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Trihalomethanes in Drinking Water and Bladder Cancer Burden in the European Union

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BACKGROUND: Trihalomethanes (THMs) are widespread disinfection by-products (DBPs) in drinking water, and long-term exposure has been consistently associated with increased bladder cancer risk.

OBJECTIVE: We assessed THM levels in drinking water in the European Union as a marker of DBP exposure and estimated the attributable burden of bladder cancer.

METHODS: We collected recent annual mean THM levels in municipal drinking water in 28 European countries (EU28) from routine monitoring records. We estimated a linear exposure–response function for average residential THM levels and bladder cancer by pooling data from studies included in the largest international pooled analysis published to date in order to estimate odds ratios (ORs) for bladder cancer associated with the mean THM level in each country (relative to no exposure), population-attributable fraction (PAF), and number of attributable bladder cancer cases in different scenarios using incidence rates and population from the Global Burden of Disease study of 2016.

RESULTS: We obtained 2005–2018 THM data from EU26, covering 75% of the population. Data coverage and accuracy were heterogeneous among countries. The estimated population-weighted mean THM level was 11.7 μg/L [standard deviation (SD) of 11.2]. The estimated bladder cancer PAF was 4.9% [95% confidence interval (CI): 2.5, 7.1] overall (range: 0–23%), accounting for 6,561 (95% CI: 3,389, 9,537) bladder cancer cases per year. Denmark and the Netherlands had the lowest PAF (0.0% each), while Cyprus (23.2%), Malta (17.9%), and Ireland (17.2%) had the highest among EU26. In the scenario where no country would exceed the current EU mean, 2,868 (95% CI: 1,522, 4,060; 43%) annual attributable bladder cancer cases could potentially be avoided.

DISCUSSION: Efforts have been made to reduce THM levels in the European Union. However, assuming a causal association, current levels in certain countries still could lead to a considerable burden of bladder cancer that could potentially be avoided by optimizing water treatment, disinfection, and distribution practices, among other possible measures. https://doi.org/10.1289/EHP4495

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Introduction

Drinking water disinfection is essential for public health protection against waterborne infections. However, disinfection byproducts (DBPs) are formed as an unintended consequence of water disinfection. DBPs form a complex mixture of hundreds of chemicals (Hebert et al. 2010; Richardson et al. 2007) to which virtually the entire population in developed countries is exposed through ingestion, inhalation, or dermal absorption when drinking or using municipal tap water and swimming in pools. Chlorine is the most widespread disinfectant used worldwide, and trihalomethanes (THMs) and haloacetic acids (HAAs) are the DBP classes formed at the highest concentrations after chlorination. Apart from disinfection methods, the characteristics of raw water (e.g., the content of natural organic matter) and the condition of the distribution system also determine the type and levels of DBPs found in municipal water (Villanueva et al. 2015, Charisiadis et al. 2015).

Several DBPs have been shown to be genotoxic in *in vitro* assays and carcinogenic in animal experiments (Richardson et al. 2007), and the World Health Organization (WHO) International Agency for Research on Cancer (IARC) classifies chloroform and other widespread DBPs as possible human carcinogens (IARC 1991). A series of previous epidemiological studies has provided estimates of the relationship between DBPs exposure and the risk of cancer and adverse reproductive outcomes (Villanueva et al. 2015). Different meta-analyses and pooled analyses (Costet et al. 2011; King and Marrett 1996; Villanueva et al. 2003, 2004) of studies in Europe and North America provide consistent evidence that long-term exposure to THMs, used as a surrogate of DBPs, is associated with an increased bladder cancer risk. In the most recent international meta-analysis of case–control studies, men exposed to annual mean THM levels >25 μg/L had a 35% increased bladder cancer risk [95% confidence interval (CI): 9, 66], and those exposed to >50 μg/L had a 51% increased risk (95% CI: 26, 82) compared to levels <5 μg/L (Costet et al. 2011). However, there are limited large cohort studies prospectively evaluating the association with bladder cancer to unequivocally conclude a causal association, and the epidemiological evidence concerning other cancer sites is inconsistent (Villanueva et al. 2015).

Together with bromate, total THM concentrations representing the sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform are the only DBPs regulated in the European Union, with a maximum contaminant level of 100 μg/L (EC 1998). Although regulated and monitored, information on the levels in drinking water is not easily available in most European countries, and there is no published report on current levels of exposure in the European Union. Epidemiological studies conducted in different European settings indicate large variability in the levels within (Villanueva et al. 2017) and between (Jeong et al. 2012) countries. The European research project Health impacts of long-term exposure to disinfection byproducts in drinking water (HIWATE) reported that in 2010, THM levels in drinking water in seven cities from five European countries ranged from below the limit of detection (Modena, Italy) to above the current regulatory maximum limit (Barcelona, Spain) (Jeong et al. 2012). This variability was based primarily on variations in the characteristics of raw water, drinking water disinfection methods, and conditions of the water distribution system (Charisiadis et al. 2015).

Burden of disease measures, such as the number of cases attributable to a given environmental exposure, characterize public health relevance and can be used in health impact assessment and economic analysis elaborating the influence of predicted future changes in DBP levels (due to, for example, lower water quality or new regulations). Burden of disease estimates for bladder cancer due to DBP exposure have been previously assessed in France (Corso et al. 2017) and the United States (Regli et al. 2015; U.S. EPA 2005), indicating that around 16% of bladder cancer incidence is currently attributable to exposure to DBPs in drinking water.

In the context of the European Project EXPOsOMICS (Turner et al. 2018; Vineis et al. 2017), our objective was to calculate Europe-wide estimates of the current concentrations of THMs in drinking water as a marker of DBP exposure and to estimate the attributable burden of bladder cancer using different exposure scenarios.

Methods

Study Area

The study area comprises the 28 countries of the European Union in 2016 (404,672,106 inhabitants over 20 years of age) (IHME 2016b). These countries are Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Trihalomethane Data Collection

We designed a questionnaire to collect routine monitoring data on the concentration of total and individual THMs (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) in drinking water (in micrograms per liter) at the tap, distribution network, or water treatment plant from the latest year(s) available. We requested information on the annual average concentration, standard deviation, median, range, and the number of measurements at national or regional levels. The questionnaire also ascertained the institution/person providing the information, reporting year and geographic region, population served, main disinfectants used, and maximum permissible level for THMs according to the country's legislation. In addition, the corresponding raw THM data were requested. We sent this questionnaire between May 2016 and April 2019 to the national contact people in the organizations maintaining water quality data, including public health institutes and universities. We explored other data sources (e.g., open data online, reports, scientific literature, etc.) in order to complement the information provided by the questionnaires. Due to the ecological design of the study and the anonymity of data, ethics approval was not sought.

Table 1 describes the countries that completed the questionnaire and provides drinking water information available from other sources. For Croatia, Finland, Hungary, Lithuania, and Malta, we received only the completed questionnaire, while for 11 countries (Belgium, Cyprus, Czech Republic, Estonia, Greece, Italy, Latvia, Poland, Portugal, Slovenia, and the United Kingdom), we also received raw monitoring data at different reporting levels (tap, city/village, water zone, province, and region). For Germany, Greece, and Luxemburg, we used municipal and water authorities' online data and reports. For Italy, we obtained partial data provided directly from participating municipalities, complemented by online data. For Cyprus, Denmark, the Netherlands, Slovakia, and Sweden, we directly obtained data after personal communication with the respective authorities or researchers. For France, Ireland, and Spain, recent country-level THM information was published (Water_Team 2014; Corso et al. 2017; Palau and Guevara 2014); hence, reference people were not contacted. Nine countries reported nonweighted THM measurements or means (Croatia, Denmark, Finland, Germany, Hungary, Malta, the Netherlands, Slovakia, and Sweden), while

Table 1. Water sources and disinfection methods of drinking water, and other information on drinking water specimens for trihalomethanes (THM) measurements included in the study of 28 European countries (EU28).

