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Article

Assessment of Highly Polar Chemicals in Dutch and Flemish Drinking Water and Its Sources: Presence and Potential Risks

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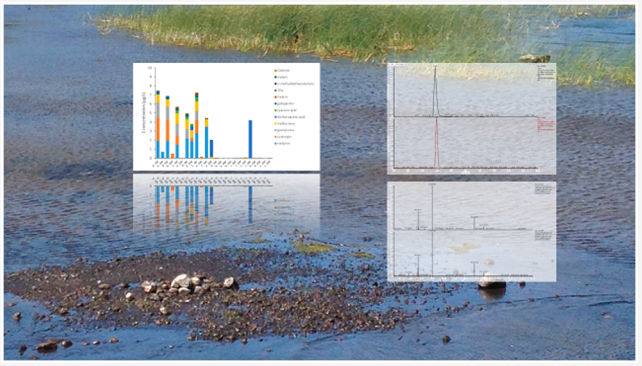
ABSTRACT: Highly polar chemicals are mobile in an aqueous environment. Analytical methods for these compounds in water are lacking. A combined target/nontarget screening method based on hydrophilic interaction LC coupled to high-resolution MS was developed. Thirty-two highly polar chemicals (including melem and melam) can thus be quantitatively measured in surface water and drinking water, and the MS data can be screened for unknown compounds. This is the first time a method for the determination of melem and melam in water has been described. The method is complementary to existing target and nontarget methods for less polar substances and can be applied for (drinking) water quality assessment. In a screening study in The Netherlands and Flanders, 12 of the 32 compounds were encountered in groundwater, surface water, and drinking water at levels between 0.01 and 4.2 μg/L. Concentrations in drinking water were compared with (provisional) guideline values to assess whether these may pose a concern for human health. In one drinking water sample, the concentration of dichloroacetic acid exceeded the provisional guideline value, indicating that health effects cannot be excluded on the basis of lifetime exposure. For most chemicals, reliable drinking water guideline values could not be derived due to the limited available of toxicity data.



KEYWORDS: *melamine, melem, melam, dichloroacetic acid, HILIC, nontarget analysis, drinking water treatment, guideline values*

INTRODUCTION

The presence of highly polar organic substances in sources of drinking water presents a potential threat for drinking water quality and human health. These substances are highly mobile and pass through natural and technical barriers, such as river banks or purification processes. They can spread further in the urban water cycle because of their hydrophilicity and low sorption coefficients, and the relative contribution of polar chemicals to the total chemical profile present in water samples increases going from wastewater to groundwater to drinking water.[1] Their removal from source waters requires specific technologies, such as membrane filtration or advanced oxidation processes. As these expensive technologies are often unavailable, monitoring of source waters and regulation of the substances are necessary, in particular in the case of persistent ones, because they may eventually reach finished waters. Persistent chemicals are continuously released from multiple sources,[2] and this release will lead to continuously increasing levels of contamination, which may result in effects on human health and the environment.[3] The list of potentially occurring persistent mobile organic compounds (PMOCs) that have not yet been investigated is still very long.[4] Information gaps have been identified for PMOCs. These include a lack of analytical methods, occurrence and toxicity data, and derivation of acceptable exposure levels.[5] The knowledge of highly polar organic compounds is much more limited[6] compared with that of the better known, traditional environmental contaminants like polychlorinated biphenyls and other persistent, bioaccumulative and toxic (PBT) substances and polar compounds like pharmaceuticals and pesticides.

Limited research has been performed on the analysis and monitoring of highly polar chemicals in water.[7−13] Analytical separation techniques like supercritical fluid chromatography,[7,14−17] chromatography using a bi-[18] or trifunctional mixed-mode column[8] combining RP, anion, and cation exchange,[8] chromatography with a core−shell biphenyl stationary phase,[9] and hydrophilic interaction liquid chromatography (HILIC),[10,11] often in combination with high-

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resolution mass spectrometry (HRMS) have been applied to study highly polar compounds in water samples. HRMS has been shown to be particularly useful in the identification of emerging substances.[19−22] In particular for organic acids and bases, new analytical methods need to be developed to enable the monitoring of their levels in drinking water sources. Many of the small organic acids have very low pK_as and as a result occur in their deprotonated, anionic form in environmental waters.

In this study, we aimed to further close the analytical and monitoring knowledge gaps for PMOCs and gain insight into the presence and fate of PMOCs during drinking water treatment. Therefore, we developed a combined target and nontarget screening method based on HILIC hyphenated with HRMS. With this method, 32 PMOCs, including small organic acids and bases, can be quantitatively measured in surface water and drinking water, while at the same time, the high-resolution mass spectrometric data obtained can be screened for additional, unknown highly polar compounds. The method was applied in a screening study of raw sources of drinking water and the corresponding produced drinking water. For the compounds detected in drinking water, their concentrations were compared with (provisional) drinking water guideline values to assess whether measured concentrations may pose a concern and to prioritize chemicals for abatement or monitoring.

EXPERIMENTAL METHODS

Chemicals. All solvents were of analytical grade quality. Acetonitrile and methanol (ultragradient HPLC grade) were obtained from Avantor Performance Materials B.V. (Deventer, The Netherlands). Formic acid (HPLC quality) was purchased from Sigma-Aldrich (Steinheim, Germany). Ultrapure water was obtained by purifying demineralized water in an Elga Purelab (High Wycombe, United Kingdom) Chorus ultrapure water system.

