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Study on the Occurrence of Artificial Sweeteners, Parabens, and Other Emerging Contaminants in Hospital Wastewater Using LC-QToF-MS Target Screening Approach

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Abstract: The presence of 220 emerging contaminants belonging to different classes (artificial sweeteners, personal care products, coffee and tobacco-related compounds, and industrial chemicals) was investigated in hospital wastewater for the first time. Twenty samples were collected within two sampling periods from two points of a Greek General Hospital. Target compounds were analyzed using a solid-phase extraction protocol followed by UHPLC-ESI-QToF-MS analysis. Analytical results showed that 23 micropollutants were detected at least once in hospital wastewater samples in Period 1, while 27 compounds were detected at least once in Period 2. The coffee and tobacco-related compounds were the most frequently detected substances, followed by artificial sweeteners, parabens, and industrial chemicals. The highest mean concentrations were recorded for the artificial sweeteners cyclamic acid (377 μg/L) and saccharine (295 μg/L), followed by caffeine (193 μg/L), nicotine (162 μg/L), and the industrial chemical lauryl diethanolamide (153 μg/L). The group of artificial sweeteners contributed up to 55.1% (Point A/Period 1) to the total concentration of studied chemicals. The detection of high concentrations of artificial sweeteners in hospital effluents reveals that hospitals should be considered as important point-sources of these contaminants.

Keywords: monitoring; hospital wastewater; emerging contaminants; parabens; artificial sweeteners; personal care products; coffee and tobacco-related compounds; industrial chemicals; target analysis; LC-QToF-MS

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1. Introduction

The management of hospital wastewater (HWW) is a matter of important concern both due to the produced volume as well as their characteristics. According to Eurostat [1], in 2019, there were 2.38 × 10^6 hospital beds in EU countries, while the HWW production rate ranged between 400 and 1000 L per hospital bed and day [2]. HWW is characterized by concentrations of major pollutants (COD, BOD, TSS, TN, TP) that are close to the concentrations found in municipal wastewater. However, additional to these pollutants, HWW may contain hazardous materials such as various groups of pharmaceuticals, radioactive substances, different types of pathogens, antibiotic-resistant bacteria, and antibiotic resistance genes [3–5].

Regarding the occurrence of organic micropollutants in HWW, so far, most published papers have focused on the analysis and presence of pharmaceuticals highlighting hospitals as important point-sources of these contaminants [6–9]. In addition to pharmaceuticals,

some other groups of synthetic organic chemicals can also be found in HWW. Artificial sweeteners are used as excipients in drug manufacturing to mask the taste of medications. In a previous study related to the excipients contained in medications marketed in Brazil, it was found that saccharine and sorbitol were contained in 38.3% and 36.9% of the studied pharmaceuticals, respectively, while sodium cyclamate and aspartame were found in others [10]. In the same study, methylparaben and propylparaben were also found in 33 and 26 out of 73 pharmaceutical formulations. It is worth mentioning that parabens are used during pharmaceutical production as antimicrobial preservatives. In another study conducted in Italy for the excipients contained in oral medicinal products used for gastrointestinal indications, the use of sweeteners such as saccharine, aspartame, sorbitol, mannitol as well as parabens was revealed [11], while a recent study conducted in Japan reported that parabens were the most commonly used potentially harmful excipients in enteral, parenteral, and topical formulations [12]. Despite the extended use of the aforementioned compounds in drug manufacturing, to the best of our knowledge, there are no studies investigating their concentration levels in HWW. Taking into account that parabens act as weak endocrine disrupter chemicals [13] while concern has been raised for the potential ecotoxicity of artificial sweeteners [14], the analysis of these groups of contaminants in HWW could allow for better identification of their sources to the environment.

Scarce information also exists in the literature for the occurrence of other organic industrial chemicals as well as tobacco-related compounds in HWW. For instance, triethyl citrate is used in the pharmaceutical industry for coating [15], while benzododecinium is used as antiseptic and disinfectant compound [16]. As far as we know, no published data are available for their occurrence in HWW. Benzotriazoles and benzothiazoles are widely used in corrosion-inhibiting products and dishwashing detergents [17]. In a recent study, Gönder et al. [18] determined mean concentration of benzotriazole equal to 24.8 μg/L in HWW originated from a Turkish hospital which is much higher than the few ppbs that are commonly detected in municipal wastewater [19]. Concerning tobacco-related compounds, few data are also available for the occurrence of nicotine and its metabolites in HWW. In a recent study, Ekpeghere et al. [20] reported the occurrence of nicotine or its metabolites in all samples collected from three Korean hospitals at concentrations that ranged up to some ppbs.