	Water source								
Country	Ground (%)	Surface (%)	Other (%)	Type of other water	Disinfection method(s)	Data source(s)	THM data source	Water tests collection point	Level of THM reporting
Austria	100	0	0	Bank filtration in emergencies	Chlorine, chlorine dioxide, UV radiation (predominately)	Personal communication, published report	Imputed	NA	NA
Belgium	65	35	0	—	Chlorine, UV radiation, ozone (limited)	Questionnaire, raw data, personal communication, published report	Monitoring	Tap	Water zone, city/village
Bulgaria	35	65	0	—	Chlorine, UV radiation (limited)	NA	EU mean	NA	NA
Croatia	70	30	0	—	Chlorine	Questionnaire	Monitoring	Distribution system, tap	Country
Cyprus	10	58	31	Seawater	Chlorine	Questionnaire, raw data	Research	Tap	Tap
Czech Republic	50	50	0	—	Chlorine, hypochlorite	Questionnaire, raw data	Monitoring	Tap	Water zone
Denmark	100	0	0	—	No disinfection, UV radiation (limited)	Personal communication	Monitoring	Water works (outlet), distribution system	Country
Estonia	54	36	0	—	Chlorine in 2 cities	Questionnaire, raw data	Monitoring	Water plant, distribution system, tap	Water zone
Finland	41	43	16	14% artificial recharge of groundwater, 2% bank filtration	No disinfection, chlorine, hypochlorite, chlorine dioxide, chloramine, UV radiation, ozone (limited)	Questionnaire	Monitoring	Tap	Country
France	66	34	0	Four marginal sea water catchments	Chlorine, hypochlorite, chlorine dioxide, ozone	Published report	Monitoring	Water plant (outlet)	Country
Germany	68	15	15	8% artificial recharge of groundwater, 7% bank filtration	Chlorine, chlorine dioxide, hypochlorite, ozone	Published reports	Monitoring	Water plant, distribution system, tap	Water plant, distribution system
Greece	29	71	0	—	Chlorine, hypochlorite, chlorine dioxide, ozone	Questionnaire, raw data, published reports	Monitoring	Tap	Tap
Hungary	45	4	51	38% bank filtration, 13% other	Chlorine, hypochlorite, chlorine dioxide	Questionnaire	Monitoring	Distribution system, tap	Country
Ireland	11	82	7	Spring water	Chlorine, UV radiation	Online database	Monitoring	Tap	Tap
Italy	54	39	7	Bank filtration	Chlorine dioxide, ozone, hypochlorite	Questionnaire, published reports, raw data	Monitoring	Source, water plant, water tank, well, tap, public fountain	Source, water plant, water tank, well, tap, public fountain
Latvia	59	30	11	Artificial recharge of groundwater	Chlorine, hypochlorite, ozone	Questionnaire, raw data	Monitoring	Tap	Tap
Lithuania	93	0	7	Artificial recharge of groundwater	Chlorine in half of one city	Questionnaire	Monitoring	Distribution system	City
Luxemburg	66	33	0	—	Chlorine, hypochlorite, chlorine dioxide, UV radiation, ozone, ultrafiltration	Published reports	Monitoring	Tap, distribution system, water tank	Municipality, tap
Malta	27	0	73	Desalination	Chlorine	Questionnaire	Monitoring	Tap	Country
Netherlands	54	39	7	Bank filtration	Ozone, UV radiation	Personal communication	Monitoring	Water plant	Country
Poland	62	24	14	—	Chlorine, chlorine dioxide, hypochlorite, ozone, UV radiation	Questionnaire, raw data	Monitoring	Water works, water plant	Province
Portugal	34	66%	0	—	Chlorine, chlorine dioxide	Questionnaire, raw data	Monitoring	Tap	Water zone

Table 1. (*Continued.*)

	Water source								
Country	Ground (%)	Surface (%)	Other (%)	Type of other water	Disinfection method(s)	Data source(s)	THM data source	Water tests collection point	Level of THM reporting
Romania	33	64	3	2.2% bank filtration	Chlorine, chlorine dioxide	Published research articles, personal communication	Research	Water plant, distribution system, tap	City
Slovakia	85	15	0	—	Hypochlorite, chlorine	Personal communication	Monitoring	Tap	Country
Slovenia	67	33	0	—	Chlorine, chlorine dioxide, UV radiation, ozone	Questionnaire, raw data	Monitoring	Tap	Water zone
Spain	60	38	0.50	Seawater	Chlorine, chlorine dioxide, ozone, permanganate	Published report	Monitoring	Water plant, water tower, distribution system, tap	Country
Sweden	17	61	22	Artificial recharge of groundwater	No disinfection, chlorine, hypochlorite, chloramine, UV radiation	Personal communication	Monitoring	Water plant	Country
United Kingdom	14	64	22	—	Chlorine, chloramine	Questionnaire, raw data	Monitoring	Tap	Region
EU28	52	37	10	Seawater, artificial recharge of groundwater, bank filtration water, spring water	Chlorine, hypochlorite, chlorine dioxide, ozone, UV radiation, aeration, permanganate	—	—	Tap, water zone, water plant, water tower, distribution system, well, public fountain	Tap, water zone, water plant, distribution system, country

Note: Reporting years and numbers of measurements for countries with monitoring data are indicated in Table 2. Data from European Topic Centre on Inland Coastal and Marine waters, 2015 (EU and country reports) (ETC ICM 2015), ad hoc questionnaires, personal communication with contributors, and published reports. —, no data; NA, not available; UV, ultraviolet.

for the rest, population-weighted THM measurements were reported or calculated.

In Austria, Bulgaria, and Romania, key people were not identified or did not participate, or recent THM data were not available. For these three countries, we performed an online literature review to identify recent scientific and gray literature in English or in the national language using Google Translate. We used PubMed, Google Scholar, Mendeley (www.mendeley.com), and official websites using the following keywords in the Google search engine: (country name) AND [(drinking water) OR (potable water)] AND [(trihalomethanes) OR (THMs) OR (disinfection byproducts) OR (chlorination byproducts)]. The literature search identified reports of THM levels measured before the year 2000 for Austria (Premazzi et al. 1997), where expected THM levels are very low, since 99.7%% of drinking water is from underground sources and ultraviolet (UV) radiation is the predominant disinfection method (A Indra, personal communication). Hence, we included Austria in the estimation of the EU average. We could not find THM data for Bulgaria. In Romania, we obtained published THM data from 2006–2015 for 8 individual cities and for small supply areas in 10 counties (Cohl et al. 2015; Dirtu et al. 2016; Kovacs et al. 2007; Thach et al. 2012).

We obtained additional data (mean, minimum, study area, population coverage, collection points, and disinfection methods) related to the study of Dirtu et al. 2016 after personal communication with the researcher (D. Dirtu, personal communication). We calculated the population-weighted average considering the population covered by these studies (7.4% of the total population in Romania) and assigned this weighted THM mean estimate for Romania as a whole. Because we had limited data for Romania and no data for Bulgaria, we did not include these countries when estimating the average annual THM exposure for the European Union as a whole. When estimating PAFs and numbers of THM-attributable bladder cancer cases, we used a population-weighted average based on published THM values for Romania and assigned the EU average THM exposure level and standard deviation (SD) for Bulgaria (Table S1).

Trihalomethane Indices

When available, we used raw data to calculate the country average, SD, and median THM levels, and we weighted the estimations by the population served in each reporting area using the function weight = area population in STATA (version 12; Stata Corp.). For Cyprus, Germany, Greece, Italy, Luxemburg, and Romania, we built separate databases in Microsoft Excel 2010 using the available THM reports to estimate the population-weighted average THM for the reported areas, which we then assigned to the whole country. We obtained the distributions of country-specific population size and age in 2016 from the Global Burden of Disease 2016 study (IHME 2016b). The area-specific population size was either included in the provided database or report or we obtained it from the latest published country census. We excluded the outliers and assigned half the value of the reporting laboratory's detection limit when measurements were undetected. For countries that provided information on individual THMs only (chloroform, bromodichloromethane, dibromochloromethane, and bromoform,) we calculated the total THMs by adding the individual THMs. We used the mean values of THMs instead of the median values, despite the skewedness of some data, because many countries provided mean values and published literature commonly reports means. For the minimum and maximum values, we used the nonweighted THM levels to show the actual range. When only the mean THM of a country was provided to us, we used it as is.

For the estimation of the EU population-weighted mean of THMs, we used the information from 26 EU countries that provided data, thus excluding Bulgaria and Romania, since the data were nonrepresentative (in Romania, the population coverage was 7.4%) or not available (Bulgaria). We used both country-specific weighted and nonweighted mean THMs, depending on the availability of data, and weighted the EU mean by the population of each country using the function weight = country population in STATA 12. We created country-specific THM concentration maps using ArcGIS (version 10.3.1; Esri.).