Reference Standard Solutions. Thirty-two model PMOCs were used for optimization and validation of the method. The compounds were chosen on the basis of their potential environmental relevance, intended use, (possible) persistence, and polarity. Reference standards were obtained from Toronto Research Chemicals (Toronto, ON) and Sigma-Aldrich (Zwijndrecht, The Netherlands). Compound names and accurate masses of the protonated molecule ($[M + H]^+$), the molecular ion (M^+), or deprotonated molecule ($[M - H]^-$) are listed in Table S1 for the reference standards. Stock solutions of the reference standards and internal standards (chlormequat-d_9 and sotalol-d_7) were prepared at a concentration of ∼100 mg/L in acetonitrile. The internal standards were used (i) to correct for the variability of the injection volume and (ii) to study matrix effects for the target and nontarget analysis. For compounds that did not dissolve completely in acetonitrile, water or methanol was added to improve the solubility. Working solutions were prepared in ultrapure water and acetonitrile [5:95 (v/v)]. Stock solutions were stored at −20 °C. Working solutions were stored at 7 °C for a maximum of 1 week.

Sampling and Sample Preparation. For method optimization, tap water was obtained from the town of Nieuwegein (The Netherlands). Surface water samples were taken from the Lekkanaal at Nieuwegein, which is connected to the River Rhine, in a stainless steel container that had previously been thoroughly washed and rinsed. The surface water samples were stored at 4 °C in the dark for a maximum of 1 week. For nontarget screening, a blank sample, consisting of 1 L of ultrapure water in the sample bottle, was processed using the same protocol that was used for the water samples from the sampling campaign. This was done four times per matrix, and samples were analyzed in duplicate (eight measurements). An aliquot of 5 mL of each water sample was transferred to a glass tube. The aliquot was evaporated to 250 μL using an automated blow-down apparatus (Barkey optocontrol) with a gentle N_2 stream (block temperature set at 300 °C, actual N_2 temperature of ∼80 °C). Next, 50 μL of the internal standard solution, containing 100 μg/L chlormequat-d_9 and sotalol-d_7, and 4.7 mL of acetonitrile were added to the sample, resulting in a final concentration of internal standards of 1 μg/L in a 95:5 (v/v) acetonitrile/water solvent. Samples were filtered using a 0.2 μm regenerated cellulose filter (Phenomenex) and transferred to an autosampler vial prior to LC-MS analysis. The sampling for the screening study is described below.

LC-MS Conditions. For chromatographic separation, a high-purity silica Zorbax Hilic plus column (150 mm × 2.1 mm inside diameter, particle size of 1.8 μm, Agilent) preceded by a Krudkatcher ULTRA HPLC In-line filter (Phenomenex, 0.5 μm) was used. The column temperature was maintained at 25 °C. Eluent A consisted of 95% ultrapure water and 5% acetonitrile (v/v) with 5 mM ammonium formate at pH 3. Eluent B consisted of 95% acetonitrile and 5% ultrapure water (v/v) with 5 mM ammonium formate at pH 3. The linear gradient started from 100% B to 90% B over 4 min. Next, the gradient was from 90% B to 20% B over 11 min, and the level of B remained at 20% for 6 min. The level of B was increased to 100% in 1 min, and the column was equilibrated at 100% B for 8 min. The flow rate was 0.3 mL/min, and 100 μL of the sample was injected onto the LC column. Blank samples containing internal standards in ultrapure water were run every 10−15 samples to check for contamination and carryover.

A Tribrid Orbitrap Fusion mass spectrometer (ThermoFisher Scientific, Bremen, Germany) provided with an electrospray ionization source was interfaced to a Vanquish HPLC system (ThermoFisher Scientific). With every batch run, mass calibration was performed using a Pierce ESI positive and negative ion calibration solution to obtain a mass error of <2 ppm. The vaporizer and capillary temperature were maintained at 350 and 300 °C, respectively. Sheath, auxiliary, and sweep gases were set to arbitrary units of 45, 5, and 5, respectively. The source voltage was set to 3.0 kV in the positive mode and −2.5 kV in the negative mode. The RF lens was set to 50%. Full scan high-accuracy mass spectra were recorded in the range of m/z 80−1300 with the resolution set at 120000 full width at half-maximum (fwhm), and quadruple isolation was used for acquisition. Data-dependent acquisition was performed using a high-collision dissociation (HCD) energy at 35% and a FT resolution of 15000 fwhm.

Data Analysis. *Target Analysis.* Data processing for target analysis was performed using Xcalibur version 2.2 (ThermoFisher Scientific). The compounds were identified by comparing the accurate mass of the molecular ion, two accurate MS2 fragment ions (when available), and the retention time of the signals of a target compound in the matrix to those obtained for the standard reference solutions. Target compounds were quantified using an external calibration line consisting of nine points ranging from 0.05 to 50 μg/L. To check for matrix effects, the peak areas of the

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ACS EST Water 2021, 1, 928−937

internal standards were monitored. No substantial matrix effects were observed. The mass extraction window was ±10 ppm for all target compounds.

Nontarget Screening. Data analysis for suspect and nontarget screening was performed using Compound Discoverer 2.1 (ThermoFisher Scientific) for peak picking, componentization, chlorine pattern scoring, suspect screening (using the target list of 32 target compounds, and ChemSpider), and automatic MS2 fragment searches in mzCloud. Only detects were considered with a signal intensity that was 5 times higher than those of the compounds detected in the bottle and instrument blanks. Sotalol-d_7 was used for quantification in the positive mode. Its response in all samples was found to be satisfactorily constant and apparently insensitive to matrix effects. An overview of the Compound Discoverer workflow and the data processing parameters is provided in the Supporting Information. The identity was confirmed by comparing the retention time, accurate mass, and fragmentation pattern of the unknown compound with those of the reference standard, and identification levels described by Schymanski et al.[23] were used.

