

EPIDEMIOLOGIC STUDIES OF DISINFECTANTS AND DISINFECTANT BY-PRODUCTS

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Keywords: birth defects, cardiovascular disease, cancer, chloramines, chlorine, chlorine dioxide, chloroform, disinfection, disinfection by-products, haloacetic acids, ozone, spontaneous abortion, trihalomethanes.

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Summary

The disinfection of municipal drinking water, which began in the early 1900s, has prevented untold illness and death due to cholera, typhoid, and a myriad of other diseases that can be transmitted through contaminated water supplies. More recently, researchers have found that chemical disinfectants such as chlorine can react with naturally-occurring material in the water to form unwanted by-products (DBPs), some of which may be of public health concern. Although disinfection practices vary throughout the world, chlorine has been and continues to be the most frequently used water disinfectant. It is economical and relatively easy to apply. Other chemical disinfectants include chloramines (chlorine and ammonia), ozone, and chlorine dioxide. Each of these disinfectants produce DBPs but of a different mix and concentration. Relatively few DBPs have been identified and their health risks have not been well characterized.

Some chlorinated DBPs when fed in high doses to laboratory animals have been found to cause liver and kidney effects and may even cause tumors and adverse reproductive or developmental outcomes. Chlorine dioxide by-products can affect the red blood cells, and ozone by-products can cause tumors in animals at high doses. Epidemiologic studies that allow an assessment of health risks for exposures normally experienced by human populations have reported weak to moderate associations between the long-term consumption of chlorinated water and bladder cancer.

However, there is a lack of site concordance between the epidemiologic and toxicologic data in regard to bladder cancer risks, and the causality of reported associations has not been established. Epidemiologic associations have also been reported between the chlorination of water and adverse reproductive and development outcomes, but the data are sparse. Exposure assessment has been cited as a major limitation of the epidemiologic studies. Studies have evaluated exposures to chlorinated water and trihalomethanes (THMs), but few studies have considered chloraminated or ozonated water, individual THMs or other DBPs.

Providing safe drinking water is still a significant problem, as nearly one fifth of the world's population still lacks clean water. Drinking water disinfection is an important part of the water treatment processes. Because of its effectiveness, ease of application, and low cost, chlorine continues to be an important water disinfectant. Developed countries have set limits or guidelines for various DBPs, and officials in developing countries should fully understand the basis for these more restrictive DBP regulations. Costs to reduce DBPs to such levels in developing countries can be relatively high with an uncertain health benefit. These same DBP regulations may not be appropriate for consideration by developing countries where, with relatively modest costs, a significant reduction can be made in morbidity and mortality by focusing on waterborne microbial risks. Water system managers should consider ways to reduce DBPs, but in doing so, they should balance the microbial and chemical risks. Globally, waterborne microbial risks far outweigh the possible cancer, reproductive, or developmental risks that may be associated with the chemical disinfection of drinking water, and efforts to reduce DBPs in any country should not result in a disproportionate increase in microbial risks.

1. Introduction

During the past 25 years, concerns have been expressed about possible health risks associated with the chemical disinfection of drinking water and DBPs. The formation of DBPs is influenced by water quality (e.g., naturally occurring organic matter, bromide, pH, temperature, ammonia, carbonate alkalinity) and water treatment conditions (e.g., disinfectant dose, contact time, removal of organic matter before the point of disinfectant application). Moreover, the composition of these complex mixtures may change seasonally. Research has largely focused on chlorine and chlorinated DBPs. For chlorinated DBPs, the relative amounts of organic matter, bromide and chlorine will affect the species distribution of THMs, HAAs, and HANs. Generally, chlorinated THM, HAA and HAN species dominate over brominated species, although the opposite may be true when high-bromide waters are chlorinated. A significant percentage of chlorinated DBPs have not been identified.