Based on the above, the main objective of this article was to study the occurrence of artificial sweeteners, parabens, personal care products, coffee and tobacco-related compounds, and other industrial chemicals in HWW. For this reason, 20 samples were collected in total during two sampling periods from two different points of a Greek General Hospital, analyzed by LC-QToF-MS, and screened for the presence of 220 emerging contaminants. The differences in the frequency of detection and the concentration levels of the 27 compounds during different sampling periods and sampling points were discussed. The observed concentrations were compared to those determined in municipal wastewater to show whether hospitals act as hot spots for these compounds.

2. Materials and Methods

2.1. Standards and Chemicals

The analytical standards of the quantified 27 compounds were of >99% purity and were supplied by Sigma-Aldrich Company (Taufkirchen, Germany). The main chemical-physical characteristics of the target analytes, including their molecular formulas, molecular weight, pK_a, $logK_{ow}$, and CAS numbers are provided in Table S1. The list was comprised of 4 artificial sweeteners, 6 personal care products, 5 coffee and tobacco-related compounds, and 12 compounds belonging to industrial chemicals. Individual stocks of standard solutions (1 mg/mL) were prepared in methanol and stored in the dark at −18 °C. Then, working standard solutions of all analytes were prepared, stored at 4 °C, and renewed monthly.

Acetonitrile (ACN), methanol (MeOH), and isopropanol were LC-MS grade and supplied from Merck (Darmstadt, Germany). Ammonium acetate (LC-MS grade), ammonium formate, and formic acid (purity 99%) were supplied by Sigma-Aldrich (Germany), while

ammonia solution (25%, for analysis) was obtained from CHEM-LAB NV (Zedelgem, Belgium). RC syringe filters (4 mm diameter, 0.2 μm pore size), empty solid phase extraction (SPE) propylene tubes (6 mL), and frits (20 μm, 6 mL) used, were supplied by Phenomenex (Torrance, CA, USA). The sorbent materials Sepra ZT (Strata-X), Sepra ZT-WCX (Strata-X-CW), and ZT-WAX (Strata-X-AW) were purchased by Phenomenex (USA), while Isolute ENV+ was supplied from Biotage (Hengoed, UK). Ultrapure water was taken from a Milli-Q system (Millipore Direct-Q UV, Bedford, MA, USA).

2.2. Study Site and Sample Collection

HWW samples were collected from a General Hospital located on Creta Island (Greece). It has a capacity of 440 beds and serves more than 40,000 hospitalized patients yearly, providing a full spectrum of health services. The following departments are found in the studied hospital: Internal Medicine, Cardiology, Intensive Care Unit, Hematology, Endocrinology, Family Planning Unit, Oncology, Gastroenterology, Neurology, Ophthalmology, Pediatric Clinic, Outpatient Clinic, Radiology, Physiotherapy, and Sterilization.

Composite 24-h raw wastewater samples were taken from two discharge points (Points A and B) in November 2020 (Period 1) and February 2021 (Period 2) with the aid of an automatic sampler. The mean daily HWW volume was 10 m^3/d in Point A, which serves the Internal Medicine, Hematology, and Oncology departments, and 60 m^3/d in Point B, which services the entire hospital. Each sampling campaign was carried out over a period of five consecutive days. In total, twenty (20) HWW samples were collected in pre-cleaned high-density polyethylene bottles. Samples were immediately transferred to the laboratory in portable coolers for conventional physico-chemical and emerging contaminants analysis. Table S2 summarizes the abbreviations of sampling points, the locations, and the exact dates of sampling.

2.3. Conventional Physico-Chemical Analyses

Conventional physico-chemical parameters such as pH, Biochemical Oxygen Demand (BOD), Chemical Oxygen Demand (COD), Total Suspended Solids (TSS), Total Nitrogen (TN), and Total Phosphorus (TP) were quantified following Standard Methods, as described by Arvaniti et al. [4].