Analytical Method Validation. The LOD of the whole method was determined by spiking reference standards in drinking water and in surface water at concentrations of 0.01, 0.05, 0.2, 1, and 5 μg/L. The LOD is defined by using the standard deviation of the repeatability for the lowest concentration that was detected, and taking into account a confidence interval of 99% with one-side probability. The limit of quantitation (LOQ) for each compound was then determined by using the LOD multiplied by 3. The repeatability and recovery were determined by spiking drinking water and surface water with the 32 compounds at a level of 1 μg/L (n = 8), which were analyzed together with the corresponding drinking and surface water blanks. Recoveries were calculated by comparing the concentrations obtained from external standard calibration with the initial spiking level, after subtraction of the corresponding blank sample.

Screening Study. In March and April 2017, 24 grab samples of surface waters, groundwater, and drinking waters were taken from the raw water inlet and the finished waters of 11 drinking water companies in The Netherlands and one in Flanders (Belgium) (called locations A−L). These samples include seven surface waters, two river bank filtrates, and three groundwaters used for the production of drinking water and the 12 associated produced drinking waters from each location. During sampling, two blank samples consisting of ultrapure water were prepared in the sample bottle and stored for analysis. Regression analysis was performed with concentration data (and employing 0.5 × LOD values in the case of concentrations below the LOD) using the Pearson product moment correlation coefficient facility from Excel.

Evaluation of the Potential Human Health Risk. For substances detected in the screening study, evaluation of the human health concern was conducted using the procedure and data sources presented by Baken et al.[24] In short, reported (statutory) drinking water guideline values (GLVs) were retrieved, or provisional drinking water guideline values (pGLVs) were calculated on the basis of acceptable daily intake levels (formula I) or virtually safe doses (VSDs) corresponding to an extra lifetime cancer risk level of 10^{-6} (formula II) established by acknowledged authorities. When acceptable intake levels were absent, they were derived from toxicological study results {no observed (adverse) effect level [NO(A)EL] or benchmark dose level (BMDL) values}, if available. Genotoxicity was evaluated on the basis of classifications provided by international authorities or available experimental data. When no information about genotoxicity was available, the genotoxic potential was predicted using OECD QSAR Toolbox version 4.1 (LMC), ToxTree version 2.6.13 (Ideaconsult Ltd.), ToxRead version 0.11 (Mario Negri), and VEGA via AMBIT2 version 3.1.0 (Ideaconsult Ltd.) to identify structural alerts or perform read across.[25,26]

I. pGLV (μg/L) = {tolerable daily intake (TDI), acceptable daily intake (ADI), reference dose (RfD), derived no effect level (DNEL) [μg (kg of body weight)$^{-1}$ day^{-1}] × 70 kg of body weight × 20% drinking water allocation}/(2 L of drinking water consumption).

II. pGLV (μg/L) = (10^{-6} extra lifetime cancer risk level × 70 kg of body weight)/(2 L of drinking water consumption).

The reliability of (p)GLVs was considered high when it concerned a (statutory) health-based GLV reported by an acknowledged authority, moderate when it concerned a pGLV reported by an acknowledged authority or when it was based on a TDI, ADI, RfD, or DNEL, and low when it was based on NO(A)EL and/or inadequate or incomplete toxicity data.

Next, the benchmark quotient (BQ) was calculated as the ratio between the mean or maximum reported drinking water concentration and the (p)GLV. A BQ value of ≥1 indicates a potential human health concern if the water were to be consumed over a lifetime. A BQ value of ≥0.1 warrants further investigation, monitoring, and/or mitigation, because a small change in water quality may cause the BQ to increase above 1.[27] When no drinking water concentration was available, the highest concentration detected in surface water was used to calculate the BQ.

When drinking water guideline values and data to derive a pGLV were lacking, the threshold of toxicological concern (TTC) approach was applied to evaluate whether chemicals detected in drinking water present a potential human health risk. To that end, drinking water concentrations were compared to generic drinking water target levels for organic contaminant concentrations of 0.1 and 0.01 μg/L based on TTC values for nongenotoxic and (predicted) genotoxic chemicals, respectively.[22,28]

RESULTS AND DISCUSSION

HILIC Target and Nontarget Screening Method for PMOCs. *Method Performance.* A simultaneous target analysis and a nontarget screening were developed for analysis of highly polar chemicals in water. The method is based on sample pretreatment, followed by hydrophilic interaction liquid chromatography (HILIC) coupled to high-resolution mass spectrometry. Thirty-two PMOCs were used for optimization and validation of the analytical method. Chromatograms obtained in positive and negative mode are shown in Figure S1. The benefits and limitations of HILIC for polar organics were recently discussed.[29,30]

The pretreatment method comprised evaporation of the water sample and, subsequently, reconstitution of the sample in a solution containing a high organic solvent concentration. The water sample is not concentrated by this procedure, but the composition of the sample changes from 100% water to a high-concentration organic solvent, i.e., 95% acetonitrile and 5% water (v/v), which is compatible with injection onto the