Use of chloramine generally leads to significantly reduced levels of chlorinated DBPs and may lead to the formation of cyanogen chloride; however, chloramine is a less effective disinfectant. Ozone can react with bromide to form brominated DBPs, including bromate, and in the presence of organic matter, aldehydes, ketoacids and carboxylic acids are formed. If both organic matter and bromide are present, ozonation may lead to the formation of bromoform. The major chlorine dioxide DBPs include chlorite and chlorate ions, which are derived from decomposition of the disinfectant as opposed to reaction with precursors. Table 1 shows the occurrence of several representative DBPs measured in public drinking waters in the United States.

This article provides a review of the epidemiologic evidence for human health effects that may be associated with the disinfection of drinking water. An epidemiologic study attempts to link human health effects with exposure to a specific agent (e.g., DBCM), agents (e.g., THMs or other DBP mixtures), or technologies (e.g., chlorination of water). The health risks of populations or selected individuals are studied at the levels that are actually found in water systems. Investigators estimate exposure levels of the agent(s) or duration of exposure to the technology for the relevant time period (e.g., decades before the onset of cancer or months before an adverse reproductive outcome). In contrast, toxicologic studies expose experimental animals at much higher levels under controlled conditions. Both types of health studies are important to understand human health risks. There is also a need to better understand the chemistry of chemical disinfectants and their associated DBPs.

DBP	Median µg/L	90th Percentile µg/L
Chloroform	25	60
BDCM	10	23
CDBM	2.5	22
Bromoform	0.1	7
MCAA	1.3	3.3
DCAA	13	30
TCAA	8	28

BCAA	4	10
MBAA	0.1	1.3
DBAA	0.6	6
Chloral Hydrate	3.6	15
DCAN	3	10
MX	0.02	0.05
Bromate	2	20
Formaldehyde	15	25
Chlorite	400	800

bromodichloromethane (BDCM), chlorodibromomethane (CDBM), monochloro- (MCAA), dichloro- (DCAA), trichloro- (TCAA), bromochloro- (BCAA), monobromo- (MBAA), and dibromoacetic acid (DBAA) dichloroacetonitrile (DCAN)

Table 1. Disinfection By-products Measured in U.S. Drinking Waters

2. Epidemiologic Study Designs

Numerous ecological or descriptive epidemiologic studies of populations receiving chlorinated water have been conducted. In these studies, information about exposure and disease is available only for the population not the individual. Results from ecological studies are difficult to interpret because critical information can be lost in the process of aggregating health or exposure information for population groups. Inferences from an ecological analysis may not pertain either to the individuals within the group or to individuals across the groups. The limitations of ecological studies are well known, and usually, this type study is conducted to formulate specific hypotheses that are then evaluated by analytical epidemiologic studies of individuals. For each person included in the analytical study, information is obtained about their disease status, exposure to various contaminants, and other characteristics or risk factors. The analytical study differs primarily in the supportive evidence that can be provided about a possible causal association. Analytical studies can estimate the magnitude of risk. To focus the discussion, only results of analytical studies are reviewed here. Reviews of ecological studies are provided in the bibliography.

In a longitudinal analytical study (cohort and case-control), the time sequence can be inferred between exposure and disease. In a cross-sectional study, exposure and disease information relate to the same time period, and this type of study is more appropriate for assessing health effects that may occur relatively soon after an exposure. The cohort study begins with the identification of an exposure of interest. Two or more groups of people are assembled for study strictly according to their exposure status, and incidence rates for various health-related outcomes are compared for exposed and unexposed groups. This study design allows an evaluation of multiple health-related endpoints, but a disadvantage is that large numbers of people must be followed, especially when studying environmental exposures and relatively rare outcomes such as birth defects and cancer. The case-control study begins with the identification of persons experiencing specific health-related outcomes. A control or referent group of persons without the outcome is selected for comparison, and information is collected about each study participant's exposures and risk

factors. Cases and controls are sampled from the general or a select (e.g., hospital) population within a specified geographic area; multiple exposures and risk factors are evaluated.