2.4. Extraction and Analysis of Contaminants

The contaminants were extracted from the wastewater matrix following a validated analytical protocol, previously published by Gago-Ferrero et al. [21]. In brief, after pH adjustment to 6.5 with HCl, and cartridge equilibration with MeOH and water, 100 mL of HWW were passed through in-house cartridges packed with four sorbent materials (200 mg Oasis HLB, 150 mg Isolute ENV+, 100 mg Strata-X-AW, and 100 mg Strata-X-CV). The elution was conducted with 4 mL of MeOH/ethyl acetate (50/50, v/v) containing 2% ammonia, followed by 2 mL of MeOH/ethyl acetate (50/50, v/v) containing 1.7% formic acid. The eluent was evaporated to dryness under a stream of N_2 at 45 °C, and the final extract was reconstituted to 0.5 mL with MeOH/water (50/50, v/v) and filtered through 0.2 μm RC filter. A thorough quality assurance and quality control (QA/QC) protocol was followed during the sample preparation and instrumental analysis to assure the efficient recovery of the tested compounds, the separation efficiency of the analytes of interest, and the good operation of the HRMS system. Detailed information on the applied QA/QC steps are provided in the Supplementary Materials (Section A).

The instrumental analysis was performed using an Ultra-High Performance Liquid Chromatography (UHPLC) system (UltiMate 3000 RSLC, Thermo Fisher Scientific, Dreieich, Germany) coupled to a Quadrupole-Time of Flight Mass Spectrometer (QToF-MS) (Maxis Impact, Bruker Daltonics, Bremen, Germany). An Acclaim RSLC C_{18} column (2.1 × 100 mm, 2.2 μm) from Thermo Fisher Scientific, connected to an ACQUITY UPLC BEH C_{18} 1.7 μm, VanGuard pre-column from Waters, thermostated at 30 °C, was used for the chromatographic separation of the analytes, while electrospray ionization (ESI)

was employed in both positive and negative polarities. Full scan MS data were recorded (m/z range: 50–1000 Da), whereas both data-dependent and data-independent MS/MS acquisition modes were applied for every sample. Detailed information on the gradient elution program and the applied ESI and MS parameters have been reported in a previous study [22], and summarized in the Supplementary Materials (Table S3).

2.5. Data Treatment and Statistical Analysis

The frequency of appearance of each contaminant was calculated as the ratio of the number of samples with a concentration higher than the detection limit for a given contaminant over the total number of samples.

Generally, for undetected compounds and compounds below LOQ, several strategies are commonly applied to calculate the mean concentrations of micropollutants in a group of samples [23,24]. In this study, if the minimum value of the target compounds was below the method's LOQ, it was given the corresponding LOQ/2 value, according to Directive 2009/90/EC [25]. Additionally, a zero value was considered when calculating the mean concentration for the samples in which target compounds were not detected [26,27].

Statistical analysis was conducted using the *t*-test at p-value < 0.05 to assess the statistical differences in the major pollutants' concentrations between each sampling campaign.

The acquired HRMS chromatograms were screened using a dataset of 220 artificial sweeteners, personal care products, industrial chemicals, coffee and tobacco-related compounds and their metabolites/transformation products, included in the wide-scope target database of the National and Kapodistrian University of Athens [28]. This database was built through the analysis of the respective reference standards and includes information on the precursor and fragment ions and retention time. The identification data for the detected compounds are listed in Table S4 and the respectively extracted ion chromatograms of their precursor ions are presented in Figure S1. For reporting a positive hit in the tested samples, the following thresholds should be met for the screened compounds: mass accuracy of the precursor ion < 2 mDa, retention time shift ± 0.2 min, good isotopic fitting, and detection of qualifier ions (adduct and fragment ions ± 5 mDa).

The standard addition method using also representative structurally related isotope-labeled compounds was performed for the quantification of the detected compounds, whereas method performance criteria, including limits of detection and quantification, repeatability (expressed as % relative standard deviation (RSD), % recovery, and matrix effect, are provided in Table S5.

3. Results and Discussion

3.1. Conventional Physico-Chemical Parameters

Several conventional physico-chemical parameters were monitored at each point during the two campaigns to estimate the water quality characteristics of the HWW. Their minimum, median, mean, and maximum values for all 20 HWW samples are presented in Table 1. The mean pH value was significantly higher at Point A compared to Point B ($p < 0.05$) at both sampling periods. Moreover, significantly higher concentrations of TN and TP were found in Point A compared to Point B during the second sampling campaign. Average TN and TP values were equal to 173 and 9.1 mg/L in Point A, and 89 and 6.0 mg/L in Point B, respectively. TSS, COD, and BOD concentrations were relatively comparable between the two points and no significant differences were observed. A similar range of values has been reported for BOD, COD, TSS, and TP in various studies performed on HWW [29,30].

Table 1. Conventional physico-chemical parameters measured in HWW of Point A and Point B during two different sampling campaigns.

