Supplemental Material

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

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Table S1. Trihalomethane (THM) data collected from literature review for the countries where monitoring data were not available by national contacts.

Country	Reference	Year sampling	Area covered	THM levels reported	Mean (SD) THM level assigned (µg/L)	Comments
Austria	Premazzi, 1997	-	Country	"When surface waters are disinfected, the usual THMs concentrations in finished waters are around 10-20 µg/L"; "The total water supply in Austria is composed of equal parts of groundwater and spring water, whereas the percentage of surface water (less than 1%) is negligible.	1.1 (5.9)	We assigned a value of 15 µg/L to the 1% of population receiving surface water and an arbitrary value of 1µg/L to 99% of Austrian population receiving ground/spring water. The standard deviation corresponds to a country with a similar water source and levels (Lithuania).
Bulgaria	-	-	-	-	11.7 (11.2)	EU mean and standard deviation of THM level assigned
Romania	Kovacs 2007, Thach et al. 2012, Cohl et al. 2015, Dirtu et al. 2016 Dirtu personal communication 2018	2006, 2009, 2010-2013, 2013-2014 2013-2014	Eight cities: Cluj-Napoca, Dej, Iasi,Oradea, Târgu Mureş, Timisoara and Zalau and population served by Small Areas in 10 counties (Botosani, Suceava, Neamt, Iasi, Vaslui, Bacau, Vrancea, Galati, Braila and Tulcea). Population covered 7.4% (1,439,069 inhabitants from 19,364,092).	Mean THM (µg/L): 111.3 (Bristrita), 57.1 (Dej), 144.4 (Iasi), 29.4 (Oradea), 194.7 (Timisoara), 210.2 (Zalau) in Kovacs et al.; 48.1 (Cluj-Napoca), 81.9 (Targu Mures), 81.5 (Zalau) (Range 9.04-116.79 µg/L) in Tach et al.; 26.0 (Iasi) in Cohl et al.; 17.34 (range: 1.87-94.18) (Small supply areas in 10 counties) in Dirtu el al.	91.8 (64.2)	Population-weighted average and standard deviation considering the population served in the cities/areas covered by these studies. Average THM values were calculated for each of the cities/areas with more than one reported measurement. Then, the overall average THM was calculated weighing the mean THM of each city/area with the population of that city/area (Stata code: summarize thm [weight=populationserved], details).

Note: SD: standard deviation. EU mean : 11.7µg/L:, EU SD 11.2µg/L

Table S2. Estimated population-weighted levels of individual Trihalomethanes (µg/L) in 14 European countries, 2005-2018.

