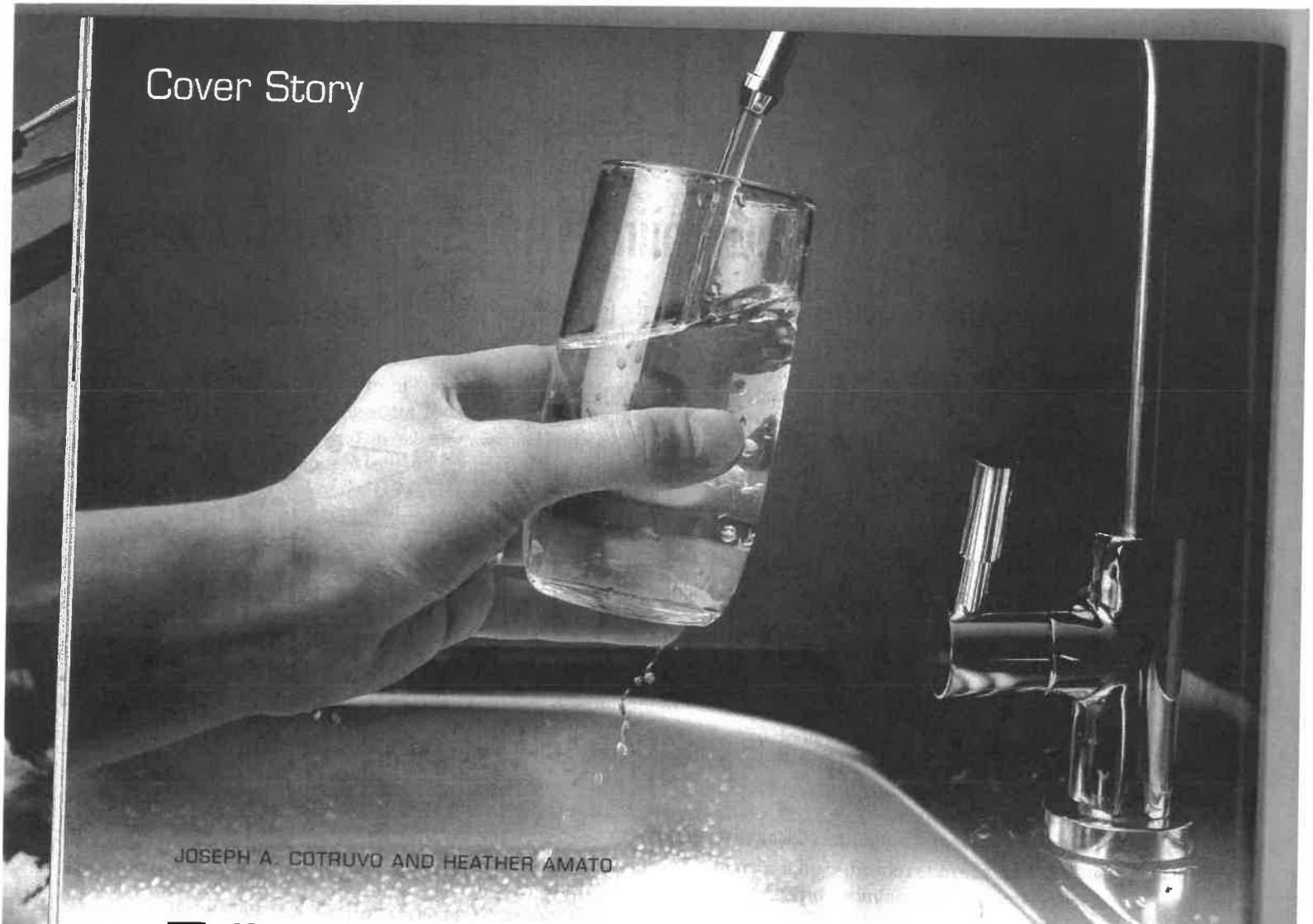


JOSEPH A. COTRUVO AND HEATHER AMATO

Trihalomethanes: Concentrations, Cancer Risks, and Regulations

WHILE THE ASSOCIATION BETWEEN TOTAL TRIHALOMETHANES AND DRINKING-WATER CANCER RISKS REMAINS DEBATABLE, MANAGING DISINFECTION BYPRODUCTS WITH SURROGATES CONTINUES TO BE AN APPROPRIATE AND PRACTICAL METHOD FOR MAINTAINING DRINKING WATER QUALITY.