Parameters	Period 1								Period 2							
	Point A				Point B				Point A				Point B			
	Min	Median	Mean	Max	Min	Median	Mean	Max	Min	Median	Mean	Max	Min	Median	Mean	Max
pH (Consort C932)	8.6	8.7	8.7 *	8.8	7.4	8.0	7.9 *	8.0	8.3	9.0	8.8 *	9.0	7.7	7.8	7.8 *	7.9
BOD_5 (mg/L) (AQUALITIC sensor system)	220	240	276	360	280	330	330	380	290	300	316	370	250	330	338	410
COD (mg/L) (APHA (2005) 5220—D)	677	804	770	823	656	669	760	1042	490	535	585	731	379	494	487	640
TSS (mg/L) (APHA (2005) 2540—D)	48	57	81	163	73	90	132	288	83	120	131	200	107	120	127	150
TN (mg/L) (LCK 238)	211	228	235	289	178	198	197	218	134	157	173 *	222	69	91	89 *	110
TP (mg/L) (APHA (2005) 4500-P-B, E)	8.5	10.7	10.9	13.4	9.0	10.7	10.4	11.5	6.0	8.2	9.1 *	13.2	4.8	5.6	6.0 *	7.9

Note: * statistical significant difference ($p < 0.05$).

3.2. Occurrence and Concentrations of Contaminants in Hospital Wastewater

Figure 1 summarizes the frequency of appearance (FoA) of the detected target compounds in the HWW samples at both sampling campaigns. In Period 1 (Figure 1), 23 compounds were found at least once in HWW samples. Out of 23 compounds, four were artificial sweeteners, four were personal care products, five were coffee and tobacco-related compounds, and 10 belonged to industrial chemicals. In addition, 16 compounds, including acesulfame, cyclamic acid, saccharine, methylparaben, propylparaben, caffeine, theobromine, nicotine, cotinine, hydroxycotinine, benzododecinium, lauryl diethanolamide, *N*,*N*-Dimethyldodecylamine, *N*,*N*-dimethyltetradecylamine, *N*-methyldodecylamine, and triethyl citrate were detected in all HWW samples, i.e., 100% FoA. Notably, 3 out of 16 compounds (theobromine, nicotine, cotinine, hydroxycotinine) belonging to caffeine and nicotine metabolites, were omnipresent in the tested samples (100% FoA). In Period 2 (Figure 1), all 27 target compounds were detected at least once in wastewater samples. Eighteen out of 27 compounds were detected in all samples, while the remaining 9 compounds were found in more than 40% of the collected samples. It is also important to note that transformation products (TPs)/metabolites of caffeine and nicotine were also detected in all samples of this period, whereas galaxolidone, a TP of galaxolide, was detected in more than 80% of the collected samples. This observation demonstrates the importance of monitoring TPs in conjunction to their parent compounds in wastewater. Additionally, as observed in both sampling campaigns, the most predominant compounds were from the group of coffee and tobacco-related compounds (5 out 5 with 100% FoA), followed by the group of artificial sweeteners (3 out 4 with 100% FoA). From all other categories of emerging contaminants, 2 out of 6 personal care products, methylparaben and propylparaben, were detected in all analyzed samples, while the other four were detected occasionally (ranging from not detected to 90% FoA). From industrial chemicals, 5 out of 12 compounds presented 100% FoA in both sampling campaigns (Figure 1). Notably benzophenone-3 and galaxolidone, which belong to personal care products, as well as *N*,*N*-dimethyldodecylamine-N-oxide and *N*,*N*-dimethyltetradecylamine-N-oxide, which belong to industrial chemicals were detected only in the second sampling period (Period B). Details regarding the number of detected compounds in each sampling site and period are provided in the Supplementary Materials (Figure S2).