Bladder Cancer and Trihalomethane Exposure–Response Function

The exposure–response function was based on data from Costet et al. (2011), the most recent and complete epidemiological data set on the relationship between residential THM exposure and bladder cancer. This is an international pooled analysis and meta-analysis including six case–control studies: two from the United States (Cantor et al. 1998; Lynch et al. 1989) and one each from Canada (King and Marrett 1996), France (Cordier et al. 1993), Finland (Koivusalo et al. 1998), and Spain (Villanueva et al. 2007). We estimated population-attributable fractions (PAFs) for each country based on an exposure–response function derived using pooled data from an analysis of residential THM exposure and bladder cancer (Costet et al. 2011) that included subjects from six case–control studies: two from the United States (Cantor et al. 1998; Lynch et al. 1989) and one each from Canada (King and Marrett 1996), France (Cordier et al. 1993), Finland (Koivusalo et al. 1998), and Spain (Villanueva et al. 2007). We pooled data from 9,458 subjects with estimates of long-term average residential THM levels, including 3,481 cases (2,776 men, 705 women) and 5,977 controls (4,199 men, 1,778 women) 30–80 years of age with THM data for ≥70% of the 40-y exposure window. We derived an odds ratio (OR) of 1.004 (95% CI: 1.002, 1.006) for a 1-μg/L increase in THM in men and women combined, adjusted for study center, age, sex, educational level, smoking status, high-risk occupation, daily fluid intake, and coffee consumption, as in Costet et al. (2011). Showering, bathing, or swimming information was not available for all studies and was not included in the analysis. We used generalized additive models (GAMs) to confirm the linearity of the exposure–response association. These models showed no significant departure from linearity ($p = 0.1461$) (see Figure S1), and we used logistic regression to estimate country-specific ORs and 95% CIs.

Attributable Bladder Cancer Cases

We followed the burden of disease approach of WHO and the United Nations Environment Programme (WHO 2015) to estimate the PAF and the annual number of bladder cancer cases attributable to THM exposure. For our primary analysis, we used the pooled OR = 1.004 for a 1-μg/L increase in THM as the exposure–response function for bladder cancer in men and women ≥20 years of age. In addition, we conducted sensitivity analyses limited to men and women 30–79 years of age, consistent with the age range of the population used to derive the pooled OR (30–80 y). For each country i, we first converted the pooled OR for a 1-μg/L increase to a country-specific OR_i for bladder cancer in association with the country-specific mean THM level (THM_i) vs. no exposure (Mueller et al. 2017):

$$\mathrm{OR}_i = \exp\left[(\ln 1.004) \times \mathrm{THM}_i\right]$$

We estimated the percent PAF_i for each country assuming 100% exposure to the mean THM level (OR_i) vs. no exposure ($\mathrm{OR}_{\mathrm{ref}} = 1.0$) (WHO 2014):

$$\mathrm{PAF}_i = \left[(\mathrm{OR}_i - 1.0)/\mathrm{OR}_i\right] \times 100$$

and estimated the number of THM-attributable bladders cancer cases per year for each country i as

$$\text{attributable cases}_i = \text{annual cases}_i \times \mathrm{PAF}_i$$

using country-specific bladder cancer incidence rates, numbers of bladder cancer cases, and population size (men and women age ≥20 y or 30–79 y, as appropriate) data from the 2016 Global Burden of Disease study (IHME 2016a, 2016b).

Exposure Scenarios and Health Impact Assessment

To account for uncertainties in the exposure estimates, we conducted a sensitivity analysis for countries with population coverage below 50% (Bulgaria, Greece, Italy, Romania, and the United Kingdom) using the average of 26 European countries (EU26) instead. In alternative analyses, we conducted a sensitivity analysis for all countries, where the lowest exposure scenario was simulated by setting the exposure level at mean THM level − 1 SD (and set to 0 μg/L if this calculated level was negative), and the highest exposure scenario was simulated by setting the exposure level at mean THM level + 1 SD for each country. Countries without available SD data (Austria, Bulgaria, Finland, France, Germany, Malta, the Netherlands, Slovakia, and Sweden) were assigned the SD of the EU population-weighted average (11.2 μg/L) with the exception of Austria, which was assigned the SD for Lithuania (5.9 μg/L), a country with a similar water source and THM levels. We also calculated the number of bladder cancer cases that would be avoided if no country would exceed the EU THM mean.

Statistical analyses were performed with Microsoft Excel 2010, the statistical software STATA 12.0, and RStudio (for GAM models, the mgcv package) (version 3.4.4; RStudio Team) (Wood 2006).

Results

Trihalomethane Levels

Drinking water source and disinfection methods used in the study countries are shown in Table 1. The vast majority of participating countries use chlorination (chlorine, hypochlorite) as the main disinfection method alone or in combination with other methods (ozone, UV radiation, etc.). Chlorine dioxide is additionally used in Italy, and in Lithuania, chlorine is used only in half of one of the cities and is supplied with surface water. In Denmark, aeration and filtration are mainly used, and in the Netherlands, ozone and UV radiation are applied. Some differences between countries are also present in the various water testing collection points and the geographical level for reporting THM levels (Table 1).

We obtained recent (2005–2018) information—with the exception of Austria (1997)—on THM levels in drinking water through routine monitoring for 26 of the 28 countries in the European Union (Table 2), covering 75% of the EU26 population. Among these countries, the population-weighted mean THM level was 11.7 μg/L [SD: 11.2, median: 10, interquartile range (IQR): 3.1–24.2]. The actual measurements ranged from 0.0 μg/L in multiple countries to 301 μg/L in Portugal, 439 μg/L

Table 2. Estimated mean total trihalomethane (THM) levels in drinking water in 26 EU countries.

Country[a]	Population[b]	MCL (μg/L)	Reporting year(s)	Number of measurements	Mean THM (μg/L)	SD (μg/L)	Median (μg/L)	Min (μg/L)	Max (μg/L)	Population served[c]	Population coverage (%)[c]
Austria[,d,e]	8,692,636	—	1997	NA	1.1	5.9	—	—	—	8,692,636	100
Belgium	11,367,990	100	2011–2014	6,015	13.2	4.0	15.9	0.0	85.1	10,556,971	93
Croatia[d]	4,221,725	100	2015	736	10.2	5.9	4.6	0.1	93.4	3,569,000	85
Cyprus	910,587	100	2012–2013	597	66.2	33.2	60.8	0.2	182.0	580,000	64
Czech Republic	10,631,077	100	2015	1,694	12.8	9.6	12.7	0.0	85.5	8,351,792	79
Denmark[d,f]	5,724,401	25	2014–2016	5,177	0.02	0.07	0.01	0.01	2.2	5,619,000	98
Estonia	1,317,494	100	2015	215	13.7	12.8	21.5	0.0	127.0	842,589	64
Finland[d]	5,507,289	100	2015	204	7.6	NA	NA	0.0	93.0	4,400,000	80
France	64,939,098	100	2005–2011	88,350	11.7	NA	NA	NA	NA	64,939,098	100
Germany[d]	82,048,579	50	2011–2013	25,382	0.5	NA	0.5	0.0	NA	74,152,913	90
Greece	10,868,170	100	2007–2017	>297	26.3	9.2	29.8	0.0	43.7	4,498,781	41
Hungary[d]	9,909,325	50	2015	5,909	10.0	20.0	4.0	0.0	771.0	9,500,000	96
Ireland	4,641,095	100	2014	1,530	47.3	25.4	43.4	0.0	255.0	3,836,798	83
Italy	60,501,702	30	2012–2017	>2,630	3.1	3.6	1.5	0.0	129.5	13,511,378	22
Latvia	1,981,699	100	2015	205	7.2	2.6	5.4	0.2	12.9	1,397,656	71
Lithuania	2,895,874	100	2015	3	1.0	5.9	0.0	NA	NA	2,872,298	99
Luxembourg	579,190	50	2011–2018	61	7.5	3.0	6.8	0.4	21.2	341,774	59
Malta[d]	420,113	100	2017	40	49.4	—	49	0.1	79.0	475,701[g]	100
Netherlands[d]	17,141,153	25	2015	161	0.2	NA	NA	0.0	1.2	17,018,408	99
Poland	38,641,788	100	2016	9,554	5.7	6.7	3.4	0.0	146.0	31,120,597	81
Portugal	10,474,821	100	2015	3,795	23.8	19.3	20.0	0.1	301.0	10,017,800	96
Slovakia[d]	5,456,895	100	2015	390	10.0	NA	NA	0.0	90.0	4,753,000	87
Slovenia	2,064,986	100	2015	457	2.9	4.5	1.2	0.0	42.1	1,844,236	89
Spain	46,481,496	100	2013	19,003	28.8	28.6	23.5	0.0	439.0	39,473,151	85
Sweden[d]	9,887,967	100	2011–2013	4,665	10.0	NA	8.0	0.5	100.0	9,903,122	100
United Kingdom	65,375,433	100	2010–2015	29,914	24.2	7.1	26.5	0.0	100.5	28,700,000	44
Total nonweighted[h]	482,682,585	—	—	>206,984	15.2	16.8	10	0.01	771	360,968,699	75
Total population, weighted		—	—	—	11.7	11.2	10	NA	NA	—	—

Note: Mean, SD, and median values are population-weighted (except if otherwise indicated). Min and max are actual measurements (nonweighted). For Greece and Italy, some municipal reports provided annual means but did not specify the number of measurements. For Sweden, additionally, 3,311 measurements had THM values below 1 μg/L but were not included in the mean THM value provided for this study. —, no data; max, maximum; MCL, maximum contaminant level; min, minimum; NA, not available; SD, standard deviation.

