Occurrence and variability of iodinated trihalomethanes concentrations within two drinking-water distribution networks☆,☆☆

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HIGHLIGHTS

- Iodinated trihalomethanes were studied in two water distribution systems.
- Low levels of iodinated trihalomethanes in tap water
- Large variability of iodinated trihalomethanes within the water distribution system

GRAPHICAL ABSTRACT
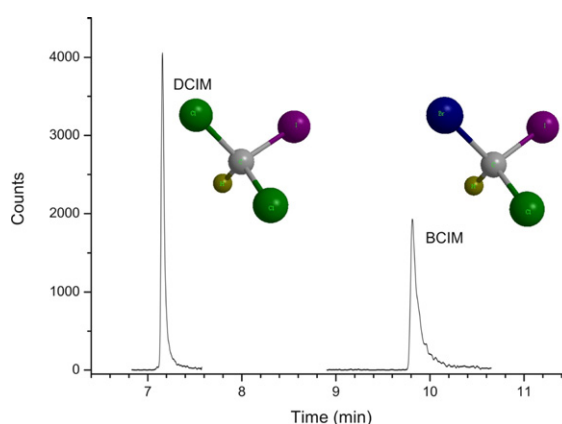
ABSTRACT

Non-iodo-containing trihalomethanes (TTHM) are frequently detected in chlorinated tap water and currently regulated against their carcinogenic potential. Iodinated THM (ITHM) may also form in disinfected with chlorine waters that are high in iodine content, but little is known about their magnitude and variability within the drinking-water pipe distribution network of urban areas. The main objective of this study was to determine the magnitude and variability of ITHM and TTHM levels and their corresponding daily intake estimates within the drinking water distribution systems of Limassol and Nicosia cities of Cyprus, using tap samples collected from individual households ($n = 37$). In Limassol, mean household tap water ITHM and TTHM levels was 0.58 and 38 $\mu g\,L^{-1}$, respectively. Dichloroiodomethane (DCIM) was the dominant species of the two measured ITHM compounds accounting for 77% of total ITHM and in the range of 0.032 and 1.65 $\mu g\,L^{-1}$. The range of DCIM concentrations in Nicosia tap water samples was narrower (0.032 – 0.848 $\mu g\,L^{-1}$). Mean total iodine concentration in tap water samples from the seaside city of Limassol was 15 $\mu g\,L^{-1}$ and approximately twice to those observed in samples from the mainland Nicosia city. However, iodine concentrations did not correlate with the

Abbreviations: DBP, Disinfection by-product; THM, Trihalomethanes; HAA, Haloacetic acid; NOM, Natural organic matter; TCM, Trichloromethane (chloroform); BDCM, Bromodichloromethane; DBCM, Dibromochloromethane; TBM, Tribromomethane (bromoform); DCIM, Dichloroiodomethane; BCIM, Bromochloroiodomethane; TTHM, Total Trihalomethanes; ITHM, Iodinated Trihalomethanes; CHO, Chinese Hamster Ovaries (ToxTest); CDI, Chronic Daily Intake; U.S. EPA, United States Environmental Protection Agency.

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Drinking-water
Bromine
Chlorine

ITHM levels. The calculated chronic daily intake rates of ITHM were low when compared with those of TTHM, but because of their widespread occurrence in tap water and their enhanced mammalian cell toxicity, additional research is warranted to assess the magnitude and variability of human ITHM exposures.

1. Introduction

Trihalomethanes (THM) is a frequently-occurring class of disinfection by-products (DBP), and it has been historically regulated in disinfected (chlorinated) tap water (Nieuwenhuijsen et al., 2000). Halogenated THM typically form upon water disinfection comprising of chlorinated-(chloroform), or mixtures of chloro/bromo-, or iodinated-THM compounds (Richardson et al., 2007). Upon oxidation of dissolved iodide during water treatment, hypoiodous acid (HOI) may form, which may react with natural organic matter (NOM) producing iodinated trihalomethanes (ITHM) (Bichsel and Von Gunten, 2000; Richardson et al., 2007). The first report on the occurrence of ITHM in drinking-water was published in the 1970s (Brass et al., 1977). Hydrophobic and high-molecular mass NOM, with high aromatic carbon content was found to readily react with chlorine towards the formation of non-iodine THM, while iodine and bromine have been observed to be more reactive with hydrophilic and low-molecular mass NOM, forming brominated and iodinated DBPs (Hua and Reckhow, 2007a, 2007b). Based on their carcinogenic potency, the four non-iodo THM are currently regulated in the EU, i.e., chloroform, bromodichloromethane, dibromochloromethane and bromoform, and their sum is known as total trihalomethanes (TTHM) (European Council Directive 98/83/EC, 1998). When TTHM were assessed for cytotoxicity in chronic Chinese hamster ovaries (CHO) assays, toxicity speciation showed bromoform > dibromochloromethane > bromodichloromethane > chloroform, suggesting the influence of bromine atoms in enhancing the overall cytotoxicity of THMs (Plewa et al., 2008). Compared to chloro- and bromo-THMs, ITHM were found to be even more cytotoxic, but not genotoxic, with the exception of chlorodiiodomethane (Richardson et al., 2008). This order of toxicity correlated well with the leaving tendency of the halogens in S_N2 reactions with iodo-groups being much better substitution groups than bromo- and chloro-groups (Richardson et al., 2008).

The water levels of dissolved bromide and iodide may also affect both the concentration and speciation of formed THM (Villanueva et al., 2012; Richardson et al., 2008). For example, it was shown that the formation of total organic iodine (TOI) from chloramination of the hydrophobic acid fraction of river water samples, increased in a linear fashion with increasing iodide concentration, while holding the bromide levels constant (Kristiana et al., 2009). Other factors that may also influence the magnitude of formation of ITHM are: i) pH (increase in pH from 6 to 8 favored the formation of THM and vice versa) (Liang and Singer, 2003, Hansen et al., 2012), ii) water temperature; higher temperatures favored the formation of THM (Richardson, 2003, Zhang et al., 2013), iii) the disinfection practice; chloramination favored the formation of ITHM (Krasner et al., 2006, Richardson et al., 2008), iv) the residence time of drinking water in the distribution system and v) the characteristics of the water distribution system such as its age, pipe material type and the presence of re-chlorination reservoir stations (Legay et al., 2010). Kinetic studies observed that the formation of ITHM was highly dependent upon the disinfection method used. Chlorination was found to favor the formation of chlorinated and brominated THM rather than ITHM due to the oxidation of hypoiodous acid to iodate, occurring at a fast rate when chlorine was used for disinfection (Jones et al., 2011). When chloramination was used as the main disinfection process, the oxidation of hypoiodous acid to iodate was much slower (Jones et al., 2011) and because monochloramine hardly oxidizes bromide (Criquet et al., 2012) the formation of ITHM was enhanced. Apart from the disinfection method, the presence of iodide and the pH may also influence the formation and speciation of ITHM (Jones et al., 2012a, 2012b, Cancho et al., 2000).

