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Health Effects of Trihalomethanes as Chlorinated Disinfection by Products: A Review Article

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Abstract**—**Trihalomethanes (THMs) were among the first disinfection byproducts to be discovered in chlorinated water. The substances form during a reaction between chlorine and organic matter in the water. Trihalomethanes are suspected to have negative effects on birth such as, low birth weight, intrauterine growth retardation in term births, as well as gestational age and preterm delivery. There are also some evidences showing these by-products to be mutagenic and carcinogenic, the greatest amount of evidence being related to the bladder cancer. However, there exist inconsistencies regarding such effects of THMs as different studies have provided different results in this regard. The aim of the present study is to provide a review of the related researches about the above mentioned health effects of THMs.

Keywords**—**Trihalomethans, by-products, disinfection, carcinogenic

I. INTRODUCTION

IT is reported that nearly half of the population in the developing countries suffers from health problems associated with lack of potable drinking water as well as the presence of microbiologically contaminated water [1]. Disinfection by chlorination is the most important step in water treatment for public supply as chlorine remains in the water as long as it is not consumed. However, chlorine also reacts with the natural organic matter (NOM) present in the water and produces a number of byproducts with harmful long-term effects. Disinfection by-products (DBPs) are formed when disinfectants (chlorine, ozone, chlorine dioxide, or chloramines) react with naturally occurring organic matter, anthropogenic contaminants, bromide, and iodide during the production of drinking water [2]. Despite much research on DBPs in recent years, we have been aware of them only since the early 1970s [3]. Use of chlorination reduces the risk of pathogenic infection but may pose chemical threat to human health due to disinfection residues and their byproducts. DBPs will be produced upon chlorination only if the water contains DBP precursors. During chlorination of water containing natural organic matter a complex mixture of chlorine byproducts is formed and more than 300 different types of DBPs have been identified [4]. In 1974, Rook reported on the identification of the first DBPs-chloroform and the other trihalomethanes (THMs)-that are formed in chlorinated drinking water [5]. In 1976, the US Environmental Protection Agency (EPA) published the results of a national survey that showed that chloroform and the other THMs were ubiquitous in chlorinated drinking water.

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Also in 1976, the US National Cancer Institute published results linking chloroform to cancer in laboratory animals. As a result, an important public health issue was born [3].

Generally, the THMs, including chloroform, bromodicholormethane, dibromochlormethane, and bromoform are the most prevalent in chlorinated surface water. The THMs were the first DBPs identified. Together, the THMs and HAAs are the two most prevalent classes of DBPs formed in chlorinated drinking water; accounting for approximately 25% of the halogenated DBPs. However, the focus of this study is mainly on the health effects of the trihalomethanes as one of the most important by-products of chlorination.

In almost 30 years since THMs were first identified, DBPs have been actively investigated. Significant research efforts have been directed toward increasing our understanding of DBP formation, occurrence, and health effects. Most of the exposure to trihalomethanes comes from consumption, either from drinking water or cooking with it. Swimmers can absorb these compounds through their skin. Some trihalomethane compounds can also become volatile and evaporate into the air when one showers. These can then be inhaled [3].

As stated by Casals (2010), Trihalomethanes are known to cause dangerous side effects to the human body. Not only can these be ingested from drinking water, but also inhaled while bathing and from swimming in water that has been treated with chlorine. Trihalomethanes are carcinogens, also referred to as organochlorides. This type of chemical does not degrade or get digested. Your body will store it in your fat tissues. They have been found to secrete through breast milk, blood and semen. These types of carcinogens have been shown to cause DNA mutations, interfere with the immune system and cell growth. Trihalomethanes are known to cause rectal, bladder and breast cancers. There is a higher risk of asthma when exposed to trihalomethanes as well as eczema, and eroding dental enamel. They are also proven to cause a higher rate of miscarriage and birth defects [6].

Much of the previous health effects research directed toward understanding the effects of chronic exposure to DBPs has focused on cancer or mutagenicity. New concerns, however, have been raised by epidemiological studies about potential adverse reproductive and developmental effects, such as low birth weight, intrauterine growth retardation, and spontaneous abortion [7]. In addition, other routes of exposure to DBPs are now being recognized as significant. For example, recent work has revealed that a person can receive twice the exposure to THMs through showering (by inhalation) and equivalent exposure through dermal absorption (bathing, etc.) as compared with ingesting 2 liters of water [8]. New human-exposure studies are being conducted in which blood and urine are being monitored for DBP exposures [9]-[10].