[a] Bulgaria and Romania are not included because there was no data (Bulgaria) or data based on literature review (Romania).

[b] Country population reported by the Global Burden of Disease Study 2016 (all ages, both sexes) (IHME 2016b).

[c] Population served and population coverage in the reporting year(s), corresponding to the country population for which THM information is available.

[d] Nonweighted mean and SD.

[e] Imputed levels (see Table S1 for details).

[f] Only chloroform is monitored in Denmark; THM values correspond to chloroform values only.

[g] Higher population served vs. total population is due to different data sources (study questionnaire vs. GBD) and reporting years (2017 vs. 2016).

[h] The population of these 26 EU countries represents 95% of the total population in the EU28. The average coverage of included countries is 75%.

in Spain, and 771 μg/L in Hungary (corresponding in this last case to one confirmed and atypical observation). Nine countries (Croatia, Denmark, Finland, Germany, Hungary, Malta, the Netherlands, Slovakia, and Sweden) provided mean THM data at the national level; hence, the population-weighted mean could not be calculated. The population coverage among the 26 countries, shown in Table 2, ranged from 22% in Italy to 100% in different countries (average coverage: 80%). The lowest mean THM values were observed in Denmark (0.02 μg/L), the Netherlands (0.2 μg/L), Germany (0.5 μg/L), Lithuania (1.0 μg/L), Austria (1.1 μg/L), Slovenia (2.9 μg/L), Italy (3.1 μg/L), and Poland (5.7 μg/L). The highest mean THM values were observed in Cyprus (66.2 μg/L), Malta (49.4 μg/L), Ireland (47.3 μg/L), Spain (28.8 μg/L), and Greece (26.3 μg/L) (Figure 1). Maximum reported concentrations exceeded the EU regulatory limit (100 μg/L) for 9 of 22 countries with available data (Table 2). However, the proportion of samples exceeding this limit was low, and average noncompliance in the nine countries was 0.7% overall, 0.3% in large water systems, and 1.1% in small water systems (EIONET).

Based on the literature search, we assigned Austria a mean (SD) THM level of 1.1 μg/L (5.9) and the EU26 mean to Bulgaria (11.7 μg/L) and SD (11.2). For Romania, the estimated mean (SD) from the published studies was 91.8 μg/L (64.2), but the population coverage was limited (7.4%) (Table S1).

Specific data on individual THMs are shown in Table S2. A total of 14 countries provided chloroform levels, 13 provided bromodichloromethane levels, and 12 provided bromoform and dibromochloromethane levels. The population-weighted average was 6.8 μg/L for chloroform (SD: 6.1; IQR: 1.6–14.2), 2.9 μg/L for bromodichloromethane (SD: 3.2; IQR: 0.3–6.3), 2.3 μg/L for dibromochloromethane (SD: 2.2, IQR: 0.5–4.3), and 1.9 μg/L for bromoform (SD: 2.5; IQR: 1.1–2.5). The average population coverage among the 14 countries with available data was 72% for chloroform, 71% for dibromochloromethane, and 70% each for bromodichloromethane and bromoform.

Attributable Bladder Cancer Cases

The estimated population fraction of bladder cancer attributable to THM exposure (both sexes, ≥20-y age group) ranged from 0.01% (95% CI: 0.004, 0.013) in Denmark to 23.2% (95% CI: 12.4, 32.7) in Cyprus and 30.7% (95% CI: 16.8, 42.3) in Romania, which was the country with the highest estimated THM level based on data reported for 7.4% of the population (Table 3). The estimated annual bladder cancer cases attributable to THM exposure ranged from zero in Denmark to 1,482 in Spain (Table 3). In total, we estimated that 6,561 bladder cancer cases per year (95% CI: 3,389, 9,537) would be attributable to THM exposure in the European Union, which represents 4.9% (95% CI: 2.5, 7.1) of the total annual bladder cancer cases in this age group. Spain (22.6%), the United Kingdom (20.7%), and Romania (16.0%) accounted for the largest estimated number of attributable cases. For men and women 30–79 years of age, we

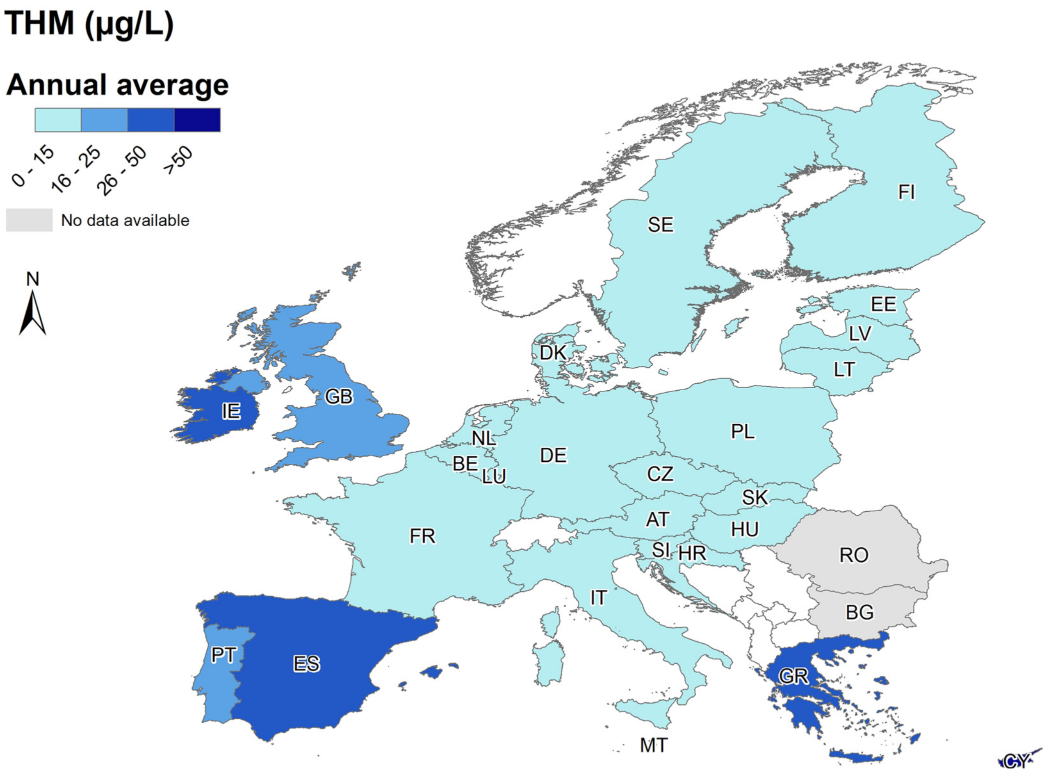

Figure 1. Map of national average total trihalomethanes (THM) levels in drinking water in European Union countries, 2005–2018. Note: See Table 1 and Table S1 for details of the estimated THM averages in the different countries. AT, Austria; BE, Belgium; BG, Bulgaria; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GB, United Kingdom; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia.

estimated that 4,518 bladder cancer cases per year (95% CI: 2,339, 6,555) would be attributable to THM exposure in the European Union as a whole, accounting for 4.9% (95% CI: 2.6, 7.1) of all EU bladder cancer cases among men and women in this age group (Table S3).

Sensitivity Analysis, Exposure Scenarios, and Health Impact Assessment

In the sensitivity analysis in which countries with population coverage <50% (Bulgaria, Greece, Italy, Romania, and the United Kingdom) were assigned the EU26 mean (11.7 µg/L), the number of attributable cases in the European Union (both sexes, ≥20-y age group) was estimated to be 5,711 (95% CI: 2,908, 8,414) cases with a PAF of 4.2% (95% CI: 2.2, 6.2) (Table 3).

Replacing country-specific mean THM values with alternative low-exposure (mean − SD or 0 if negative, resulting EU mean = 0.5 µg/L) and high-exposure (mean + SD; EU mean = 22.9 µg/L) scenarios resulted in 1,907 (95% CI: 972, 2,808) and 12,101 (95% CI: 6,351, 17,346) estimated attributable cases per year, respectively, among men and women ≥20 years of age (Table 4). Similarly, in the 30- to 79-y age group, the number of attributable cases ranged from 1,308 (95% CI: 667, 1,925) in the lowest-exposure scenario to 8,334 (95% CI: 4,387, 11,918) in the highest-exposure scenario (Table S4).

Reducing estimated mean THM values to the current EU mean (11.7 µg/L) for 13 countries with higher THM exposures reduced the estimated number of attributable cases by 2,868 per year (95% CI: 1,522, 4,060), a 43.7% reduction relative to the primary estimate for men and women ≥20 years of age (Table 5). The largest absolute reduction would occur in Romania (891 cases), Spain (860 cases), and the United Kingdom (685 cases). The largest reduction relative to the current number of attributable cases occurred in Romania (85.1%), Cyprus (80.3%), Malta (74.5%), and Ireland (73.5%). In the 30- to 79-y age group, 2,016 (95% CI: 1,074, 2,843) annual attributable bladder cancer cases would be avoided (Table S5).

Discussion

We conducted the first Europe-wide assessment of THM levels in drinking water and estimated the THM-attributable burden of bladder cancer using monitoring data covering 75% of the population in 26 EU countries. We estimated an annual average THM level of 11.7 µg/L (SD: 11.2) and a PAF of 4.9% (95% CI: 2.5, 7.1; country-specific range: 0–23%), corresponding to 6,561 (95% CI: 3,389, 9,537) bladder cancer cases per year among men and women ≥20 years of age. Reducing estimated mean THM levels to the EU average for 13 countries with higher exposures reduced the estimated number of attributable cases by 43.7% (2,868 fewer cases per year).

Although national averages may hide disparities within countries, i.e., areas supplied with ground vs. surface water may have lower THM levels, we prioritized width to depth in the data collection in order to compare the average situation between countries. We used the population-weighted mean where possible to harness this possible difference. The annual THM average was above 25 µg/L in only 5 of 26 countries with monitoring data: Cyprus, Malta, Ireland, Spain, and Greece. Chlorine is the main disinfectant used to treat drinking water in Cyprus, Ireland, and Greece (where surface water is the primary source) and in Spain (where groundwater is the primary source). In Malta, where desalination is the primary source of drinking water, THMs consist primarily of bromoform. Interventions should focus on

Table 3. Estimated population-attributable fraction (PAF) and number of bladder cancer (BC) cases attributable to total trihalomethanes (THM) levels in 28 EU countries, men and women, 20 years of age and above.

								Sensitivity analysis for countries with <50% coverage (assigned EU26 mean)		
Country	Population[a]	Annual BC cases[a]	Mean THM (μg/L)	OR (95% CI)[b]	PAF [% (95% CI)]	Attributable cases (95% CI)	Contribution[c]	PAF [% (95% CI)]	Attributable cases (95% CI)	Contribution[b,c]
Austria	7,024,117	2,084	1.1[d]	1.004 (1.002, 1.007)	0.4 (0.2, 0.7)	9 (5, 14)	0.1%	0.4 (0.2, 0.7)	9 (5, 14)	0.2%
Belgium	8,808,207	3,188	13.2	1.054 (1.027, 1.082)	5.1 (2.6, 7.6)	163 (83, 241)	2.5%	5.1 (2.6, 7.6)	163 (83, 241)	2.9%
Bulgaria	6,028,262	1,468	11.7[d]	1.048 (1.024, 1.072)	4.6 (2.3, 6.8)	67 (34, 99)	1.0%	4.6 (2.3, 6.8)	67 (34, 99)	0.2%
Croatia	3,364,105	1,144	10.2	1.042 (1.021, 1.063)	4.0 (2.0, 5.9)	46 (23, 68)	0.7%	4.0 (2.0, 5.9)	46 (23, 68)	0.8%
Cyprus	707,247	162	66.2	1.302 (1.141, 1.486)	23.2 (12.4, 32.7)	38 (20, 53)	0.6%	23.2 (12.4, 32.7)	38 (20, 53)	0.7%
Czech Republic	8,566,358	2,764	12.8	1.052 (1.026, 1.080)	5.0 (2.5, 7.4)	138 (70, 204)	2.1%	5.0 (2.5, 7.4)	138 (70, 204)	24%
Denmark[e]	4,417,579	2,017	0.02	1.000 (1.000, 1.000)	0.0 (0.0, 0.0)	0 (0, 0)	0.0%	0.0 (0.0, 0.0)	0 (0, 0)	0.0%
Estonia	1,055,356	247	13.7	1.056 (1.028, 1.086)	5.3 (2.7, 7.9)	13 (7, 19)	0.2%	5.3 (2.7, 7.9)	13 (7, 19)	0.2%
Finland	4,314,703	890	7.6	1.031 (1.015, 1.047)	3.0 (1.5, 4.4)	27 (13, 40)	0.4%	3.0 (1.5, 4.4)	27 (13, 40)	0.5%
France	49,073,604	16,161	11.7	1.048 (1.024, 1.072)	4.6 (2.3, 6.8)	737 (373, 1,092)	11.2%	4.6 (2.3, 6.8)	737 (373, 1,092)	12.9%
Germany	67,512,197	20,093	0.5	1.002 (1.001, 1.003)	0.2 (0.1, 0.3)	40 (20, 60)	0.6%	0.2 (0.1, 0.3)	40 (20, 60)	0.7%
Greece	8,819,379	3,386	26.3	1.111 (1.054, 1.171)	10.0 (5.1, 14.6)	338 (173, 493)	5.1%	4.6 (2.3, 6.8)[f]	155 (78, 229)[f]	2.7%
Hungary	7,976,719	2,250	10.0	1.041 (1.041, 1.062)	3.9 (2.0, 5.8)	88 (45, 131)	1.3%	3.9 (2.0, 5.8)	88 (45, 131)	1.5%
Ireland	3,338,589	667	47.3	1.208 (1.099, 1.327)	17.2 (9.0, 24.6)	115 (60, 164)	1.7%	17.2 (9.0, 24.6)	115 (60, 164)	2.0%
Italy	49,506,336	27,294	3.1	1.012 (1.006, 1.019)	1.2 (0.6, 1.8)	336 (169, 501)	5.1%	4.6 (2.3, 6.8)[f]	1245 (631, 1845)[f]	21.8%
Latvia	1,602,227	406	7.2	1.029 (1.014, 1.044)	2.8 (1.4, 4.2)	11 (6, 17)	0.2%	2.8 (1.4, 4.2)	11 (6, 17)	0.2%
Lithuania	2,330,161	447	1.0	1.004 (1.002, 1.006)	0.4 (0.2, 0.6)	2 (1, 3)	0.0%	0.4 (0.2, 0.6)	2 (1, 3)	0.0%
Luxembourg	452,860	128	7.5	1.030 (1.015, 1.046)	2.9 (1.5, 4.4)	4 (2, 6)	0.1%	2.9 (1.5, 4.4)	4 (2, 6)	0.1%
Malta	334,530	97	49.4	1.218 (1.104, 1.344)	17.9 (9.4, 25.6)	17 (9, 25)	0.3%	17.9 (9.4, 25.6)	17 (9, 25)	0.3%
Netherlands	13,334,551	5,163	0.2	1.001 (1.000, 1.001)	0.1 (0.0, 0.1)	4 (2, 6)	0.1%	0.1 (0.0, 0.1)	4 (2, 6)	0.1%
Poland	31,003,748	7,687	5.7	1.023 (1.012, 1.035)	2.3 (1.1, 3.4)	174 (88, 259)	2.6%	2.3 (1.1, 3.4)	174 (88, 259)	3.0%
Portugal	8,469,059	2,021	23.8	1.100 (1.049, 1.153)	9.1 (4.6, 13.3)	183 (94, 268)	2.8%	9.1 (4.6, 13.3)	183 (94, 268)	3.2%
Romania	15,346,980	3,411	91.8[e]	1.443 (1.201, 1.732)	30.7 (16.8, 42.3)	1,047 (572, 1,442)	16.0%	4.6 (2.3, 6.8)[f]	156 (79, 231)[f]	2.7%
Slovakia	4,350,449	957	10.0	1.041 (1.020, 1.062)	3.9 (2.0, 5.8)	37 (19, 56)	0.6%	3.9 (2.0, 5.8)	37 (19, 56)	0.7%
Slovenia	1,667,591	300	2.9	1.012 (1.006, 1.017)	1.1 (0.6, 1.7)	3 (2, 5)	0.1%	1.1 (0.6, 1.7)	3 (2, 5)	0.1%
Spain	37,275,483	13,648	28.8	1.122 (1.059, 1.118)	10.9 (5.6, 15.8)	1,482 (763, 2,160)	22.6%	10.9 (5.6, 15.8)	1,482 (763, 2,160)	26.0%
Sweden	7,677,260	2,195	10.0	1.041 (1.020, 1.062)	3.9 (2.0, 5.8)	86 (43, 127)	1.3%	3.9 (2.0, 5.8)	86 (43, 127)	1.5%
United Kingdom	50,314,449	14,702	24.2	1.102 (1.050, 1.156)	9.2 (4.7, 13.5)	1,356 (695, 1,984)	20.7%	4.6 (2.3, 6.8)[f]	671(340, 994)[f]	11.8%
Total EU28	404,672,106	134,976	11.7[g]	—	4.9 (2.5, 7.1)	6,561 (3,389, 9,537)	100.0%	4.2 (2.2, 6.2)	5,711 (2,908, 8414)	100.0%

