APPLICATION NOTE 73390

Determination of haloacetic acids, bromate, and dalapon in drinking water using ion chromatography coupled to high-resolution accurate-mass (IC-HRAM) mass spectrometry

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Keywords: Dionex ICS-6000, Dionex IonPac AS31 column, Q Exactive HF Hybrid Quadrupole-Orbitrap mass spectrometer, disinfection byproducts, HAAs

Goal

To demonstrate the capability and performance of a Thermo Scientific™ Q Exactive™ HF hybrid quadrupole-Orbitrap mass spectrometer-based IC-HRAM MS method to identify and quantify nine haloacetic acids, bromate, and dalapon in drinking water

Introduction

Disinfection processes for removing or killing pathogenic microorganisms were introduced in the early twentieth century for drinking water treatment. They have helped reduce the incidences of waterborne diseases such as poliomyelitis and cholera. However, the applied disinfectants can react with the natural organic matter and anthropogenic contaminants in the water to form disinfection by-products (DBPs).

Haloacetic acids (HAAs) are one of the most commonly detected classes of DBPs[1-2] and have captured considerable attention due to their adverse biological effects on human and aquatic organisms.[3] Chlorinated, brominated, and iodinated HAAs are formed when chloride, bromide, and iodide ions are present in the raw water source. Of the nine chlorinated and/or brominated HAAs,

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five are currently regulated by the U.S. Environmental Protection Agency (EPA) (HAA5): monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), and dibromoacetic acid (DBAA). Consequently, the U.S. EPA has established a maximum contamination level (MCL) of 60 µg/L for HAA5 in drinking water.[4] The remaining four HAAs are currently unregulated: bromochloroacetic acid (BCAA), bromodichloroacetic acid (BDCAA), dibromochloroacetic acid (DBCAA), and tribromoacetic acid (TBAA). Bromate can arise as a byproduct of the ozonation of bromide-containing water depending on the conditions (pH, temperature, etc.) prevalent at the treatment site.[5] According to regulations, drinking water plants must determine the concentration of DBPs in drinking water prior to release. U.S. EPA Method 557 has been validated for the determination of HAAs, bromate, and dalapon.[6]

By comparison to the conventional U.S. EPA methods using GC with ECD, the combination of ion chromatography (IC) and mass spectrometry (MS) offers sensitive and rapid detection without the need for sample pretreatment. In this study, we develop a fast, simple, and sensitive quantitation assay with high confidence for determination of HAAs, bromate, and dalapon in drinking water using a recently introduced Thermo Scientific™ Dionex™ IonPac™ AS31 column, Thermo Scientific™ Dionex™ ICS-6000 HPIC™ system, and a Q Exactive HF mass spectrometer. Thermo Scientific™ Q Exactive™ hybrid quadrupole-Orbitrap™ series mass spectrometers offer analysts a range of scan modes that provide functionality comparable to the modes provided by conventional tandem quadrupole mass spectrometers. Our study compared three types of targeted quantitation experiments including full-scan MS with data-dependent tandem mass spectrometry (full MS/ddMS^2 with inclusion list), targeted selected ion monitoring (SIM) with data-dependent tandem mass spectrometry (t-SIM/ddMS^2), and parallel reaction monitoring (PRM or t-MS^2). Compared to QQQ MS methods that involve optimization of SRM transitions in numerous time windows, Orbitrap mass spectrometer-based quantitation methods do not require special tuning and optimization nor comprehensive MS knowledge to set up, and eliminate the need for the additional make-up flow of organic solvents, and thus simplify operation. Our method also has greater confidence provided by higher resolving power due to reduced likelihood of false detection of the analytes of interest. Full-scan HRAM MS data can be acquired across the full mass range of interest, which provides unique ability to detect non-target compounds and to analyze data retrospectively.

Experimental

Equipment and consumables

IC

- Thermo Scientific™ Dionex™ ICS-6000 HPIC system including:
  - Dionex ICS-6000 DP Pump module
  - Dionex ICS-6000 EG Eluent Generator module with high-pressure degasser module
  - Dionex ICS-6000 Low Temperature DC Detector/ Chromatography module with two injection valves
  - CD Conductivity Detector
  - Tablet control
- Thermo Scientific™ Dionex™ AS-AP Autosampler with Tray Temperature Control (P/N 074926), Sample Syringe, 250 µL (P/N 074306) and Buffer line, 1.2 mL (P/N 074989)
- Thermo Scientific™ Dionex™ EGC 500 KOH Eluent Generator Cartridge (P/N 075778)
- Thermo Scientific™ Dionex™ CR-ATC 600 Continuously Regenerated Anion Trap Column (P/N 088662)
- Thermo Scientific™ Dionex™ ADRS 600 Anion Dynamically Regenerated Suppressor (2 mm, P/N 088667)
- Dionex IC PEEK Viper Fitting Tubing Assembly Kit (2 mm, P/N 302965)
- Dionex AS-AP Autosampler Vials 10 mL (P/N 074228)

Mass spectrometer

- Q Exactive HF Hybrid Quadrupole-Orbitrap Mass Spectrometer
- Peak® Scientific Genius 1022 nitrogen generator (P/N 10-6022 (230v))

Software

Data acquisition

- Thermo Scientific™ Xcalibur™ 4.2 software with SII 1.5 for Xcalibur software

Or

- Thermo Scientific™ TraceFinder™ 5.0 software

Data processing

- TraceFinder 5.0 software

Conditions

Parameter	Value
IC system	Dionex ICS-6000 HPIC system
MS detector	Q Exactive HF Hybrid Quadrupole-Orbitrap Mass Spectrometer
Columns	Dionex IonPac AG31 Guard, 2 × 50 mm (P/N 303148) Dionex IonPac AS31 Analytical, 2 × 250 mm (P/N 303147)
Eluent source	Thermo Scientific™ Dionex™ EGC 500 KOH Eluent Generator Cartridge with Thermo Scientific™ Dionex™ CR-ATC 600
Gradient eluent	*Time (min)* / *[KOH] (mM)* / *Divert valve (one of two injection valves)* -0.5 / 17.0 / Eluent to Waste 0.0 / 17.0 4.01 / Eluent to MS 7.0 / 17.0 8.6 / Eluent to Waste 11.1 / Eluent to MS 18.0 / 85.0 18.73 / Eluent to Waste 21.73 / Eluent to MS 40.0 / 85.0 / Eluent to Waste 40.1 / 17.0 47.0 / Stop Run
Flow rate	0.3 mL/min
Injection volume	100 µL
Temperature	4 °C (autosampler tray temperature), 15 °C (column compartment), 20 °C (detector compartment)
System backpressure	~3750 psi (25.85 MPa)
Detection	Suppressed conductivity, Dionex ADRS 600 Suppressor (2 mm), AutoSuppression, 64 mA, external water mode via one Dionex ICS-6000 DP Pump, external water flow rate (0.60 mL/min)
Background conductance	~ 0.3 µS/cm
Run time	47 min
Mass spectrometric detection	
Ion source	Electrospray ionization (ESI), negative mode
HESI source	Sheath gas flow rate: 40 Aux gas flow rate: 8 Sweep gas flow rate: 0 Spray voltage (kV): 3 Capillary temp. (°C): 220 S-lens RF level: 50 Aux gas heater temp (°C): 325
Three types of experiments[7]	1. Full MS/ddMS^2 with inclusion list, Table 1 2. t-SIM/ddMS^2, Table 2 3. PRM, Table 3