The health effects of trihalomethanes are controversial within the scientific community. Studies with lab animals have shown increased cancers at high doses, but such studies cannot always be extrapolated to humans. Other studies have compared the rates of cancers to levels of TTHM exposure in large numbers of people, and these results have also been contradictory. There have also been contradictory studies of the effects of these substances on human development and reproduction [11]. This article aims, as far as possible, to make a review of the various studies conducted on the health effects of trihalomethans especially regarding carcinogenecity, mutagenecity and birth effects. As stated in Lenntech (2001), many disinfection by-products are bio accumulative. They are not destroyed by the body and can accumulate in body tissues. Research on health effects of disinfection byproducts aims at the following themes: 1- Health effects on humans that drink disinfected drinking water. The research is carried out through epidemic studies. These are mostly concerned with long-term effects. Humans are exposed to small concentrations of disinfection byproducts for many years. 2- Toxicity of separate disinfection byproducts and mixtures of disinfection byproducts. This research is carried out on laboratory animals.

II. Trihalomethans and Carcinogenecity

Studies on associations between THMs, cancer and other health effects have produced conflicting and inconclusive evidence. In this regard, the highest association is found between trihalomethans and bladder cancer. Association between the ingestion of chlorinated drinking water in excess with risk of bladder and rectal cancer followed by mortality has been reported in several epidemiological studies [12]. An apparent association between bladder cancer, reproductive disorders and trihalomethane occurrence has also been established [13].

The most precise information about risk of cancer and contamination of drinking water comes from water quality surveillance. A study was conducted to determine the types of cancer associated with surface water and strength and consistency of such association [14]. Cancer of the colon, rectum, and urinary bladder was noticed to be linked with many settings of water sources containing the elevated level of chlorine byproducts. In addition, several other cancer sites namely stomach, brain, pancreas, lung and liver were also found to be linked with chlorinated byproducts (CBPs).

A comparison of different studies to individual consumption of chlorinated drinking water and the association of bladder cancer show there is a connection between lengthy exposure to chlorinated drinking water and bladder cancer. This risk increases after exposure for many years. This risk is not very big, but because many people are exposed to chlorinated drinking water for many years, this risk is significant because cases of bladder cancer can be attributed to disinfection byproducts. A meta-analysis of several researches shows that there is a positive correlation between exposure to disinfection byproducts in drinking water and human bladder and anal cancer. Nine percent of all cases of bladder cancer and fifteen percent of anal cancer are attributed to chlorinated drinking water and disinfection byproducts. This comes down to 10,000 cases annually [15].

One study estimated that chlorination by-products result in 10,700 bladder and rectal cancers a year [16]. Cancers of the colon, rectum and bladder have been linked to chlorinated drinking water [17]. In 1990 and 1991 in Colorado (United States) a population research was carried out on the relation between disinfection of drinking water with chlorine or chloramines and the occurrence of bladder cancer. 327 people with bladder cancer were compared to 261 people suffering from another type of cancer. On the basis of interviews and data of the Health Organization a drinking water exposure profile was created. This study showed that a relation exists between years of exposure to chlorinated drinking water and the development of bladder cancer. This risk increased after more years of exposure. After exposure of thirty years the risk on bladder cancer was 1.8 times bigger than when no exposure had occurred. The concentration trihalomethanes, nitrate and residual chlorine were not associated with the risk on bladder cancer [18]. One study in Ontario, Canada found some evidence suggesting that people exposed to very high levels of THMs over long periods of time (more than 35 years) had an increased risk of developing bladder cancer [19]. Another study in the USA also found some evidence to link bladder cancer with long-term exposure to THMs but only in men and smokers [20]. Chang, et al, (2007), conducted a study to evaluate whether exposure to disinfection by-products (DBP) is associated with bladder cancer. A matched case-control study was used to investigate the relationship between the risk of death from bladder cancer and exposure to total trihalomethanes (TTHM) in drinking water in 65 municipalities in Taiwan. The results of this study show that there was a significant positive correlation between the concentration of TTHM in drinking water and risk of death from bladder cancer. Gerald et al (2007) examined the relation between the estimated concentrations in drinking water of disinfectant byproduct (DBP) trihalomethanes (THMs) and the risk for urinary bladder cancer in a case-control study of 567 white men aged 35 to 90 years, in western New York State. Higher levels of consumption of THMs led to increased risk for cancer of the urinary bladder. Results were most significant for bromoform, and risk was highest for those who consumed the greatest amount of water at points within the distribution system with the oldest post disinfected tap water.