Country	Population[a]	Coverage (%)	Chloroform Mean ± SD	Chloroform Median (min-max)	Bromodichloromethane Mean ± SD	Bromodichloromethane Median (min-max)	Dibromochloromethane Mean ± SD	Dibromochloromethane Median (min-max)	Bromoform Mean ± SD	Bromoform Median (min-max)
Belgium	11,367,990	40	3.5±2.0	4.4 (0.2-54.0)	1.5±0.3	1.4 (0.0-7.4)	1.9±2.0	1.1 (0.0-12.2)	2.5±1.2	2.0 (0.0-8.9)
Croatia	4,221,725	86	6.3±4.9	3.2 (0.1-57.9)	1.9±0.9	0.9 (0.1-13.3)	1.7±1.5	0.8 (0.1-21.1)	2.2±2.6	0.6 (0.1-27.2)
Cyprus	910,587	50	16.6±8.5	15.9 (0.1-43.1)	21.8±11.0	20.3 (0.0-55.8)	20.7±12.2	19.0 (0.1-64.2)	7.1±7.0	4.3 (0.1-40.3)
Denmark[b]	5,724,401	98	0.02±0.07	0.01 (0.01-2.2)	-	-	-	-	-	-
Greece	10,868,170	40	18.1±5.5	19.6 (0.0-35.2)	7.1±1.8	7.7 (0.0-10.2)	2.5±0.4	2.6 (0.0-9.9)	0.4±1.4	0.0 (0.0-37.0)
Hungary	9,909,325	97	6.0±20.0	1.0 (0.0-718)	2.0±3.0	0.0 (0.0-50.0)	2.0±3.0	0.0 (0.0-57.0)	1.0±3.0	0.0 (0.0-36.0)
Italy	60,501,702	9	1.6±2.3	0.3 (0.0-26.3)	0.3±0.7	0.1 (0.0-8.9)	0.5±1.0	0.3 (0.0-10.8)	1.1±1.7	0.8 (0.0-14.9)
Luxembourg	579,190	59	3.2±1.4	3.1 (0.1-10.0)	2.0±0.8	1.9 (0.1-6.2)	1.6±0.6	1.5 (0.1-6.3)	0.6±0.4	0.5 (0.2-3.7)
Malta	420,113	100	0.7±na	0.5 (0.1-1.5)	5.7±na	0.3 (0.1-45.0)	0.9±na	0.7(0.1-2.7)	48.6±na	48.0(0.1-77.0)
Poland[c]	38,641,788	65	4.4±7.0	2.2 (0.0-119.0)	1.5±1.6	1.0 (0.0-30.0)	1.5±1.3	1.0 (0.0-24.0)	1.3±1.0	1.0 (0.0-79.0)
Portugal	10,474,821	97	13.2±12.5	10.0 (0.1-168.0)	6.6±5.1	5.3 (0.1-102.0)	4.3±4.1	3.5 (0.1-41.9)	2.4±3.3	1.4 (0.0-61.4)
Slovakia	5,456,895	88	0.0±na	0.0 (0.0-60.0)	0.0±na	0.0 (0.0-10.0)	-	-	-	-
Slovenia	2,064,986	89	1.4±3.0	0.4 (0.1-38.0)	0.7±0.7	0.3 (0.0-6.9)	0.6±0.9	0.3 (0.0-9.7)	0.4 (1.9)	0.1 (0.1-23.0)
Spain	46,481,496	85	14.2±na	na (0.0-673)	6.3±na	na (0.0-69.1)	4.6±na	na (0.0-80.0)	3.1 (na)	-
Total	**207,203,077**	**54**	**6.8±6.1**	**4.4 (0.0-718)**	**2.9±3.2**	**1.5 (0.0-102.0)**	**2.3±2.3**	**1.5 (0.0-80.0)**	**1.8 (1.0)**	**1.3 (0.0-140)**

Note: SD: standard deviation, min: minimum, max: maximum, na: not available. Mean, SD and Median values are population-weighted (except if otherwise indicated). Min, Max: actual measurements (non-weighted)

[a] Source: Country population reported by Global Burden of Disease 2016 Study (GBD) in 2016 (all ages, both sexes) (IHME b)

[b] Only chloroform is monitored in Denmark

[c] Poland: coverage of 49% for DBCM, 62% for BDCM, 47% for Bromoform

Figure S1. Exposure-response relationship between average trihalomethane (THM) levels (µg/L, x-axis) and bladder cancer odds ratio (OR) (y-axis). Smoothed spline from a generalised additive model adjusted for study center, age, sex, educational level, smoking status, high-risk occupation, daily fluid intake, and coffee consumption. Tick marks above the x-axe represent observations, and the dashed lines represent the 95% confidence intervals (CIs).