Cross-sectional, cohort, and case-control studies have been conducted to assess risks that may be associated with the disinfection of drinking water. However, the studies have differed in the amount and quality of information obtained. In some studies, interviews and questionnaires were used to obtain information about various risk factors, relevant exposures to disinfected drinking water in the appropriate trimester of pregnancy, and water consumption. However, in many studies, information available from vital statistics was used and water exposures were community-based rather than individual-based. That is, DBP exposures were estimated by using measures of THMs from samples collected at the water treatment plant or from limited sampling points in the water distribution system rather than samples collected at each study participant's tap. Frequently, THMs were used as a surrogate for chlorinated DBPs, or analyses were not comprehensive (e.g., only chloroform or THMs were analyzed). In some instances, the timing of water sample collection was not optimal for assessing relevant exposure. For example, samples were collected a year or more before or even after the pregnancy, or samples were collected within the most recent few years before the cancer diagnosis. Recently, modeling techniques have been developed and tested to estimate several DBPs based on water source characteristics, treatment, and disinfection practices. Several investigators are now re-analyzing previously conducted studies using these water quality models.

3. Uncertainty of Risk Estimates

3.1. Random Error

A small p -value or, for a relative risk (RR) or odds ratio (OR), a confidence interval (CI) that does not include unity (1.0) suggests that random error or chance is an unlikely explanation for the observed association. However, statistical significance does not imply that an association is biologically significant or causal. Chance can never be completely ruled out as a possible explanation for an observed association. An association from a well-conducted study with a reasonably large number of study participants, even though it lacks statistical significance, can provide information about a prior hypothesis. However, statistically stable estimates of the RR are needed to provide evidence about the magnitude of a causal association.

3.2. Systematic Error

Even if chance is an unlikely explanation, an association may be spurious because of systematic bias. The direction of the bias can sometimes be determined (e.g., the bias reduced or increased the magnitude of the association), and a sensitivity analysis can be conducted to estimate the extent to which bias may affect the risk. Bias can be prevented by careful design and conduct.

When information about exposure and disease is collected by methods that are not comparable for each participant, an association may be observed due to information bias. For example, in studies of birth defects, mothers of malformed infants may more

completely recall exposures (e.g., drug use, alcohol consumption, and water consumption) than mothers of non-malformed infants. The amount of time lapsed between the exposure and the collection of information is also important to prevent recall bias.

An incorrect diagnosis of disease or assessment of exposure can result in the misclassification of disease or exposure. If the misclassification is not differentially distributed among study participants, risk estimates will be biased toward the null value. That is, the association may be missed or its magnitude underestimated. Non-differential exposure misclassification occurs primarily because of poorly defined exposure. For example, persons may not accurately recall water consumption, or water quality is measured at times that are not optimal or at surrogate locations that do not represent places where exposure took place. Differential misclassification, however, can result in either an under- or over-estimate of the risk, depending on how the misclassification is distributed among the study participants. For example, an overestimate of the risk occurs if the assessed exposure for cases is higher than their actual exposure or the assessed exposure for controls is lower than their actual exposure.

To avoid exposure misclassification, studies should consider personal exposures to DBPs and other water contaminants for the etiologically relevant time period when the exposure might affect the development of the fetus, reproductive health of the mother or father, or development of cancer or noncancer effects. When assessing long-term water exposures for cancer studies, a complete residential history is needed. Exposures should be based on contaminant levels at the tap and estimates of historical water quality. Characterization of water quality should also include an assessment of all water contaminants that may pose a risk for the outcomes studied and potential exposures must also be considered from beverages such as bottled water and beverages. Personal exposure estimates can be based on water consumption patterns, personal habits, household activities, and available biomarkers to confirm exposures or estimate the contaminant dose. Some women may change water sources (i.e., use bottled water) or alter other personal habits and behaviors, such as alcohol consumption, when they learn they are pregnant, and this should also be considered when designing studies of reproductive effects. The residence of a mother at the time of child birth has been used to estimate fetal exposure to drinking water contaminants, however, use of the birth address assumes that a change of residence did not occur and that water exposures were similar during the entire course of the pregnancy. This assumption may be incorrect. Some persons may consume large quantities of tap water while others consume only bottled water. Water quality and consumption may also at places of employment. Exposure assessments should also consider multiple routes of exposure (i.e., inhalation, dermal contact, and ingestion exposure) which are a concern primarily for DBPs, that are volatile and/or nonpolar (e.g THMs).