At a global scale there are geographic differences in the prevalence of rectal cancer, and the highest rates generally occur in economically developed areas (e.g., Australia, Japan, New Zealand, and North America) compared with less developed areas (e.g., Africa and China). This is most often explained by environmental factors related to diet [21]. There are also geographic disparities within the United States; for example, Devesa, Grauman, Blot, G. Pennello, Hoover, and Fraumeni [1999] summarized geographic patterns of urinary bladder and rectal cancers in the U.S. for the period 1950–94 and noted that throughout the period, high rates clustered in the northeastern United States. Other potential risk factors for rectal cancer include tobacco consumption, [22]- [23] alcohol consumption [24]-[25]; genetic disposition [Slattery, Sweeney, Murtaugh, Ma, Caan, Potter, Wolff, 2006; Lynch & Lynch, 2002]occupational exposures, [26]-[27] diet [28]-[29] and disinfectant by-products (DBPs), the focus of the present study.

Research on the connection of intestinal cancer and disinfection by-products in drinking water show that there is an elevated risk on intestinal cancer when chlorinated drinking water is used. King and Marret examined 5000 people in Ontario (Canada), of which 950 were bladder-, intestinal or anal cancer. Data on the concentration of trihalomethanes in water were used. Other factors, including eating habits were investigated as well. This study proved that people who were exposed to concentrations of 50 μg/L or more had 1.5 times bigger risk developing intestinal cancer [19]. A study carried out in Iowa (USA) in 1986 and 1989 with data from intestinal and anal cancer patients shows there is no elevated risk on intestinal cancer after long time exposure to chlorinated drinking water or trihalomethanes. For anal cancer there is an elevated risk however. This risk is even bigger for people who eat little fibrous food. A lack of physical exercise also elevates the risk on anal cancer [30].

Some studies indicate that chlorination by-products in drinking water may contribute slightly to breast cancer risk. Melnick, (1994), for example, found a possible correlation between certain DBPs in drinking water and breast cancer. However, the majority of studies regarding the effects of THMS on breast cancer, show a negative correlation. Pamela (1998) conducted an ecologic study describing the association between total trihalomethane levels in publicly supplied water and the incidence of female invasive breast cancer. Total trihalomethane levels were not associated materially with breast cancer risk, adjusting for potential confounders. When stratified by race, the observed association for the aforementioned total trihalomethane category was not very different in black women than in white women. These ecologic data are compatible with trihalomethanes in drinking water being either unrelated or weakly related to breast cancer risk.

Regarding animals, all four of the regulated THMs are carcinogenic in rodents [31]-[32]-[33]. Only two have been administered in the drinking water, bromodichloromethane and chloroform, and both were negative in the mouse via this route. However, in the rat, bromodichloromethane produced liver tumors, and chloroform produced renal tumors when exposure was via the drinking water [34]. These studies provide an important mechanistic link to a type of cancer associated with drinking-water exposure in humans. IARC has found bromoform [35] and chlorodibromomethane [33] to be group 3, which is not classifiable as to their human carcinogenicity. In contrast, both chloroform [36] and bromodichloromethane [36] have been classified by IARC as 2B, possibly carcinogenic to humans. The U.S. EPA's Integrated Risk Information System (IRIS) describes bromodichloromethane as B2, probable human carcinogen.

Chloroform, a disinfection byproduct of chlorine, is one of the most investigated trihalomethanes. Toxicological research [37] shows that chloroform causes damage to liver and finally causes cancer when it is daily directly applied into the stomach of laboratory animals. The amount of chloroform is too big for the liver to break down completely. The liver is damaged and death of cells and regenerative cell growth occur. The risk on cell mutation and cancer in exposed organs is increased. Another research was carried out in which laboratory animals were exposed to the same amount of chloroform dissolved in drinking water.

They did not develop cancer. This was probably due to the fact that throughout the day animals were exposed to small amounts of drinking water with chloroform. The liver was able to break down the chloroform without getting damaged [38].