Note: CI, confidence interval; OR, odds ratio.

[a] Country population and bladder cancer cases reported by Global Burden of Disease Study in 2016 (≥20-y age group, men and women) (IHME 2016a, 2016b).

[b] Country-specific ORs were derived by converting the pooled OR for a 1-μg/L THM increment (OR = 1.004), derived using pooled data for men and women age 30–80 from Costet et al. 2011) to a country-specific OR_i for bladder cancer in association with the country-specific mean exposure vs. no exposure $\{OR_i = \exp[(\ln 1.004) \times THM_i]$; $\% PAF_i = [(OR_i - 1)/OR_i] \times 100$; $\text{attributable cases}_i = \text{annual cases}_i \times PAF_i\}$.

[c] Country contribution: contribution (percent) of each country to the total attributable cases.

[d] Imputed levels (see Table S1 for details).

[e] Only chloroform is monitored in Denmark; THM values correspond to chloroform values only.

[f] Bulgaria, Greece, Italy, Romania, United Kingdom (countries included in the sensitivity analysis for countries with <50% coverage).

[g] EU mean corresponds to the population-weighted average based on the 26 countries for which THM data were available (Table 2).

Table 4. Estimated number of bladder cancer (BC) cases in Europe attributable to total trihalomethane (THM) levels in the lowest and highest exposure scenarios, men and women, age 20 years and above, in 28 European countries (EU28).

				Mean THM (μg/L)			Attributable cases	
Country	Population[a]	BC incidence (no. per 100,000)[a]	Annual BC cases[a]	Current mean ± SD	Lowest scenario mean (mean − 1 SD)[b]	Highest scenario mean (mean + 1 SD)[b]	Lowest scenario [*n* (95% CI)]	Highest scenario [*n* (95% CI)]
Austria	7,024,117	30	2,084	1.1 ± 5.9[c]	0.0	7.0	0 (0, 0)	57 (29, 85)
Belgium	8,808,207	36	3,188	13.2 ± 4.0	9.2	17.1	115 (58, 170)	211 (107, 311)
Bulgaria	6,028,262	24	1,468	11.7 ± 11.2[c]	0.5	22.9	3 (1, 4)	128 (66, 188)
Croatia	3,364,105	34	1,144	10.2 ± 5.9	4.3	16.1	19 (10, 29)	71 (36, 105)
Cyprus	707,247	23	162	66.2 ± 33.2	33.0	99.4	20 (10, 29)	53 (29, 72)
Czech Republic	8,566,358	32	2,764	12.8 ± 9.6	3.2	22.4	35 (18, 53)	236 (121, 346)
Denmark[d]	4,417,579	46	2,017	0.0 ± 0.1	0.0	0.1	0 (0, 0)	1 (0, 1)
Estonia	1,055,356	23	247	13.7 ± 12.8	1.0	26.5	1 (0, 1)	25 (13, 36)
Finland	4,314,703	21	890	7.6 ± 11.2	0.0	18.8	0 (0, 0)	64 (33, 95)
France	49,073,604	33	16,161	11.7 ± 11.2	0.5	22.9	32 (16, 48)	1,412 (723, 2069)
Germany	67,512,197	30	20,093	0.5 ± 11.2	0.0	11.7	0 (0, 0)	917 (464, 1,358)
Greece	8,819,379	38	3,386	26.3 ± 9.2	17.1	35.6	223 (114, 329)	448 (232, 649)
Hungary	7,976,719	28	2,250	10.0 ± 20.0	0.0	30.0	0 (0, 0)	254 (131, 370)
Ireland	3,338,589	20	667	47.3 ± 25.4	21.9	72.7	56 (29, 82)	168 (90, 235)
Italy	49,506,336	55	27,294	3.1 ± 3.6	0.0	6.7	0 (0, 0)	716 (361, 1,066)
Latvia	1,602,227	25	406	7.2 ± 2.6	4.6	9.7	7 (4, 11)	16 (8, 23)
Lithuania	2,330,161	19	447	1.0 ± 5.9	0.0	6.9	0 (0, 0)	12 (6, 18)
Luxembourg	452,860	28	128	7.5 ± 3.0	4.5	10.5	2 (1, 3)	5 (3, 8)
Malta	334,530	29	97	49.4 ± 11.2	38.2	60.6	14 (7, 20)	21 (11, 29)
Netherlands	13,334,551	39	5,163	0.2 ± 11.2	0.0	11.4	0 (0, 0)	230 (116, 340)
Poland	31,003,748	25	7,687	5.7 ± 6.7	0.0	12.4	0 (0, 0)	371 (188, 549)
Portugal	8,469,059	24	2,021	23.8 ± 19.3	4.5	43.1	36 (18, 53)	319 (167, 459)
Romania	15,346,980	22	3,411	91.8 ± 64.2[c]	27.7	156.0	357 (183, 520)	1,581 (913, 2,070)
Slovakia	4,350,449	22	957	10.0 ± 11.2	0.0	21.2	0 (0, 0)	78 (40, 114)
Slovenia	1,667,591	18	300	2.9 ± 4.5	0.0	7.4	0 (0, 0)	9 (4, 13)
Spain	37,275,483	37	13,648	28.8 ± 28.6	0.2	57.4	13 (7, 20)	2,793 (1478, 3,964)
Sweden	7,677,260	29	2,195	10.0 ± 11.2	0.0	21.2	0 (0, 0)	178 (91, 261)
United Kingdom	50,314,449	29	14,702	24.2 ± 7.1	17.2	31.3	974 (496, 1,435)	1,727 (892, 2,511)
Total EU28	404,672,106	33	134,976	11.7 ± 11.2	0.5	22.9	1,907 (972, 2,808)	12,101 (6,351, 17,346)

Note: BC incidence, annual, per 100,000 population. CI, confidence interval; SD, standard deviation.

[a] Country population and BC incidence and cases reported by the Global Burden of Disease Study in 2016 (≥20-y age group, men and women (IHME 2016a, 2016b).

[b] Lowest THM level scenario: mean THM − 1 SD, with negative values forced to 0. Highest THM level scenario: mean + 1 SD. When the SD was not available for a given country, the average SD (11.2 μg/L) for Europe was assigned. This was the case for Bulgaria, Finland, France, Germany, Malta, the Netherlands, Slovakia, and Sweden. Austria was assigned the SD for Lithuania (5.9 μg/L).

[c] Imputed levels (see Table S1 for details).

[d] Only chloroform is monitored in Denmark; THM values correspond to chloroform values only.

further reductions in THM levels in these countries. Previous studies in European regions found THM levels similar to the ones in our study in Italy, Lithuania, Spain, and the United Kingdom, but Greece (the island of Crete) showed lower levels, and France (Rennes region) showed higher levels than the national averages reported in the present study (Goslan et al. 2014; Krasner et al. 2016). Outside the European Union, recently reported THM levels varied from 6.2 μg/L in Dharan, Saudi Arabia (2012) (Chowdhury 2013) to 21.1 μg/L in Tetovo, North Macedonia (2011) (Bujar et al. 2013, 2017), 35.4 μg/L in Ankara, Turkey (2016) (Babayigit et al. 2016), 43.9 μg/L in Quebec, Canada (2000–2001) (Rodriguez et al. 2004), and 260 μg/L in Islamabad, Pakistan (2012) (Amjad et al. 2013).