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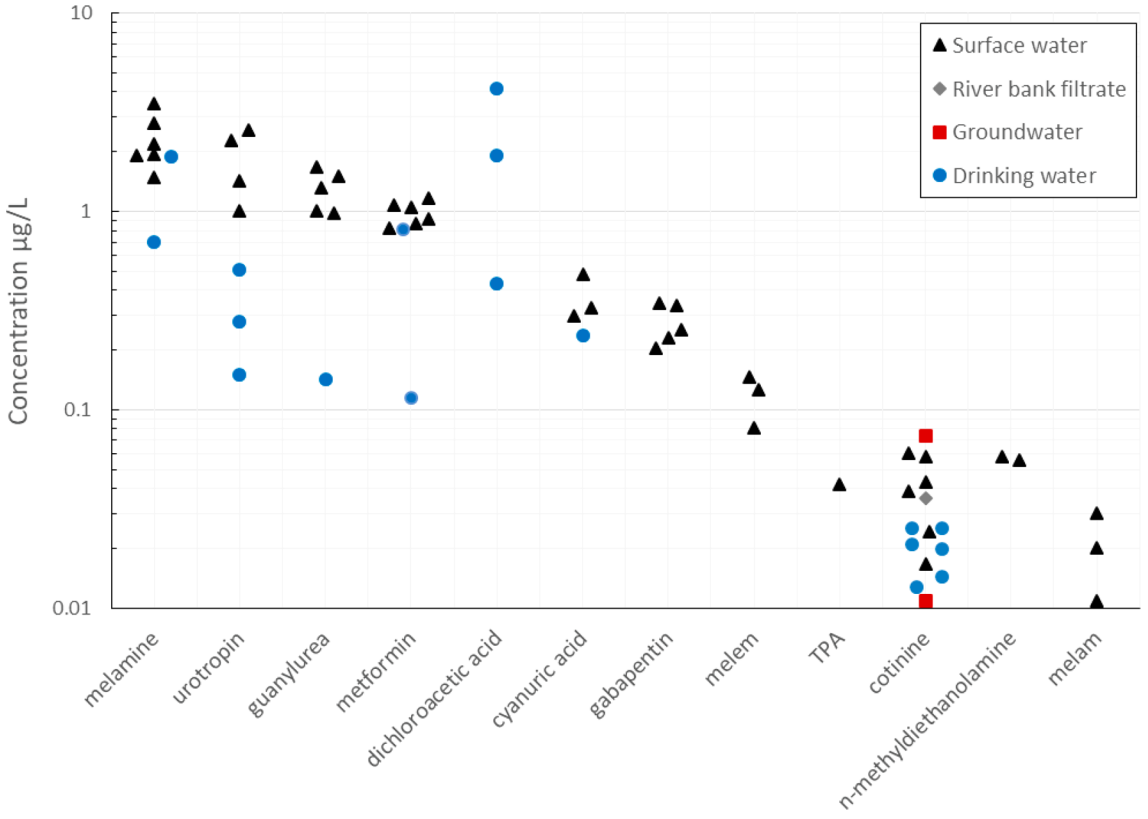

Figure 1. Concentrations of polar contaminants found with target HILIC-MS analysis in surface waters (SW; n = 7), river bank filtrate (RBF; n = 2), groundwater (GW; n = 3), and drinking water (DW; n = 12). For LODs and LOQs, see Table S1.

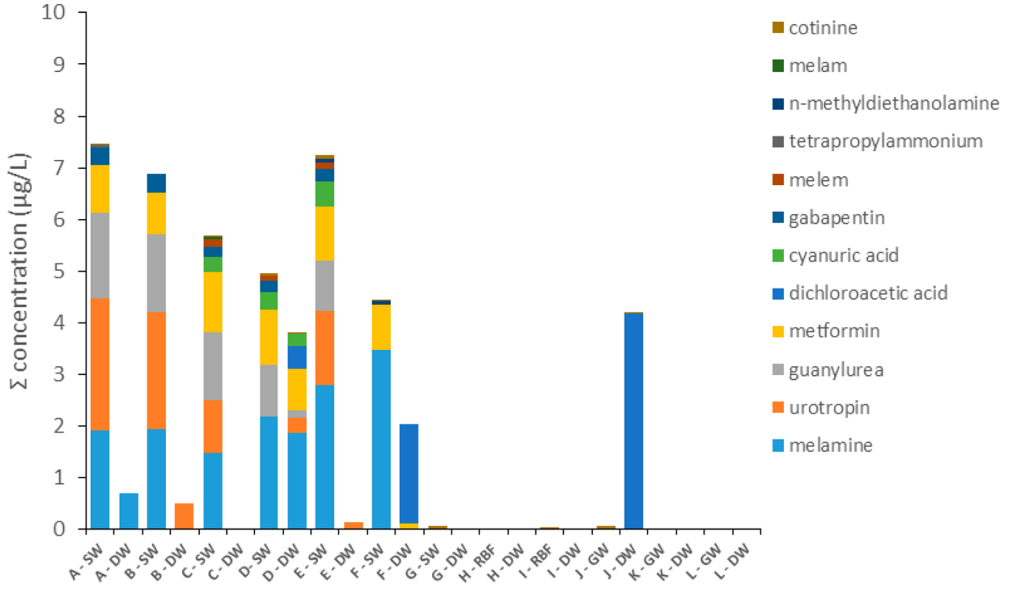

Figure 2. Summed concentrations of the polar contaminants detected with target HILIC-MS analysis in surface water (SW), river bank filtrate (RBF), and groundwater (GW) and the corresponding produced drinking water (DW), grouped for each location (A–L).

HILIC column. Other sample treatment methods, like freeze-drying,[8] two-stage SPE procedures,[7] and multilayer SPE,[31] have been described to concentrate PMOCs and are also worth exploring.