Chloroform is the only regulated THM for which there is enough evidence to develop a risk assessment based on its mode of action [39]. Numerous studies have shown that chloroform is not genotoxic and that tumors, when they arise, develop only at doses that produce significant cellular toxicity, cell death, and regenerative proliferation [40]-[41]. Chloroform has induced kidney tumors in male rats and liver tumors in male and female mice only at doses that resulted in cytotoxicity. The tumors were postulated to be secondary to sustained or repeated oxidative metabolism-mediated cytotoxicity and secondary regenerative hyperplasia. This oxidative pathway can produce the electrophilic metabolite phosgene, which can lead to tissue injury and cell death by reaction with tissue proteins and cellular macromolecules as well as phospholipids, glutathione, free cysteine, histidine, methionine, and tyrosine.

The Environmental Protection Agency (EPA) concludes that as long as exposure to chloroform remains under given threshold values that cause cell damage, the risk for cancer is very low. Standards set for chloroform in drinking water are far below these values (EPA, 1998).The IRIS discussion of chloroform (http://www.epa.gov/iris/subst/0025.htm) indicates that three different types of quantitative assessments are possible. The weight-of-evidence assessment concludes that ''chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues. However, chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration.''

Although there is insufficient information for the other regulated THMs to develop a specific mode of action, mutational events and cellular death and regeneration may be necessary for the carcinogenicity of the brominated THMs. Recent data on the pharmacokinetics of bromodichloromethane in humans showed that the maximum blood concentrations of bromodichloromethane were 25–130 times higher from dermal exposure compared to oral exposure [42], emphasizing the importance of route of exposure in risk assessment of the brominated THMs [43]-[44].

Because the brominated chemicals are more active than chlorinated chemicals in the animal models and because the brominated trihalomethanes are formed as a result of bromide ions in the source water, epidemiological studies of colorectal cancer in regions with high bromide content in the source water (e.g., coastal regions) would yield greater insight on risks associated with exposure to trihalomethanes.

III. Trihalomethans and Birth Effects

There have been some epidemiological evidences of a relationship between the exposure to DBPs and adverse reproductive outcomes in human beings and animal studies [45]. However, there is no conclusive evidence in humans that THMs affect the outcome of a pregnancy and there is very limited and inconclusive evidence that high doses of THMs might be lead to having a baby with slightly lower birth weight

[46]. The only evidence linking THMs and adverse health effects relates to experiments where laboratory animals were exposed to high concentrations of the chemicals. These showed some evidence of liver and kidney damage [47]. The levels of THMs used in the experiments were far higher than would be found in Scottish tap water.

The number of epidemiological studies on exposure to disinfection byproducts and the influence on reproduction and birth defects is small. However, these studies show there is a connection between exposure to trihalomethanes and spontaneous abortion, birth defects and growth delay. A research was carried out on exposure during pregnancy to chlorinated drinking water with a high amount of natural organic matter and non-chlorinated drinking water with a small amount of natural organic matter. Birth data from 137,145 Norwegian births between 1993 and 1995 were used. The study showed no connection between exposure to chlorinated drinking water and a risk for low birth weight and small body length. The risk of premature birth was slightly smaller with exposure to chlorinated drinking water than non-chlorinated drinking water.

Data from 56,513 births in Massachusetts (USA) in 1990 were used to investigate the effect of exposure to trihalomethanes in drinking water on foetal development. Exposure causes a low birth weight and small body length, also known as foetal growth delay. Comparison of trihalomethane concentration shows that 80µg/l or more lower the birth weight with 32 gram. No evidence was found on exposure to trihalomethanes and premature birth [48].

Dodds and King (2001), conducted a retrospective cohort study based on data from a population based perinatal database in Nova Scotia, Canada and from the results of routine water monitoring tests to evaluate the risk of birth defects relative to exposure to specific trihalomethanes in public water supplies. The birth defects analyzed included neural tube defects, cardiovascular defects, cleft defects, and chromosomal abnormalities. Two of the four trihalomethane compounds occur in large enough concentrations to be analyzed (chloroform and bromodichloromethane (BDCM)). The result revealed that exposure to bromodichloromethane at concentrations of 20 µg/l or over was associated with an increased risk of neural tube defects, whereas exposure to chloroform was not. Exposure to bromodichloromethane of 20 µg/l and over was associated with decreased risks of cardiovascular anomalies. There was a suggestion of an increased risk of chromosomal abnormalities associated with exposure to chloroform, and no evidence of any association between either trihalomethane compound and cleft defects.