Over the last 20 y, many EU countries managed to decrease the THM levels in their public drinking water by changing treatment methods including disinfection and by improving the quality of the water resources and the distribution network infrastructures (Palacios et al. 2000; Premazzi et al. 1997; Llopis-González et al. 2010; Gómez-Gutiérrez et al. 2012). In France, for example, water utilities have made efforts to reduce soluble organic matter in surface water sources, and chlorine dosage has been optimized to keep residual chlorine in the distribution network with minimal DBP formation (Corso et al. 2018; Courcier et al. 2014). In Italy, chlorine dioxide is widely used, contributing to lower levels of THMs but also to higher levels of chlorite and chlorate (Fantuzzi et al. 2007). In other countries, the use of ozone (e.g., the Netherlands, Germany, and France), UV radiation (Austria), or chloramines (e.g., Finland, Sweden) alone or in combination with chlorine result in lower concentrations of THMs.

However, each chemical or disinfection process contributes to the formation of other disinfectant-specific by-products, e.g., aldehydes, ketones, keto aldehydes, carboxylic acids, keto acids (after ozonation), bromate (after ozonation in presence of bromide), nitrosamines (after chlorination and chloramination), or chlorite/chlorate (after chlorine dioxide) (Kristiana et al. 2013; Richardson et al. 2000; Sorlini et al. 2014; von Gunten 2003). Disinfectants are highly reactive by definition, and any one of them will lead to the formation of DBPs (Hua and Reckhow 2007). Most of them are not regulated, and many are considered carcinogenic and/or genotoxic and have been associated with bladder cancer (e.g., nitrosamines) (Richardson et al. 2007), but their effect on human health has not been sufficiently studied.

DBPs constitute a complex mixture of hundreds of chemicals (Richardson et al. 2007), and THMs have been used in epidemiological studies as surrogates of total DBP content. THMs have limitations as markers of total DBPs since they are not the most toxic (Plewa et al. 2008), are present in mixtures with other DBPs and their effects cannot be fully separated (Rice et al. 2009), and correlations with specific DBPs are variable (Villanueva et al. 2012). However, the exposure–response relationship is only available for total THMs.

Table 5. Estimated number of attributable bladder cancer (BC) cases if no country would exceed the current EU total trihalomethanes (THM) mean level (11.9 µg/L), men and women, age 20 years and above, in 28 European countries (EU28).

		Current scenario		Reduced exposure scenario				
Country	Annual BC cases[a]	Mean THM (µg/L)	Attributable cases (95% CI)	Mean THM (µg/L)	Attributable cases (95% CI)	Reduction in attributable cases (95% CI)[b]	Percent reduction	Country contribution reduction (%)[c]
Austria[d]	1,908	1.1	9 (5, 14)	1.1	9 (5, 14)	0 (0, 0)	0.0	0.0
Belgium[e]	2,909	13.2	163 (83, 241)	11.7	145 (74, 216)	18 (9, 26)	10.8	0.5
Bulgaria[d]	1,445	11.7	68 (34, 101)	11.7	67 (34, 99)	0 (0, 0)	0.0	0.0
Croatia	1,102	10.2	46 (23, 68)	10.2	46 (23, 68)	0 (0, 0)	0.0	0.0
Cyprus[e]	151	66.2	38 (20, 53)	11.7	7 (4, 11)	30 (16, 42)	80.3	1.1
Czech Republic[e]	2,664	12.8	138 (70, 204)	11.7	126 (64, 187)	11 (6, 17)	8.3	0.3
Denmark[f]	1,896	0.02	0 (0, 0)	0.02	0 (0, 0)	0 (0, 0)	0.0	0.0
Estonia[e]	236	13.7	13 (7, 19)	11.7	11 (6, 17)	2 (1, 3)	14.4	0.1
Finland	816	7.6	27 (13, 40)	7.6	27 (13, 40)	0 (0, 0)	0.0	0.0
France	14,409	11.7	737 (373, 1,092)	11.7	737 (373, 1,092)	0 (0, 0)	0.0	0.0
Germany	18,513	0.5	40 (20, 60)	0.5	40 (20, 60)	0 (0, 0)	0.0	0.0
Greece[e]	3,116	26.3	338 (173, 493)	11.7	155 (78, 229)	183 (95, 264)	54.2	6.4
Hungary	2,172	10.0	88 (45, 131)	10.0	88 (45, 131)	0 (0, 0)	0.0	0.0
Ireland[e]	621	47.3	115 (60, 164)	11.7	30 (15, 45)	84 (45, 119)	73.5	3.0
Italy	24,693	3.1	336 (169, 501)	3.1	336 (169, 501)	0 (0, 0)	0.0	0.0
Latvia	391	7.2	11 (6, 17)	7.2	11 (6, 17)	0 (0, 0)	0.0	0.0
Lithuania	430	1.0	2 (1, 3)	1.0	2 (1, 3)	0 (0, 0)	0.0	0.0
Luxembourg	120	7.5	4 (2, 6)	7.5	4 (2, 6)	0 (0, 0)	0.0	0.0
Malta[e]	91	49.4	17 (9, 25)	11.7	4 (2, 7)	13 (7, 18)	74.5	0.5
Netherlands	4,814	0.2	4 (2, 6)	0.2	4 (2, 6)	0 (0, 0)	0.0	0.0
Poland	7,410	5.7	174 (88, 259)	5.7	174 (88, 259)	0 (0, 0)	0.0	0.0
Portugal[e]	1,867	23.8	183 (94, 268)	11.7	92 (47, 137)	91 (47, 131)	49.6	3.1
Romania[d,e]	3,349	91.8	1,047 (572, 1,442)	11.7	156 (79, 231)	891 (493, 1,211)	85.1	31.4
Slovakia	922	10.0	37 (19, 56)	10.0	37 (19, 56)	0 (0, 0)	0.0	0.0
Slovenia	276	2.9	3 (2, 5)	2.9	3 (2, 5)	0 (0, 0)	0.0	0.0
Spain[e]	12,374	28.8	1,482 (763, 2,160)	11.7	623 (315, 923)	860 (448, 1,237)	58.0	30.0
Sweden	1,969	10.0	86 (43, 127)	10.0	86 (43, 127)	0 (0, 0)	0.0	0.0
United Kingdom[e]	13,143	24.2	1,356 (695, 1,984)	11.7	671 (340, 994)	685 (355, 991)	50.5	23.8
Total EU28	123,805	11.7	6,561 (3,389, 9,537)	7.5	3,693 (1,867, 5,478)	2,868 (1,522, 4,060)	43.7	100.0

Note: Reduced scenario: no country exceeds the current EU THM mean (11.7 µg/L); the EU mean level was assigned to countries with current THM levels above the EU mean. CI, confidence interval.

[a] Bladder cancer cases reported by Global Burden of Disease Study in 2016 (≥20-y age group, men and women) (IHME 2016a).

[b] Reduction-attributable cases: the number of BC cases attributable to THMs were reduced in the reduced exposure scenario.

[c] Country contribution: contribution (percentage) of each country to the total attributable cases.

[d] Imputed levels (see Table S1 for details).

[e] Countries where current THM average level is above the EU mean (11.7 µg/L).

[f] Only chloroform is monitored in Denmark; THM values correspond to chloroform values only.