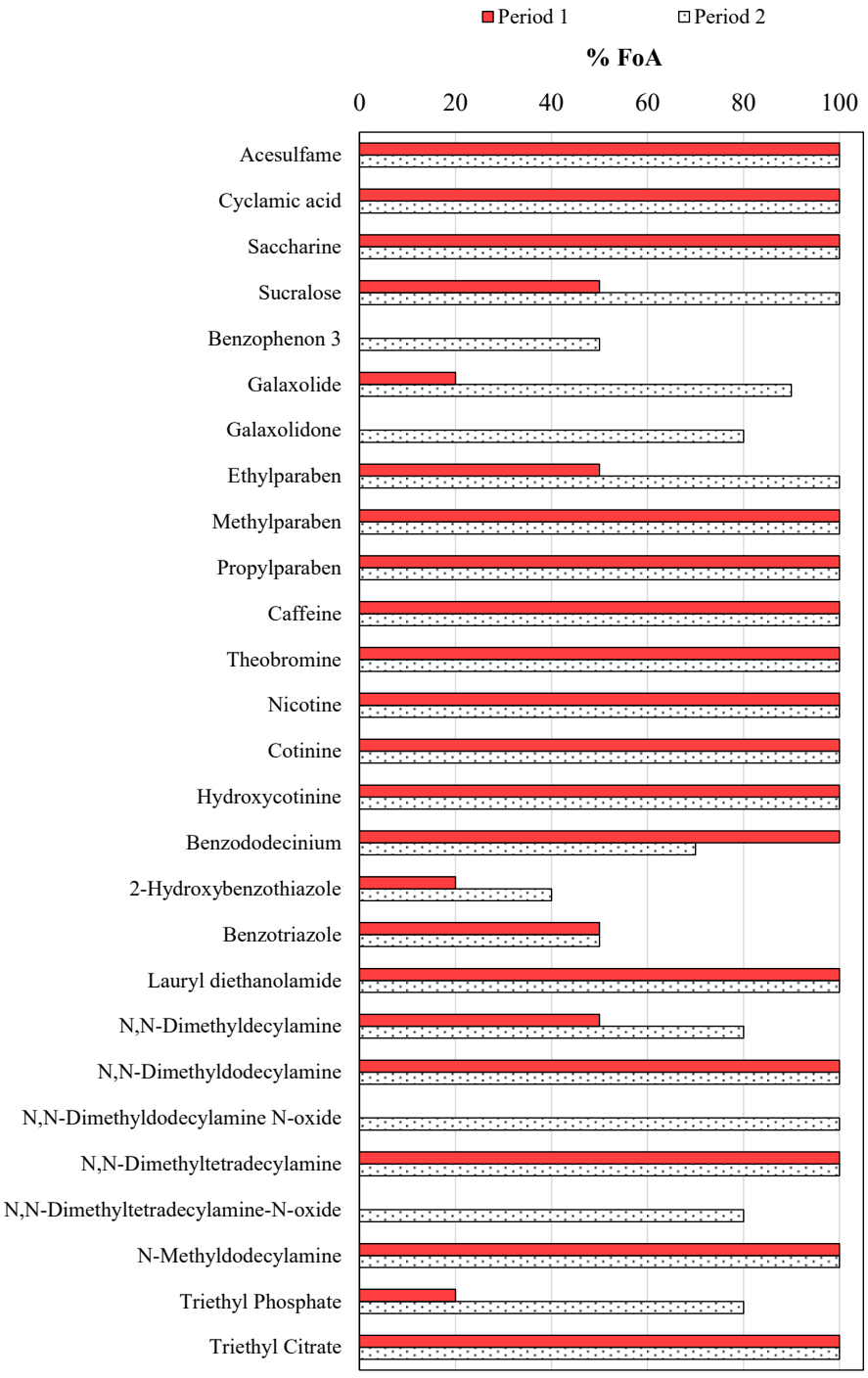

Figure 1. Frequency of appearance (FoA%) of detected emerging contaminants in HWW for Period 1 and 2.

The average concentrations of measured substances, along with the minimum and maximum values for all monitored sites and periods, are presented in Table 2.

Table 2. Minimum, maximum, and average concentrations (μg/L) of detected emerging contaminants in the HWW at both sampling sites and periods.