Drinking water chlorination remains one of the greatest public health benefits of science and engineering. Chlorination is a simple, low-cost, and broadly effective technique for disinfecting drinking water and reducing waterborne disease risks. When combined with filtration, chlorination systems provide remarkable reductions in waterborne disease such that source water–related gastrointestinal waterborne disease outbreaks have virtually disappeared when these unit processes operate as designed.

Forms of chlorine include gaseous chlorine, sodium hypochlorite, calcium hypochlorite, chlorinated isocyanurates, and chloramines (combined ammonia and chlorine). Chlorine is chemically reactive and an oxidizing and halogenating agent. In the early 1970s, studies indicated that chlorinated water produced halogenated disinfection byproducts (DBPs) as a function of the levels of natural total organic carbon (TOC) and contact time, pH, and temperature (Bellar et al. 1974, Rook 1974). Use of monochloramine, formed by combining chlorine and ammonia, increased as a secondary disinfectant following this discovery. Monochloramine (i.e., combined chlorine) is much less reactive than free chlorine or hypochlorite, producing lower levels of fewer and different DBPs while retaining some biocidal efficacy during water distribution.

Four trihalomethanes (THMs)—trichloromethane (TCM; chloroform), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and tribromomethane (TBM; bromoform)—have been a concern since they were found to form in drinking water following reactions between chlorine species and TOC in source waters. Brominated DBPs are produced following chlorine oxidation of bromide to HOBr/OBr$^-$, an effective brominating agent, and the mixed-halogen total trihalomethanes (TTHMs) depend on precursor concentrations and relative reaction rates.

Along with haloacetic acids (HAAs), TTHMs comprise the major portion of the mass of halogenated DBPs, and their concentrations are regulated in numerous countries. TTHMs were originally regulated in the United States (USEPA 1979) by the US Environmental Protection Agency (USEPA) as a readily analyzed indicator of other DBPs that might be present in much greater numbers but at much lower concentrations. The maximum contaminant level (MCL) of 0.10 mg/L (100 µg/L) was set as the limit for TTHMs in drinking water, taken as the sum of the four most common THMs. The TTHM MCL, a distribution system–wide annual average of quarterly samples, was not really risk-based but rather was based on treatment feasibility while most importantly maintaining adequate disinfection of waterborne pathogens. The MCL applied to large systems; extensions to smaller systems came later. The regulation used TTHMs as an indicator of the presence of other DBPs to drive treatment changes to concurrently reduce other DBPs, an approach analogous to requiring measurement and reduction of *Escherichia coli* bacteria as indicators for sanitary pathogenic microorganisms.

Disinfectant chemistry is complex, and different disinfectants produce arrays of different DBPs. Noting the efficacy of chloramines to reduce DBP formation, many water suppliers shifted from chlorine to chloramine residuals in their distribution systems. Some water suppliers also changed their primary disinfectants from free chlorine to ozone or chlorine dioxide.

USEPA's MCL was found to be feasible, although it was later reduced to 0.08 mg/L (80 µg/L), and five HAAs were added (USEPA 1998). HAAs represent a substantial portion of DBPs, have potential health risk issues, and may be indicators for other DBPs. The MCLs for TTHMs and HAAs were reaffirmed (USEPA 2006) but made more restrictive when the compliance method was calculated on a sampling location–specific basis rather than a system-wide average, although the latter had been previously affirmed on appeal.

CARCINOGENICITY AND REPRODUCTIVE AND DEVELOPMENTAL TOXICITY HISTORY OF TTHMs

USEPA's 1979 TTHM regulation was initiated from the National Toxicology Program's (NTP's) whole animal bioassay results that chloroform was carcinogenic in rats and mice tested at high doses by corn oil gavage (NTP 1976). That numerical TTHM MCL was not based on quantitative toxicology but on analytical and water treatment feasibility and with the intent of using it as a surrogate for reducing other unmeasured DBPs concurrently produced. The other three THMs were grouped with chloroform by structural analogy and similar formation chemistry as there were only limited data from then new and basic in vitro mutagenicity tests.