For compounds that are ionized in the positive ionization mode, retention times (see Table S1) are distributed evenly throughout the LC gradient, i.e., ranging from 2.10 to 11.3 min. The retention for compounds measured in the negative ionization mode, e.g., chemicals with an acidic moiety, is less pronounced on this HILIC column, as they all elute very early, i.e., between 1.69 and 2.10 min. The high resolution of the mass spectrometer makes it possible to distinguish these compounds within this tight time window, although this window is far from ideal for nontarget screening purposes.

Five compounds were analyzed in negative ionization mode (5-fluorouracil, cyanuric acid, dichloroacetic acid, naphthalene-

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ACS EST Water 2021, 1, 928–937

Table 1. Confirmation of the Identity of Highly Polar Compounds Using Reference Standards

chemical	CAS Registry No.	frequency of detection (of 24 samples)	Schymanski level of ID[21]	comment
N,*N*-diphenylguanidine	102-06-7	11	1	
metoprolol	51384-51-1	6	1	
(−)-nicotine	54-11-5	6	1	
guanine	73-40-5	5	1	
choline	62-49-7	4	1	
tramadol	27203-92-5	2	1	
triisopropanolamine	122-20-3	2	1	
phenazone	60-80-0	2	1	
1,3-di-*o*-tolylguanidine	97-39-2	2	2/3	possibly a structural isomer because of the same MS^2 spectra but a different RT
O-desmethylvenlafaxine	93413-62-8	1	1	
triethanolamine	102-71-6	1	1	
2,2,6,6-tetramethyl-4-piperidinol	2403-88-5	1	1	

1,5-disulfonic acid, and sotalol-d_7). During method development, more compounds in the negative mode such as ethyl sulfate, triflic acid, tryptophan, phenylalanine, tyrosine, ammelide, maleic hydrazide, and niacin were tested. Ethyl sulfate and triflic acid were removed from the method, due to poor retention on this HILIC column. For the other compounds, the retention was satisfactory; however, these compounds were not sufficiently relevant to be included in the method (amino acids), or the sensitivity was better in the positive mode.

The method performance of the whole analytical method was determined in drinking and surface water. The validation results, shown in Table S1, are satisfactory. The LOQs of the 32 PMOCs range from 0.006 to 0.73 μg/L with an average of 0.14 μg/L for drinking water. For surface water, the values are slightly higher; i.e., the LOQs vary from 0.005 to 1.3 μg/L with an average of 0.23 μg/L. The RSD for all compounds, except for maleic hydrazide in drinking water, is <20%. The recoveries are on average 98% and 89% for drinking and surface water, respectively. Two compounds (ammelide and maleic hydrazide) in drinking water and six in surface water (acephate, ammelide, gemcitabine, maleic hydrazide, naphthalene-1,5-disulfonic acid, and urotropin) fall outside the recovery range of 75−125%, which is a generally accepted range for recovery. While in particular the results for maleic hydrazide and gemcitabine indicate that further analytical optimization for both compounds is required (all other compounds fall within the range of 50−150%), the method developed in this study can be used to identify the presence of these compounds in water.

Screening Study: Target Analysis. In the 24 samples collected from drinking water sources and their corresponding drinking water, 12 of the 32 target compounds were detected (Figure 1). The seven surface water samples appeared to contain the largest number of compounds and the highest concentrations. Melamine, urotropin, and cyanuric acid as well as the pharmaceutical metformin and its transformation product guanylurea were detected at concentrations exceeding 1 μg/L in surface waters. In the sample of river bank filtrate and in the four groundwater samples, only cotinine (0.01 and 0.07 μg/L), a metabolite of nicotine, was detected. In 10 of the 12 drinking waters sampled, seven polar compounds were detected, two of which were detected at concentrations of >1 μg/L, namely, melamine and dichloroacetic acid (Figure 1).

In general, concentrations of the PMOCs decreased as a result of drinking water treatment (Figure 2).

Dichloroacetic acid, melamine, metformin, urotropin, cyanuric acid, guanylurea, and cotinine were detected in drinking water, at concentrations between 0.01 μg/L for cotinine and 4.2 μg/L for dichloroacetic acid. One compound, i.e., dichloroacetic acid, appears to be introduced during drinking water treatment and was detected at concentrations of 0.4−4.2 μg/L in drinking water from stations D, F, and J. This byproduct is formed during disinfection[32,33] by chlorination used at the three production locations to prevent fouling in pipelines used for the transport of surface water to the treatment station (location D) or at the drinking water distribution system (locations F and J). Chlorination is not used for the disinfection of water in the production process of tapwater in The Netherlands. The metabolite of nicotine, cotinine, was detected in most drinking water samples (locations C, D, and I−L) at concentrations of 0.01−0.03 μg/L. Cotinine is frequently reported in wastewaters, and removal from source waters appears to be incomplete.[34] In a nationwide study in the United States, median levels of cotinine in source waters and drinking water from drinking water plants were 15 and 10 ng/L, respectively.[35] Metformin and its metabolite, guanylurea, are frequently reported in source waters.[8] Urotropin has only scarcely been reported in source waters and drinking water.[28]

In the study presented here, cyanuric acid was detected in one drinking water sample at a concentration of 0.24 μg/L (location D). The drinking water sample from location D contained the highest number of PMOCs ($n = 7$), compared to the other drinking water samples ($n \leq 2$). At location D, drinking water is produced from surface water without employing a natural barrier by soil passage. Soil passage may enhance treatment efficiency.