Compounds	Period 1						Period 2					
	Point A			Point B			Point A			Point B		
	Min	Max	Average	Min	Max	Average	Min	Max	Average	Min	Max	Average
Artificial sweeteners												
Acesulfame	108	279	201	38.7	161	115	18.3	72.2	36.7	7.69	24.1	14.9
Cyclamic acid	346	782	579	204	512	412	103	271	174	29.3	114	68.4
Saccharine	163	787	491	34.5	189	130	23.2	233	98.9	6.53	29.4	13.5
Sucralose	<LOD	24.2	9.38	<LOD	8.16	3.24	1.21	8.23	4.56	1.21	7.97	3.57
Personal care products												
Benzophenon 3	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.978	0.481	<LOD	0.142	0.0284
Galaxolide	<LOD	0.209	0.0759	<LOD	<LOD	<LOD	<LOD	0.0915	0.0540	0.0170	0.0170	0.0170
Galaxolidone	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ethylparaben	0.472	2.13	1.16	<LOD	<LOD	<LOD	0.095	1.61	0.560	0.0397	0.158	0.0986
Methylparaben	72.7	168	133	32.2	135	87.2	20.8	56.2	36.8	1.05	27.8	15.2
Propylparaben	41.6	108	76.6	17.5	70.6	43.9	11.8	21.9	16.2	4.82	12.3	7.57
Coffee and tobacco-related compounds												
Caffeine	198	433	279	130	404	213	82.4	143	108	36.0	85.1	65.7
Theobromine	33.8	108	67.2	55.1	129	81.6	10.6	33.6	21.4	9.29	14.6	11.5
Nicotine	97.9	250	144	71.2	543	179	10.4	58.2	31.1	2.32	21.9	11.2
Cotinine	10.6	14.8	12.7	8.75	17.8	11.9	0.600	4.20	2.84	0.782	4.05	2.52
Hydroxycotinine	34.3	66.3	47.8	27.3	78.7	41.8	21.2	31.7	27.0	7.34	16.3	12.7

Table 2. *Cont.*

Compounds	Period 1						Period 2					
	Point A			Point B			Point A			Point B		
	Min	Max	Average	Min	Max	Average	Min	Max	Average	Min	Max	Average
Industrial chemicals												
Benzododecinium	5.88	88.3	29.8	4.24	28.0	19.5	<LOD	17.9	8.51	<LOD	9.05	4.39
2-Hydroxybenzothiazole (2-OH-BTH)	<LOD	7.71	2.02	<LOD	<LOD	<LOD	<LOD	0.259	0.0517	<LOD	0.259	0.155
Benzotriazole (BTR)	<LOD	<LOD	<LOD	4.46	15.6	10.4	<LOD	<LOD	<LOD	0.0881	2.20	0.885
Lauryl diethanolamide (Lauryl-DEA)	0.668	444	181	15.7	364	204	1.87	18.6	9.99	5.52	9.88	8.20
N,*N*-Dimethyldecylamine (*N*,*N*-diMe-DA)	<LOD	<LOD	<LOD	0.0473	0.095	0.0735	<LOD	0.0443	0.0133	0.0111	0.37	0.153
N,*N*-Dimethyldodecylamine (*N*,*N*-diMe-DDA)	0.275	2.56	1.09	5.98	17.7	11.5	0.738	2.76	1.89	0.609	1.41	0.986
N,*N*-Dimethyldodecylamine N-oxide (*N*,*N*-diMe-DDA-N-oxide)	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.493	15.2	8.42	0.0596	3.94	1.10
N,*N*-Dimethyltetradecylamine (*N*,*N*-diMe-TDA)	12.3	176	63.0	24.0	126	94.6	1.40	7.96	5.18	0.987	4.93	2.80
N,*N*-Dimethyltetradecylamine-N-oxide (*N*,*N*-diMe-TDA-N-oxide)	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	6.65	2.70	<LOD	0.765	0.219
N-Methyldodecylamine (N-Me-DDA)	0.0907	0.652	0.315	0.655	1.86	1.35	0.100	1.01	0.541	0.0511	0.326	0.124
Triethylphosphate	<LOD	3.04	0.607	<LOD	12.7	2.54	0.0480	1.29	0.706	0.00	0.533	0.250
Triethylcitrate	1.05	5.07	2.83	0.976	3.39	2.22	0.0804	0.847	0.423	0.173	0.392	0.258

More details about the found concentrations of the emerging contaminants during different days of monitoring are reported in the Supplementary Materials (Table S6). Among all analytes, the highest concentrations were found for the artificial sweetener saccharine (787 μg/L; Point A, Period 1) and cyclamic acid (782 μg/L; Point A, Period 1), followed by the stimulant nicotine (543 μg/L; Point B; Period 1), and the industrial chemical lauryl diethanolamide (444 μg/L; Point A; Period 1). Overall, considering all sampling campaigns, the observed concentrations were higher in Point A compared to Point B and for Period 1 compared to Period 2. More specifically, the highest sum concentration was calculated for Point A and Period 1 (2322 μg/L), followed by Point B and Period 1 (1665 μg/L), Point A and Period 2 (597 μg/L), and Point B and Period 2 (247 μg/L). The contributions of each category of emerging contaminants to the total concentration are presented in Figure 2.