Some other THMs besides chloroform showed some level of carcinogenicity under animal testing conditions. However, TCM (Jorgenson et al. 1985) and BDCM (NTP 2006) were found not to be carcinogenic when retested in water rather than corn oil. USEPA concluded that TCM and DBCM were not likely to be carcinogenic below a dose threshold (USEPA 1998). The World Health Organization (WHO) Guidelines for Drinking-Water Quality (GDWQ) do not treat TCM, DBCM, and TBM as genotoxic non-threshold carcinogens and also state that "as BDCM was negative for carcinogenicity in a recent NTP bioassay in which it was dosed in drinking-water, exceedances of the guideline value (currently 0.06 mg/L) are not likely to result in an increased risk of cancer" (WHO 2017). The International Agency for Research on Cancer (IARC) rated BDCM as 2B (IARC 1991). Canada withdrew its cancer risk–based guideline for BDCM in April 2009 (Health Canada 2017, 2009, 2008). IARC determined that TCM was rated 2B, possibly carcinogenic to humans, and consistent with a mechanism of action that involved prior cytotoxicity (i.e., a dose threshold; IARC 1999). DBCM and TBM (Group 3) did not have sufficient evidence to be classified as possibly carcinogenic to humans.

Chloroform has been evaluated for inhalation toxicology in male and female mice in 90-day studies. The no-observed-adverse-effect level for liver cell proliferation, the most sensitive endpoint in female mice, was 10 ppm (Larson et al. 1996); the study authors concluded that no increase in liver cancer would occur in female mice at that inhaled dose.

Population studies suggesting possible reproductive and developmental

> Observed associations between TTHMs and bladder cancer have been incorrectly interpreted by some as causal.

effects have been mixed and inconsistent. In the 2006 revision, USEPA concluded that "the current reproductive and developmental health effects data do not support a conclusion at this time as to whether exposure to chlorinated drinking water or disinfection by-products causes developmental or reproductive health effects," although it went on to say that it supports a potential health concern. In the Six-Year Review (2017), USEPA updated the information on reproduction and developmental toxicity of TTHMs. In general, most of the animal and human studies were inconclusive or negative, and effects in animal studies usually occurred at very high doses and often equivalent to the maternal toxicity levels, which may indicate an indirect adverse effect. Nevertheless, USEPA stated that it continues to support a potential health concern (USEPA 2017).

Health Canada had proposed a guideline of 16 µg/L for BDCM on cancer risk; however, this was later withdrawn on the basis of the NTP BDCM results in water (Health Canada 2017). Reproductive and developmental effect studies concluded that animal effects were observed at high maternally toxic doses and concluded that the weight of evidence did not support an association between those effects and exposure to BDCM at drinking water levels (Health Canada 2008).

Maximum contaminant level goals (MCLGs) in the United States are nonregulatory benchmarks set at the level at which no known or anticipated adverse health effects would occur, including a margin of safety. USEPA sets MCLGs for genotoxic carcinogens at zero as an "aspirational" goal; other chemical MCLGs have finite values. WHO establishes GDWQ for genotoxic carcinogens at the hypothetical 1/100,000 70-year lifetime risk benchmark. The current individual US MCLGs are as follows: TCM, 0.07 mg/L; BDCM, zero; DBCM, 0.06 mg/L; TBM, zero. These have not been reassessed since before 2006. WHO's current health-based guideline values are TCM, 0.3 mg/L; BDCM, 0.06 mg/L; DBCM, 0.1 mg/L; and TBM, 0.1 mg/L (WHO 2017). The USEPA threshold calculation for chloroform used a 20% relative source contribution (RSC) from drinking water; WHO used a 75% RSC, which accounts for most of the four-fold differences in the two values.

> The potential for a measurable drinking water contribution to bladder cancer risk is not obvious, and causality associated with drinking water has not been established.