Melamine, melem, melam, and cyanuric acid belong to the group of triazines, chemicals characterized by one or multiple benzene rings, at which three carbon atoms are displaced by nitrogen atoms. Melem is a condensation product and melam a reaction product of melamine. Cyanuric acid is formed as an impurity during melamine production but can also result from disinfection during water treatment.[36] Concentrations in drinking water of melamine, melem, melam, and cyanuric acid observed in the study presented here are significantly correlated [$p \leq 0.05$, Pearson correlation test (see Table S2)]. It must be noted that for this calculation values of 0.5 × LOD

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ACS EST Water 2021, 1, 928−937

Table 2. Toxicological Risk Estimation of PMOCs Observed in This Study for Which a (provisional) Drinking Water Guideline Value Is Available

chemical (CAS Registry No.)	(p)GLV[a] (μg/L)	genotoxic potential	benchmark quotient (BQ)	source of (p)GLV[c]	reliability of (p)GLV	explanation of (p)GLV
melamine (108-78-1)	5	no	≤0.38	RIVM (2016)[d]	moderate	A pGLV of 50 μg/L was derived by RIVM based on a BMDL10 of 16 mg (kg of bw)$^{-1}$ day^{-1} for bladder stones in a 13-week study in rats and an uncertainty factor of 300, which was subsequently decreased by a factor of 10 because of the uncertainty in the synergistic effects of structural analogues.
melam (3576-88-3)	2330	no	≤0.00001[b]	ECHA[e]	low	pGLV based on a NOAEL of 1000 mg (kg of bw)$^{-1}$ day^{-1} in a 90-week subchronic and reproductive toxicity study in rats reported in the REACH registration dossier and an uncertainty factor of 300. An additional uncertainty factor of 10 was applied for potential synergistic effects of structural analogues.
cyanuric acid (108-80-5)	40000	no	≤0.00001	WHO (2011)[f]	high	WHO GLV based on a NOEL of 154 mg (kg of bw)$^{-1}$ day^{-1} for heart and urinary tract lesions in a 2-year rat study and an uncertainty factor of 100.
dichloroacetic acid (79-43-6)	50	yes[k]	≤0.08	WHO (2011)[f]	moderate	WHO pGLV based on an extra lifetime cancer risk level of 10^{-5} and practical achievability.
	4		≤1.05		high	WHO pGLV adjusted to an extra lifetime cancer risk level of 10^{-6} (Dutch standard).
urotropin (100-97-0)	1050	equivocal	≤0.0005	EFSA (2014)[g]	low	pGLV based on an ADI of 0.15 mg (kg of bw)$^{-1}$ day^{-1} derived from a NOAEL of 15 mg (kg of bw)$^{-1}$ day^{-1} in dogs and an uncertainty factor of 100. EFSA (2014) considers this study to be of insufficient quality but did not identify suitable alternatives.
metformin (657-24-6)	392	no	≤0.002	RIVM (2014)[h]	moderate	pGLV based on a provisional ADI of 56 μg (kg of bw)$^{-1}$ day^{-1} derived by RIVM (2014) from the smallest therapeutic dose of 390 mg/day, an uncertainty factor of 100, and a bw of 70 kg. RIVM concludes that no data on reproductive toxicity are publicly available.
guanylurea (141-83-3)	39.2	equivocal	≤0.004	RIVM (2014)[h]	low	pGLV based on pGLV of parent substance metformin derived by RIVM (2014) and an additional uncertainty factor of 10 due to insufficient (geno)toxicity information.
gabapentin (60142-96-3)	1800	no	≤0.0002[b]	WHO (2016)[i]	moderate	pGLV based on a provisional ADI of 275 μg (kg of bw)$^{-1}$ day^{-1} derived from the WHO defined daily dose of 1.8 g, and an uncertainty factor of 100.
N,*N*-diphenylguanidine (102-06-7)	2.5		≤0.012	Ministry of Infrastructure and Water Management (2011)[j]	low	Maximal tolerable concentration (MTC) in (hot) tap water according to Dutch legislation. The derivation of the MTC value is not reported.
	397	equivocal	≤0.00007	ECHA[e]	low	pGLV based on a NOAEL of 17 mg (kg of bw)$^{-1}$ day^{-1} in a 90 day toxicity study in rats reported in the REACH registration dossier, a standard uncertainty factor of 100, and a factor 3 due to the lack of a chronic toxicity study. Insufficient information about genotoxicity is available.

[a](p)GLV is the (provisional) drinking water guideline value. [b]BQ was based on the highest concentration detected in surface water due to the lack of a drinking water concentration. [c]Only for cyanuric acid, dichloroacetic acid, and *N*,*N*-diphenylguanidine was a drinking water guideline value published by acknowledged (inter)national authorities, and a pGLV has been published for melamine. For all other substances, a pGLV was derived from toxicity data provided in the source of the pGLV reference. [d]Risicobeoordeling en afleiding voorlopige richtwaarde voor melamine in drinkwater. RIVM advies aan ILT (09-08-2016); National Institute for Public Health and the Environment: Bilthoven, The Netherlands, 2016. [e]ECHA Information on Chemicals. https://echa.europa.eu/home (accessed 2017-12-15). [f]*WHO Guidelines for Drinking-water Quality*, 4th ed.; World Health Organization: Geneva, 2011. [g]Scientific Opinion on the re-evaluation of hexamethylene tetramine (E 239) as a food additive. European Food Safety Authority. *EFSA J.* **2014**, *12* (6), 3696. [h]Environmental risk limits for pharmaceuticals. Derivation of WFD water quality standards for carbamazepine, metoprolol, metformin and amidotrizoic acid. RIVM Letter Report 270006002/2014. C.T.A. Moermond; National Institute for Public Health and the Environment: Bilthoven, The Netherlands, 2014. [i]WHO Collaborating Centre for Drug Statistics. 2016. https://www.whocc.no/atc_ddd_index/?code=N03AX12&showdescription=yes (accessed 2017-12-15). [j]Ministerial Regulation materials and chemicals drinking water- and warm tap water supply. BJZ2011048144; Ministry of Infrastructure and Water Management: The Hague, The Netherlands, 2011. [k]https://www.who.int/water_sanitation_health/dwq/chemicals/dichloroaceticacid0505.pdf.

