As discussed earlier, individuals with a pre-existing medical condition may have reduced resistance to subsequent infection or toxic insult. Most of the studies conducted by EPA relating to health status have focused on individuals with weakened immune systems. The immune system is complex, involving a variety of different types of cells and processes that comprise an individual's defense system against infection or disease. Because of this complexity, many different approaches are used to test immune status following exposure to a toxic or pathogenic agent. To assist risk assessors in evaluating the results of these tests, EPA compiled information on the various assays and prepared a compendium that describes their strengths and weaknesses (EPA, 1998h).

EPA is conducting several different types of studies in the laboratory, clinic and field to evaluate the impact of host immune status on sensitivity. For individuals with weakened immune systems, particularly those with acquired immunodeficiency syndrome (AIDS) and patients on immunosuppressive drugs, infections with the pathogen *Cryptosporidium* can be life-threatening. EPA scientists and grantees are conducting research on various animal models to examine the impact of compromised host immune condition on infection with this parasite. Pilot epidemiology studies are evaluating the role of drinking water as a source of *Cryptosporidium* infections in a hospital setting and in a population that is positive for the virus that causes AIDS. EPA researchers and collaborators have also studied the role of drinking water as a source of another opportunistic pathogen that poses a special risk to people with weakened body defenses. In a recently published study (Aronson *et al.*, 1999), investigators found *Mycobacterium avium* in potable water from selected homes, large buildings and hospitals. Many of the isolates from the water and from immunocompromised patients were found to share similar patterns of genetic material. The methodology used in this study was inadequate for establishing a clear link between *M. avium* infections and exposure through the drinking water, but the results do provide a basis for additional studies being planned by EPA to further evaluate this issue.

EPA has supported several studies to determine the infectious dose and role of protective immunity in healthy human volunteers exposed to the pathogens *Cryptosporidium* and Norwalk virus. This research has suggested that a low number of pathogens is required to establish infections in healthy adults, and that (at least for *Cryptosporidium*) the immune system plays an important role in protecting people who have been exposed previously (Chappell *et al.*, 1999). These results further highlight the special risks that some pathogens can pose to individuals whose defense systems are compromised.

It has been well established that an individual with a weakened immune system is at greater risk of infection and serious illness following exposure to a microbial pathogen. If a chemical in drinking water is immunotoxic, this could render the individual more sensitive to infection with a waterborne pathogen. In the collaborative EPA/NTP toxicity screening program, researchers are evaluating the potential of five DBPs (dibromoacetic acid, sodium bromate, sodium chlorite, dichloroacetic acid and chloroform) and the disinfectant chloramine to cause immunotoxic effects in experimental animals. Screening studies have been completed on two of

the DBPs to date. Dibromoacetic acid was found to alter the immune response in an initial high dose study, and additional tests are now being conducted to further evaluate if effects can be observed at lower doses (NTP, 1999). Sodium bromate did not alter the immune responsiveness of treated animals (NTP, 2000).

4.5 Exposure

A critically important area of research to help identify sensitive subpopulations in DBP epidemiology studies is the development of improved data and methods for estimating exposures. Several approaches are being used, including: 1) developing and applying geographic information systems to better manage exposure and health data; 2) incorporating lifestyle questions (e.g., water consumption and use) into survey questionnaires to better gauge exposures to DBPs by the oral, dermal and inhalation routes; 3) using distribution system modeling techniques to estimate DBP exposures at or near the homes of study participants; and 4) determining concentrations of DBPs in blood samples for comparison with levels found in drinking water taken from the distribution system and home. EPA is also merging activity pattern data with existing multiple route exposure models to better estimate the variability in total exposure to DBPs for different population groups.

EPA is coordinating several studies to characterize multiple-source, multiple-route exposures to environmental contaminants across seven states. This effort involves a consortium of research organizations in the National Human Exposure Assessment Survey (NHEXAS). Two of the studies include representative samples of the general population, and a third study will compare urban and rural populations. Classes of contaminants being evaluated include pesticides, volatile organic compounds, and metals.

In conducting risk assessments on special populations of interest, it is important to consider information on levels of drinking water intake that may be specific to that particular group of individuals. Several approaches are being used to develop these intake data. EPA has conducted an extensive review of data on drinking water intake rates from the U.S. Department of Agriculture's Continuing Survey of Food Intake by Individuals (EPA, 2000). Intake of tap water, bottled water and water from other sources was evaluated. Water consumed directly as well as water used in the preparation of juices, coffee, reconstituted soup mixes and other similar foods were considered. The data were found to generally support the Agency's use of 2 L/day for adults and 1 L/day for children as upper-percentile tapwater intake rates. Pregnant women do not differ significantly in their water ingestion compared to women of child-bearing age. However, lactating women ingest significantly more water than pregnant or control (non-pregnant, non-lactating) women. When considering water ingestion in units of milliliters of water ingested per kilogram of body weight per day, babies younger than one year old have an ingestion rate that is approximately three to four times higher than that of the general population. It is reasonable to assume individuals who engage in vigorous work or exercise, particularly in warmer climates, have a higher daily intake of water than the general population. An analysis of consumption according to the source of the water indicates that community water supplies

account for 75% of the water consumed, followed by bottled water (13%) and spring, well and cistern water combined (10%).