Occurrence of ITHM in various water resource matrices was reported, for example, in wastewater effluents (Gong and Zhang, 2015), water treatment plants (Cancho et al., 2000; Serrano et al., 2015), desalination units (Le Roux et al., 2015), drinking water treatment plants (Plewa et al., 2004; Krasner et al., 2006; Richardson et al., 2008; Jeong et al., 2012; Ding et al., 2013a, 2013b; Wei et al., 2013a, 2013b). Brief information on literature reporting ITHMs in various water resources is presented in Table 1. However, to our best knowledge, no study is available on monitoring ITHMs spatially along drinking water distribution systems and in kitchen tap water at household level. Drinking-water supply in Cyprus originates from surface water behind dams and it is supplemented with post-chlorinated reverse osmosis treated seawater in periods of high water demand (spring, summer). Cyprus, is characterized by elevated average TTHM levels in its tap water (range: 3–130 μg L^{-1}, Mean (SD): 65 (24) μg L^{-1}) (Charisiadis et al., 2015). Being a Mediterranean island, Cyprus' seaside urban areas may be subject to high dissolved iodide levels in source water acting as precursors for ITHM formation. The seaside city of Limassol was chosen along with the mainland city of Nicosia, which is one hour away from the coast. No data is currently available on the magnitude and variability of ITHM in the region of the Eastern Mediterranean and particularly for the magnitude and variability of water ITHM levels within the distribution network of a city. This study also systematically collected all studies of quantitative ITHM analyses in tap water around the globe through a systematic literature search. The main objective of this study was to determine the magnitude and variability of ITHM and TTHM levels within the drinking water distribution systems of Limassol and Nicosia cities and their corresponding daily intake estimates, using drinking-water samples collected from individual households, after obtaining residents' written informed consent. The relative contribution of each of the three routes (ingestion, dermal absorption and inhalation) of exposure to the daily intake estimates for ITHM and TTHM was also assessed, based on their water concentrations found in water, and the corresponding frequency of water use activities, such as, drinking tap water, bathing and showering as recorded with questionnaire data.

Gas chromatography (GC) has been the choice of instrumentation for analysis of volatile and semi-volatile ITHMs in various water matrices. For example, ITHMs were detected and quantified using GC coupled with electron capture detection (Bichsel and Von Gunten, 2000; Krasner et al., 2006; Hua and Reckhow, 2007a, 2007b; Jones et al., 2012a, 2012b) and GC coupled with mass spectrometry detection (Plewa et al., 2004; Richardson et al., 2008; Duirk et al., 2011). Polar and semi-polar ITHMs in water matrices were analyzed with liquid chromatography coupled with mass spectrometry detection (Ding and Zhang, 2009; Ding et al., 2013a, 2013b; Gong and Zhang, 2015). Analytical method parameters and instrumentation used in representative studies are presented in Table 1. We applied GC coupled to a tandem mass spectrometer (MS/MS) for the analysis of TTHMs and ITHMs in drinking water samples collected at household level along two different drinking water distribution systems in two major cities of Cyprus. Out of the six ITHM (iodoform-IF, dichloroiodomethane-DCIM, bromochloroiodomethane-BCIM, chlorodiiodomethane-CDIM, dibromoiodomethane-DBIM, bromodiiodomethane-BDIM), we quantified two viz., dichloroiodomethane (DCIM) and bromochloroiodomethane (BCIM) because (i) these are the most frequently occurring

Table 1

Quantitative comparison of reported iodinated trihalomethanes concentrations and ranges ($\mu g\ L^{-1}$) in finished drinking-water samples collected around the globe (at the water treatment plant exit and/or within the water distribution network). Empty table cells denote that the related information was not sought in the corresponding study, or this measurement was not actually taken.