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ACS EST Water 2021, 1, 928−937

or 0.5 × LOQ were used when concentrations below the LOD or between te LOD and LOQ, respectively, were observed. Measurements below the LOD are also representative of the (non-) occurrence of these compounds and were therefore included in this calculation. Melamine and the derivatives ammeline, ammelide, and cyanuric acid have been reported in precipitation, surface waters, and tapwater in New York State[37] with 2−5-fold higher concentrations in precipitation than in surface water, and concentrations in surface waters (~0.1 μg/L) similar to those reported in the study presented here.

Screening Study: Nontarget Screening. Next, the HRMS raw data were processed in a nontarget screening workflow (see Figure S2) using Compound Discoverer, to determine if, in addition to the 32 target compounds, other highly polar compounds could be detected in the samples. In total, 145 features were detected, i.e., compounds with a unique combination of an accurate mass and a retention time. The identity of 11 features could be confirmed using reference standards (see Table S3 and Figures S3−S14). Table 1 provides confirmation levels of the identity of PMOCs using reference standards. The following compounds were identified accordingly using Compound Discoverer: metoprolol, (−)-nicotine, guanine, choline, tramadol, triisopropanolamine, phenazone, *O*-desmethylvenlafaxine, triethanolamine, 2,2,6,6-tetramethyl-4-piperidinol, and 1,3-di-*o*-tolylguanidine (*N*,*N*-diphenylguanidine).

These results show that the simultaneous method developed in this study can also be used for an improved screening and structure elucidation of unknown, nonlisted, polar compounds. Adding more internal standards to improve our ability to cope with matrix effects would further strengthen the method, although finding suitable internal standards for HILIC is challenging.

Evaluation of the Potential Human Health Risk. The concentrations of 12 PMOCs detected in drinking water and one additional compound identified in the nontarget screening, namely *N*,*N*-diphenylguanidine, were compared with (provisional) drinking water guideline values to assess whether measured concentrations may pose a concern. *N*,*N*-Diphenylguanidine was included because it has been found to be widespread in environmental samples in both this study and others.[13,38]

Only for cyanuric acid, dichloroacetic acid, and *N*,*N*-diphenylguanidine was a drinking water guideline value published by acknowledged (inter)national authorities, and a pGLV has been published for melamine. For five other substances, pGLVs were derived from toxicity data with varying degrees of reliability. A BQ was calculated for these nine substances. The results are summarized in Table 2. A BQ of ≥1, which indicates that a health risk cannot be excluded upon lifetime exposure, was calculated for dichloroacetic acid in a single drinking water sample. The highest concentration observed of melamine resulted in a BQ of >0.1, suggesting that the presence of this chemical in drinking water should be further studied. The seven other chemicals did not occur at concentrations that individually pose an appreciable human health risk based on measured concentrations.

Concentrations of the four remaining substances (for which no toxicity data were available to derive a pGLV) were compared to the TTC-based drinking water target levels. Table 3 shows that the highest detected concentrations of melem and tetrapropylammonium in surface water exceed these target levels. A potential human health risk cannot be excluded when

Table 3. Toxicological Risk Estimation of Four PMOCs Identified in This Study, for Which a (provisional) Drinking Water Guideline Value Is Lacking

chemical (CAS Registry No.)	genotoxic potential	concentration > TTC-based drinking water target level?	comments
melem (1502-47-2)	unknown; prediction: negative	yes[a]	Concentrations detected in surface water are <1 μg/L, which may be sufficiently protective for nongenotoxic chemicals in drinking water according to the evaluation of Baken et al.[24,b]
cotinine (486-56-6)	unknown; prediction: negative	no	For parent substance nicotine, a pGLV of 5.6 μg/L can be derived from an ADI of 0.0008 mg (kg of bw)$^{-1}$ day^{-1} (EFSA, 2011).[9,c] This pGLV is not exceeded by the maximum concentration of cotinine in drinking water. If the toxicity of cotinine would be comparable to that of nicotine, cotinine concentrations in drinking water would not present a health risk.
N-methyldiethanolamine (105-59-9)	negative; prediction: negative	no[a]	
tetrapropylammonium (multiple CAS Registry Nos.)	unknown; prediction: negative	yes[a]	Concentrations detected in surface water are <1 μg/L, which may be sufficiently protective for nongenotoxic chemicals in drinking water according to the evaluation of Baken et al.[24,b]

[a]The highest concentration detected in surface water was used due to the lack of an available drinking water concentration. [b]Baken, K. A.; Sjerps, R. M. A.; Schriks, M.; van Wezel, A. P. Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern. *Environ. Int.* **2018**, *118*, 293−303. [c]EFSA. Setting of temporary MRLs for nicotine in tea, herbal infusions, spices, rose hips and fresh herbs. *EFSA J.* **2011**, *9* (3), 2098.