THM RISKS

Some epidemiology studies have suggested—but not consistently—that colon, rectal, and especially bladder cancers could be associated with TTHM exposure (e.g., Hrudey 2012, 2008). However, the assumption that TTHMs are indicators of bladder cancer risk in humans has not been confirmed, and existing data suggest that TTHMs are not good surrogates for some other chlorination byproducts that may increase bladder cancer risk (Bull 2012, Bull et al. 2009). Observed associations between TTHMs and bladder cancer have been incorrectly interpreted by some as causal. Hrudey (2008) concluded that "none of the THMs, nor any other concurrently identified DBPs, have both the capability of acting to cause bladder tumors and sufficient potency and exposure concentration to yield bladder cancer predictions that would accord with epidemiological predictions." USEPA (2003) estimated in its Stage 2 Disinfection Byproducts Rule analysis that lower and upper confidence limits of bladder cancer risk for chlorination of drinking water ranged from 2 to 17%. Bull (2012) concluded that the potential effects of THMs on bladder cancer would be about two orders of magnitude lower than the observed cancer rates reported by some epidemiological studies. Thus, if there is some correlation between chlorination of drinking water and bladder cancer, it would likely be due to other factors.

Bull (2012) stated that results from meta-analyses suggested estimates of approximately 1/1,000 lifetime risk of developing bladder cancer from consumption of chlorinated drinking water. Based on their assessments of several epidemiology studies, Regli et al. (2015) estimated an increased lifetime bladder cancer risk of 0.0001 per incremental µg/L of TTHM, assuming increased source water bromide levels of 50 µg/L. However, USEPA (2006) cautioned that the level of confidence in its calculations did not preclude that the actual number of bladder cancer cases related to drinking water could be zero because causation had not been proved. That lack of causality was restated in USEPA's most recent Six-Year Review document (USEPA 2017).

Brominated THMs and other substances are metabolized by glutathione S-transferase theta 1-1 (GST-T1-1), and some may produce a mutagenic product, so the possibility of a genotoxic mechanism may exist (Ross & Pegram 2004). Some studies in Spain reported a higher risk of bladder cancer among a population subset with genetic polymorphisms coding for activation of brominated THMs, oxygenation of some HAAs, and

metabolism of many industrial chemicals and oxidation of THMs (Cantor et al. 2010). Bull (2012) states that genetic polymorphisms provide substantive evidence that chlorinated drinking water contributes to bladder cancer, but for a number of mechanistic reasons, it does not provide strong evidence that THMs are causally related to bladder cancer.

Cellular-level in vitro studies employing cytotoxicity and genotoxicity have evaluated numerous DBPs for their biological activities. Such studies usually suffer from the lack of consideration of whole animal post-ingestion metabolism and in vivo organ dosages at target organs and cells, in addition to DNA repair processes. Nevertheless, they indicate very low in vitro activity for THMs (Huang et al. 2017, Plewa & Wagner 2009).

Woo et al. (2002) provided a structure–activity assessment of 209 DBPs for carcinogenic potential. None received high ratings; high–moderate ratings were attributed to three MX (halofuranone) chemicals; moderate ratings were attributed to one MX, five haloalkanes/haloalkenes, six halonitriles, two haloketones, one haloaldehyde, one halonitroalkane, and one nonhalogenated aldehyde. The MX compounds are mutagenic in *Salmonella* assays but are not considered very carcinogenic because they are likely rapidly detoxified after ingestion. The remaining 189 DBPs were assigned low–moderate (58), low (98), or marginal (33) concern.

Hrudey et al. (2015) reviewed 10 higher-quality case control studies with some study overlaps, eight of which suggested an association with bladder cancer with odds ratios for men between 1.4 and 2.5, along with two meta-analyses. They stated that

> Quantitative risk estimates derived from toxicological risk assessment for CxDBPs (chlorination DBPs) currently cannot be reconciled with those from epidemiologic studies, notwithstanding the complexities involved, making regulatory interpretation difficult. . . . Replication of epidemiologic findings in independent populations with further elaboration of exposure assessment is needed to strengthen the knowledge base needed to better inform effective regulatory approaches.

They also concluded that "no causal agent with sufficient carcinogenic potency has been identified, nor has a mechanistic model been validated." It is possible that imprecise DBP exposure variables and other assumptions and consequences of multiple contributing risk factors may be larger than the magnitude of potential water treatment–related risks being studied, thus making further studies of the same type not necessarily likely to resolve the issue.