	Authors	Treatment	Country	Water source	Analytical Method	# Samples	Parameter	CHCl$_2$I (DCIM)	CHBrClI (BCIM)	CHBr$_2$I (DBIM)	CHClI$_2$ (CDIM)	CHBrI$_2$ (BDIM)	CHI$_3$ (IF)
1	Le Roux et al. (2015)	Thermal multi– stage flash distillation and reverse osmosis	Saudi Arabia	Seawater	LLE and GC–ECD, USEPA551.1	2 desalination plants	Mean ± std. deviation ($\mu g\ L^{-1}$)	<LOD	<LOD	1.73 ± 1.15	<LOD	0.60 ± 0.03	<LOD
							Range ($\mu g\ L^{-1}$)	NR*	NR	NR	NR	NR	NR
							LOD ($\mu g\ L^{-1}$)	0.09	0.09	0.09	0.09	0.09	0.09
2	Richardson et al. (2008)	Most plants used chloramination	USA, Canada	Rivers and Groundwater	SPME and GC–EI–MS (Silva et al., 2006, method)	23 cities' water plants	Mean ± std. deviation ($\mu g\ L^{-1}$)	0.83 ± 1.3	1.28 ± 1.55				
							Range ($\mu g\ L^{-1}$)	0.06–5.4	0.06–5.7				
							LOD ($\mu g\ L^{-1}$)	0.06	0.06				
3	Wei et al. (2013a, 2013b)	Peroxidation coagulation, sedimentation, sand filter, chloramines	China	Yangtze river and Huangpu river	USEPA 551.1	13 water plants	Median (winter/summer) ($\mu g\ L^{-1}$)						0.85/0.4 (Yangtze river) 0.18/0.01 (Huangpu river)
							Range (winter/summer) ($\mu g\ L^{-1}$)						0.16–0.4 (Yangtze river)/ 0.01– 0.01 (Huangpu river) 0.49–1.25 (Yangtze river)/ 0.23–0.56 (Huangpu river)
							LOD ($\mu g\ L^{-1}$)						Low $\mu g\ L^{-1}$ range
4	Goslan et al. (2009)	Coagulation, lime softening, sedimentation, chlorine/chloramines	Scotland	River and reservoir (upland)	USEPA 551.1	7 water plants and distribution	Median ($\mu g\ L^{-1}$)	Sum = 0.9					
							Range ($\mu g\ L^{-1}$)	0.01–3.7					
							LOD ($\mu g\ L^{-1}$)	0.01					
5	Luo et al. (2014)	Settling, filtering, ozonation	China	Qiangwei river	SPME–GC–MS	2 water plants	Mean ± std. deviation ($\mu g\ L^{-1}$)	1.80 ± 1.22	0.84 ± 0.53	0.1 ± 0.05	0.13 ± 0.13	0.009 ± 0.002	<LOD
							Range ($\mu g\ L^{-1}$)	NR	NR	NR	NR	NR	NR
							LOD ($\mu g\ L^{-1}$)	0.07	0.05	0.002	0.005	0.05	0.05
6	Ding et al. (2013a, 2013b)	No details on water treatment. Seven out of 70 plants used chloramines while the rest used Cl$_2$.	China	Rivers, lakes and reservoirs and a few groundwaters	LLE–GC–ECD USEPA 551.1	31 cities, 70 water plants	Median ($\mu g\ L^{-1}$)	<LOD					<LOD
							Range ($\mu g\ L^{-1}$)	<LOD–5.58					NR
							LOD or LOQ ($\mu g\ L^{-1}$)	LOQ=0.1 for all					LOQ=0.1
7	Serrano et al., 2015	Peroxidation, sedimentation, filtration, chloramination, and chlorine dioxide	Spain	Guadalmellato reservoir	LLE–GC–MS USEPA 551.1	1 water plant and distribution	Median ($\mu g\ L^{-1}$)	0.12 ± 0.01					
							Range ($\mu g\ L^{-1}$)	0.14–0.25(spring) 0.16–0.29(summer) 0.11–0.27(fall) 0.07–0.11(winter)					
							LOD ($\mu g\ L^{-1}$)	0.02					
8	Wei et al., 2013b	Biological treatment, coagulation, biological activated carbon, chloramination	China	Inland river	USEPA 551.1	1 water plant, 7 samples	Mean ± std. deviation ($\mu g\ L^{-1}$)	1.42 ± 0.05					
							Range ($\mu g\ L^{-1}$)	NR					
							LOD ($\mu g\ L^{-1}$)	NR					
9	Cancho et al., 2000	Prechlorination, settling, sand filtration, ozonation, granular activated carbon, postc hlorination	Spain	Llobregat river	LLE–GC–ECD	1 water plant, 21 samples	Mean ± std. deviation ($\mu g\ L^{-1}$)	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
							Range ($\mu g\ L^{-1}$)	NR	NR	NR	NR	NR	NR
							LOD ($\mu g\ L^{-1}$)	0.01	0.03	0.02	0.01	0.01	0.01
10	Krasner et al., 2006	Coagulation, lime softening, membrane softening, biological filtration, chlorination, ozonation, chlorine dioxide disinfection and chloramination	U.S.A.	Surface water and two colored groundwaters	LLE–GC–ECD	12 water plants, up to 5 seasons of sampling	Median ($\mu g\ L^{-1}$)	Sum of six = 0.4					
							Range ($\mu g\ L^{-1}$)	<LOD – 19.0					
							Minimum reporting limit ($\mu g\ L^{-1}$)	0.1–0.5	0.25–3.0	0.25–0.64	0.1–0.5	0.1–0.5	0.1–2.0
11	This Study	Coagulation, sedimentation, filtration, chlorination	Cyprus	Surface water (dams)	LLE–PTV–GC–MS/MS	2 water plants and distribution	Mean ± std. deviation ($\mu g\ L^{-1}$)	0.475 ± 0.30	0.11 ± 0.07				
							Range ($\mu g\ L^{-1}$)	0.03–1.65	<LOD – 0.45				
							LOD ($\mu g\ L^{-1}$)	0.06	0.015				

[a] NR not reported in the paper.

ITHM compounds in finished tap water and (ii) DCIM received a high score for research prioritization among more than 100 DBPs, based on criteria such as frequency of occurrence, toxicity and regulatory aspects (Hebert et al., 2010). The four regulated (non-iodo) THMs were also quantified to serve as the reference THM group.

2. Methods

2.1. Study design and water sampling

Sodium sulfate, sodium phosphate dibasic, potassium phosphate monobasic, ammonium chloride, decafluorobiphenyl (surrogate), acetone and methanol GC grade were purchased from Sigma-Aldrich. t-Butyl methyl ether (MTBE) GC grade was purchased from Panreac (Barcelona, Spain). Dichloroiodomethane (DCIM) and bromochloroiodomethane (BCIM) were purchased from CanSyn Chemicals (Toronto, Canada). The four regulated THM mix, containing trichloromethane (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and tribromomethane (TBM) was purchased from Restek (Bellefonte, USA). 4-bromofluorobenzene (internal standard) was purchased from Supelco (Bellefonte, USA). Ultrapure water prepared by a reverse osmosis system purchased from Temak (Athens, Greece).

A total of 37 tap water samples were collected from 37 different households in both Limassol and Nicosia, the two largest cities of Cyprus, during April–May of 2013. The households were randomly selected from city neighborhoods with confirmed water supply origin and being within the city's pipe network system. The crude average distance range of the closest versus the most distant household from the chlorination tank was calculated to be about 5–15 km distance for both cities. Household tap water samples were obtained from the main kitchen faucet after flushing for 1 min, and ensuring no bubbles or overflowing of water occurred during water filling in the 60 mL polypropylene vials with minimum headspace. For each sampling point, three 60 mL polypropylene vials were filled. The first group of vials contained buffer and dechlorination agents according to the U.S. EPA method 551.1 (United States Environmental Protection Agency (US.EPA), 1995). Approximately in every sampling vial, 50 mL water sample, 7 mg of Na_2HPO_4, 700 mg of KH_2PO_4, and 4 mg of NH_4Cl were added as the required preservatives for THM analyses according to the US EPA method 551.1, as previously described (Charisiadis et al., 2014, 2015). The second vial contained 0.5 mL boric acid as a preservative, for nitrate determination, and the third vial contained the water volume needed for conducting several physicochemical measurements. Based on questionnaire responses from our earlier cross-sectional study in Nicosia (n = 380 subjects), the frequency of water use activities, such as, drinking tap water, bathing and showering was included in our chronic daily intake calculations (Charisiadis et al., 2014). In addition, four samples were also collected from the finished water produced at Dhekelia seawater reverse-osmosis desalination plant in Cyprus. The primary disinfectant used was chlorine, while the chlorine dosing at the plant differs by season with a mean value of about 1–1.5 ppm (Dr. Konstantinou, Dhekelia plant technical officer, personal communication). Duplicate measurements of residual chlorine, temperature and dissolved oxygen measurements were obtained in situ. Samples were temporarily stored in ice chests and they were immediately analyzed for a suite of physicochemical properties upon arrival at the laboratory; the rest of vials were stored in the −80 °C freezer until THM and total iodine analysis.