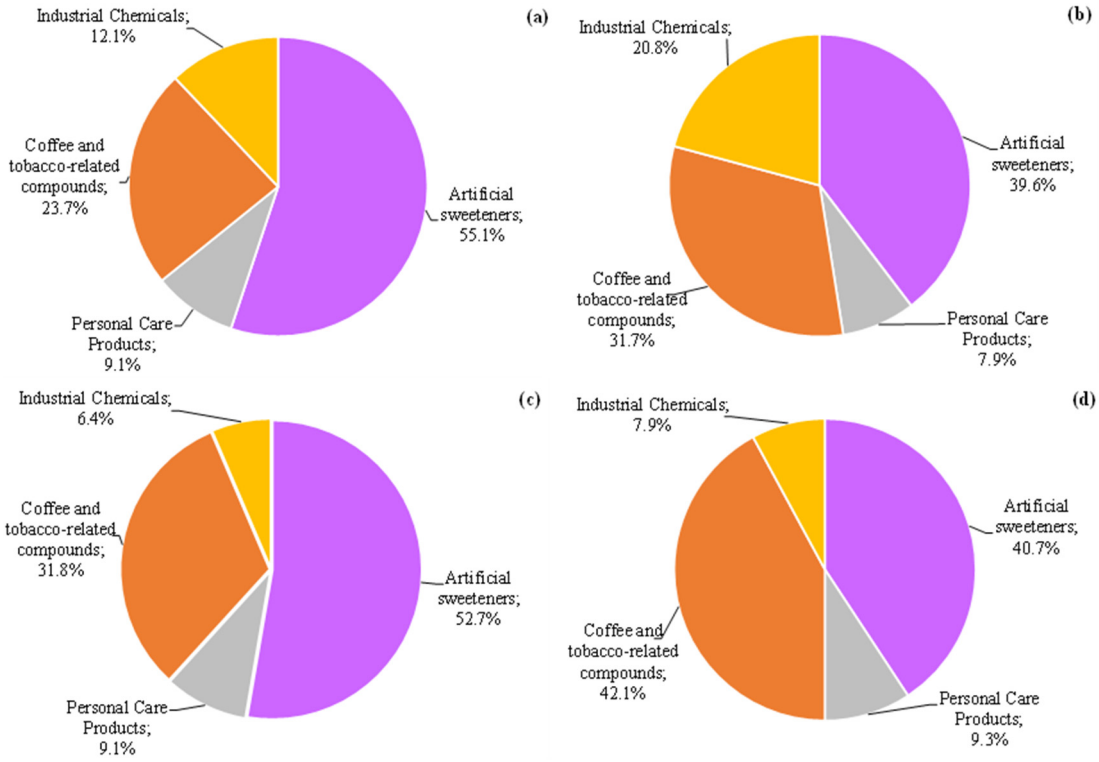

Figure 2. Contribution of each class of compounds to the total concentration of emerging contaminants detected in (**a**) Point A/Period 1, (**b**) Point B/Period 1, (**c**) Point A/Period 2, and (**d**) Point B/Period 2.

Artificial sweeteners added the most to the total concentration of emerging contaminants with percentages ranging between 39.6% (Point B/Period 1) and 55.1% (Point A/Period 1). Additionally, a high percentage of the total concentration was attributed to the presence of the group of coffee and tobacco-related compounds which ranged between 23.7% (Point A/Period 1) and 42.1% (Point B/Period 2). As regards personal care products and industrial chemicals, these compounds contributed similarly to the total amount, generally not exceeding 10%. However, in sampling Point B (Period 1), a higher contribution of the industrial chemicals (20.8%) was observed, which is attributed to the elevated concentrations of some compounds such as benzotriazole, lauryl diethanolamide, and *N*,*N*-Dimethyltetradecylamine. In Figure 3, Box and Whiskers graphs represent the concentration of target detected analytes in μg/L for Points A and B of each sampling period, where concentration levels ranged from some ng/L to a few mg/L.