https://dx.doi.org/10.1021/acsestwater.0c00237
ACS EST Water 2021, 1, 928−937

similar concentrations would occur in drinking water; however, these substances were not detected above the reporting limit in the drinking water samples. In addition, concentrations of melem and tetrapropylammonium were <1 μg/L, which may already be sufficiently protective for nongenotoxic chemicals in drinking water according to the evaluation of Baken et al.[24]

Most of the (p)GLVs used in this evaluation need to be regarded as indicative, because they are based on either limited or incomplete toxicity data (melam, *N*,*N*-diphenylguanidine, and urotropin), therapeutic doses (metformin and gabapentin), or toxicity data for related chemicals (guanylurea). In addition, a default allocation factor of 20% of the total exposure was applied to derive pGLVs. The actual contribution of drinking water to the exposure may differ for each substance. In particular for highly polar compounds, the relative contribution of the drinking water exposure route may be higher, which would result in a higher pGLV.

The structurally related chemicals melamine, melem, melam, and cyanuric acid were simultaneously detected in several surface water samples. For melamine and melam, an additional uncertainty factor of 10 has been used in the derivation of the pGLV because of potential synergistic effects.[39] When an additional uncertainty factor would be applied for cyanuric acid, as well, a pGLV of 4 mg/L would be calculated, which is close to the guideline value of 0.28 μM (3.6 mg/L) used by the Dutch Ministry of Infrastructure and Waterworks for the evaluation of industrial discharges into surface waters.[40] More insight into mixture effects of these structural analogues is required to establish safe combined exposure levels. In a recent preliminary hazard assessment, it was concluded that drinking water is a minor contributor to melamine and cyanuric acid exposure in humans and that ecological risks were minimal.[34]

For part of the PMOCs observed, no pGLV could be derived due to the lack of toxicity data. TTC-based drinking water target levels were used instead to assess whether health effects are expected to be negligible. It should be noted that such target levels are intended for use as an early warning tool and for prioritization of chemicals with unknown toxicity in drinking water and its resources and do not represent target levels for all emerging contaminants.[22] Further substance-specific toxicological evaluation of these chemicals is necessary to assess their potential genotoxicity and to derive a (p)GLV and BQ value.

Outlook. On the basis of the results of this study, monitoring of concentrations of dichloroacetic acid, melamine, melem, and tetrapropylammonium in drinking water and sources is recommended. Dichloroacetic acid was present at a concentration for which health risks cannot be excluded upon lifelong exposure in one drinking water sample. For most chemicals, reliable health-based drinking water guideline values could not be derived. More information about the toxicity of and exposure to highly polar chemicals is required to obtain further insight into the toxicological relevance of the presence of these substances in drinking water.

The structurally related chemicals melamine, melem, melam, and cyanuric acid were simultaneously detected in several surface water samples. Although analytical methods have been published for the determination of some of these triazines, e.g., in food[41] and surface waters,[42] for several compounds, such as melam and melem, to the best of our knowledge this is the first time a method has been developed for their determination in environmental and drinking waters. More insight into their mixture effects is required to establish safe combined exposure levels.

The goal of the screening study presented here was to trace both target and newly emerging polar substances in the water production chain. The HILIC method developed here is complementary to existing C18 chromatography-based screening methods, and some compounds can be analyzed by both chromatographic methods. It is very challenging to develop a single method that covers the whole chemical space of highly polar compounds, from strongly acidic to neutral and strongly basic compounds, and also including amphoteric and ionic compounds (e.g., quaternary amines). No one has thus far succeeded. For compounds measured in the negative ionization mode, e.g., strong acids like cyanuric acid, naphthalene-1,5-disulfonic acid, and triflic acid, the HILIC nontarget screening method is not optimal because those compounds show limited retention on the column used.[43] For those compounds, exploring other separation options, for example, other types of HILIC columns, different separation conditions, including SFC, mixed-mode chromatography columns, and WAX columns (weak anion exchange), is therefore strongly advised. Exploring more possibilities for sample pretreatment/concentration for highly polar compounds is also recommended. It can be envisioned that at least two methods are needed to cover the whole space of highly polar organic chemicals. These methods can then be applied to screen for novel highly polar chemicals in relevant environmental samples and to study the fate of these compounds during drinking water treatment.

CONCLUSION

A combined target/nontarget screening method was developed for analysis of highly polar chemicals. With this method, 32 highly polar chemicals (including melem and melam) can be quantitatively measured in surface water and drinking water, while at the same time, the high-resolution mass spectrometric data obtained could be screened for unknown compounds. Melem and melam, which are a condensation product and a reaction product, respectively, of melamine and for which hitherto no analytical methods were available, were observed in several samples. The method can be used for a better (drinking) water quality assessment. To that end, an effort was made to derive (provisional) drinking water guideline values. For most chemicals, reliable drinking water guideline values could not be derived due to the limited availability of toxicity data. The screening study covering 12 drinking water sites in The Netherlands and Flanders showed that 12 of the 32 compounds were encountered in samples of surface water, groundwater, and drinking water at levels between 0.01 and 4.2 μg/L. In one drinking water sample, the concentration of dichloroacetic acid exceeded the provisional drinking water guideline value, indicating that health effects cannot be excluded upon lifetime exposure.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsestwater.0c00237.

Method performance and compound characteristics, statistical data on the correlation between concentration measurements, the workflow used in nontarget mass

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spectrometry screening, and chromatograms and mass spectra (PDF)

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Notes

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