3. Systematic literature search

A comprehensive search in Scopus (1960 onwards) was performed in order to identify studies reporting analysis and measurements of iodinated THM in drinking-water. Keywords for the search were ((iodin* OR chlorinated OR iodo*) AND trihalomethanes*). Resulting

articles were assessed for inclusion by reading either the abstract or full text or both. Further, the cited bibliography in each of these articles of interest was screened to obtain relevant back referenced citations for possible inclusion. The following exclusion criteria were used for our systematic analysis: i) articles containing data and information about other than ITHM, such as polar and non-polar iodo-DBP, ii) review articles, iii) articles reporting work on spiked d-H_2O or spiked source water in lab experiments, iv) articles on ITHM occurrence in either seawater samples, or shale gas and chlorinated saline wastewater samples, or recycled water, or medical imaging waste, and v) qualitative studies reporting yes/no on the presence of ITHM compounds. The inclusion criteria were: i) studies reporting on the occurrence of ITHM in finished drinking-water (tap) and ii) any form of quantitative ITHM analysis.

From the detailed search, we found 30 studies reporting ITHM in drinking water and other matrices, out of which a total of 11 articles fulfilled our inclusion criteria.

3.1. Drinking-water measurements and statistical analyses

Water pH and electrical conductivity were determined using the Mettler–Toledo InLab Expert Pro-ISM IP67 and Mettler–Toledo InLab 738 ISM electrodes, respectively, both connected on a Mettler–Toledo SevenGo Duo pro™ pH/ORP/Ion/Conductivity meter SG78. Residual chlorine was measured on-site using a portable Lovibond MaxiDirect Photometer, while dissolved oxygen and temperature measurements were obtained with the InPro6050 Dissolved Oxygen (DO) sensor coupled with a MettlerToledo SevenGo pro TM SG6 dissolved oxygen meter. Ammonium, chloride, cupric and nitrate concentrations in tap water were determined using their respective ion selective electrodes (Mettler-Toledo perfectION™ series and Mettler-Toledo InLab Pro reference electrode). A 20 mL aliquot from each sample containing boric acid was used for nitrate determination and 2×20 mL aliquots from the no-preservative containing samples were used for pH, conductivity, ammonium, chloride and copper analyses. Prior to the analysis, each electrode was checked for functionality using standard procedures and the required solutions were freshly prepared daily. For ion determination, exactly 400 μL of ionic strength adjusting (ISA) solution was added to each 20 mL sample. The ISA solutions used were 5 M $NaNO_3$ for chloride and cupric, 2 M $(NH_4)_2SO_4$ for nitrates and 0.4 M Na_2SO_4 for ammonium. Three drops of 1 M HNO_3 were added into the 20 mL samples intended for chloride and cupric analysis, using a plastic dropper to a final pH < 4. Total iodine and bromine content in tap water samples was analyzed with a modified method of Kataoka et al. (2008) using an inductively coupled plasma mass spectrometer (Thermo X-Series II, Thermo Scientific Inc., Germany).

The water ITHM analytical protocol was based upon the U.S. EPA Method 551.1 and a previously published in-house method on water TTHM (Charisiadis et al., 2014, 2015) and urine THM (Charisiadis and Makris, 2014), while the large volume injection optimization was based upon a recently optimized methodology in our laboratory (Kalyvas et al., 2014). All the stock and working solutions that contained the standards for ITHM and TTHM, surrogate, and internal standards were kept protected from light, prepared fresh and stored at −20 °C in glass vials. Briefly, a liquid–liquid extraction protocol was performed by mixing 15 mL water sample (spiked with surrogate solution at a final concentration of 10 μg L^{-1}) with 2 mL of MTBE, addition 6.0 g of sodium sulfate, shaking gently for 5 min in a lab shaker at 100 rpm. Following, samples were centrifuged for 1 min at 500 rpm for a clear phase separation. Half mL of the upper phase was transferred into a GC vial containing the internal standard solution at a final concentration of 200 μg L^{-1}.

For ITHM analysis, an Agilent 7890A gas chromatograph coupled with Agilent 7000B triple quadrupole GC-MS/MS system was used while the analyte separation was achieved using a 30 m $\times$ 0.25 mm $\times$ 0.25 μm HP 5MS (5%-phenyl-methylpolysiloxane) column (Agilent Technologies, Inc.). A programmed temperature vaporization (PTV) program was used where 50 μL sample were injected at a rate of

6000 μL min^{-1} while the inlet was maintained at 50 °C for 1 min, ramped to 170 °C at a rate of 200 °C min^{-1} for 1.5 min and then ramped to 300 °C at a rate of 200 °C min^{-1}. Solvent was evaporated for 1 min at a flow rate 15 mL min^{-1} at 0 psi and after 4 min of sample loading on the column; the purge valve was opened at a flow 30 mL min^{-1}; carrier gas (helium) was set at 0.9 mL min^{-1}. The column oven temperature program was set to 35 °C, then ramped to 45 °C at a rate of 15 °C min^{-1}, ramped to 75 °C at a rate of 3 °C min^{-1}, ramped to 100 °C at a rate of 8 °C min^{-1}, ramped to 150 °C at a rate of 100 °C min^{-1} and to 280 °C for 1.5 min at a rate of 100 °C min^{-1}. The mass spectrometer source temperature was set at 250 °C and the transfer line at 200 °C. Solvent delay was set to 6.5 min and the total run time was 18 min. Time segments, retention times, dwell time, precursor and product ion used and related collision energies for each ITHM and TTHM compound can be found in Table SI-1.

For TTHM analysis, the injection volume was 1 μL using the spiltless injector mode. Carrier gas was helium at 1 mL min^{-1}. The inlet was maintained at 200 °C and then ramped to 300 °C with 150 °C min^{-1}. The column oven temperature programs were set to 30 °C for 5 min, then ramped to 150 °C for 2 min at a rate of 60 °C min^{-1}, then ramped to 180 °C for 0.1 min at a rate of 30 °C min^{-1}, and ramped to 300 °C for 1.0 min at a rate of 50 °C min^{-1}. Carrier gas was helium at 1 mL min^{-1}. Solvent delay was set to 4.5 min. The total run time was 12 min. Electron impact (EI) ionization was performed at electron energy of 70 eV. MS/MS was performed in the MRM mode (Table SI-1). The quadrupole mass detector was operated at 150 °C. The ion source temperature was set to 250 °C; the transfer line was set to 200 °C for ITHM analysis and to 250 °C for TTHM analysis. The peaks were identified on the basis of their fragmentation patterns using the NIST Mass Spectral Search Program and the system was controlled by the software Mass Hunter Workstation (Agilent Technologies, Inc.). Procedural calibration standards were prepared in deionized water containing the aforementioned preservatives. The curve was constructed by including ten water samples for TTHM (from 0.77 to 99 μg L^{-1}) and eight samples for ITHM (from 0.04 to 5 μg L^{-1}) using GC–MS/MS in the MRM mode (Table SI-2); quantitative analysis was based on ratio analysis of peak area of the analyte divided by peak area of the internal standard.

The analytical method's limits of detection and quantification (LOD and LOQ) for all analytes were: 64 and 192 ng L^{-1} (DCIM), 14 and 43 ng L^{-1} (BCIM), 130 and 390 ng L^{-1} (TCM), 110 and 320 ng L^{-1} (BDCM), 130 and 380 ng L^{-1} (DBCM), 110 and 340 ng L^{-1} (TBM) (Table SI-2). The TTHM spike recoveries at 10 μg L^{-1}, final concentration were 99%, 92%, 87% and 91% for the TCM, BDCM, DBCM and TBM, respectively, while for the two ITHM, the spike recoveries at final concentrations of 700, 500, and 400 ng L^{-1} were 98%, 104%, 99%, and 97%, 97%, 92%, respectively, for the DCIM and BCIM compounds; the mean surrogate recovery during the ITHM runs was 97%. The inter-day variability of DCIM and BCIM (n = 4) measurements were 8.1% and 6.7%, 8.4% and 4.4%, and 7.1% and 1.5%, at final concentrations levels of 400, 500 and 700 ng L^{-1}, respectively. The inter-day variability of TCM, BDCM, DBCM and TBM (n = 4) measurements were 6.1%, 8.0%, 7.0%, and 7.2%, respectively, at final concentrations level of 10 μg L^{-1}. The intra-day variability of TCM, BDCM, DBCM and TBM (n = 8) measurements were 5.5%, 8.2%, 6.4%, and 9.1%, respectively, at final concentrations level of 10 μg L^{-1}.

For the statistical analyses, JMP Pro 10 statistical software was used. The concentrations of DCIM and BCIM were added to generate the variable "Total ITHM" and the same procedure was followed for TCM, BDCM, DBCM and TBM to generate the variable "Total THMs". Missing values were treated by imputing measurements below the LOD and LOQ as LOD/2 and LOQ/2 respectively. The distributions of all variables were explored for normality. Univariate analyses between variables following a normal distribution were performed using the Pearson correlation test; otherwise the Spearman rank test was used.

3.1.1. Exposure assessment

All routes of exposure (ingestion, dermal contact and inhalation) were considered to calculate chronic daily intake (CDI) values for the THM compounds (both non-iodinated and iodinated). The ingestion route was considered for the scenario of tap water consumption and/ or for the preparation of cold and hot beverages (coffee, tea, juice, etc.). Dermal uptake and inhalation routes were considered for the scenario of bathing and showering. Only the ingestion route was considered for ITHM, due to lack of information in the literature about their skin permeability constants and volatilization factors. The calculation for each route was expressed as (United States Environmental Protection Agency (US.EPA), 2011):

$$CDI_{ingestion} = \frac{Cw * IRw * EF * ED}{BW * AT}$$

$$CDI_{dermal} = \frac{Cw * SA * Kp * ET * CF * EF * ED * EvD}{BW * AT}$$

$$CDI_{inhalation} = \frac{Ca * IRa * EF * ED * ET * EvD}{BW * AT}$$

where:

CDI	Chronic daily intake (mg kg^{-1} day^{-1})
Cw	Concentration of specific THM in the tap water of a specific sample (μg L^{-1})
IR$_w$	Intake rate of tap water (0.6 L day^{-1})
EF	Exposure frequency (350 days year^{-1}) (United States Environmental Protection Agency (US.EPA), 2011)
ED	Exposure duration (70 years) (United States Environmental Protection Agency (US.EPA), 2011)
ET	Exposure time (0.19 h event^{-1})
EvD	Daily exposure events (event day^{-1})
CF	Conversion factor of cm^3 to L (0.001 L cm^{-3})
SA	Skin surface area available for contact for an adult during bathing or showering (19,300 cm^2, United States Environmental Protection Agency (US.EPA), 2011).
K$_p$	Dermal permeability constant measured at 25 °C, TCM: 0.16, BDCM: 0.18, DBCM: 0.2, TBM: 0.21 (cm h^{-1}) (Xu et al., 2002)
CA	Concentration of THM in the air of the studied zone (μg m^{-3})
IR$_a$	Inhalation rate (0.83 m^3 h^{-1}, United States Environmental Protection Agency (US.EPA), 2011).
BW	Body weight (70 kg, United States Environmental Protection Agency (US.EPA), 2011).
AT	Averaging Time (365 days year^{-1} * 70 years = 25,550 days, United States Environmental Protection Agency (US.EPA), 2011)

The levels for each individual THM in the air during showering and bathing were calculated as: Chloroform levels in the indoor air were calculated using the following empirical equation (Nazir and Khan, 2006),

$$Ca_{chloroform} = (10.446 * Cw_{chloroform}) - 99.599$$

while for the rest of THM, a volatilization factor of 0.5 L m^{-3} was multiplied by their Cw to estimate air concentrations during showering and bathing (Legay et al., 2011). It should be noted however that the above equation could not be used for lower concentrations of chloroform in water (<9.5 μg L^{-1}), because at such low levels the partitioning of water chloroform to air is considered negligible (Nazir and Khan, 2006), and thus, it was not included in the CDI calculations.