NOTE: The portion of the graph indicating OR<1 is a computational artefact. This model was only used to confirm the linearity of the exposure-response relationship, and was not used to derive the country-specific ORs, that were estimated from a logistic regression adjusted for the same co-variables.
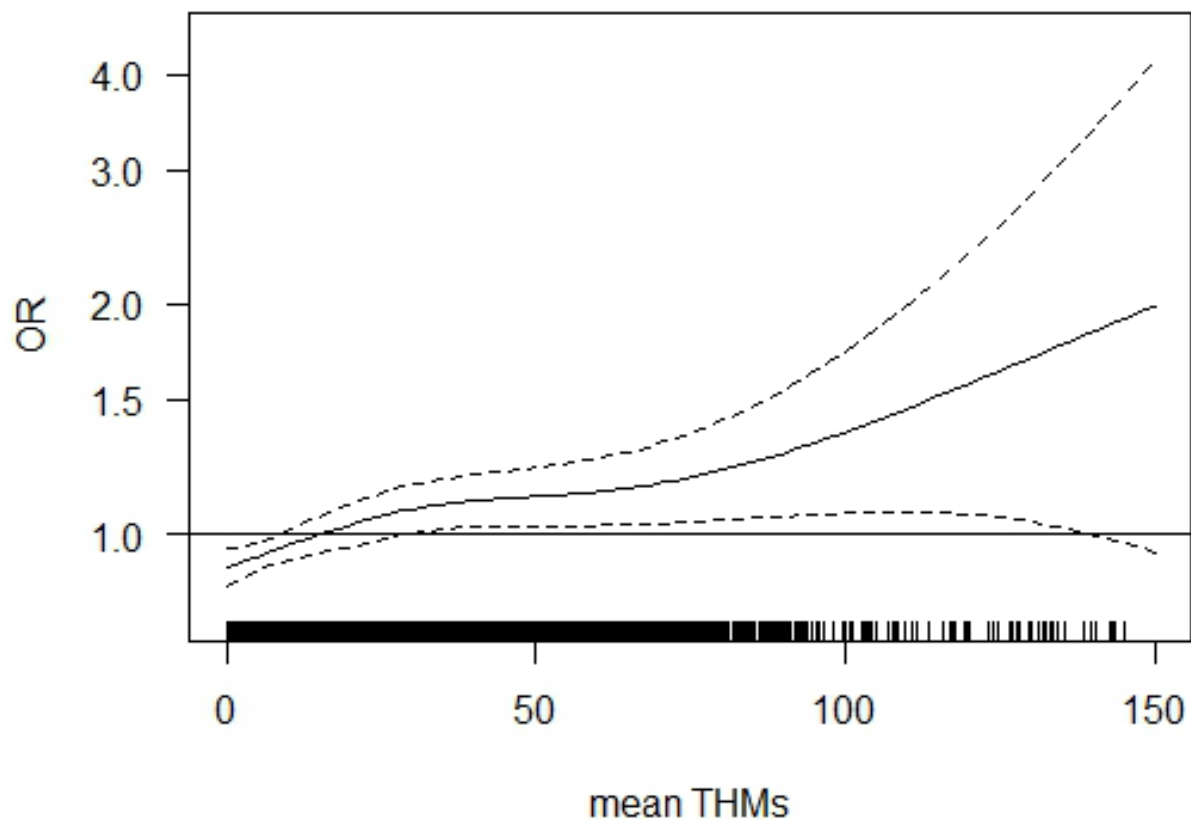
Table S3. Estimated population attributable fraction (PAF) and number of bladder cancer (BC) cases attributable to trihalomethanes (THM) levels in 28 EU countries, men and women, age 30-79 years.