Data on drinking water consumption patterns for various age groups and on the contribution of contaminants from drinking water exposures are also being evaluated from the NHEXAS project and other data sources. The results will be compiled into an updated childhood exposure factors data base. In addition, methods are being developed to better scale physiological parameters for children versus adults, which will lead to improved quantitative estimates of risk for children.

To assess total dietary exposure to contaminants, EPA has developed a PC-based Dietary Exposure Potential Model (DEPM). The model can help identify food and drinks that are relatively high contributors to contaminant exposure by consumption, and it can provide a relative exposure estimate for the consumption of tapwater only or tapwater used in food/drink preparation and food. The DEPM can also provide an estimate of exposure for populations based on age, ethnic origin, and region for contaminants included in various residue surveys. Currently, EPA is using the model in its risk assessment of arsenic to identify foods high in total arsenic content.

5. CONCLUSIONS

EPA is conducting and supporting a wide range of studies to identify and characterize groups that may be at greater health risk than the general population following exposure to contaminants in drinking water. Important factors that are being investigated include life stage (i.e., fetuses, infants and children, the elderly), gender, genetic traits, health status and exposure. Research to date has emphasized waterborne pathogens and chemicals from a public health and regulatory perspective, with efforts now expanding to address "emerging" contaminants that may be considered in future regulatory decision making. Because of the importance and broad scope of this issue, EPA has established collaborations and has leveraged funding for research with various Federal agencies, the water industry and other research entities.

The EPA studies that have been completed to date are providing important data to improve risk assessments and guide future research activities on sensitive subpopulations. New insights are expected within the next few years as the results of ongoing studies become available. To fully identify and characterize groups that may be more sensitive than the general population to contaminants in drinking water, the results of EPA studies need to be considered in the context of the larger body of scientific literature on sensitive subpopulations.

Major highlights of EPA's sensitive subpopulation studies on waterborne pathogens and chemicals in drinking water are summarized below:

Waterborne pathogens. The results of an analysis of physiological and exposure-related characteristics of infants and children suggest that this subpopulation may be more sensitive than

the general population to waterborne pathogens. This is consistent with data collected on the demographics of foodborne illnesses, but the data from waterborne disease outbreaks in the U.S. are less conclusive. The results of several epidemiology studies and surveys that are currently underway should provide important information on the risks that pathogens in drinking water pose to infants, children, and other age groups. Individuals with pre-existing disease, particularly those with weakened immune systems, are known to be at increased risk following exposure to opportunistic pathogens such as *Cryptosporidium*. EPA is conducting research in the laboratory and field to further evaluate the impact of host immune status on sensitivity to these agents.

Chemicals. Studies conducted by EPA and others have raised concerns about a potential risk of adverse reproductive outcomes following maternal exposure to DBPs. EPA research has also shown that exposure of laboratory animals to high levels of certain pesticides can cause adverse developmental effects. Current laboratory and field research on pesticides will contribute to a better understanding of the potential risks of these contaminants to subpopulations of special concern. In studies to evaluate the health effects of sulfate, EPA researchers and collaborators found that piglets (as a model for human infants) and previously unexposed adults were not particularly sensitive to the effects of this contaminant in drinking water.

Considerable progress has been made since the enactment of the 1996 SDWA Amendments in the development of improved methods for evaluating toxicity, assessing exposures, and conducting risk assessments of contaminants and subpopulations of special concern. These new tools will enable Agency scientists to generate critical data and conduct scientifically sound risk assessments in support of the requirements of SDWA and other regulatory statutes.

Based on a consideration of potential public health risks and the findings of studies to date, near-term research priorities include studies of DBP exposures and adverse reproductive outcomes, risks to infants and children from exposure to waterborne pathogens, and risks to individuals whose health status is compromised. A greater emphasis will be placed on research to examine the elderly as a possible sensitive subpopulation. Efforts will be made to take advantage of new advances in molecular biology to study genetic factors involved in environmentally-induced disease. The development and application of improved methods for toxicity evaluations, exposure assessment and risk assessment will also continue to be priorities. The results of these studies will help to provide a sound scientific basis for regulations and guidance to protect the public health of the 250 million people, including sensitive subpopulations, who get their water from public water systems.

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