4. Results

The average water pH was 7.7 and 7.9 in Limassol and Nicosia cities, while the water temperature was ~25 °C (Table 2). Mean residual chlorine concentrations were negligible (0.04 mg L^{-1}), suggesting that microbial and/or chemical scales present in the pipe network nearly consumed the disinfectant dose in all sampling locations. It was possible that part of the colorimetrically-detected residual chlorine levels could be ascribed to chloramine interference due to relatively high (>1 mg L^{-1}) ammonium levels in tap water; however, total mean residual chlorine concentrations were negligible in tap water of the households (0.04 mg L^{-1}). Mean dissolved nitrate, ammonium, chloride and copper concentrations were well below their respective maximum contaminant level for tap water (Table 2).

Total iodine levels in tap water collected from eighteen households in Nicosia showed little variability (standard deviation of 1.6 μg L^{-1}) around the mean of 8 μg L^{-1}, while nearly 2× higher total iodine levels were observed in tap water from Limassol households (n = 20) with a mean of 15 μg L^{-1} and a standard deviation of 2.4 μg L^{-1}, reflecting the geographic location of the city and its proximity to seawater. Interestingly, mean total bromine levels in tap water between the two cities did not differ (66 vs. 52 μg L^{-1} in Nicosia and Limassol, respectively).

Desalination-produced finished water before being subject to post chlorination showed that levels of both TTHM and ITHM were <LOD. The water ITHM and TTHM concentrations in the households of both cities (n = 37) were normally-distributed. In Limassol, mean household tap water ITHM and TTHM were 0.58 and 38 μg L^{-1}, respectively, with DCIM being the dominant species of the two measured ITHM, accounting for 77% of total ITHM (Table 3). A wide range of DCIM levels in tap water was observed from 0.032 (LOD/2) to 1.65 μg L^{-1} in Limassol. The range of DCIM concentrations in Nicosia was narrower (0.032 (LOD/2) to 0.85 μg L^{-1}). Total ITHM levels were comparable between Limassol (0.58 μg L^{-1}) and Nicosia (0.59 μg L^{-1}), with no statistically significant difference (p > 0.05, t-test). The mean TTHM concentrations were slightly higher in Nicosia than Limassol (mean concentration 43 vs. 38 μg L^{-1}), but the difference was not statistically significant (p > 0.05, t-test). More specifically, the range of individual TTHM concentrations was: Limassol: TCM 1.3–13.3 μg L^{-1}, BDCM 2.7–16.7 μg L^{-1}, DBCM 3.4–16.5 μg L^{-1} TBM 3.7–19.9 μg L^{-1}; Nicosia: TCM 3.3–31.1 μg L^{-1}, BDCM 2.3–28.5 μg L^{-1}, DBCM 0.065 (LOD/2)– 22.5 μg L^{-1}, TBM 0.055 (LOD/2)–4.8 μg L^{-1}.

The composition of TTHM varied between the two cities, with TBM being present at higher concentrations in Limassol, which is a seaside city often high in precursor bromide and iodine levels in source water. The mean concentrations of TCM at Limassol households were half of those observed in Nicosia, being similar in magnitude to TBM levels. Comparatively, TCM and TBM made up to 24% and 29%, respectively of the TTHM content in Limassol and 35% and 7%, respectively, in Nicosia. The correlation analysis revealed a statistically significant (p < 0.001) positive correlation (ρ = 0.72) between ITHM and TTHM using data from both cities (Table SI-3). With the notable exception of TBM, the rest of TTHM compounds correlated well with the ITHM (Table SI-3). Using data from both cities, water ITHM concentrations correlated well with certain routine physicochemical properties of tap water (Table 4); ITHM levels were positively correlated with dissolved oxygen (p < 0.05) (Table 4).

In the absence of data for dermal and inhalation routes of exposure, only oral ingestion was considered for ITHM, with a mean CDI estimate of 0.005 μg kg^{-1} day^{-1}, nearly two orders of magnitude less than the CDI for TTHM through the same exposure route (0.3 μg kg^{-1} day^{-1}) (Table SI-4). Dermal uptake was the main route of exposure to TTHM, giving the highest CDI estimate (mean 0.48 μg kg^{-1} day^{-1}), while the oral ingestion-based mean CDI was 0.3 μg kg^{-1} day^{-1} followed by inhalation (~0.1 μg kg^{-1} day^{-1}). Mean exposure levels through ingestion and dermal contact were at the same levels between Limassol and Nicosia, except for the inhalation route that contributed to a higher percentage to TTHM exposure in Nicosia than Limassol.

5. Discussion

This is the first study in the Eastern Mediterranean region that quantified the magnitude and variability of ITHM levels in tap water collected from individual households within the water distribution network of two cities in Cyprus (n = 37). The novelty of the study also lies in its design where in addition to the typical sampling locations at the exit of waterworks (compared to literature reviewed in Table 1). Water samples in this study came from households within a pipe water network receiving the same finished water, where improved human THM exposure assessment at the point of water use can be performed. The measured concentrations of ITHM in tap water of both cities were in the sub μg L^{-1} range (~0.50 μg L^{-1}), being similar to those measured in other parts of the globe (Table 1). In specific, mean DCIM levels

Table 2
Frequency distributions of routine physicochemical properties of tap water samples in two cities.

City	Variable	Mean	Std. deviation	P25	P75	P90	Min	Max	Median
Limassol (n = 20)	Temperature (°C)	24.9	2.24	22.7	26.9	27.1	20.9	27.1	25.9
	DO (mg L^{-1})	7.38	0.490	7.29	7.67	7.78	5.62	7.81	7.54
	Residual Cl (mg L^{-1})	0.043	0.026	0.02	0.04	0.07	0.01	0.11	0.04
	pH	7.77	0.304	7.71	7.84	8.12	6.662	8.30	7.78
	EC (μS cm^{-1})	879	73.2	824	941	1000	762	1004	870
	Cl$^-$ (mg L^{-1})	62.4	12.0	58.0	63.4	78.9	35.3	84.1	63.4
	Cu^{2+} (μg L^{-1})	2.87	3.29	1.06	3.08	7.67	0.62	14.7	1.87
	NO$_3^-$ (mg L^{-1})	13.9	2.78	12.2	15.9	18.6	8.89	18.9	13.8
	NH$_4^+$ (mg L^{-1})	1.21	0.187	1.10	1.36	1.45	0.736	1.49	1.21
	Total bromine (μg L^{-1})	51.5	7.10	50.1	55.8	59.3	32.3	63.3	52.8
	Total iodine (μg L^{-1})	15.1	2.43	13.6	14.9	16.8	9.1	19.8	14.9
Nicosia (n = 17)	pH	7.87	0.229	7.87	7.95	8.07	7.02	8.08	7.91
	EC (μS cm^{-1})	725	78.7	664	780	828	600	904	732
	Cl$^-$ (mg L^{-1})	49.7	8.53	41.3	55.5	61.9	31.4	62.0	52.1
	Cu^{2+} (μg L^{-1})	19.8	14.4	9.19	29.7	50.0	2.18	50.3	14.4
	NO$_3^-$ (mg L^{-1})	8.01	1.62	6.82	9.42	10.3	5.14	10.4	8.21
	NH$_4^+$ (mg L^{-1})	1.06	0.332	0.867	1.12	1.56	0.758	2.18	0.959
	Total bromine (μg L^{-1})	66.2	75.5	39.3	58.9	145.7	25.1	352.2	45.6
	Total iodine (μg L^{-1})	8.31	1.62	7.66	9.19	10.3	4.08	11.6	8.32