Table 1a. Full MS/ddMS² method inclusion list

Mass [*m/z*]	Formula [M]	Species	CS [z]	Polarity	Start [min]	End [min]	(N)CE
92.97488	$C_2H_3O_2Cl$	- H	1	Negative	5.00	7.50	
136.92437	$C_2H_3BrO_2$	- H	1	Negative	6.00	8.00	52
126.90363	BrO_3		1	Negative	7.00	9.00	78
140.95156	$C_3H_4Cl_2O_2$	- H	1	Negative	11.00	13.00	13
126.93591	$C_2H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
172.88335	C_2H_2[81]$BrClO_2$	- H	1	Negative	13.00	15.00	22
216.83283	C_2H_2[79]Br[81]BrO_2	- H	1	Negative	14.00	16.00	17
116.90711	CCl_3		1	Negative	22.00	24.50	23
162.85454	C_3[81]$BrCl_2$		1	Negative	24.00	27.00	17
206.80403	C_3[79]Br[81]BrCl		1	Negative	26.00	30.50	58
250.75351	C_3[79]Br_2[81]Br		1	Negative	31.00	36.00	49
94.97193	$C_2H_3O_2$[37]Cl	- H	1	Negative	5.00	7.50	
93.97824	[13]$C_3C_3H_3O_2Cl$	- H	1	Negative	5.00	7.50	
137.92772	[13]$C_3C_3H_3BrO_2$	- H	1	Negative	6.00	8.00	52
127.93926	[13]$C_3C_3H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
117.91046	[13]CCl_3		1	Negative	22.00	24.50	23

Note: Formula [M] stands for the structure of the active compound, CS [z] for the charge state of the ion to be fragmented, and (N)CE for normalized collision energy

Table 1b. Properties of the full MS/ddMS² method

Method properties		
Global setting	User role	Standard
	Use lock masses	Best
	Chrom. peak width (FWHM)	20 s
Time	Method duration	47 min
Properties of full MS/ddMS² (TOPN), part 1		
General	Run time	0 to 47 min
	Polarity	Negative
	Default charge state	1
	Inclusion	On
	Tags	-
Full MS	Resolution	120,000
	AGC target	3e6
	Maximum IT	247 ms
	Scan range	50 to 300 *m/z*

Properties of full MS/ddMS² (TOPN), part 2		
dd-MS²/ dd-SIM	Resolution	60,000
	AGC target	1e5
	Maximum IT	119 ms
	Loop count	5
	TopN	5
	Isolation windows	4.0 *m/z*
	Fixed first mass	-
	(N)CE/stepped (N)CE	nce: 10, 30, 60
dd settings	Minimum AGC target	8.00e3
	Intensity threshold	6.7e4
	Apex trigger	-
	Charge exclusion	-
	Peptide match	-
	Exclude isotopes	On
	Dynamic exclusion	10.0 s
	If idle	Do not pick others

Table 2a. t-SIM/ddMS² method inclusion list

Mass [*m/z*]	Formula [M]	Species	CS [z]	Polarity	Start [min]	End [min]	(N)CE
92.97488	$C_2H_3O_2Cl$	- H	1	Negative	5.00	7.50	
136.92437	$C_2H_3BrO_2$	- H	1	Negative	6.00	8.00	52
126.90363	BrO_3		1	Negative	7.00	9.00	78
140.95156	$C_3H_4Cl_2O_2$	- H	1	Negative	11.00	13.00	13
126.93591	$C_2H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
172.88335	C_2H_2[81]$BrClO_2$	- H	1	Negative	13.00	15.00	22
216.83283	C_2H_2[79]Br[81]BrO_2	- H	1	Negative	14.00	16.00	17
116.90711	CCl_3		1	Negative	22.00	24.50	23
162.85454	C_3[81]$BrCl_2$		1	Negative	24.00	27.00	17
206.80403	C_3[79]Br[81]BrCl		1	Negative	26.00	30.50	58
250.75351	C_3[79]Br_2[81]Br		1	Negative	31.00	36.00	49
94.97193	$C_2H_3O_2$[37]Cl	- H	1	Negative	5.00	7.50	
93.97824	[13]$C_3C_3H_3O_2Cl$	- H	1	Negative	5.00	7.50	
137.92772	[13]$C_3C_3H_3BrO_2$	- H	1	Negative	6.00	8.00	52
127.93926	[13]$C_3C_3H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
117.91046	[13]CCl_3		1	Negative	22.00	24.50	23

Table 2b. Properties of the t-SIM/ddMS² method

Method properties		
Global setting	User role	Standard
	Use lock masses	Best
	Chrom. peak width (FWHM)	20 s
Time	Method duration	47 min
Properties of t-SIM/ddMS², part 1		
General	Run time	0 to 47 min
	Polarity	Negative
	Default charge state	1
	Inclusion	On
SIM	Resolution	120,000
	AGC target	3e6
	Maximum IT	249 ms
	Loop count	5
	Isolation windows	4.0 *m/z*

Properties of t-SIM/ddMS², part 2		
dd-MS²	Resolution	60,000
	AGC target	1e5
	Maximum IT	119 ms
	Loop count	5
	TopN	5
	Isolation windows	4.0 *m/z*
	Fixed first mass	-
	(N)CE/stepped (N)CE	nce: 10, 30, 60
dd settings	Minimum AGC target	8.00e3
	Intensity threshold	6.7e4
	Apex trigger	-
	Charge exclusion	-
	Peptide match	-
	Exclude isotopes	On
	Dynamic exclusion	10.0 s

Table 3a. PRM method inclusion list

Mass [*m/z*]	Formula [M]	Species	CS [z]	Polarity	Start [min]	End [min]	(N)CE
92.97488	$C_2H_3O_2Cl$	- H	1	Negative	5.00	7.50	
136.92437	$C_2H_3BrO_2$	- H	1	Negative	6.00	8.00	52
126.90363	BrO_3		1	Negative	7.00	9.00	78
140.95156	$C_3H_4Cl_2O_2$	- H	1	Negative	11.00	13.00	13
126.93591	$C_2H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
172.88335	C_2H_2[81]$BrClO_2$	- H	1	Negative	13.00	15.00	22
216.83283	C_2H_2[79]Br[81]BrO_2	- H	1	Negative	14.00	16.00	17
160.89694	$C_2HCl_3O_2$	- H	1	Negative	22.00	24.50	23
162.85454	C_1[81]$BrCl_2$		1	Negative	24.00	27.00	17
206.80403	C_1[79]Br[81]BrCl		1	Negative	26.00	30.50	58
250.75351	C_1[79]Br_2[81]Br		1	Negative	31.00	36.00	49
94.97193	$C_2H_3O_2$[37]Cl	- H	1	Negative	5.00	7.50	
93.97824	[13]$C_1C_1H_3O_2Cl$	- H	1	Negative	5.00	7.50	
137.92772	[13]$C_1C_1H_3BrO_2$	- H	1	Negative	6.00	8.00	52
127.93926	[13]$C_1C_1H_2Cl_2O_2$	- H	1	Negative	12.00	14.00	19
161.90029	[13]$C_1C_1HCl_3O_2$	- H	1	Negative	22.00	24.50	23

Table 3b. Properties of the PRM method

Method properties		
Global setting	User role	Standard
	Use lock masses	Best
	Chrom. peak width (FWHM)	20 s
Time	Method duration	47 min
Properties Targeted-SIM/ddMS², part 1		
General	Run time	0 to 47 min
	Polarity	Negative
	Default charge state	1
	Inclusion	On

Properties Targeted-SIM/ddMS², part 2		
MS²	Resolution	60,000
	AGC target	1e5
	Maximum IT	119 ms
	Isolation windows	0.7 *m/z*
	Fixed first mass	-
	(N)CE/stepped (N)CE	nce: 10

Reagents and standards

Reagents

- Deionized (DI) water, Type I reagent grade, 18 MΩ·cm resistivity or better filtered through a 0.2 µm filter immediately before use
- Thermo Scientific™ Pierce™ LTQ Velos ESI Positive Ion Calibration Solution (P/N 88323)
- Thermo Scientific™ Pierce™ Negative Ion Calibration Solution (P/N 88324)

Standards

- Haloacetic Acid Mix (9 components), 1000 mg/L each in methyl tert-butyl ether, Restek (Restek P/N 31896)
- Dalapon (2,2-dichloropropionic acid), 1000 mg/L in methanol, Restek (Restek P/N 32253)
- Bromate standard, 1000 mg/L (P/N 303168)
- Monochloroacetic acid MCAA-2-13C, 1000 mg/L (P/N 069406)

- Monobromoacetic acid MBAA-1-13C, 1000 mg/L (P/N 069407)
- Dichloroacetic acid-DCAA-2-13C, 1000 mg/L (P/N 069408)
- Trichloroacetic acid TCAA-2-13C, 1000 mg/L (P/N 069409)
- Ammonium chloride, (Crystalline/Certified ACS), Fisher Chemical (Fisher Scientific P/N A661-500)
- Sodium bicarbonate, (Crystalline/Certified ACS), Fisher Chemical (Fisher Scientific P/N S233-500)
- Sodium chloride, (Crystalline/Certified ACS), Fisher Chemical (Fisher Scientific P/N S271-500)
- Sodium nitrate, (Crystalline/Certified ACS), Fisher Chemical (Fisher Scientific P/N S343-500)
- Sodium sulfate anhydrous, (Granular/Certified ACS), Fisher Chemical (Fisher Scientific P/N S421-500)

Preparation of reagents and standards

Reagent water (RW)

Purified water, which does not contain any measurable quantity of the method analytes or interfering compounds at or above 1/3 the minimum reporting level (MRL) for the target analyte, is very important for the successful execution of this method. For this work, DI water was further purified using a bench model Millipore water purification system (Millipore Corp., Billerica, MA, Model No. MilliQ® Gradient A10 or equivalent).

Laboratory synthetic sample matrix (LSSM)

Prepare the LSSM at the concentrations listed in Table 4. The required concentrations of nitrate (20 mg/L), bicarbonate (150 mg/L), chloride (250 mg/L), and sulfate (250 mg/L) are based on the mass of the anion, not the sodium salt. The NH_4Cl preservative is included in the matrix.

Internal standard primary dilution standard (internal standard PDS) (1.0 mg/L)

Prepare the internal standard PDS by adding enough of each internal standard stock standard (1000 mg/L) to a known volume of reagent water to make the final concentration 1.0 mg/L. Store the PDS in a glass vial with a PTFE/silicone septum. During method development, add 160 µL of the internal standard PDS to each 40 mL field sample, QC sample, or calibration standard to produce a final concentration of 4.0 µg/L. The aqueous internal standard PDS is stable for 60 days when stored at 4 °C.

Analyte primary dilution solution (analyte PDS) (1.0 mg/L)

Prepare the analyte PDS by dilution of the analyte stock standard solutions (1000 mg/L) into reagent water. Store the PDS in a glass vial with a PTFE/silicone septum. The analyte PDS is used to prepare calibration standards and to fortify samples with the method analytes. An example preparation of the analyte PDS is provided in Table 5.

Table 4. LSSM preparation

Compound	Empirical formula	Salt (gfw)[a]	Anion (gfw)	Salt mass (mg)	H_2O (L)	Conc. stock (mg/L)[b]	Conc. LSSM (mg/L)[c]
Ammonium chloride (preservative)	NH_4Cl	53.49		500	0.5	1000	100
Nitrate	NO_3^-	84.99	62.00	137	0.5	200	20
Bicarbonate	HCO_3^-	84.01	61.02	1030	0.5	1500	150
Chloride	Cl^-	58.44	35.45	2060	0.5	2500	250
Sulfate	SO_4^{2-}	142.04	96.06	1850	0.5	2500	250

[a]gfw = gram formula weight of the sodium salt
[b]Stock concentration = (salt mass)(gfw anion)/(gfw salt)(0.5 L)
[c]1:10 dilution of stock (e.g., 50 mL to 500 mL), LSSM = Laboratory synthetic sample matrix

The single laboratory lowest concentration minimum reporting level (LCMRL) solutions

LCMRL is defined as the lowest spiking concentration such that the probability of spike recovery in the 50% to 150% range is at least 99%. In our study, it is determined in reagent water using the LCMRL calculator provided by EPA.[8] The LCMRL calculator recommends seven spiking levels with four replicates per level for a total of 28 analyses for each compound. The spiking levels of single laboratory LCMRLs for the analytes in this method are listed in Table 6. Note: Depending on the source and purity, labeled HAA internal standards may contain a small percentage of the corresponding native analyte. Usually, such contributions are insignificant when performing the method within the normal calibration range of 0.1 to 20 µg/L. However, the contribution may be significant when attempting to determine LCMRLs. The final concentration of the labeled internal standard with 99% purity at 4.0 µg/L might contribute at most 0.04 µg/L of the corresponding MCAA, MBAA, DCAA, and TCAA. We estimated the purity of the labeled internal standards using a Q Exactive HF Hybrid Quadrupole-Orbitrap Mass Spectrometer.

Calibration standard solutions

This method uses a procedural calibration technique. In this type of calibration the stardards are processed through the entire method, including the sample preparation and the addition of preservatives. Prepare calibration standards by diluting the analyte PDS into reagent water containing 100 mg/L NH_4Cl (preservative). A calibration range of 0.1 to 20 µg/L is recommended as a starting point and is adequate for most drinking water sources. Add 160 µL of the 1 mg/L internal standard PDS to each 40 mL calibration standard.

Table 5. Analyte PDS (1.0 mg/L) preparationt

Analyte stock	Stock concentration (mg/L)	Stock volume (mL)	Final volume (mL reagent water)	Analyte PDS concentration (mg/L)
Bromate, aqueous	1000 as bromate anion	0.05	50	1.0
Dalapon in methanol	1000	0.05	50	1.0
Haloacetic acids in methyl-tertbutyl ether	1000	0.05	50	1.0

Note: Storage stability of the analyte PDS was evaluated during method development at a single concentration of 1.0 µg/mL. The aqueous analyte PDS is stable for 60 days when stored at 4 °C. Other PDS concentrations may be selected. However, it is recommended that the laboratory independently assess the stability of the aqueous PDS to determine a safe storage time.

Table 6. LCMRL fortification levels

Compound	t-SIM/ddMS²	PRM	Full MS/dd-MS²
MCAA	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L
MBAA	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L
Bromate	1, 2.5, 3.75, 5, 7.5, 10, 25 ng/L	1, 2.5, 3.75, 5, 7.5, 10, 25 ng/L	10, 25, 37.5, 50, 75, 100, 250 ng/L
Dalapon	2.5, 3.75, 5, 7.5, 10, 25, 37.5 ng/L	25, 37.5, 50, 75, 100, 250, 375 ng/L	10, 25, 37.5, 50, 75, 100, 250 ng/L
DCAA	0.05, 0.075, 0.1, 0.25, 0.375, 0.5, 0.75 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L
BCAA	3.75, 5, 7.5, 10, 25, 37.5, 50 ng/L	5, 7.5, 10, 25, 37.5, 50, 75 ng/L	10, 25, 37.5, 50, 75, 100, 250 ng/L
DBAA	2.5, 3.75, 5, 7.5, 10, 25, 37.5 ng/L	3.75, 5, 7.5, 10, 25, 37.5, 50 ng/L	10, 25, 37.5, 50, 75, 100, 250 ng/L
TCAA	0.075, 0.1, 0.25, 0.375, 0.5, 0.75, 1 µg/L	0.05, 0.075, 0.1, 0.25, 0.375, 0.5, 0.75 µg/L	0.075, 0.1, 0.25, 0.375, 0.5, 0.75, 1 µg/L
BDCAA	7.5, 10, 25, 37.5, 50, 75, 100 ng/L	5, 7.5, 10, 25, 37.5, 50, 75 ng/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L
DBCAA	3.75, 5, 7.5, 10, 25, 37.5, 50 ng/L	3.75, 5, 7.5, 10, 25, 37.5, 50 ng/L	0.1, 0.25, 0.375, 0.5, 0.75, 1, 2 µg/L
TBAA	3.75, 5, 7.5, 10, 25, 37.5, 50 ng/L	2.5, 3.75, 5, 7.5, 10, 25, 37.5 ng/L	-

Note: The stability of calibration standards was evaluated during method development at concentrations of 2.0 and 5.0 µg/L. The aqueous calibration standards are stable for 14 days when stored at 4 °C in glass vials with PTFE/silicone septa. The laboratory should independently assess the stability of the aqueous calibration standards to determine safe storage time.

Precision and accuracy study

Precision and accuracy were demonstrated by the measurement of nine HAAs, bromate, and dalapon fortified at 1.0 and 15 µg/L in reagent water, 1.0 and 15 µg/L in laboratory synthetic sample matrix, and 2.0 and 10 µg/L in tap water. The percent relative standard deviation (RSD) of the concentrations of the replicate analyses must be ≤20% for all method analytes. The average percent recovery of the replicate analyses must be within ±30% of the true value.

Relative standard deviation (RSD) and recovery were calculated using the equation:

$$\text{RSD} = \frac{\textit{Standard Deviation of Measured Concentration}}{\textit{Average Concentration}} \times 100$$

$$\%\ \text{Recovery} = \frac{\textit{Average Measured Concentration}}{\textit{Fortified Concentration}} \times 100$$

Results and discussion

IC-HRAM MS separation

In this study, a fast IC-MS method was developed to separate nine HAAs, bromate, and dalapon on a Dionex IonPac AS31 column set at 15 °C that is optimized to ensure reproducible recovery for HAAs. MBAA, DBCAA, and TBAA degrade readily in aqueous eluent at high pH. Such conditions may exist in the mobile phase of ion exchange columns. The reaction is temperature dependent. For this reason, the separation is performed at sub-ambient temperature, specifically 15 °C. At 15 °C, degradation in the column eluent is minimized. The eluent flow rate was 0.3 mL/min and the elution method started at 17 mM KOH for 7 min, then increased to 85 mM KOH from 7 to 18 min, held at 85 mM KOH until 40 min to elute TBAA, and returned to 17 mM KOH at 40 min to re-equilibrate the column for 7 min before the next injection. The total run time was 47 min. The KOH eluent was neutralized using a Dionex ADRS 600 2 mm dynamically regenerated suppressor before conductivity and MS-detection. The injection volume was 100 µL, and field samples, QC samples, and calibration standards were always maintained at or below 6 °C, including the time these were in the autosampler awaiting injection.

MS data acquisition was performed in three different modes: full-scan MS with data-dependent tandem mass spectrometry (full MS/ddMS2 with inclusion list), targeted SIM with data-dependent tandem mass spectrometry (t-SIM/ddMS2), and parallel reaction monitoring (PRM). The ion source conditions are shown in “Conditions” and the three modes used to analyze target analytes are shown in Tables 1–3. IC-HRAM MS data were acquired using Thermo Scientific™ Xcalibur™ 4.2 software with SII 1.5 for Xcalibur software and processed using Thermo Scientific™ TraceFinder™ 5.0 software, which allows easy creation of the acquisition and processing methods for high-throughput quantitative analysis along with data reviewing and reporting. Identification parameters for the HAAs are listed in Table 7. HAAs were identified according to their retention time and the exact mass of pseudo molecular ions ($[M\text{-}H]^-$). In the case of trihalogenated HAAs (TCAA, BDCAA, DBCAA, and TBAA), the exact mass of ions formed by decarboxylation of the pseudo molecular ions ($[M\text{-}H\text{-}COO]^-$) in the ESI source or the analyzer due to the instability of these compounds was also used for identification.[9] The bromate and dalapon ions were detected as molecular ion ($[M]^-$), and pseudo molecular ion ($[M\text{-}H]^-$), respectively.

Figures 1-3 show chromatograms of a 9 HAAs, dalapon, and bromate standard solution containing the preservative and the labeled internal standards with retention times using three different acquisition modes.

Table 7. Identification parameters of HAAs analyzed by IC-HRAM MS in the ESI negative mode

Compound	Retention time (min)	Full MS/dd-MS² and t-SIM/ddMS²			PRM		
		Elemental composition	Formula	Extracted fragment exact *m/z*	Precursor ion	Formula	Extracted fragment exact *m/z*
MCAA	6.43	$C_2H_2O_2Cl^-$	$[M-H]^-$	92.97488	$C_2H_2O_2Cl^-$	$[M-H]^-$	92.97488
MCAA_IS	6.43	$[13]C_1C_1H_2O_2Cl^-$	$[M-H]^-$	93.97824	$[13]C_1C_1H_2O_2Cl^-$	$[M-H]^-$	93.97824
MBAA	7.17	$C_2H_2BrO_2^-$	$[M-H]^-$	136.92437	$C_2H_2BrO_2^-$	$[M-H]^-$	78.9183
MBAA_IS	7.17	$[13]C_1C_1H_2BrO_2^-$	$[M-H]^-$	137.92772	$[13]C_1C_1H_2BrO_2^-$	$[M-H]^-$	78.9183
Bromate	7.62	BrO_3^-	$[M]^-$	126.90363	BrO_3^-	$[M]^-$	110.9072
Dalapon	12.02	$C_3H_3Cl_2O_2^-$	$[M-H]^-$	140.95156	$C_3H3Cl_2O_2^-$	$[M-H]^-$	104.9734
DCAA	12.74	$C_2H_1Cl_2O_2^-$	$[M-H]^-$	126.93591	$C_2H_1Cl_2O_2^-$	$[M-H]^-$	82.9454
DCAA_IS	12.74	$[13]C_1C_1H_1Cl_2O_2^-$	$[M-H]^-$	127.93926	$[13]C_1C_1H_1Cl_2O_2^-$	$[M-H]^-$	83.9485
BCAA	13.61	$C_2H_1[81]BrClO_2^-$	$[M-H]^-$	172.88335	$C_2H_1[81]BrClO_2^-$	$[M-H]^-$	128.8919
DBAA	14.88	$C_2H_1[79]Br[81]BrO_2^-$	$[M-H]^-$	216.83283	$C_2H_1[79]Br[81]BrO_2^-$	$[M-H]^-$	172.8417
TCAA	22.90	CCl_3^-	$[M-H-COO]^-$	116.90711	$C_2Cl_3O_2^-$	$[M-H]^-$	116.9056
TCAA_IS	22.90	$[13]C_1Cl_3^-$	$[M-H-COO]^-$	117.91046	$[13]C_1C_1Cl_3O_2^-$	$[M-H]^-$	117.9090
BDCAA	25.10	$C_1[81]BrCl_2^-$	$[M-H-COO]^-$	162.85454	$C_1[81]BrCl_2^-$	$[M-H-COO]^-$	80.9162
DBCAA	28.29	$C_1[79]Br[81]BrCl^-$	$[M-H-COO]^-$	206.80403	$C_1[79]Br[81]BrCl^-$	$[M-H-COO]^-$	78.9183
TBAA	33.11	$C_1[79]Br_2[81]Br^-$	$[M-H-COO]^-$	250.75351	$C_1[79]Br_2[81]Br^-$	$[M-H-COO]^-$	78.9183

IS = internal standard

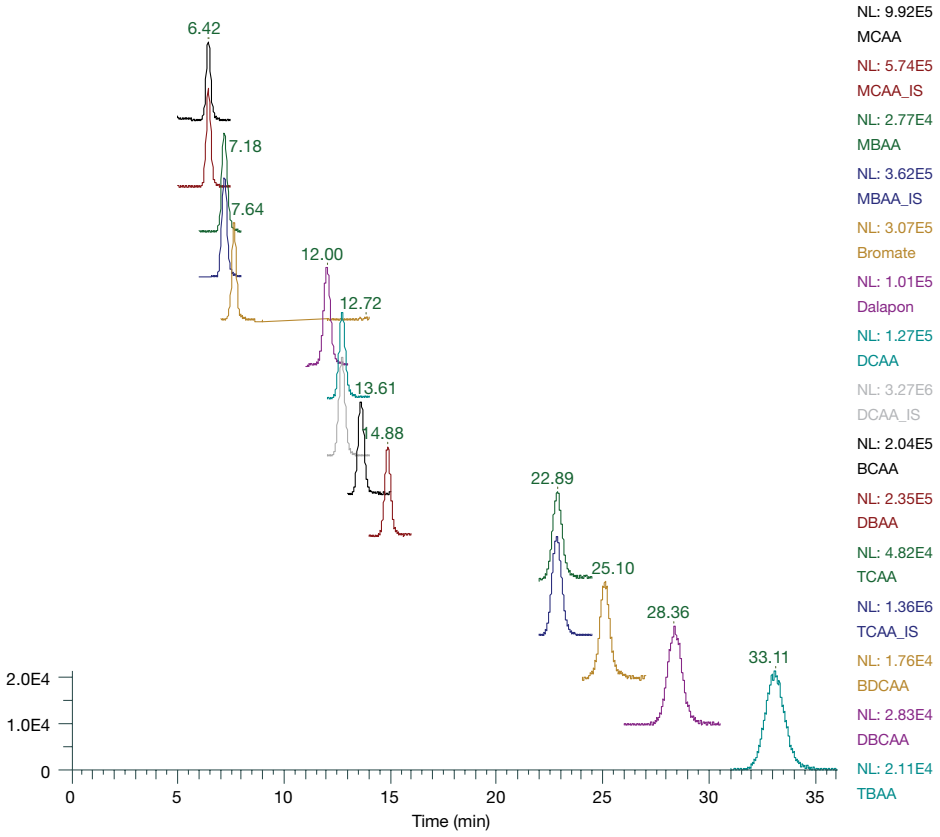

Figure 1. Chromatograms of nine HAAs, dalapon, and bromate (0.1 µg/L each) standard solution containing the preservative and the labeled internal standards (4 µg/L each) using t-SIM /dd-MS² mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

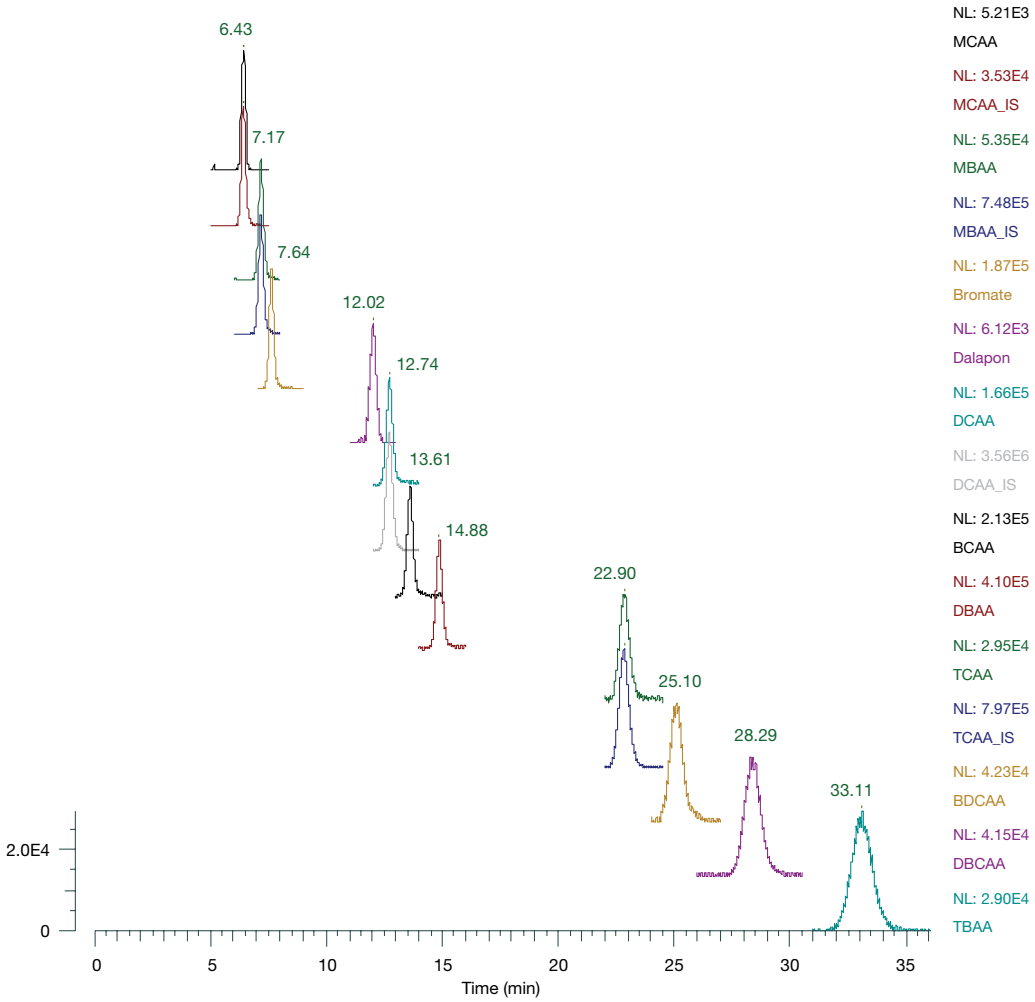

Figure 2. Chromatograms of nine HAAs, dalapon, and bromate (0.1 µg/L each) standard solution containing the preservative and the labeled internal standards (4 µg/L each) using PRM mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local.
NL: Normalization level

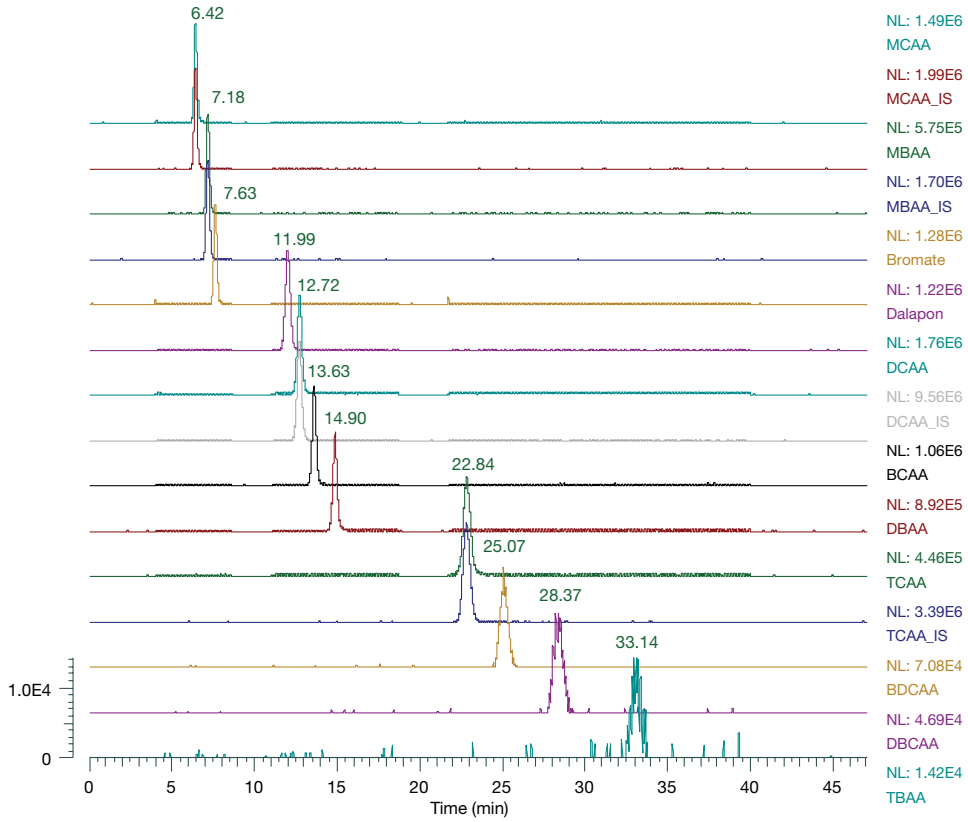

Figure 3. Chromatograms of nine HAAs, dalapon, and bromate (0.5 µg/L each) standard solution containing the preservative and the labeled internal standards (4 µg/L each) using Full MS/dd-MS² mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

Figures 4-6 show chromatograms of a drinking water sample containing the preservative and internal standards (4 µg/L each) using three different acquisition modes. Figure 7 also illustrates the ability to detect non-target compounds, such as chlorite, acetate, malonate, succinate, malate, chlorate, and bromide, without re-running samples. The results (Figures 4 and 5) show that t-SIM/ddMS² and PRM modes are sensitive to enable confirmation of the presence of all nine HAAs, bromate, and dalapon in the tap water sample. Full-scan HRAM data acquisition (Figures 6 and 7) provides benefits of simultaneous data collection for both targeted and non-targeted components, and suitability for simultaneous quantification of an unlimited number of compounds, which is not possible using QQQ SRM methods. The results demonstrate that accurate mass assignment and high resolution in both MS and MS/MS modes increase selectivity and reduce uncertainty. The selected ion for MCAA quantitation in PRM mode is the precursor ion because the product ion of MCAA is *m/z* 34.9683 below the mass range 50 to 6,000 *m/z* for the Q Exactive HF MS (Scan range: last mass ≤ 15 × first mass). Full-scan HRAM data acquisition captures all sample data, enabling the identification of "unexpected" compounds and retrospective data analysis without the need to re-run samples.