Country	Population[a]	Annual BC cases	Mean THM, μg/L	OR (95%CI)[b]	PAF, % (95% CI)	Attributable cases (95% CI)	Country contribution %[c]
Austria	5,449,050	1,438	1.1[d]	1.004 (1.002, 1.007)	0.4 (0.2, 0.7)	6 (3, 9)	0.1
Belgium	6,749,010	2,115	13.2	1.054 (1.027, 1.082)	5.1 (2.6, 7.6)	108 (55, 160)	2.4
Bulgaria	4,776,529	1,241	11.7[d]	1.048 (1.024, 1.072)	4.6 (2.3, 6.8)	57 (29, 84)	1.3
Croatia	2,656,373	872	10.2	1.042 (1.021, 1.063)	4.0 (2.0, 5.9)	35 (18, 52)	0.8
Cyprus	515,978	116	66.2	1.302 (1.141, 1.486)	23.2 (12.4, 32.7)	27 (14, 38)	0.6
Czech Republic	6,834,999	2,207	12.8	1.052 (1.026, 1.080)	5.0 (2.5, 7.4)	110 (56, 163)	2.4
Denmark[e]	3,424,844	1,524	0.02	1.000 (1.000, 1.000)	0.0 (0.0, 0.0)	0 (0, 0)	0.0
Estonia	806,831	178	13.7	1.056 (1.028, 1.086)	5.3 (2.7, 7.9)	10 (5, 14)	0.2
Finland	3,345,284	606	7.6	1.031 (1.015, 1.047)	3.0 (1.5, 4.4)	18 (9, 27)	0.4
France	37,679,844	10,571	11.7	1.048 (1.024, 1.072)	4.6 (2.3, 6.8)	482 (244, 715)	10.7
Germany	53,140,291	13,576	0.5	1.002 (1.001, 1.003)	0.2 (0.1, 0.3)	27 (14, 41)	0.6
Greece	6,919,836	2,193	26.3	1.111 (1.054, 1.171)	10.0 (5.1, 14.6)	219 (112, 320)	4.8
Hungary	6,306,548	1,835	10.0	1.041 (1.020, 1.062)	3.9 (2.0, 5.8)	72 (36, 107)	1.6
Ireland	2,702,262	478	47.3	1.208 (1.099, 1.327)	17.2 (9.0, 24.6)	82 (43, 118)	1.8
Italy	39,013,809	17,495	3.1	1.012 (1.006, 1.019)	1.2 (0.6, 1.8)	215 (108, 321)	4.8
Latvia	1,230,519	308	7.2	1.029 (1.014, 1.044)	2.8 (1.4, 4.2)	9 (4, 13)	0.2
Lithuania	1,762,309	330	1.0	1.004 (1.002, 1.006)	0.4 (0.2, 0.6)	1 (1, 2)	0.0
Luxembourg	351,465	91	7.5	1.030 (1.015, 1.046)	2.9 (1.5, 4.4)	3 (1, 4)	0.1
Malta	263,795	74	49.4	1.248 (1.104, 1.344)	17.9 (9.4, 25.6)	13 (7, 19)	0.3
Netherlands	10,402,899	3,755	0.2	1.001 (1.000, 1.001)	0.1 (0.0, 0.1)	3 (2, 4)	0.1
Poland	24,141,473	6,144	5.7	1.023 (1.012, 1.035)	2.3 (1.1, 3.4)	139 (70, 207)	3.1
Portugal	6,758,380	1,333	23.8	1.100 (1.049, 1.153)	9.1 (4.6, 13.3)	121 (62, 177)	2.7
Romania	12,318,158	2,861	91.8[d]	1.443 (1.201, 1.732)	30.7 (16.8, 42.3)	878 (480, 1209)	19.4
Slovakia	3,414,420	773	10.0	1.041 (1.020, 1.062)	3.9 (2.0, 5.8)	30 (15, 45)	0.7
Slovenia	1,334,179	201	2.9	1.012 (1.006, 1.017)	1.1 (0.6, 1.7)	2 (1, 3)	0.1
Spain	29,715,133	8,598	28.8	1.122 (1.059, 1.188)	10.9 (5.6, 15.8)	934 (481, 1361)	20.7
Sweden	5,802,874	1,488	10.0	1.041 (1.020, 1.062)	3.9 (2.0, 5.8)	58 (29, 86)	1.3
UK	38,145,133	9,313	24.2	1.102 (1.050, 1.156)	9.2 (4.7, 13.5)	859 (440, 1257)	19.0
Total EU28	**315,962,225**	**91,715**	**11.7**[fe]		4.9 (2.6, 7.1)	**4518 (2339, 6555)**	100.0

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

[a] Source: Country population and bladder cancer cases reported by Global Burden of Disease Study in 2016 (GBD 2016) (30-79 years age group, men and women) (IHME a, b)

[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 ($OR_i = \exp[(\ln 1.004) * THM_i]$; % $PAF_i = ((OR_i - 1)/OR_i)*100$; attributable cases$_i$ = annual cases$_i$ * PAF_i."

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

[d] Imputed levels (See supplemental material Table 1 for details).

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

[f] EU mean corresponds to the population-weighted average based on the 26 countries that provided THM data (Table 2 main paper).

Table S4. Estimated number of bladder cancer (BC) cases attributable to trihalomethane (THM) levels in the lowest and highest exposure scenarios, men and women, age 30-79 years.