Table 3
Distributions of iodinated, and non-iodo trihalomethanes in the distribution network of two major cities of Cyprus.

City	Trihalomethane	Mean	Stdev.	P25	P75	P90	Min	Max	Median
Limassol (n = 20)	DCIM	0.446	0.302	0.352	0.474	0.553	0.032	1.65	0.370
	BCIM	0.133	0.088	0.128	0.138	0.166	0.007	0.446	0.133
	ITHM	0.579	0.328	0.478	0.606	0.901	0.039	1.79	0.505
	TCM	8.98	3.62	5.7	12.5	13.3	1.3	13.3	9.75
	BDCM	10.4	4.57	5.48	14.0	15.7	2.7	16.7	11.3
	DBCM	7.34	3.89	4.83	7.9	16.0	3.4	16.5	6.3
	TBM	11.0	4.38	7.28	13.7	18.2	3.7	19.9	11.0
	TTHM	37.6	10.1	29.9	45.2	53.2	21.3	57.3	37.8
Nicosia (n = 17)	DCIM	0.506	0.241	0.345	0.678	0.848	0.032	0.848	0.497
	BCIM	0.080	0.073	0.007	0.137	0.165	0.007	0.201	0.127
	ITHM	0.586	0.287	0.412	0.775	0.999	0.039	1.05	0.624
	TCM	15.2	8.95	6.5	23.5	30.8	3.3	31.1	13.8
	BDCM	14.5	7.89	8.6	21.7	24.9	2.3	28.5	13.2
	DBCM	10.7	6.22	7.35	15.6	18.3	0.065	22.5	10.9
	TBM	2.86	1.5	2.45	3.7	4.56	0.055	4.8	3.1
	TTHM	43.3	21.8	27.5	60.4	78.0	8.72	86.2	35.8

in finished water of a 23-city-based U.S. study was 0.8 µg L^{-1} (Richardson et al., 2008), and 0.12 µg L^{-1} in Spain (Serrano et al., 2015), while the sum of DCIM and BCIM was 0.9 µg L^{-1} in Scotland (Goslan et al., 2009). Much higher water DCIM levels were observed in China, reaching mean levels of 1.4 µg L^{-1} and 1.8 µg L^{-1} (Luo et al., 2014; Wei et al., 2013b); most of aforementioned water systems used chloramination, while the plant with the highest DCIM levels (1.8 µg L^{-1}) used ozonation (Luo et al., 2014). The highest levels of BCIM were measured in a U.S. study (1.28 µg L^{-1}) (Richardson et al., 2008), while the BCIM levels after ozonation in China were 0.84 µg L^{-1} (Luo et al., 2014), and this study in Cyprus exhibited the lowest BCIM levels (mean of two cities: 0.11 µg L^{-1}). Seawater treatment in Saudi Arabia resulted in measurable levels of ITHM only for DBIM and BDIM, while the rest four ITHM were <LOD (Le Roux et al., 2015). Seawater desalination treatment in Saudi Arabia resulted in very high DBIM levels in finished water of 1.73 µg L^{-1} (Le Roux et al., 2015), while the only other study that detected DBIM was in China reporting mean levels of 0.1 µg L^{-1} (Luo et al., 2014). The CDIM species was only detected in the Chinese study of Luo et al., 2014 at low levels of

0.13 µg L^{-1}. Iodoform was only detected in a Chinese study having a mean value of 0.6 µg L^{-1} for both seasons in water originating from Yangtze river and a mean value of 0.1 µg iodoform L^{-1} for both seasons in water originating from Huangpu river (Wei et al., 2013a, 2013b); rest of aforementioned studies did not detect IF or did not report it. In the case of BDIM, it was only detected in the Saudi Arabian study with a mean of 0.6 µg L^{-1} that used seawater-based desalination treatment (Le Roux et al., 2015); rest of studies either did not detect it or did not report it.

Most of the ITHM occurrence studies in tap water were conducted in samples taken from the exit of water treatment plants, while only a few studies have focused on the ITHM occurrences within pipe water distribution networks. This study focused on the ITHM occurrence in the water distribution system along with the studies in Spain and Scotland by Serrano et al. (2015) and Goslan et al. (2009), respectively; these three studies focused only on the DCIM and BCIM species of ITHM in the finished tap water with similar mean sum values in Cyprus, Scotland and Spain being 0.6, 0.9 and 0.12 µg L^{-1}, respectively.

The very low levels of ITHM when compared with those of the regulated TTHM has probably contributed to the fact that no regulatory

Table 4
Non-parametric Spearman correlation coefficients between iodinated and other THM and routine physicochemical measurements.