In 2016, a total of 135,011 bladder cancer cases occurred in the European Union, of which 134,976 (99.97%) were in the ≥20-y age group (IHME 2016a). Current THM levels would lead to an estimated considerable attributable proportion of cases, 4.9% (95% CI: 2.5, 7.1), or 6,561 cases (95% CI: 3,389; 9,537). Spain was the country with the greatest estimated contribution (23% of attributable EU cases) followed by the United Kingdom (21%) and Romania (16%), explained largely by high incidence rates (Spain, Romania), large population size (the United Kingdom ranks the second EU country in inhabitants), or high average THM levels (Romania). However, the quality of THM data for Romania was low (few published studies with very low population coverage) and may not accurately reflect the current country average. Romania accounted for 16% of all attributable bladder cancer cases; therefore, if THM levels were overestimated for Romania, attributable bladder cancer cases would have been overestimated for the country and for the European Union as a whole. We estimated a PAF of 4.6% for France (737 attributable cases/year), which is lower than estimates reported by Corso et al. (2017) (PAF = 16%; 1,485 attributable cases/year) based on a nationwide study that used 2011 estimates of bladder cancer incidence in men from the French network of cancer registries [FRANCIM (INCa and InVS 2011) vs. the 2016 Global Burden of Disease study used in our analysis], THM levels at the outlet of all French water treatment plants from the national database SISE-Eaux (http://www.data.eaufrance.fr/concept/sise-eaux) (vs. the national mean estimates in the present analysis), and categorical ORs from the pooled analysis of data for men reported by Costet et al. (2011) vs. the continuous exposure–response function that we derived using pooled data for both men and women from Costet et al. (2011). In addition, for Bulgaria, we could not find any published data at all, and we assigned the EU mean, but it is a small country (1.5% of the EU population) and therefore has little influence in the overall European estimates.

We calculated the burden of bladder cancer based on current THM levels, assuming no changes in future THM levels, bladder cancer incidence, and population size and distribution. Thus, our estimations should be interpreted as future projections rather than estimates of the actual burden of disease, since recent THM data do not necessarily reflect past exposures. For future estimates, sources of error include changes in population structure and incidence rates, since the European population is growing and getting older (Eurostat), and the bladder cancer incidence is expected to increase in some European countries and decrease in others over the next decade (Antoni et al. 2017; Wong et al. 2018). We used incidence data for bladder cancer from the Global Burden of Disease 2016 study, which uses multiple sources depending on the country (e.g., WHO mortality data, national registries, vital statistics, modeling from neighboring regions, etc.). Accuracy may differ, since not all keep nationwide cancer registries or there may be discrepancies with national databases. In the French study, for example (Corso et al. 2017), bladder cancer cases were considerably lower in all ages ($n = 9{,}100$ in 2011, men only) than the ones reported in the Global Burden of Disease 2016 study ($n = 13{,}959$ in 2016, men only).

We used pooled data for 3,481 cases and 5,977 controls from 7 case–control studies included in a meta-analysis by Costet et al. (2011) to derive the continuous exposure–response function that was the basis of our country-specific ORs for bladder cancer in association with country-specific mean THM estimates. Although this is the most comprehensive pooled analysis currently available, it is limited to case–control studies and does not include a recent U.S. study of 1,213 bladder cancer cases and 1,418 controls (Beane Freeman et al. 2017).

An underlying assumption of this research study is the causal relationship between THMs and bladder cancer. Many DBPs have been classified as mutagenic or genotoxic based on *in vitro* assays or experimental studies of animals (Richardson et al. 2007). In addition, a study of 49 adults reported that micronuclei counts in peripheral lymphocytes and urine mutagenicity were associated with higher levels of individual brominated THMs in exhaled breath following 40 min of swimming (Kogevinas et al. 2010), while another study of 43 adults (Espín-Pérez et al. 2018) reported that changes in exhaled DBPs following a 40-min swim in a chlorinated pool were associated with microRNA and gene expression patterns that may indicate an increased risk of bladder cancer. However, some uncertainties in the association still exist, e.g., the putative agent(s) is yet to be identified, the biological pathways are not completely established, and the inconsistent association in some studies in women is not well understood. Additionally, the precision of the exposure–response relationship decreases at higher exposure levels, given the smaller statistical power at the higher-exposure end, as shown in Figure S1. This may lead to inaccurate estimates in countries with high THM levels. Polymorphisms in DBP-metabolizing genes have been shown to modify the exposure–response relationship (Cantor et al. 2010), but these population differences are unlikely to affect our overall results.

Our analyses are based on men and women combined. While most of the case–control studies included in the pooled analysis report a null or inverse association among women, there are also case–control studies showing higher risks in women than men (Beane Freeman et al. 2017). Future studies may want to consider comparing estimates based on sex-specific exposure–response functions to estimates for men and women combined.

We have not considered the proportion of use of bottled or filtered water, which, in some countries, may be substantial and account for exposure misclassification through the ingestion route (Wright et al. 2006), nor the exposure to DBPs through inhalation and dermal exposure during household cleaning activities (Charisiadis et al. 2014), showering or bathing, or in swimming pools (Villanueva et al. 2007), which contributes to increased THM exposure because the available data set of Costet et al. 2011 did not include this information for all studies. Although models are adjusted for the main risk factors of bladder cancer, the potential for residual confounding cannot be ruled out.

The biggest challenge has been the collection of representative THM data at the national level in the 28 EU countries for a comparable recent period. In particular, the data for Romania are a limitation, and the estimated PAF and attributable cases for Romania were markedly reduced when using the EU mean in place of the original estimate. In addition, using the EU mean for all countries with <50% coverage (Greece, Italy, Romania, and the United Kingdom) resulted in a net decrease in the overall PAF and attributable case estimates. Potential exposure misclassification may result from reliance on monitoring data covering 75% of the population that may lead both to over- or underestimation of the THM average. For some countries, a variable proportion of the noncovered population may use private wells with low THM levels. For example, in the Czech Republic, 94% of the population is served by public water supply systems, but we had THM data only for 74%. Similarly in Greece, for large cities including Thessaloniki and Larisa, THM data were not available. However, we do not have this type of information for all the countries, and we cannot generalize and anticipate the impact on the EU population-weighted THM estimate.

The reporting situation differs widely among countries. According to the European Council (EC) Drinking Water Directive, countries are obliged to report the drinking water quality to the public and the EC in a 3-year report. However, only the number of THM analyses and percentage of noncompliant measurements are presented and not the actual monitoring or even descriptive data (EC 1998). Only some countries maintain a centralized electronic database of THM measurements and only Ireland (U.S. EPA 2015) and Denmark (GEUS) have this database publicly available. Denmark provides information only for chloroform since it is the only DBP regularly measured. Danish drinking water is not chlorinated, but chloroform has been found in groundwater and can either originate from anthropogenic pollution or be of natural origin, i.e., from forest soil (Hunkeler et al., 2012). Open data are available for some countries in a decentralized way, which forced us to do an extensive internet search of municipality and water utility websites (e.g., Italy, Greece), including manual data extraction from published individual laboratory reports (e.g., Luxemburg).

Not all municipalities or water utilities report their water quality analysis results, and among the ones that do, only a subset includes THMs values. For example, for Italy, we checked relevant websites covering 54% of the Italian population, and, of these, only 35% included THM information. It is therefore important for these countries to set up centralized electronic databases to monitor drinking water quality and for these databases to be publicly available, both to the EC and also to the public and scientific community. This is also in line with the proposal for the new EC directive (EC 2018) on the quality of water intended for human consumption that requires the establishment of centralized databases and better publicity of the results of water quality analyses. However, in the new directive, there is no provision to lower the maximum permissible limit for THMs of 100 μg/L or to include information on the actual monitoring results in these databases, although it proposes to regulate additional DBPs such as HAAs, chlorite, and chlorate.

Another source of heterogeneity in THM levels is the diversity of monitoring sampling sites (e.g., treatment plant, distribution network, and consumers' taps). This is relevant since THM levels may differ, i.e., levels may increase with residence time in the distribution network and distance to the tap, presence of additional chlorination, distribution network maintenance, etc. (Charisiadis et al. 2015). Only 12 of 26 countries report THM measurements collected at consumers' taps only. The rest report measurements from specimens collected in a variety of places (water treatment plants, water tanks, distribution network, and taps), and annual averages may not accurately reflect levels at the consumers' taps. Routine monitoring is less frequent in small water supplies, sometimes only once per year, and may not reflect the annual average exposure. However, it involves a relatively small amount of population, and this potential source of error would be minor in the overall estimates. Furthermore, for some countries, we could not calculate the population-weighted average due to lack of appropriate data and used the nonweighted one in the estimation of the EU mean. The weighted average may be different from the nonweighted average, depending on the size of the population served by each water distribution system and its respective THM levels.

Conclusion

The current average THMs levels in drinking water in all EU countries were below the European regulatory limits, although maximum levels showed exceedance in nine countries. Assuming a causal association, our results suggest that current THM exposures in the European Union may lead to a considerable number of bladder cancer cases that could be avoided by optimizing water treatment, disinfection, and distribution, among other measures, without compromising the microbiological quality of drinking water. The main efforts in reduction of THM levels should be made in countries with the highest proportion of exceedance and highest average THM levels.

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