Inaccurate diagnoses of disease and the incomplete ascertainment of cases can also result in misclassification bias. Cases may be missed because of the poor sensitivity of diagnostic information and incomplete reporting of the outcome. Like the misclassification of exposure, the poor or inaccurate assessment of health-related outcomes result in either differential or non-differential misclassification bias.

When criteria used to enroll persons in the study are not comparable, the observed association between exposure and disease may be due to selection bias. Selection bias may

occur when exposure or disease status is related to the inclusion or exclusion of persons from a study. Important information about DBP exposure or other important characteristics may also be incomplete or not available for some study participants causing them to be excluded from the analysis. When a large proportion of eligible study participants are excluded from the study, the question of bias depends on whether persons who participate are different in regard to exposure, health outcome, or other characteristics than those who did not participate.

3.3. Confounding

An observed association may be due to confounding rather than to the exposure being evaluated. Several potential risk factors (e.g., cigarette smoking, maternal age, socioeconomic status, and alcohol consumption) may confound the association between DBPs and health outcomes. Bias due to confounding can be controlled or assessed during data analysis if sufficient information is collected about known or suspected confounding characteristics. The magnitude of an association can be helpful in assessing possible residual confounding that may be associated with environmental exposures. A RR or OR of 0.9 to 1.2 is essentially too weak to be detected by epidemiologic methods. It is also difficult to interpret a weak association (RR or OR=1.2 to 1.5 or 0.7 to 0.9) because one or more unidentified confounding characteristics can easily be responsible for the association. Associations that are moderate (RR or OR= 1.5 to 3.0 or 0.4 to 0.7) and strong (RR or OR= 3.0 to 10.0 or 0.1 to 0.4) are less likely to be completely explained by unidentified confounding.

4. Cancer Risks

4.1. Cohort Studies

In Washington County, Maryland, a well-defined, homogenous population was followed for a 12-year period (1963-1975). No statistically significant associations were found between 27 causes of death, including 16 cancer sites, and residence in an area where chlorinated surface water was used. Moderately large, but not statistically significant, associations were reported for bladder (RR=1.6; CI=0.5-6.3) and liver (RR=1.8; CI=0.6-6.8) cancer among women and bladder cancer (RR=1.8; CI=0.8-4.8) among men. Among men who had resided in the same domicile for at least 12 years, the risk of bladder cancer was elevated but the risk estimate was very imprecise (RR=6.5; CI=1.0->100). These associations are difficult to interpret because of the likelihood of random error.

In Iowa, a cohort of 41,836 postmenopausal women was assembled in 1986 and followed for eight years. Drinking water exposures were estimated from answers provided by 36,127 women to two questions asked in 1989: what is your main source of drinking water at home and how long have you been drinking this water. Analyses were limited to the 27,339 women who reported drinking water for more than the previous ten years. For women who reported use of municipal surface water sources, a moderately strong association was found for colon cancer (RR=1.7; CI=1.1-2.7), and a weak association was found for breast cancer (RR=1.3; CI=1.0-1.8). No increased risk was observed for bladder cancer (RR=0.7; CI=0.2-2.9) or cancer of the rectum and anus (RR=0.9; CI=0.4-2.1). An exposure-response relationship was also found; increased chloroform levels in municipal