Country	Population[a]	BC incidence (/100,000)[a]	Annual BC cases[a]	Mean THM (µg/L)			Attributable cases	
				Current mean ± SD	Lowest scenario (Mean – 1 SD)[b]	Highest scenario (Mean + 1 SD)[b]	Lowest scenario (95% CI)	Highest scenario (95% CI)
Austria	5,449,050	26	1,438	1.1±5.9[c]	0.0	7.0	0 (0, 0)	40 (20, 59)
Belgium	6,749,010	31	2,115	13.2±4.0	9.2	17.1	76 (38, 113)	140 (71, 206)
Bulgaria	4,776,529	26	1,241	11.7±11.2[c]	0.5	22.9	2 (1, 4)	108 (55, 159)
Croatia	2,656,373	33	872	10.2±5.9	4.3	16.1	15 (7, 22)	54 (28, 80)
Cyprus	515,978	23	116	66.2±33.2	33.0	99.4	14 (7, 21)	38 (21, 52)
Czech Rep.	6,834,999	32	2,207	12.8±9.6	3.2	22.4	28 (14, 42)	188 (96, 276)
Denmark[d]	3,424,844	45	1,524	0.0±0.1	0.0	0.1	0 (0, 0)	1 (0, 1)
Estonia	806,831	22	178	13.7±12.8	1.0	26.5	1 (0, 1)	18 (9, 26)
Finland	3,345,284	18	606	7.6±11.2	0.0	18.8	0 (0, 0)	44 (22, 64)
France	37,679,844	28	10,571	11.7±11.2[c]	0.5	22.9	21 (11, 32)	924 (473, 1353)
Germany	53,140,291	26	13,576	0.5±11.2[c]	0.0	11.7	0 (0, 0)	620 (314, 918)
Greece	6,919,836	32	2,193	26.3±9.2	17.1	35.6	145 (74, 213)	290 (150, 420)
Hungary	6,306,548	29	1,835	10.0±20.0	0.0	30.0	0 (0, 0)	207 (107, 301)
Ireland	2,702,262	18	478	47.3±25.4	21.9	72.7	40 (20, 59)	120 (65, 169)
Italy	39,013,809	45	17,495	3.1±3.6	0.0	6.7	0 (0, 0)	459 (231, 683)
Latvia	1,230,519	25	308	7.2±2.6	4.6	9.7	6 (3, 8)	12 (6, 17)
Lithuania	1,762,309	19	330	1.0±5.9	0.0	6.9	0 (0, 0)	9 (4, 13)
Luxembourg	351,465	26	91	7.5±3.0	4.5	10.5	2 (1, 2)	4 (2, 6)
Malta	263,795	28	74	49.4±11.2	38.2	60.6	10 (5, 15)	16 (8, 22)
Netherlands	10,402,899	36	3,755	0.2±11.2	0.0	11.4	0 (0, 0)	167 (85, 248)
Poland	24,141,473	25	6,144	5.7±6.7	0.0	12.4	0 (0, 0)	296 (150, 439)
Portugal	6,758,380	20	1,333	23.8±19.3	4.5	43.1	24 (12, 35)	211 (110, 303)
Romania	12,318,158	23	2,861	91.8±64.2[c]	27.7	156.0	299 (154, 436)	1326 (766, 1736)
Slovakia	3,414,420	23	773	10.0±11.2	0.0	21.2	0 (0, 0)	63 (32, 92)
Slovenia	1,334,179	15	201	2.9±4.5	0.0	7.4	0 (0, 0)	6 (3, 9)
Spain	29,715,133	29	8,598	28.8±28.6	0.2	57.4	8 (4, 12)	1760 (931, 2497)
Sweden	5,802,874	26	1,488	10.0±11.2	0.0	21.2	0 (0, 0)	120 (61, 176)
UK	38,145,133	24	9,313	24.2±7.1	17.2	31.3	617 (314, 909)	1094 (565, 1591)
Total EU28	315,962,225	29	**91,715**	**11.7±11.2**[e]	**0.5**	**22.9**	**1308 (667, 1925)**	**8334 (4387, 11918)**

Note: SD: Standard Deviation. CI: Confidence interval. BC incidence: annual, per 100,000 inhabitants.

[a] Source: country population and bladder cancer incidence and cases reported by Global Burden of Disease Study in 2016 (GBD 2016) (30-79 years age group, men and women (IHME a, b).

[b] Lowest THM level scenario: mean THM – 1 SD, with negative values forced to 0. Countries without SD data that were assigned the EU SD (11.2) were Bulgaria, Finland, France, Germany, Malta, Netherlands, Slovakia, Sweden. Austria was assigned the SD for Lithuania (5.9 µg/L).

[c] Imputed levels (See supplemental material Table 1 for details).

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

[e] EU mean corresponds to the population-weighted average based on the 26 countries that provided THM data (Table 2 main paper).

Table S5. Estimated number of attributable bladder cancer (BC) cases if no country would exceed the current EU Total Trihalomethanes (THM) mean level (11.7 µg/L), men and women, age 30-79 years, EU-28.