BLADDER CANCER

Bladder cancer rates vary substantially by region and country. Europe and North America have the highest incidence rates, followed by North and West Africa. Age-standardized rates for bladder cancer in the European Union in 2008 were 27.4/100,000 males and 5.6/100,000 females. The highest rates were in Spain, Denmark, Czech Republic, and Germany; the lowest were in Slovenia, Finland, and the United Kingdom (Ferlay et al. 2010). Comparable US incidence was 19.8/100,000 for 2014 (CDC 2017). Race and ethnicity appear to be significant risk factors in the United States; the rate per 100,000 was 21.1 for whites, 11.4 for blacks, 10.7 for Hispanics, 8.1 for Asian/Pacific Islanders, and 8.4 for American Indian/Alaska Native (CDC 2017).

Bladder cancer incidence is correlated with age; about 90% of bladder cancers occur in people over 55 years of age, 70% occur over age 65, and median age at diagnosis is 73 (KenResearch 2017). Five-year survival is 77.3% (NCI 2017). Numerous risk factors contribute to age-related incidences of bladder cancer, including predominantly smoking, exposure to aromatic amines, and several occupations (Action Bladder Cancer UK 2017). Some reports suggest that bladder cancer risk may be about 40% in type 2 diabetes patients, and more so in men than women (Diapedia 2014, Zhu et al. 2013, Larsson et al. 2006).

Diabetes, smoking, age, gender, ethnicity, and chemical contributors may interact to affect the risk of bladder cancer. Other small risk factors like arsenic and polycyclic aromatic hydrocarbon exposures add to contributions from certain medical treatments (ACS 2016). Men are about two to four times more likely to contract bladder cancer than women in their lifetimes; smokers are at least three times as likely as nonsmokers to contract bladder cancer; smoking causes about half of all bladder cancers in both men and women (ACS 2016); and there are numerous other contributors to bladder cancer risk. Some mixed-results studies suggest that drinking more fluids, including drinking water, tends to lower risks (ACS 2016, Michaud et al. 2007). Most dietary components have not been

> Bladder cancer risk from drinking water, if any, is likely small, and it is probably overwhelmed by many other larger risk factors such as smoking, diabetes, and others.

associated with bladder cancer (Cancer Research UK 2017).

Arsenic is a risk factor for bladder cancer at high exposures. Mendez et al. (2016) associated bladder cancer with arsenic in drinking water at >150 µg/L but at <150 µg/L with lower confidence. Other studies have not shown increased cancer risk when arsenic occurs at levels of 3–60 µg/L (Lamm et al. 2004) or <100–200 µg/L, especially for nonsmokers (Tsuji et al. 2014). Median US drinking water levels over the period from 2006 to 2010 were 1.5 µg/L (95th percentile was 15.4 µg/L; Mendez et al. 2016). USEPA's MCL and WHO's GDWQ value are 10 µg/L (WHO 2017, USEPA 2016).