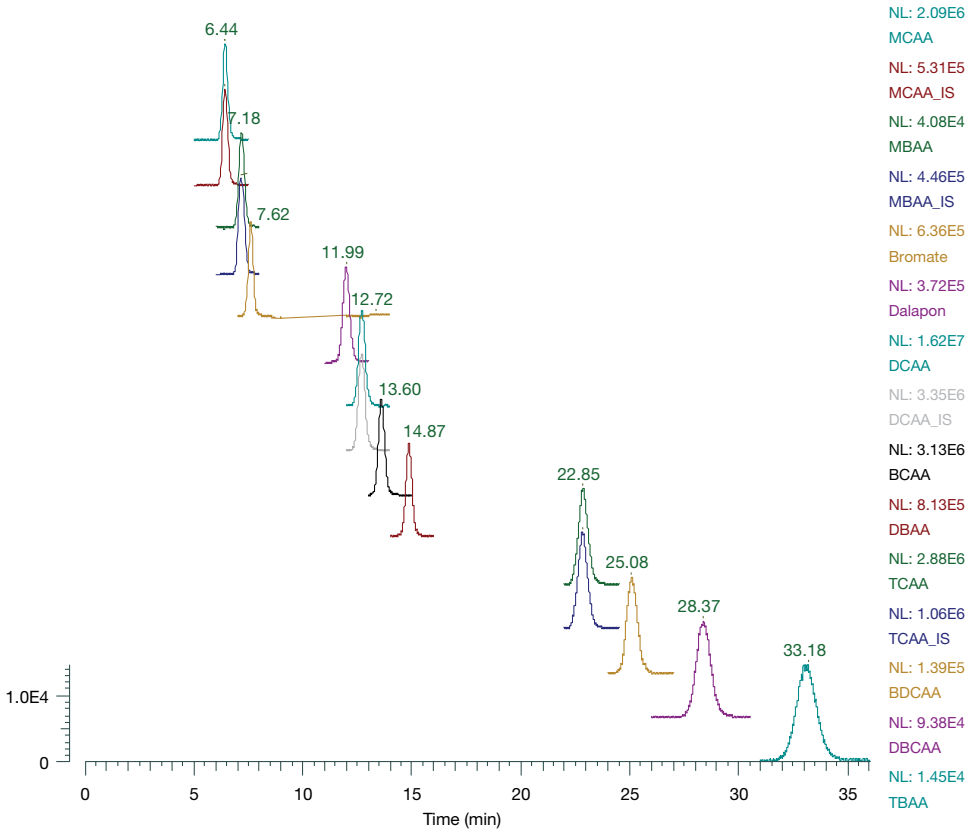

Figure 4. Chromatograms of a drinking water sample containing the preservative and internal standards (4 µg/L each) using t-SIM/dd-MS² mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

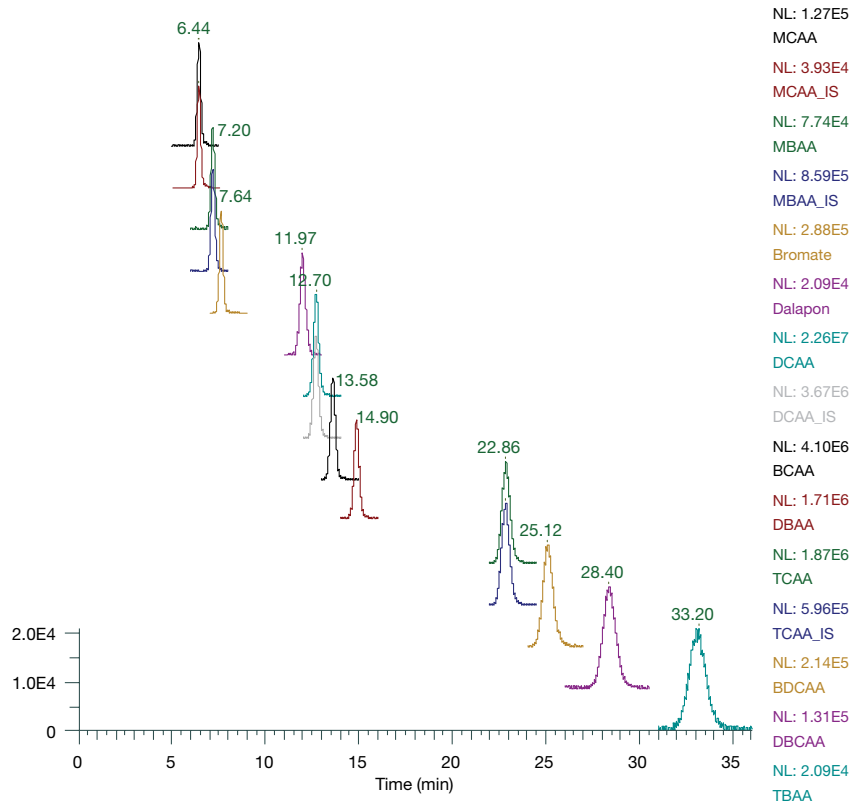

Figure 5. Chromatograms of a drinking water sample containing the preservative and internal standards (4 µg/L each) using PRM mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

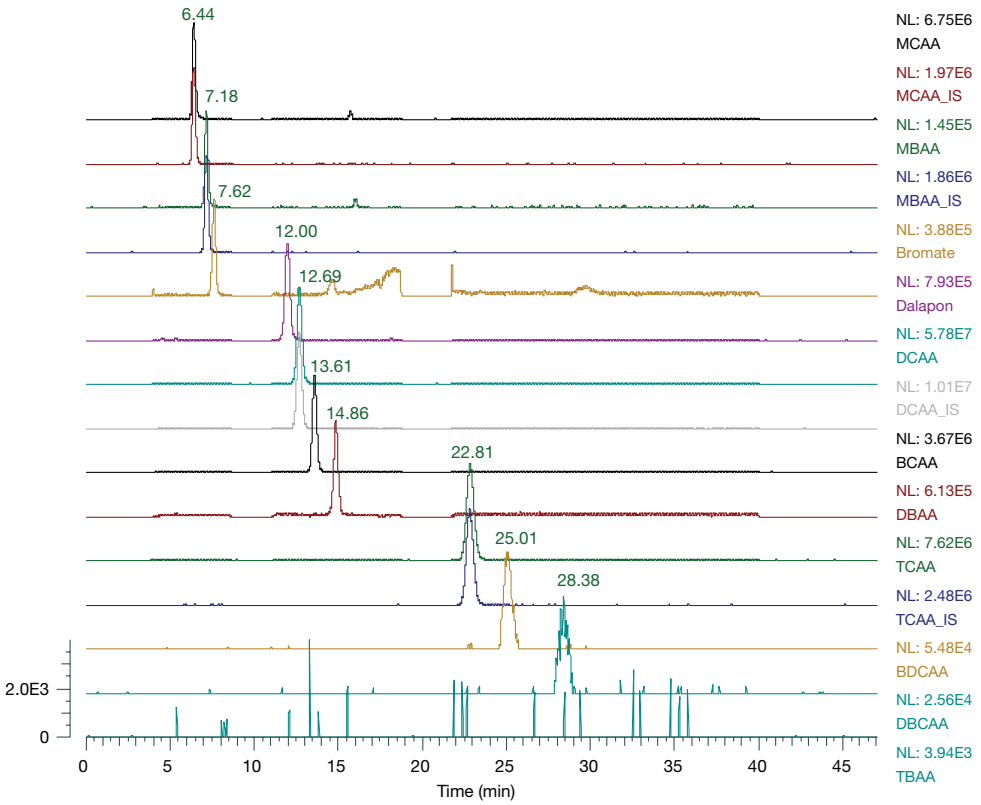

Figure 6. Chromatograms of a drinking water sample containing the preservative and internal standards (4 µg/L each) using Full MS/dd-MS² mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