Location	Trihalomethane component	Temperature (°C)	DO (mg L^{-1})	pH	EC (µS/cm)	Cl$^-$ (mg L^{-1})	Cu^{2+} (µg L^{-1})	NO$_3^-$ (mg L^{-1})	NH$_4^+$ (mg L^{-1})	Total bromine (µg L^{-1})	Total iodine (µg L^{-1})
Limassol	DCIM	0.44	0.29	0.00	−0.68**	−0.21	0.22	−0.53*	0.25	0.21	−0.54*
	BCIM	0.22	0.32	0.01	−0.12	0.02	0.03	0.07	0.38	0.43	−0.12
	ITHM	0.38	0.46*	−0.10	−0.41	−0.05	0.09	−0.23	0.35	0.46*	−0.32
	TCM	0.29	0.22	0.35	−0.56**	−0.12	0.38	−0.19	0.00	0.40	−0.54*
	BDCM	0.37	0.36	0.22	−0.68***	−0.14	0.42	−0.26	0.12	0.43	−0.66**
	DBCM	0.12	0.11	0.17	−0.53*	−0.25	0.26	−0.18	−0.03	0.36	−0.55*
	TBM	−0.38	0.03	0.01	0.57**	0.45*	−0.25	0.56*	0.03	0.00	0.43
	TTHM	0.21	0.29	0.24	−0.48*	−0.04	0.27	−0.09	0.08	0.43	−0.49*
Nicosia	DCIM	0.00	0.00	−0.16	−0.20	0.04	−0.10	0.25	−0.39	0.20	−0.22
	BCIM	0.00	0.00	0.09	0.30	−0.48	0.01	−0.23	−0.26	−0.07	0.20
	ITHM	0.00	0.00	−0.12	−0.07	−0.11	−0.14	0.11	−0.35	0.10	−0.08
	TCM	0.00	0.00	0.17	0.34	−0.11	−0.19	−0.12	−0.19	−0.21	0.18
	BDCM	0.00	0.00	0.03	−0.13	0.01	−0.02	0.37	−0.40	0.03	−0.10
	DBCM	0.00	0.00	−0.07	−0.12	0.00	−0.01	0.25	−0.24	0.15	0.01
	TBM	0.00	0.00	0.03	−0.22	−0.11	0.08	0.30	−0.33	−0.06	−0.01
	TTHM	0.00	0.00	0.11	0.01	−0.05	−0.07	0.20	−0.37	−0.05	0.01
Both cities	DCIM	0.44	0.29	0.05	−0.42**	−0.12	0.22	−0.25	−0.28	0.11	−0.40*
	BCIM	0.22	0.32	−0.20	0.28	−0.04	−0.19	0.19	0.11	0.19	0.25
	ITHM	0.38	0.46*	−0.06	−0.23	−0.08	0.07	−0.12	−0.19	0.15	−0.22
	TCM	0.29	0.22	0.33*	−0.30	−0.27	0.32	−0.39*	−0.34*	−0.14	−0.40*
	BDCM	0.37	0.36	0.18	−0.38*	−0.16	0.27	−0.16	−0.35*	0.08	−0.39*
	DBCM	0.12	0.11	0.15	−0.46**	−0.23	0.33*	−0.23	−0.46**	0.09	−0.42**
	TBM	−0.38	0.03	−0.43**	0.72***	0.55***	−0.70***	0.81***	0.33*	0.17	0.78***
	TTHM	0.21	0.29	0.12	−0.18	−0.07	0.11	−0.06	−0.28	0.00	−0.22

* *p* < 0.05.
** *p* < 0.01.
*** *p* < 0.001.

action is taken against ITHM, despite their enhanced cell cyto-, and geno-toxicity indices as compared to their brominated and chlorinated analogs (Richardson et al., 2008). DCIM was the dominant compound of the measured ITHM, being consistent with the findings of other studies in the U.S. (Krasner et al., 2006). DCIM concentrations measured in finished water of the water treatment plant (Nicosia, Cyprus) were in the sub-µg L^{-1} range, close to DCIM levels measured (up to 0.6 µg L^{-1}) in finished chlorinated water of a plant during the U.S.-nationwide DBP occurrence study (USEPA/600/R-02/068, 2002); ITHM concentrations varied between 0.2 and 19 µg L^{-1} depending on the disinfection practice and location of the plant, while DCIM was the dominant species in most locations sampled (Krasner et al., 2006).

The speciation of TTHM in tap water samples differed between the two cities, with Limassol having higher concentrations of TBM than Nicosia ($p < 0.0001$) and at comparable levels to the rest of TTHM in contrast to other studies where TCM was the dominant THM (McGuire et al., 2002, Wang et al., 2007, Whitaker et al., 2003, Egorov et al., 2003). TTHM speciation in Nicosia samples followed the normal pattern of TCM being the most abundant THM and TBM the least, with the other two species in between. The ratio of ITHM to TTHM concentration in this study based on their respective median values was 1.3%, close to 2.0% calculated by Krasner and colleagues (Krasner et al., 2006).

Since DCIM consisted almost 80% of ITHM, only total ITHM was considered for the univariate analyses and correlations. The analysis revealed a significant ($p < 0.001$) correlation between DCIM and TTHM. This association could be partially explained by the fact that all TTHM species use natural organic matter as a precursor, as is the case with these two species (Liang and Singer, 2003). A statistically significant negative correlation was also observed between ITHM and residual chlorine concentrations ($p < 0.05$), which is in accordance with the fact that the longer presence periods and thus reaction times of the disinfectant in the water can increase the formation of THMs (Bougeard et al., 2010).

This study had certain limitations: the sample size was small and not representative of the general population of Cyprus. Another important limitation is the quantification of only two out of six iodinated trihalomethanes. The quantification of all compounds of this group could give a better picture about the concentrations of total ITHM in the drinking water distribution systems of Cyprus and perhaps could aid in showing differences in ITHM levels between the two studied cities. Several assumptions were also employed to estimate the chronic daily intakes of ITHM and TTHM, including skin surface area, skin permeability constants and inhalation rates. The values used were provided by U.S. EPA, however, physiological differences between the populations of U.S. and Cyprus are plausible. Parameters, like water temperature, ventilation of the bathroom that can affect the concentrations of THMs in the surrounding air (Nazir and Khan, 2006) or other possible TTHM exposure sources, like dish washing or cleaning activities were not taken into account.

6. Conclusions

This is the first study of iodinated THM in tap water collected from households within two distribution urban pipe networks in the Eastern Mediterranean region. This study also gathered the technical characteristics of all published studies on ITHM in finished drinking water around the globe showing that DCIM and BCIM were the most frequently occurring ITHM compounds. Mean levels of ITHM within the drinking-water distribution systems in Cypriot cities were in the sub ppb levels, but they were accompanied by a wide range of concentrations between households, possibly reflecting water distribution characteristics, but this will be the focus of a subsequent study. The wide range of measured ITHM levels among households of the city receiving the same finished water was documented for the first time and worth of exploring further in relation with their health effects. The higher mammalian toxicity of ITHM than that of TTHM along with the documented variability in

ITHM water levels should be studied in seaside cities with elevated water iodine levels in source water (brackish groundwater or seawater). The beneficial human health effects of iodine consumption in humans through drinking water and/or diet (salt) may need to be studied along with the formation of ITHM levels in tap water reaching consumer taps.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.scitotenv.2015.10.031.

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