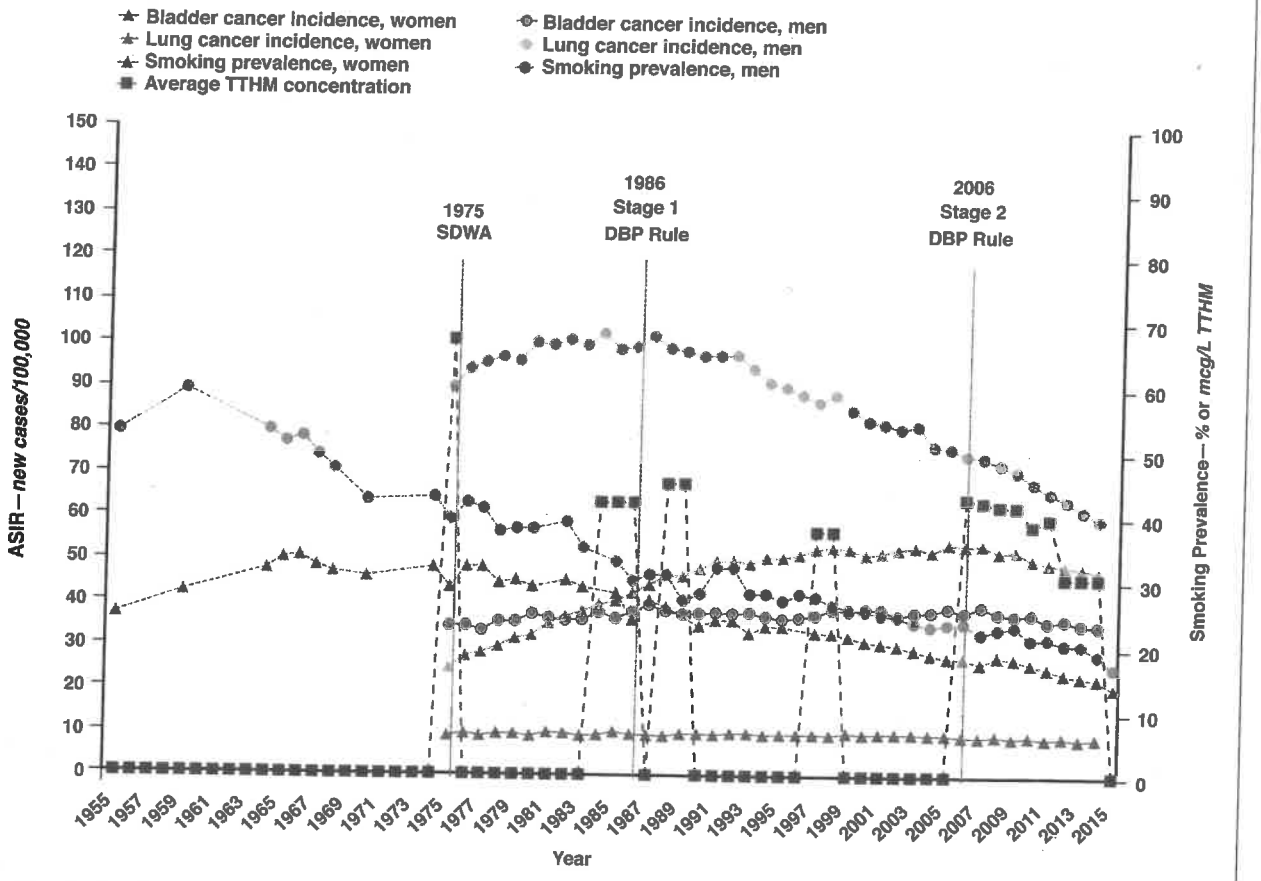
Bladder cancer rates in the United States and Canada have not changed in the more than 40 years since THMs were originally detected in the early 1970s and then regulated in 1979 (Figure 1). US male bladder cancer rates have been consistently 3.5 times female rates; male-to-female rates in Canada have been in the 3.6–4 range (Figure 2). Smoking has declined, and lung cancer rates have also declined, but this has not been manifested in the overall bladder cancer rates. It may be that the latency period for smoking-related bladder cancer is much longer than the latency period for lung cancer.

It remains uncertain whether reduced exposure to TTHMs as a result of drinking water treatment changes has resulted in lower risks to consumers, especially for bladder cancer. Given that THMs are not animal carcinogens at drinking water levels, are there other DBPs that are quantitatively related to TTHM concentrations, such that TTHM reductions might reflect concurrent reductions of those DBPs? It might be hypothesized that reduced drinking water concentrations of TTHMs could concurrently result in reduced exposures to other more potent DBPs and therefore possibly indirectly reduce attributable bladder cancer risks.

TTHMs IN US AND CANADIAN DRINKING WATER SYSTEMS

TTHM data from US locations were extracted from various national or multi-city reports and summaries, primarily from USEPA's national surveys.

FIGURE 1 US annual age-adjusted smoking prevalence, bladder and lung cancer incidence, and TTHM concentrations in drinking water systems, 1955–2015