drinking water were associated with increased risk for all cancers combined, colon cancer, lung cancer, and melanoma (test for trend $p < 0.05$). Associations were also found between chloroform levels greater than 14 $\mu\text{g/L}$ and melanoma (RR=3.4; CI=1.3-8.6), lung cancer (RR=1.6; CI=1.0-2.6), and colon cancer (RR=1.7; CI=1.1-2.5). No associations were found between colon cancer risk and BDCM, CDBM, or bromoform levels. This study had a relatively short follow-up period for the cohort, limited information about the cohort's water exposures before 1989, and potential uncontrolled confounding. In another study, age-adjusted, sex-specific cancer incidence rates for the years 1969-78 were found to be evaluated for Iowa municipalities with a population of 1000 or more and a public water supply (surface or ground) that had remained stable for at least 14 years. Although higher rates were found for several cancer sites in municipalities using surface water sources, the results were not always consistent with the hypothesis of an association between cancer and chlorinated water.

A cohort study of 621,431 persons in 56 towns in Finland assessed the relationship between historical exposure to drinking water mutagenicity and cancer incidence during 1971-93. The *Salmonella* microsome assay was used to assess the mutagenicity of the non-volatile, acid/neutral fraction of chlorinated organic material in water, and historical exposures were estimated for each five-year period from 1955 to 1970. Exposure to high levels of mutagenicity was associated with statistically significant increased cancer risks, primarily in women. In women, weak associations were found for cancers of the bladder (RR=1.5; CI=1.01-2.2), rectum (RR=1.4; CI=1.0-1.9), and breast (RR=1.1; CI=1.0-1.2); a moderate association was found for cancer of the esophagus (RR=1.9; CI=1.0-3.5). In men a weak association was found for lung cancer (RR=1.2; CI=1.1, 1.4). Past exposure to THMs, however, was not associated with a statistically significant excess risks of cancer.

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Biographical Sketches

Mr. Craun received an MS degree in sanitary engineering from the Virginia Polytechnic Institute in 1971. He is a registered professional engineer and Diplomate of the American Academy of Environmental Engineers. He also received a MPH in 1980 and a MS in epidemiology in 1984, both from Harvard University. He served with the U.S. Public Health Service during 1965-1991. In 1971, he was assigned to the U.S. Environmental Protection Agency's drinking water program and office of research and development, Cincinnati, Ohio, where he planned, directed, and conducted research to assess health effects associated with drinking water contaminants. He was awarded the PHS silver medal for his work on waterborne disease outbreaks. Since 1991, he has been a consultant on epidemiological and health-related drinking water issues for various organizations including the World Health Organization; Pan American Health Organization; The Coca-Cola Company; NSF International; Peace Corps; Great Lakes Environmental Center; International Life Sciences Institute; New York City Department of Environmental Protection.; and U.S. Department of Justice. During 1991-1994, he was the Charles Edward Via Scholar, Environmental Engineering and Sciences, Virginia Polytechnic Institute and State University. He has published over 100 scientific and professional articles including a number of books and book chapters on drinking water and health topics.

Dr. Calderon received her MS degree in microbiology from the University of Rhode Island. She received a MPH in infectious disease epidemiology from Yale School of Public Health in 1981 and a Ph.D. in Epidemiology from Yale University in 1986. Before coming to the EPA, she was on the faculty in the Division of Environmental Health at the Yale School of Public Health. She joined the USEPA in 1989. In

1992 she joined the Epidemiology Branch in the Health Effects Research Laboratory, Research Triangle Park, NC. She managed the drinking water epidemiology program that has focused on epidemiologic research on microbes, arsenic and disinfection byproducts. In 1997, she became Chief of the Epidemiology & Biomarkers Branch in the Human Studies Division, and since May 2003, she has been the Director of the Human Studies Division. She has published on both recreational waters and drinking water epidemiology, including over 60 articles, three books and six book chapters. She was awarded the EPA's Gold Medal for her work on Environmental Equity in 1992 and in 1998 a Bronze Medal for her work in support of the Office of Groundwater and Drinking Water regulatory agenda.

Both authors are internationally recognized experts in the health effects of drinking and recreation water.