Country	Annual BC cases[a]	Current scenario		Reduced exposure scenario				
		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]	1,438	1.1	6 (3, 9)	1.1	6 (3, 9)	0 (0, 0)	0.0	0.0
Belgium[e]	2,115	13.2	108 (55, 160)	11.7	97 (49, 143)	12 (6, 17)	10.8	0.6
Bulgaria[d]	1,241	11.7	57 (29, 84)	11.7	57 (29, 84)	0 (0, 0)	0.0	0.0
Croatia	872	10.2	35 (18, 52)	10.2	35 (18, 52)	0 (0, 0)	0.0	0.0
Cyprus[e]	116	66.2	27 (14, 38)	11.7	5 (3, 8)	22 (12, 30)	80.3	1.1
Czech Rep.[e]	2,207	12.8	110 (56, 163)	11.7	101 (51, 149)	9 (5, 13)	8.3	0.5
Denmark[f]	1,524	0.02	0 (0, 0)	0.02	0 (0, 0)	0 (0, 0)	0.0	0.0
Estonia[e]	178	13.7	10 (5, 14)	11.7	8 (4, 12)	1 (1, 2)	14.4	0.1
Finland	606	7.6	18 (9, 27)	7.6	18 (9, 27)	0 (0, 0)	0.0	0.0
France	10,571	11.7	482 (244, 715)	11.7	482 (244, 715)	0 (0, 0)	0.0	0.0
Germany	13,576	0.5	27 (14, 41)	0.5	27 (14, 41)	0 (0, 0)	0.0	0.0
Greece[e]	2,193	26.3	219 (112, 320)	11.7	100 (51, 148)	119 (62, 171)	54.2	5.9
Hungary	1,835	10.0	72 (36, 107)	10.0	72 (36, 107)	0 (0, 0)	0.0	0.0
Ireland[e]	478	47.3	82 (43, 118)	11.7	22 (11, 32)	60 (32, 85)	73.5	3.0
Italy	17,495	3.1	215 (108, 321)	3.1	215 (108, 321)	0 (0, 0)	0.0	0.0
Latvia	308	7.2	9 (4, 13)	7.2	9 (4, 13)	0 (0, 0)	0.0	0.0
Lithuania	330	1.0	1 (1, 2)	1.0	1 (1, 2)	0 (0, 0)	0.0	0.0
Luxembourg	91	7.5	3 (1, 4)	7.5	3 (1, 4)	0 (0, 0)	0.0	0.0
Malta[e]	74	49.4	13 (7, 19)	11.7	3 (2, 5)	10 (5, 14)	74.5	0.5
Netherlands	3,755	0.2	3 (2, 4)	0.2	3 (2, 4)	0 (0, 0)	0.0	0.0
Poland	6,144	5.7	139 (70, 207)	5.7	139 (70, 207)	0 (0, 0)	0.0	0.0
Portugal[e]	1,333	23.8	121 (62, 177)	11.7	61 (31, 90)	60 (31, 87)	49.6	3.0
Romania[d/e]	2,861	91.8	878 (480, 1209)	11.7	131 (66, 193)	747 (413, 1016)	85.1	37.1
Slovakia	773	10.0	30 (15, 45)	10.0	30 (15, 45)	0 (0, 0)	0.0	0.0
Slovenia	201	2.9	2 (1, 3)	2.9	2 (1, 3)	0 (0, 0)	0.0	0.0
Spain[e]	8,598	28.8	934 (481, 1361)	11.7	392 (199, 581)	541 (282, 780)	58.0	26.9
Sweden	1,488	10.0	58 (29, 86)	10.0	58 (29, 86)	0 (0, 0)	0.0	0.0
UK[e]	9,313	24.2	859 (440, 1257)	11.7	425 (215, 630)	434 (225, 628)	50.5	21.5
Total EU28	**91,715**	**11.7**	**4519 (2340, 6556)**	**7.5**	**2502 (1265, 3712)**	**2016 (1074, 2843)**	**44.6**	**100.0**

Note: CI: Confidence intervals. Reduced scenario: no country exceeds the current EU THM mean (11.7 µg/L); assignment of EU mean level to countries with current THM levels above the EU mean.

[a] Bladder cancer cases reported by Global Burden of Disease Study in 2016 (GBD 2016) (30-79 years age group, men and women) (IHME a).

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

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

[d] Imputed levels (See supplementary material Table 1 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 only.

References

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