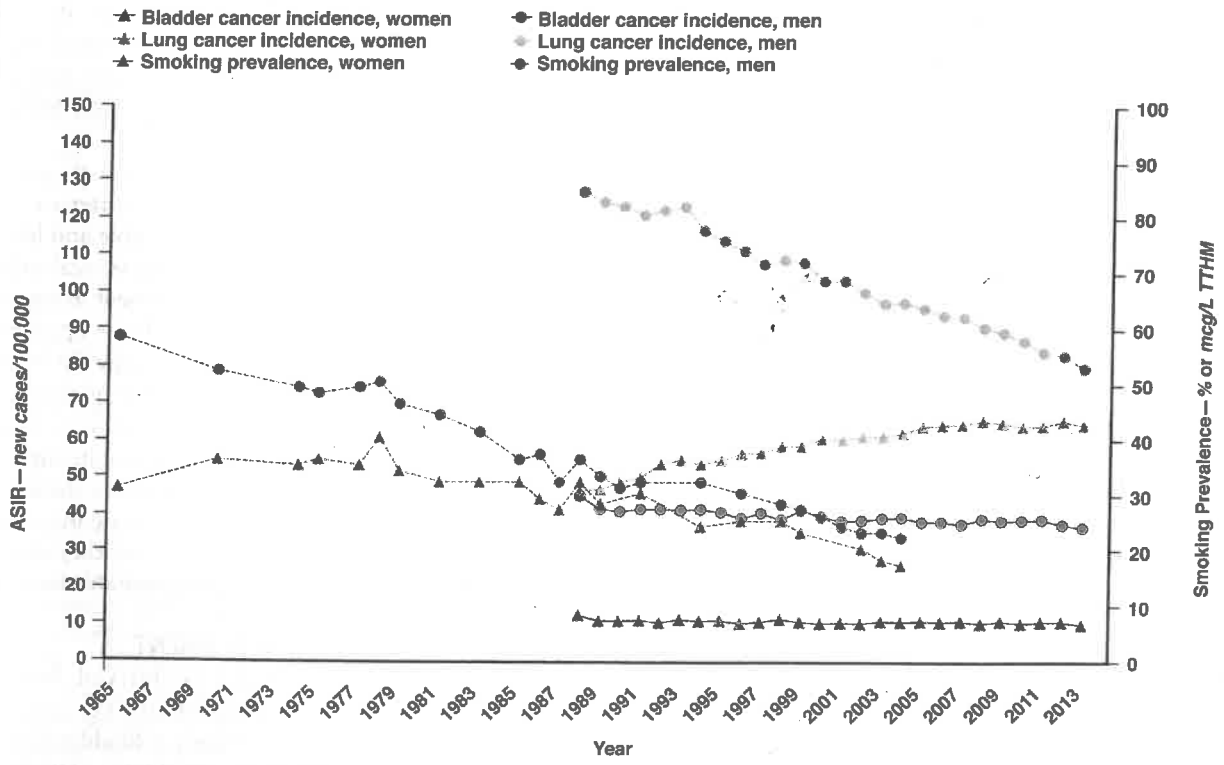
ASIR—age-specific incidence rate, DBP—disinfection byproduct, SDWA—Safe Drinking Water Act, TTHM—total trihalomethane

National annual average TTHM concentrations in micrograms per liter were either directly extracted from published reports or calculated by averaging concentrations across all water systems and all time points with available data in a given year. Table 1 provides a list of TTHM data sources for drinking water systems in the United States by time period.

The United States has multiple databases from its regulatory monitoring requirements and national surveys. The National Organics Reconnaissance Survey (NORS) (Symons et al. 1975) and the National Organics Monitoring Survey in the 1970s related TTHMs to chlorination and water conditions (Table 1). TTHM averages reflect regulatory and treatment technology changes. Average TTHMs in US drinking water supplies were 67 µg/L in 1976, 42–44 µg/L in 1986, and 30 µg/L in 2013–2015. Average TTHM levels were probably at least 67 µg/L before the mid-1970s, when there were no constraints. The highest NORS survey level exceeded 300 µg/L in a water supply in a warm climate with very high TOC water; chlorine was used as a disinfectant and to bleach colored humic substances. TTHM levels have trended downward in part because numerous water suppliers have made treatment changes as previously described.

Similar trends in TTHM reduction technology and concentrations could be expected in Canada. The current Canadian national guideline for chloroform is 100 µg/L (0.1 mg/L) using tolerable daily intake calculations. A summer–winter survey of treated and distributed water from 53 selected water plants in 1993 found that TCM, dichloroacetic acid, and trichloroacetic acid were the major DBPs detected, and HAAs often equaled or exceeded TTHM concentrations (Williams et al. 1997). The population-weighted TTHM average was 30.8 µg/L. Thirty-seven plants used conventional disinfection and alum coagulation, and 15 only disinfected. Most (35) used pre- and post-chlorine dosage; total chlorine doses ranged from 0.1 to 5.75 mg/L (winter) and 1 to 13.6 mg/L (summer). Ammonia followed pre-chlorination in 10 facilities. Facilities (7) using ozone followed by chlorine or chloramine had total chlorine dosages from 0.5 to 3.3 mg/L (winter) and 0.5 to 4 mg/L (summer). TTHM levels in the distribution systems of chlorinating treatment plants ranged from 2.8 to 221.1 µg/L (mean 34.4, winter) and 0.3 to 342.4 µg/L (mean 62.5, summer). TTHM values following chloramine/chloramine or ozone/chloramine ranged from 0.6 to 42.1 µg/L (means 9.9–13.7, winter) and 2.5 to

FIGURE 2 Annual age-adjusted smoking prevalence and bladder and lung cancer incidence in Canada, 1965–2013



ASIR—age-specific incidence rate, TTHM—total trihalomethane

TABLE 1 Data sources for annual average TTHM concentration in drinking water in the United States

Time Period	Data Source	Sample Location	Statistical Summary	Number of Water Systems
1975	NORS	Finished water	Single samples	80
1975–1976	NOMS	Finished water	Single samples	111
1984–1986	AwwaRF	Distribution system	Single samples	727
1988–1989	35-city survey	Finished water	Single samples averaged over four quarters	35
1997–1998	ICR	Distribution system	Average of six quarterly samples	479
2006–2010	Six-Year Review	Distribution system	Single samples	167,000
2012–2015	Seidel et al. 2017	Distribution system	95th percentile quarterly samples	394

Source: McGuire et al. 2003, McGuire & Graziano 2002, McGuire & Meadow 1988

AwwaRF—AWWA Research Foundation, ICR—Information Collection Rule, NOMS—National Organics Monitoring Survey, NORS—National Organics Reconnaissance Survey, TTHM—total trihalomethane

107.8 µg/L (means 32.8–66.7, summer), respectively.

A 2009–2010 survey in 65 selected Canadian facilities indicated a decline in TTHM concentrations and reported a population TTHM average of 20.7 µg/L. Systems employed chlorination (51), chloramination (12), ozonation (8), and ultraviolet light (11). The average TTHM level of surface water facilities was 20.9 µg/L, and the average TTHM concentration in groundwater was 11.6 µg/L (Tugulea 2017).

SUMMARY

THMs have not been determined to be carcinogens under drinking water conditions as indicated by animal bioassays conducted in water rather than corn oil. If THMs correlate with cancer risk, it may be because they reflect the presence of other DBPs potentially present in greater numbers but at much lower concentrations. In the United States and Canada, TTHM concentrations have declined on the basis of published reports, compliance data, and water treatment information from national regulatory authorities. The national time trend bladder cancer data since the TTHMs were discovered and regulated do not reflect a strong linkage between TTHMs and bladder cancer incidence.

Bladder cancer is a disease of older age, and its etiology is complex, with many contributing factors of varying degrees. On the basis of this review, the potential for a measurable drinking water contribution to bladder cancer risk is not obvious, and causality associated with drinking water has not been established. Epidemiological studies using imprecise drinking water TTHM exposure assessments over the long term may include assumptions that have a greater effect on outcomes than the potential risks associated with TTHMs. Bladder cancer risk from drinking water and THMs, if any, is likely small, and it is probably overwhelmed by many other larger risk factors such as smoking, diabetes, and other country-specific factors. Gender and race/ethnicity remain important confounding factors in bladder cancer incidence.

Reproductive and developmental outcomes associated with TTHMs in drinking water were also updated in USEPA's Six-Year Review, and most of the studies it included were negative or inconsistent and/or occurred at maternally toxic doses and doses well above those found in drinking water. However, USEPA has stated continuing concerns. The Six-Year Review concluded that regulatory changes were not indicated at that time for TCM, DBCM, and TBM for toxicity-based MCLGs. With regard to BDCM, the Six-Year Review acknowledged data generated since the 2006 regulation but was not specific as to whether a revised MCLG would be appropriate.

Nevertheless, even though potential TTHM drinking water cancer risks remain questionable and likely small compared with several other factors, DBP management using surrogates continues to be an appropriate and practical strategy for maintaining drinking water quality and avoiding excessive unnecessary exposures. However, as reiterated by WHO, DBP management decisions should never compromise microbial disinfection efficacy, and they should reflect costs and identifiable benefits.

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