To examine the effect of trimester specific and pregnancy average total trihalomethane (TTHM) exposure on infant birth weight, low birth weight, and intrauterine growth retardation in term births, as well as gestational age and preterm delivery in all births, Wright, Schwartz , and Dockery (2003),conducted a cross sectional analysis of 56 513 singleton infants born to residents of Massachusetts during 1990. Pregnancy average TTHM exposure over 80 micro g/l was associated with a 32 g reduction in birth weight. There was a 23 g reduction in birth weight in infants born to mothers exposed to greater than 80 micro g/l TTHM during the second trimester. For each 20 micro g/l increase in TTHM, the estimated reduction in birth was 2.8 g for pregnancy average exposure and 2.6 g for second trimester exposure. There was no evidence of an association between preterm delivery and increased TTHM levels, but there were slight increases in gestational duration associated with TTHM concentrations.

Grazuleviciene**,** Nieuwenhuijsen**,** Vencloviene, Kostopoulou-Karadanelli**,** Krasner**,** Danileviciute**,** Balcius and Kapustinskiene (2011), examined the relationship of individual exposures to THMs in drinking water on low birth weight (LBW), small for gestational age (SGA), and birth weight (BW) in singleton births. They conducted a cohort study of 4,161 pregnant women in Kaunas (Lithuania), using individual information on drinking water, ingestion, showering and bathing, and uptake factors of THMs in blood, to estimate an internal dose of THM. They found dose-response relationships for the entire pregnancy and trimester-specific THM and chloroform internal dose and risk for LBW and a reduction in BW. Chloroform internal dose was associated with a slightly increased risk of SGA; the risk increased by 4% per every 0.1 µg/d increase in chloroform internal dose.

A meta-analysis of the 5 studies published by the end of 2001 indicated that exposure to chlorination by-products may increase the risk of birth defects in general, especially neural tube and urinary tract defects. A Swedish study provided evidence of an elevated risk of cardiac defects [49], whereas two Californian case-control studies of neural tube defects, cleft lip, and cleft palate provided inconsistent results [50]. In a Norwegian nationwide cross-sectional study, the risk of ventricular septal defects, cleft lip, and obstructive urinary tract defects were related to exposure to disinfection by products [51]. A recent study in England and Wales reported that the risk of ventricular septal defects was associated with exposure to disinfection by products [52].

Hwang, Jaakkola**,** Guo (2008) conducted a population-based cross-sectional study of 396,049 Taiwanese births in 2001–2003 using information from the Birth Registry and Waterworks Registry. They compared the risk of eleven most common specific defects in four disinfection by-product exposure categories based on the levels of total trihalomethanes (TTHMs) representing high (TTHMs 20+ µg/L), medium (TTHMs 10–19 µg/L), low exposure (TTHMs 5–9 µg/L), and 0–4 µg/L as the reference category. The study suggests that prenatal exposure to disinfection by-products increases the risk of ventricular septal defects, cleft palate, and anencephalus. The finding on ventricular septal defects is consistent with previous epidemiologic studies, which strengthens the weight of evidence.

Most researches carried out on reproduction effects of disinfection byproducts aim at birth defects and spontaneous abortion. Little research has been carried out on effects on male reproduction. An American research shows that bromodichloromethane (BDCM) and chloral hydrate (CH) lower the speed and mobility of sperm in laboratory rats. The effect of BDCM at low concentrations is stronger than the effect of CH or other disinfection byproducts that lower sperm speed [53].

On the basis of birth data of births in Nova Scotia (Canada) from 1988 to 1995 and results of water monitoring tests research has been carried out on birth effects of bromodichlormethane and chloroform.

Exposure during pregnancy to bromodichloromethane concentrations of 20 or more µg/l was associated with an elevated risk on defects on the neural tube. Exposure to chloroform points out to an elevated risk of chromosomal defects. The results of this study show that research on the relation between specific disinfection byproducts and birth defects is needed [54]. Moreover, as stated by Fleckenstein (2001), according to the EPA's Stig Regli at the Office of Ground Water and Drinking Water, the results of reproductive studies are less convincing than cancer studies. Results have been inconsistent and more studies are needed.

IV. Trihalomethans and Genotoxicity

The THMs have been studied intensively over the past 30 years, and many in vitro techniques have been used to investigate their mutagenic and genotoxic properties [34]. Richardson, et, al have used the term ‘‘mutagenicity’’ to refer to assays that measure a change in DNA sequence (either gene or chromosomal mutation); and the term ‘‘genotoxicity’’ to refer to mutagenicity as well as DNA damage (DNA adducts, DNA strand breaks, etc.). Bromodichloromethane, chlorodibromomethane, and bromoform have generally not induced gene mutations in the standard test systems; the few positive results are either in single studies or were not found in repeated studies [31]. Nonetheless, some studies have found that chlorodibromomethane induced chromosomal aberrations or sister chromatid exchanges (SCEs) and that bromoform induced SCEs and micronuclei [31].

Recently these DBPs were evaluated for genotoxicity in CHO cells; they were refractory to concentrations of 5 mM. The rank order of chronic CHO cell cytotoxicity was bromoform > chlorodibromomethane > chloroform > bromodichloromethane [56]. However, unlike chloroform, these brominated THMs are activated to mutagens by GSTT1-1. in a transgenic strain of Salmonella (RSJ100); their rank order of mutagenic potency was bromoform > bromodichloromethane > chlorodibromomethane [56]. Thus, the likely absence of GSTT1-1 in most (if not all) of the studies in which these compounds were not genotoxic may account for the general negative results in the standard test systems. The dependence of these compounds on GSTT1-1 to be activated to mutagens raises important limitations regarding the standard test systems and emphasizes the need for basic research of the sort that has been applied to these brominated THMs. DeMarini, et al. [1997] proposed two possible pathways of metabolism of THMs that would result in the GC! AT transitions identified as the sole class of base substitutions induced by these THMs in strain RSJ100 of Salmonella. The authors demonstrated that GSTT1-1 had the ability to mediate the mutagenicity of bromine containing THMs but not chloroform. They suggested that the difference in mutational mechanisms between the brominated THMs and chloroform is likely due to initial metabolism in which the bromine is removed via nucleophilic displacement of bromine or reductive dehalogenation. Data in humans and animals indicate that chloroform is metabolized chiefly to phosgene except at high doses [57]. Pegram et al. [1997] demonstrated that brominated THMs could be activated by GST-mediated transformation into mutagenic intermediates. Also, chloroform displayed a low affinity for the same pathway, indicating that the THMs as a chemical class do not share the same mode of action.

More recently, the biotransformation and genotoxicity of 14C-bromodichloromethane were studied. These in vitro experiments demonstrated that GSTT1-1 catalyzed the covalent binding of bromodichloromethane to DNA and the formation of guanine adducts [43]. The cancer target tissues in the rat had greater potential formation of bromodichloromethane-derived DNA adducts compared to the rat liver due to greater flux through the GSTT1-1 pathway [43].

V. The Insufficuiency of the Reasearches Conducted Regarding the Health Effects of Disinfectant By-Product

Fleckenstein (2001) refers to the shortage and insufficiency of the researches conducted regarding the health effects of disinfectant by-products. He believes that animal studies are very incomplete. Not a single by-product chemical has been assessed for the range of possible effects, including cancer, reproductive toxicity, neurological damage, and immune system disruption. The animal data available for a handful of chemicals has uncertain relevance for humans. Fleckenstein (2001) also refers to the fact that single chemical testing on animals is "insufficient" to characterize the risks from exposure to a mix of thousands of organochlorines in chlorinated drinking water.

There is evidence that organochlorines can have synergistic effects in which a combination of chemicals is disproportionately more toxic in a mixture. Moreover, Organochlorines in the water are always present in a complex mixture, so no single chemical can be singled out as responsible for a disease. While the California study linked trihalomethane levels to increased miscarriages, this wouldn't implicate trihalomethanes specifically since the toxic effects may be from other disinfection by-products, or a combination of trihalomethanes and other chemicals. In addition, long-term health effects may take decades or generations to show up. Health effects could also be subtle (for instance, immune suppression, reduced fertility or neurological damage) that may be impossible to consistently clinically identify [58].

Finally, diseases induced by disinfection by-products may arise from other causes as well, so unless the relative contribution of by-product chemicals is very large, it is impossible to detect with confidence. The effect of all the factors (genetic, diet, exposure to other pollutants) in addition to the one under study, such as chlorinated drinking water, tends to obscure causal relationship.

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