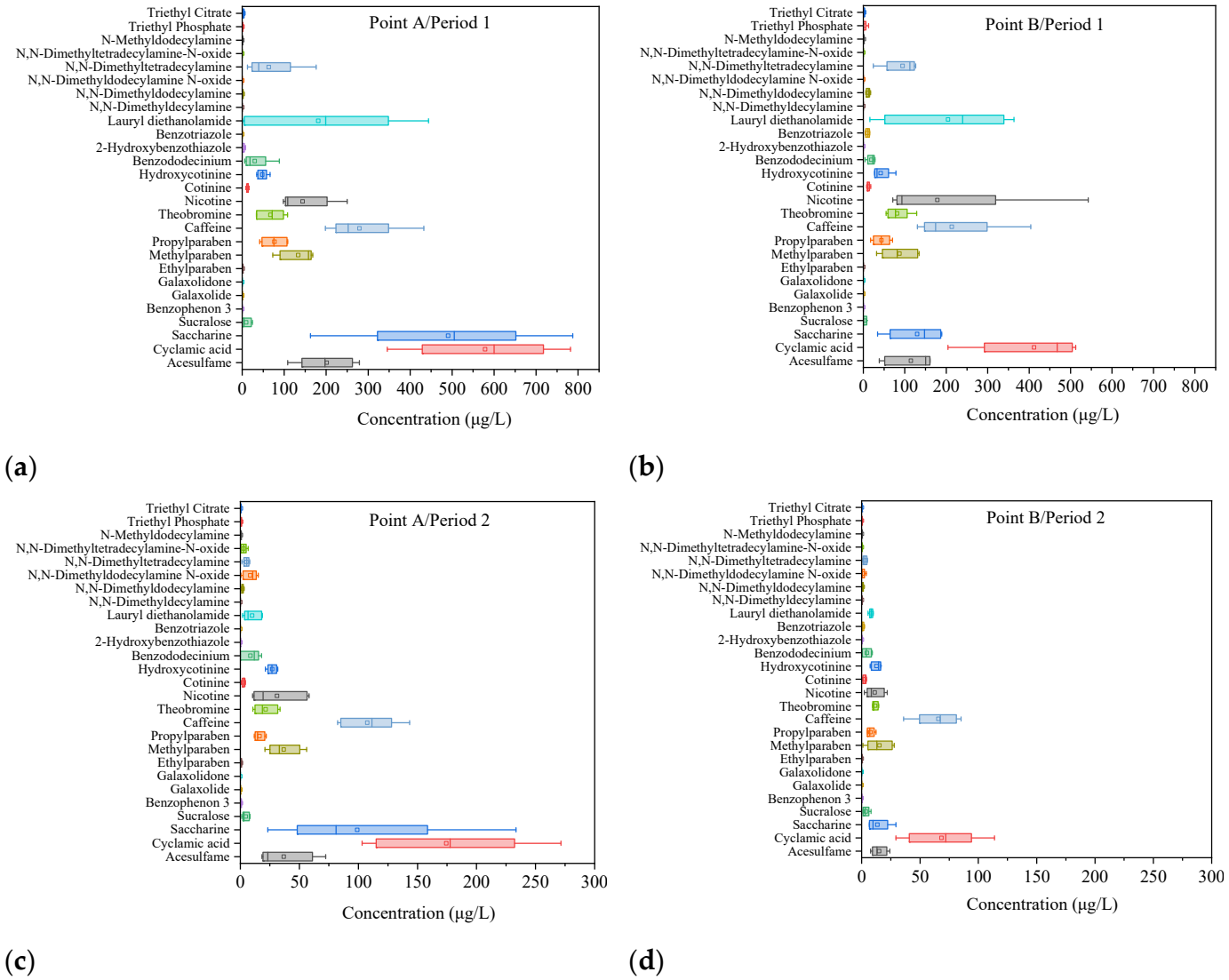

Figure 3. Box-whisker plots of the average measured concentrations for each sampling site and period. Data for Point A/Period 1 (**a**), Point B/Period 1 (**b**), Point A/Period 2 (**c**), and Point B/Period 2 (**d**) are shown. Boxes represent lower (25%) and upper quartiles (75%). The line inside the box represents the median, while square points inside the box represent the mean values, and whiskers represent 1.5× interquartile range.

The 10 most abundant compounds are depicted in Figure 4. Taking into account both sampling periods, the highest mean concentrations were recorded for cyclamic acid (377 μg/L, Point A), saccharine (295 μg/L, Point A), caffeine (193 μg/L, Point A), acesulfame (119 μg/L, Point A), lauryl diethanolamide (153 μg/L, Point B), nicotine (162 μg/L, Point B), methylparaben (85.0 μg/L, Point A), propylparaben (46.4 μg/L, Point A), caffeine metabolites, theobromine, (46.6 μg/L, Point B), and nicotine metabolite, hydroxycotinine, (37.4 μg/L, Point A).

In addition to the wide use of artificial sweeteners as excipients in medications [10,11], this is the first time that their concentrations are determined in HWW. Similarly, there is no study for lauryl diethanolamide which is used in cosmetics as foam booster and foam stabilizer. On the other hand, there is a recent article on the presence of parabens in HWW. