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AN ANALYSIS OF TRIHALOMETHANE LEVELS IN THE DISTRIBUTION NETWORKS OF THREE ROMANIAN CITIES

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Abstract: The main source of municipal water in Cluj, Târgu Mureş and Zalau is surface waters treated with chlorine. No studies have been done in these cities to describe factors that may contribute to CBP levels, or to characterize the relationship of surface water chlorination with possible health risks. We undertook sampling from water treatment plants and from a range of locations in Cluj, Târgu Mureş and Zalau, and examined the influence of city and distance from chlorination site upon THM and chloroform levels. To better understand the potential health risks posed to consumers of water from treatment plants in Romania, we used the ATSDR established MRLs to assess the risk of bladder cancer from THM and chloroform exposure using chemical analysis of THM concentrations of water obtained directly from the water treatment plants. THMs and chloroform levels in the three cities ranged from 9.04-116.79 µg/L and 9.04-78.24 µg/L, respectively. Both THMs and chloroform levels were found to be lowest in Cluj-Napoca as compared with those in the other two cities where levels appeared to be similar. Mean THM levels were 48.120 (SE=3.917), 81.883 (SE=4.014) and 81.521 (SE=4.014) in Cluj, Târgu Mureş and Zalau, respectively. Mean chloroform levels were 35.386 (SE=2.848), 64.784 (SE=2.919) and 50.778 (SE=2.919) in Cluj, Târgu Mureş and Zalau, respectively. Multivariate linear regression showed non-significant (p=0.108) effect of distance on THM levels and a significant effect of city in predicting THM levels. To our knowledge, this is the first attempt at investigating the levels of THMs, specifically chloroform, in these Romanian cities to aid in characterizing possible cancer risk to residents. Measured levels of chloroform in this study are below the US EPA standards for acute, intermediate and chronic exposures. Results from this study suggest that Romania has been successful in its efforts to adhere to UN drinking water standards. Additionally, it suggests that consumers of chlorinated drinking water in Cluj-Napoca, Târgu Mureş and Zalau are unlikely to face long-term health risks from consumption. This assumption, however, should be made cautiously due to the complex nature of the exposure and should be further studied.

Keywords: bladder cancer, chloroform, drinking water disinfection, health effects, trihalomethanes

1. INTRODUCTION

Access to safe drinking water is regarded as a basic health benefit. Thus, from a public health perspective, the proportion of a population with access to safe drinking water is an indicator of the extent to which basic needs are met. Because water is a decisive environmental factor promoting health, poor water quality poses a major threat. Disease outbreaks related to contamination of drinking water continue to occur, even in economically developed European countries, and can severely affect human health.

While the vast majority of outbreaks of waterborne diseases results from microbial (bacteriological, viral, protozoan or other biological) contamination, serious health concerns may also arise as a result of chemical contamination of drinking water. These considerations explain the need to achieve common, high standards of drinking water quality and to reduce the burden of diseases attributable to poor water, sanitation and hygiene.

Like many regions, surface water sources in Romania face microbiological and chemical contamination generated mainly by compromised management of wastes and municipal residual waters. Commonly, the quality of drinking water is negatively impacted by source contamination (accidental or not), water treatment (its absence, insufficiency or interruption) and contamination in the distribution network due to the poor technical status of the distribution network (Gurzau et al., 2010).

Chlorination has been successfully used for the control of waterborne infectious diseases for more than a century and is the most widely used cost effective method of water disinfection in Romania. However, identification of chlorination byproducts (CBPs) and their potential health hazards has created a major issue in balancing chemical toxicity with risks from pathogenic microbes (Gopal et al., 2007).

Principal among chlorination byproducts are trihalomethanes (THMs), a group of compounds derived from methane through substitution of three hydrogen atoms with halogens. Four THMs commonly found in water are chloroform, bromodichloromethane, dibromochloromethane and bromoform (Waller et al., 1998). Total concentration of THMs and formation of THM species in chlorinated water strongly depend on the composition of the raw water, operational parameters and on the occurrence of residual chlorine in the distribution system. THM formation is dependent on temperature, pH, dose, contact time, inorganic compounds, and natural organic matter. It is promoted by high temperatures, alkaline pH and high levels of free residual chlorine generally from 3mg/L or more. The presence of THMs in water is connected with and directly proportional to the organic contamination of water (frequently from anthropogenic sources) and influenced by the efficiency of the water treatment process (Gurzau et al., 2011). It is known that the health risks associated with treatment of drinking water is related to water contamination during the treatment process, final disinfection and distribution.