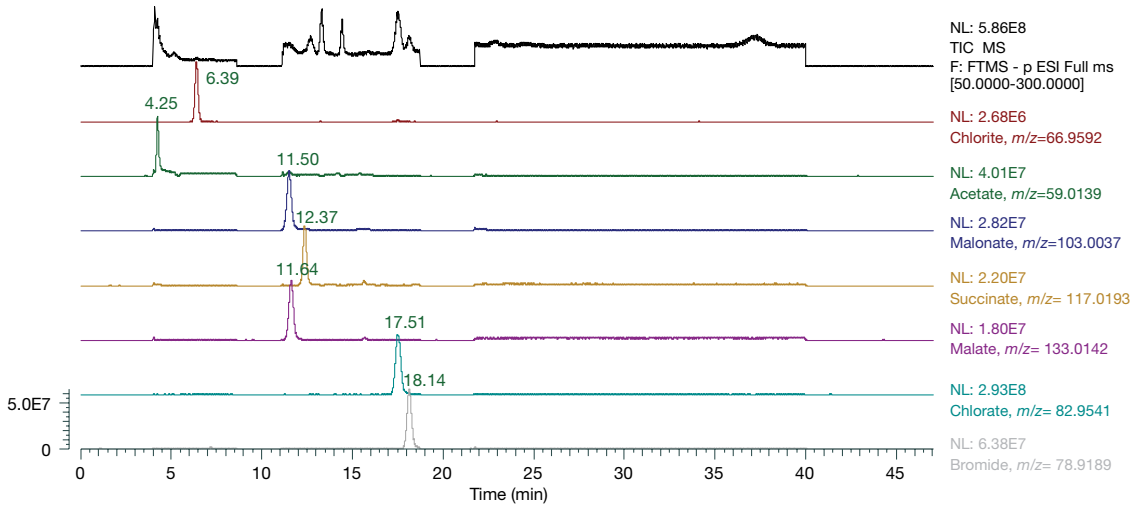

Figure 7. Non-target compounds such as chlorite, acetate, malonate, succinate, malate, chlorate, and bromide are detected in a drinking water sample using Full MS/dd-MS² mode. Here, the y-axis scale is set to absolute (where the title is intensity), and the normalization is set to local. NL: Normalization level

Determination of the single laboratory LCMRL

Single laboratory LCMRLs for the analytes using three different acquisition modes ranged from 0.0011 to 0.18 µg/L and are listed in Table 8. The results demonstrated high sensitivity of the Q Exactive mass spectrometer compared to QQQ MS/MS analysis.

Table 8. IC-HRAM MS lowest concentration minimum reporting level (LCMRL, µg/L)

Compound	EPA reported QQQ MS/MS	t-SIM/ddMS²	PRM	Full MS/dd-MS²
MCAA	0.58	0.1	0.1	0.1
MBAA	0.19	0.1	0.1	0.1
Bromate	0.042	0.0011	0.001	0.01
Dalapon	0.41	0.0025	0.025	0.01
DCAA	0.13	0.05	0.1	0.1
BCAA	0.16	0.00375	0.0054	0.012
DBAA	0.062	0.0025	0.00375	0.01
TCAA	0.25	0.075	0.05	0.075
BDCAA	0.19	0.0075	0.0077	0.11
DBCAA	0.08	0.00375	0.00375	0.18
TBAA	0.27	0.00375	0.0028	>0.375

Calibration and linearity

An internal standard mixture of ^{13}C-labeled MCAA, MBAA, DCAA, and TCAA was spiked into each sample at 4 µg/L. All calibration standards were prepared in DI water containing 100 mg/L NH_4Cl as a preservative. A mass-extracted window of 5 ppm around the theoretical *m/z* of each target analyte was used. The calibration curves were generated using the internal standard approach for all the HAA compounds in water, except for MCAA in our study. When baseline noise is significant, peak height measurement is more reliable than area integration. The calibration curve of MCAA is constructed on the peak height and external standard method. Excellent linearity results were observed for all compounds (Table 9).

Drinking water sample analysis

Tap water samples from different cities in the San Francisco Bay Area were analyzed for the presence of all analytes contained in the method. Drinking water samples were collected in accordance with the U.S. EPA Method 557 procedure,[6] with NH_4Cl added as a preservative as it reacts with residual chlorine preventing further production of HAAs after sampling. Internal standards were added, and the samples were quantified. The three quantitative methods were used to evaluate three types of drinking water samples: commercial bottled water, tap water, and tap water that has been through a filtered drinking water faucet, where the disinfectants were thought to be eliminated. The levels of each compound detected in the samples are shown in Table 10.

Table 9. IC-HRAM MS method calibrations

Compound	Internal standard assignment	t-SIM/ddMS²		PRM		Full MS/dd-MS²	
		Range (µg/L)	Coefficient of determination (r^2)	Range (µg/L)	Coefficient of determination (r^2)	Range (µg/L)	Coefficient of determination (r^2)
MCAA	MCAA[2-^{13}C]	0.375–15	0.9996	0.1–20	0.9990	0.1–20	0.9999
MBAA	MBAA[1-^{13}C]	0.1–20	0.9999	0.1–20	0.9997	0.1–20	0.9999
Bromate	MBAA[1-^{13}C]	0.025–2 0.25–15	0.9991 0.9981	0.025–2 0.25–20	0.9991 0.9996	0.025–2 0.1–15	0.9993 0.9998
Dalapon	DCAA[2-^{13}C]	0.1–20	0.9999	0.1–20	0.9998	0.1–20	0.9998
DCAA	DCAA[2-^{13}C]	0.1–20	0.9999	0.1–20	0.9999	0.1–20	0.9999
BCAA	DCAA[2-^{13}C]	0.1–20	0.9997	0.1–20	0.9996	0.1–20	0.9997
DBAA	DCAA[2-^{13}C]	0.1–20	0.9998	0.1–20	0.9997	0.1–20	0.9996
TCAA	TCAA[2-^{13}C]	0.1–20	0.9999	0.1–20	0.9998	0.25–20	0.9998
BDCAA	TCAA[2-^{13}C]	0.1–20	0.9998	0.1–20	0.9994	0.25–15	0.9991
DBCAA	TCAA[2-^{13}C]	0.1–20	0.9998	0.25–20	0.9997	0.375–15	0.9997
TBAA	TCAA[2-^{13}C]	0.075–20	0.9995	0.075–20	0.9999	0.75–15	0.9998

Table 10. HAAs, bromate, and dalapon concentrations (µg/L)

Analyte	Bottled water			Drinking water			Filtered drinking water		
	t-SIM/ ddMS²	PRM	Full MS/ dd-MS²	t-SIM/ ddMS²	PRM	Full MS/ dd-MS²	t-SIM/ ddMS²	PRM	Full MS/ dd-MS²
MCAA	<0.1	n.d.	<0.1	3.23	3.06	3.01	<0.1	n.d.	<0.1
MBAA	n.d.	n.d.	<0.1	<0.1	<0.1	<0.1	n.d.	n.d.	<0.1
Bromate	<0.025	<0.025	<0.025	0.145	0.149	0.156	0.0361	0.0373	0.043
Dalapon	n.d.	n.d.	n.d.	0.278	0.282	0.231	n.d.	n.d.	n.d.
DCAA	<0.1	<0.1	<0.1	20.0	20.2	20.2	<0.1	<0.1	<0.1
BCAA	n.d.	n.d.	n.d.	1.68	1.56	1.49	n.d.	n.d.	n.d.
DBAA	n.d.	n.d.	n.d.	0.194	0.234	0.198	n.d.	n.d.	n.d.
TCAA	n.d.	n.d.	n.d.	11.1	11.0	11.0	n.d.	n.d.	n.d.
BDCAA	n.d.	n.d.	n.d.	0.434	0.476	0.515	n.d.	n.d.	n.d.
DBCAA	n.d.	n.d.	n.d.	<0.1	<0.1	n.d.	n.d.	n.d.	n.d.
TBAA	n.d.	n.d.	n.d.	n.d.	<0.075	n.d.	n.d.	n.d.	n.d.

n.d.=not detectable

The PRM mode provides the most sensitivity and selectivity for quantification of compounds in the samples with a complex matrix. All three methods showed good quantitative performance and obtained similar values.

Precision and accuracy

Single laboratory precision and accuracy data are presented for three water matrices: reagent water (Table 11), LSSM (Table 12), and tap water (Table 13).

Single laboratory precision was measured by relative standard deviation (RSD) of replicate analyses (n=7), and accuracy was measured by percent recoveries of fortified water samples. Single laboratory precision was 0.078–8.04% and accuracy was in the range 70–130%. The accuracy for TBAA in tap water was slightly below 70% at the spiked concentration of 2 µg/L using full MS/dd-MS² mode.

Table 11. Precision and accuracy of method analytes fortified at 1.0 and 15 µg/L in reagent water

Analyte	Fortified conc. = 1.0 µg/L (n=7)						Fortified conc. = 15 µg/L (n=7)					
	t-SIM/ddMS²		PRM		Full MS/dd-MS²		t-SIM/ddMS²		PRM		Full MS/dd-MS²	
	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD
MCAA	101	1.70	98.2	3.24	98.5	1.16	98.8	5.19	103	1.94	99.5	1.98
MBAA	95.8	0.871	94.6	0.280	94.8	0.438	99.3	0.855	98.7	0.458	98.7	0.260
Bromate	106	2.95	94.1	1.46	97.0	1.13	104	6.37	96.5	2.50	103	1.73
Dalapon	95.3	2.42	98.3	1.98	95.2	0.694	99.3	2.94	104	1.37	99.3	0.948
DCAA	94.7	0.323	94.5	0.285	94.3	0.160	99.5	0.550	99.3	0.316	98.8	0.078
BCAA	102	4.37	91.8	1.48	95.7	0.956	97.3	3.28	96.1	2.75	100.5	0.666
DBAA	99.1	0.722	93.4	4.38	95.4	0.438	106	3.83	94.0	2.66	99.2	1.15
TCAA	94.6	0.289	92.8	2.41	94.6	0.755	98.9	0.411	98.2	2.22	98.0	0.366
BDCAA	96.1	1.37	91.5	1.23	94.3	1.84	102	2.25	96.1	1.11	100.4	0.618
DBCAA	95.3	1.94	92.8	0.662	94.9	1.03	104	3.97	97.6	0.985	100.7	0.970
TBAA	94.1	1.69	91.7	0.778	97.6	1.52	98.6	2.88	98.1	1.27	100.9	1.29

Table 12. Precision and accuracy of method analytes fortified at 1.0 and 15 µg/L in a synthetic sample matrix

Analyte	Fortified conc. = 1.0 µg/L (n=7)						Fortified conc. = 15 µg/L (n=7)					
	t-SIM/ddMS²		PRM		Full MS/dd-MS²		t-SIM/ddMS²		PRM		Full MS/dd-MS²	
	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD
MCAA	94.5	3.25	88.8	3.38	79.3	1.74	86.2	1.64	75.4	1.33	78.3	2.25
MBAA	109	0.821	109	0.474	110	1.13	111	0.588	111	0.932	111	0.393
Bromate	113	5.61	111	2.92	113	1.04	98.3	2.05	116	7.92	122	0.714
Dalapon	74.5	4.04	70.7	0.912	70.1	1.09	76.4	1.36	73.7	4.30	74.3	0.366
DCAA	97.3	1.95	96.6	0.633	94.8	0.571	99.3	0.694	100	0.724	99.7	0.254
BCAA	101	5.94	96.5	1.21	75.2	1.46	94.7	1.11	102	3.94	91.7	0.788
DBAA	95.8	4.3	97.8	1.39	88.3	1.36	102	2.06	102	1.73	95.6	0.900
TCAA	98.4	1.42	92.5	2.02	93.8	1.74	100	0.638	99.0	2.66	100	0.500
BDCAA	91.7	1.72	83.4	1.23	83.1	4.89	101	1.20	91.9	0.810	90.2	0.677
DBCAA	82.0	5.05	78.4	1.36	78.7	2.96	98.7	0.989	92.8	1.51	78.6	2.74
TBAA	84.5	7.64	82.2	1.17	75.9	3.07	95.9	4.13	95.0	1.00	87.3	0.542

Table 13. Precision and accuracy of method analytes fortified at 2.0 and 10 µg/L in tap water

Analyte	Fortified conc. = 2.0 µg/L (n=7)						Fortified conc. = 10 µg/L (n=7)					
	t-SIM/ddMS²		PRM		Full MS/dd-MS²		t-SIM/ddMS²		PRM		Full MS/dd-MS²	
	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD	Mean % recovery	RSD
MCAA	109	4.32	112	2.84	113	3.30	111	2.95	107	2.10	119	0.886
MBAA	107	0.471	106	0.511	115	0.328	115	0.694	114	0.692	115	0.289
Bromate	103	1.77	103	2.67	117	0.630	117	2.94	111	3.87	116	1.29
Dalapon	108	0.603	106	1.26	99.3	0.431	109	0.447	108	0.981	100	0.695
DCAA	76.3	2.30	74.9	5.81	87.2	2.98	-	-	-	-	-	-
BCAA	103	1.22	89.2	1.27	93.5	0.683	97.6	0.990	93.2	1.91	96.2	0.670
DBAA	88.6	1.30	84.4	0.803	84.5	0.456	92.6	1.60	88.0	1.45	88.5	1.15
TCAA	83.6	4.92	80.3	5.24	72.2	3.73	89.4	0.789	94.4	3.89	84.6	0.737
BDCAA	79.3	0.434	90.2	0.961	78.3	0.949	81.7	0.563	93.3	0.712	77.1	0.792
DBCAA	72.6	0.700	88.3	0.591	72.3	8.04	76.9	2.29	95.4	0.858	71.9	4.37
TBAA	76.9	1.75	87.9	0.947	64.3	1.51	79.9	0.452	95.8	0.288	75.4	0.901

Conclusion

This application note evaluated the capability and performance of a Q Exactive mass spectrometer-based IC-HRAM MS method to detect HAAs, bromate, and dalapon in drinking water. Following the guidelines of U.S. EPA Method 557, direct injection of drinking water into a Dionex ICS-6000 HPIC system coupled to a Q Exactive HF Hybrid Quadrupole-Orbitrap Mass Spectrometer system allowed for the quantitation of nine haloacetic acids, bromate, and dalapon. Running the analysis by this methodology spares the analyst from derivatization required by gas chromatography methodology. This study demonstrated great sensitivity, good precision and accuracy, and high specificity. All scan modes met the reporting level requirements for EPA Method 557. Compared to QQQ MS, the availability of high-resolution MS multiple techniques offers flexibility and convenience, bringing greater possibilities and confidence to the analysts in achieving more conclusive results to their experiments. For example, using full scan mode, it may be possible to expand EPA method 557 for accurate quantitation of additional anions such as chlorite.

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