An 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 ecologic epidemiological studies. Associations between bladder cancer, reproductive disorders and THM occurrence have also been established (Yang et al., 1998, Koivusalo et al., 1997, Tokmak et al., 2004). Studies conducted in mammals revealed that THMs induce neurotoxicity, hepatotoxicity, reproductive toxicity and nephrotoxicity (Gopal et al., 2007).

In contrast, studies in humans are inadequate to determine if chloroform, the major CBP from water treatment with chlorine, is carcinogenic. Studies in animals reveal that chloroform can cause an increased incidence of kidney tumors in male rats and increased incidence of liver tumors in male and female mice. However, this carcinogenic response occurs only at high dose levels that result in cytotoxicity, and the weight of evidence indicates that carcinogenic responses observed in animals are associated with regenerative hyperplasia that occurs in response to cytolethality (Golden et al., 1997, EPA, 2001).

Results from a study performed by Weisel and Jo confirm the necessity of knowing the biologically active agent and the site of activity of a contaminant to accurately quantify the dose received from all significant exposure routes before forming public health polices related to contaminated water supplies (Weisel & Jo., 1996). In order to better characterize any link between chloroform exposure and human health outcomes, disease risk must be evaluated in terms of present and past exposure, as well as exposure in the company of other disinfection byproducts.

To reduce the public health risk from these toxic compounds, population exposures are ideally controlled through adherence to implemented guidelines. Since its accession into the European Union, Romania has increased efforts to improve the quality of water provided to its citizens. According to current EU and US EPA legislation, the current total THMs limit in drinking water is 100µg/mL and 80µg/mL for the EU and the US, respectively. Here, we focus on analysis THM levels, specifically chloroform, in three cities in Romania where this has not yet been done: Cluj-Napoca, Târgu Mureş and Zalau.

The Gilau reservoir formed on the Somesul Mic River follows a system of reservoirs on the Somesul Cald River, receiving water from the Somesul Rece River and Agarbiciu Creek. It is the water source for the Gilau water treatment plant that provides the drinking water in Cluj-Napoca along with several other localities that include a total of approximately 500,000 inhabitants. The Varsolt reservoir, with accumulation on the Crasna River is the raw water source for the Varsolt water treatment plant that provides drinking water for Zalau and its neighboring localities which includes 79,000 inhabitants. The Mures River is the dirnking water source for the Targu Mures water treatment plant, supplying drinking water to the approximately 150,000 of Targu Mures (Gurzau et al., 2010).

The main source of municipal water in Cluj, Târgu Mureş and Zalau is surface waters treated with chlorine. No studies have been done to describe the relationship of surface water chlorination in these cities with possible health risks from consumption of this water or factors that may contribute to varying levels of CBPs in these areas. We undertook sampling from water treatment plants and from a range of locations in Cluj, Târgu Mureş and Zalau. We then examined the influence of city and distance from chlorination site upon THM and chloroform levels. To better identify the possible health risks posed to consumers of water from treatment plants in Romania, we used the Agency for Toxic Substances and Disease Registry (ATSDR) established minimal risk limits (MRLs) to assess the risk of bladder cancer from THM and chloroform exposure using chemical analysis of THM concentrations of water obtained directly from the water treatment plants. This analysis allows for a qualitative characterization of risk and provides information regarding whether an alteration in water treatment processes is necessary to ensure safe exposure levels while balancing health and economical impacts of water treatment with chlorine.

2. METHODS

Drinking water samples were collected from the water treatment station (WTS), reservoirs and random locations in the distribution networks of the WTSs in three Transylvanian cities: Cluj-Napoca, Târgu Mureş and Zalau. At the WTS, samples were obtained from different sampling points in the technological process of water treatment process. Samples of raw, decanted, filtered and chlorine-treated water were collected. Samples were collected three times, once in June, once in July and once in August 2009 and stored in 1150 mL PE white bottles (Agro-Rom Plastics). Additional samples of chlorinated water were collected in 500mL brown glass bottles with a conical ground joint with sodium thiosulfate ($Na_2S_2O_3$) added to quench residual chlorine. Free and total chlorine concentrations were read immediately during collection using a chlorine test kit from Merck.

For free chlorine concentrations below 0.1, a low level chlorine test kit from Merck was used. All samples were stored at 4°C until analysis, performed no later than 14 days after collection.

Tests for organic matter were performed 1-2 days after sample collection using International Organization for Standardization protocols: Ammonia (SR ISO 7150-1), Nitrite (SR 3048-2), Nitrate (SR ISO 7890-3) and Permanganate (SR EN ISO 8467). Mass spectrometry was used (Specord 20, Analtikjena) to determine concentrations.

Determination of THM concentration was carried out by gas chromatography (Shimadzu GC Solution) with electron capture detector (GC-ECD). The analysis was made using the headspace technique. 10 mL of sample was filled into 20 mL headspace vials and closed with Teflon lined screw caps. Samples were then equilibrated in an oven at 60°C for 45 minutes, 1 mL of the headspace was then injected into the GC (Cyanopropylphenyl Polysiloxane column, 30m x 53mml, 3um film thickness, Thermo Finnigan, USA). The column program was 35°C (hold time 3 minutes), 15°C/minutes to 200°C (hold time 3 minutes). The inlet was set at 200°C. The calibration standards were prepared for the range 0-100 μg/L in pure water. In the analysis of THMs, samples of 1mL volume of headspace were injected into the GC column with TriPlus HS auto sampler and four peaks were detected, in accordance to the four THM compounds.

Statistical analysis was performed using SAS Version 9.2 (2009). A generalized linear model was used for multi-group comparisons to compare mean chloroform levels among the cities. Linear regression was used to assess the relationship between chloroform levels and the distance of sampling point from the point of chlorination, city and the interaction between distance and city.

3. RESULTS

Table 1 shows the concentration of THMs and chloroform (μg/L) from the point of chlorination in each of the three cities and various sampling points in their distribution network.

N represents the number of observations included in analysis of the data. THMs and chloroform levels in the three cities ranged from 9.04-116.79 μg/L and 9.04-78.24 μg/L, respectively. Both THMs and chloroform levels were found to be lowest in Cluj-Napoca as compared with those in the other two cities where levels appeared to be similar. Regression analysis was then performed, results of which are summarized in table 2 and table 3.

Assuming no effect of distance on THM or chloroform levels, a generalized linear model ANOVA was used to compare mean THM levels and then to compare mean chloroform levels between cities. The F-value of the Duncan multiple range test for THM was 24.10 and the value for chloroform was 26.03, significant at the 0.05 ($p=<0.001$ for both THM and chloroform) level indicating that mean THM and chloroform levels significantly differed between cities. Mean THM levels were 48.120 (SE=3.917), 81.883 (SE=4.014) and 81.521 (SE=4.014) in Cluj, Târgu Mureş and Zalau, respectively. Mean chloroform levels were 35.386 (SE=2.848), 64.784 (SE=2.919) and 50.778 (SE=2.919) in Cluj, Târgu Mureş and Zalau, respectively.

Table 1. Trihalomethane and Chloriform Distribution in Three Romanian Cities (June-August 2009)

City		N	Mean	Median	STD	Max	Min
Cluj Napoca	THM (µg/L)	21	48.12	48.85	16.21	60.72	20.38
	Chloroform (µg/L)	21	35.39	32.98	14.09	52.24	13.45
	Distance from WTS (km)	17	16.24	16.00	2.79	22.00	5.00
Tărgu-Mures	THM (µg/L)	20	81.88	81.90	11.06	101.58	40.58
	Chloroform (µg/L)	20	64.78	64.93	8.13	78.24	28.07
	Distance from WTS (km)	15	4.00	4.00	1.96	7.50	0.50
Zalău	THM (µg/L)	20	81.52	79.50	21.18	116.79	9.04
	Chloroform (µg/L)	20	50.78	48.33	15.65	76.41	9.04
	Distance from WTS (km)	16	17.81	17.25	1.91	21.50	16.00

Table 2. Association of THM levels, city and distance from point of chlorination

Model	R-Square	Parameter Estimate	SE	P-value
Distance	0.111	-1.226	0.513	0.021
Distance Targu Mures Zalau	0.523	-1.846 12.650 37.612	1.124 15.034 6.233	0.108 0.404 <0.001
Distance Targu Mures Zalau Interaction	0.563	-3.381 -2.391 19.668 1.093	1.797 15.890 33.137 0.0952	0.067 0.881 0.556 1.257

Table 3. Association of chloroform levels, city and distance from point of chlorination

Model	R-Square	Parameter Estimate	SE	P-value
Distance	0.353	-1.578	0.315	<0.001
Distance Targu Mures Zalau	0.549	-1.523 11.335 18.080	0.786 10.517 4.360	0.059 0.287 <0.001
Distance Targu Mures Zalau Interaction	0.539	-4.602 -7.710 -18.400 1.622	2.565 22.689 47.315 1.359	0.080 0.736 0.699 0.239

Data were also analysed assuming an effect of distance on THM or chloroform levels. An unadjusted linear regression model of the association between THM levels and distance from the point of chlorination in the three cities indicated that at the 0.05 level, distance is a significant predictor of THM levels and that with each unit increase in distance, THM levels decrease by 1.226 µg/L (SE=0.513). A similar analysis was done for chloroform levels also indicating that distance was a significant predictor of chloroform levels and that with each unit increase in distance, chloroform levels decrease by 1.578 µg/L (SE=0.315). When a city comparison was included in the model using Cluj as a reference because it had the lowest measured THM and chloroform levels, Zalau showed to have significantly (p=<0.001) higher measured levels of THM and chloroform than Cluj or Târgu Mureş. Upon assessment of the presence of an interaction between the distance from point of chlorination and city, multivariate linear regression rendered all of the variables in the model insignificant at the 0.05 level. Removal of the interaction variable due to insignificance resulted in the following as final models for THM and chloroform.

THM level = 79.598 – 1.846Distance + 12.656TârguMureş + 37.612Zalau + 18.715
chloroform level = 61.888 – 1.523Distance + 11.335TârguMureş + 18.080Zalau + 13.092

The first model reveals a non-significant ($p=0.108$) effect of distance on THM levels and a significant effect of city in predicting THM levels. The second model indicates a marginally significant effect of distance ($p=0.059$) and a significant effect of city in predicting chloroform levels, independent of one another. Post-hoc statistical power calculated for all models was 99.99%.

4. DISCUSSION

In 2001, the US Environmental Protection Agency (EPA) issued a toxicological review of chloroform to support its risk assessment of the compound. ATSDR has established MRLs as a screening tool to assist public health professionals in evaluating risk. EPA and ATSDR reference values for chloroform and THMs are set below levels that, based on current information, might cause adverse health effects among those individuals most sensitive to such substance induced effects. In December 2008, the MRL for acute (1-14 days), intermediate (>14-364 days) and chronic (365 days and longer) exposure to chloroform were 0.30 mg/kg/day, 0.10 mg/kg/day and 0.01 mg/kg/day, respectively (EPA, 2001).

To our knowledge, this is the first attempt at analyzing and investigating the levels of THMs, specifically chloroform, in these Romanian cities to better understand possible cancer risk to residents. Measured levels of chloroform in this study are below the US EPA standards of 10,505 µg/L, 3,500 and 350 µg/L for acute, intermediate and chronic exposures, respectively, when applied to a 70 kg adult consuming, on average, 2 L of water a day. Results from this study suggest that Romania has been successful in its efforts to adhere to EU drinking water standards. Additionally, it suggests that consumers of chlorinated drinking water in Cluj-Napoca, Târgu Mureş and Zalau are unlikely to face long-term health risks from consumption. This assumption, however, should be made cautiously due to the complex nature of the exposure.

Epidemiological studies have found excess risk of cancer associated with levels of THM exposure in drinking water lower than standards set by the US EPA. Some of these studies have detected a weak association between exposure to chlorinated water and bladder cancer (Villanueva et al., 2006, Bove et al., 2007, King et al., 2000). Several are summarized in table 4.

Bove et al.'s study assessed cancer risk using THM data in conjunction with geographic interpolation methods to estimate tap water exposure for individuals from a related case-control study, the Upstate New York Diet Study, that was designed to compare the dietary histories of incident cases of urinary bladder and other cancers with those of controls drawn from the same western New York State populations. The mean THM level in this study was 35.07µg/L. While chloroform was the most abundant THM (mean=19.75 µg/L), results were most significant for bromoform (OR=3.05; 95% CI=1.51-5.69) and risk was highest (OR=5.85; 95% CI=1.93-17.46) for those who consumed the greatest amount of water at points within the distribution system with the oldest post-disinfected tap water.

Their study was strengthened by the fact that information on individual tap water intake measures from multiple dietary sources was obtained as well as detailed information on covariates for the study participants. The fact that only associations with tap water intake without taking into account estimated exposure doses of CBPs based on residence represents a limitation of the study. Furthermore, exposure estimates were calculated from THM data collected in the 1990s from participants who had been exposed for many years previously and thus may not be representative of true exposure (Vena et al., 1993).

Table 4. Summary of Epidemiological Studies Finding Associations at Low-Dose Exposures

Study	Study Type	Index of Exposure	Risk Estimate	Associated Effects
Bove Jr.et al. 2007	Case-Control	THM	2.34 (CI=1.01-3.66)	Urinary Bladder cancer
Villanueva et al. 2006	Case-Control	THM	1.35 (CI=0.92-1.99)	Baldder cancer
King et al. 2000b	Case-Control	THM	1.53 (CI=1.13-2.09)	Colon cancer

CI=95%Confidence Interval

Villanueva et al., (2007) conducted a multicenter hospital-based case-control study of bladder cancer between 1998 and 2001. In addition to administering a comprehensive computer-assisted personal interview to study participants, micronuclei were analyzed in exfoliate urine cells of a subset of study subjects. Results of this study showed that average ingestion THM level ranged from 0 to 240μg/L in the study population with a mean of 24μg/L. Exposure to THMs through ingestion was associated with a non-statistically significant increased risk of bladder cancer for the highest (≥35 ug/L) versus the lowest quartile of exposure with an odds ratio of 1.35 (CI=0.92-1.99). This study was strengthened by extensive data on THMs and related variables collected in the geographic study areas as well as comprehensive individual data on lifetime water consumption and water-related habits. The use of micronuclei as a biomarker concurred with experimental data and further allowed for a more accurate means of measuring THM exposure. On the other hand, the assumptions used to model past THM levels oversimplified the temporal and spatial variability of exposure within municipalities. This type of exposure misclassification is likely to be non-differential and to bias risk toward the null.

King et al., (2000) conducted a population based case-control study where they used a questionnaire and phone interview to assess exposure of study participants to THMs. The volume of tap water consumed was calculated from the reported daily consumption of water and of beverages or foods made with water, two years before the interview. Associations between colon cancer and THM exposure were observed for males but not for females in this study in contrast to other studies that did not find sex differences. The investigators concluded that among males, use of chlorinated surface waters for at least thirty years was associated with a 49% increased risk of colon cancer relative to those served by ground water for the same amount of time (95% CI = 0.10-1.00). They also found that colon cancer risk also increased with THM concentration. Those exposed to a THM level of ≥75 μg/L for ≥30years had an 87% increase compared to those exposed to levels <25 μg/L (95% CI = 0.15-2.05). The authors go on to say, however, that other descriptive and analytical epidemiological data suggest that distal colon cancers occur more frequently in males than females and that different subsites may have varying etiologies rendering distinct risk factor profiles for men and women.

In a pooled analysis of disinfection byproducts and bladder cancer, Villanueva et al., (2004) calculated an adjusted OR of 1.24 in men with exposure to an average of more than 1 μg/L THMs when compared with those who had lower or no exposure (95% CI = 1.09-1.41) over a forty year exposure window. The strongest risk estimates for bladder cancer for males in this study were observed with >35 years of exposure to THM levels of >75 μg/L. As with the previously described studies, a limitation of this study is the high likelihood of misclassification in working with past exposures and incomplete or limited water exposure histories that may reduce the power and extrapolation of findings. Moreover, any reported drinking water-cancer associations have been based on characteristics of populations compared at the group or aggregate level; thus, interpretations are subject to the ecologic fallacy.

Results from these studies when compared with current literature and established drinking water standards set by the US EPA highlight the need for further investigation of chlorination byproducts and risk assessment methods. Based on EPA reference values, chloroform levels and most THM levels measured in Cluj, Târgu Mureş and Zalau would not be associated with excess lifetime risk of cancer, while the same levels have been associated with increased risk for bladder and colon cancer in epidemiological studies. This suggests that the extrapolation of animal studies to humans may not be a wholly adequate means by which to estimate human risk from exposure to chloroform. Furthermore, it elucidates the fact that CBPs may act in concert with one another and/or other factors that may contribute to the development of bladder cancer, as the present epidemiological evidence has only evaluated the health effects of THMs as a class rather than individual substances.

The US EPA, in 1998, calculated the population-attributable risk for bladder cancer from chlorination byproducts to range from 2% to 17% (EPA, 2001). These calculations, however, were made based on the assumption that there is a causal relationship between exposure to chlorinated drinking water and risk of bladder cancer. Although some epidemiological evidence for an association between consumption of chlorinated drinking water and risk for urinary bladder indicates a slight excess of risk, subsequent evaluation of these studies by the US EPA and application of standard criteria for establishing causality from epidemiological observations led regulators to conclude that the current data were not sufficient to establish a causal relationship between exposure to chloroform in drinking water and increased risk of cancer. This conclusion and available information point to the complexity of chlorination byproducts and the possibility that chloroform may not be the only player in promoting carcinogenicity.

While there is sufficient evidence in experimental animals for the carcinogenicity of chloroform, there is inadequate evidence in humans for the carcinogenicity of chloroform; thus, further epidemiological investigation is necessary to better understand the nature of this relationship in order to provide the most informed decisions and regulations. Results from the current study and a review of the literature also suggest that future studies utilizing better methods to assess risk are necessary in order to accurately and effectively inform the public of potential hazards pertaining to consumption of chlorinated drinking water.

5. CONCLUSIONS

Strengths of this study lie in its novel nature in examining the CBP levels in these Romanian surface waters to better understand and aid in estimating risk in future studies. In analyzing trends from exposure to chloroform in these cities in Romania, it was found that there was a slightly significant association between chloroform levels and the distance of a sampling point from the point of chlorination in that network. To date, there are no studies that investigate the effect of distance on chloroform levels in chlorinated drinking water. Factors such as water flow rate, ecology of the environment surrounding the water treatment plant, and make-up and condition of pipes may influence this relationship and should be studied further to verify this observed relationship. Levels of THMs fell within an exposure range which some epidemiological studies have linked with increased risk of cancer, and some levels exceeded EPA and WHO-recommended exposure levels. Chloroform levels, on the other hand, were found to be generally lower than EPA-recommended exposure levels. Limitations of the study include its ecologic nature, thus its inability to provide information on individual levels of THM exposure within the water service areas tested. The analysis of only one sample from each sampling point also led to a lower N, perhaps influencing the significance of observed associations.

Future research to better understand risk from exposure to CBPs in these Romanian cities should include more stable estimates of exposure risk by increasing the number of measurements. Individual exposure could further be refined with application of a questionnaire designed to assess water consumption along with closely looking at which neighborhoods' exposures are captured by the sampling locations in this study. This would also provide information as to whether the current sampling points are representative of the cities and if sampling needs to be done in more locations. Such refined exposure estimates would help to elucidate possible risk based on number of residents exposed to a given THM level, or provide information to perform an epidemiological study investigating bladder or colon cancer using the THM data as the exposure variable of interest.

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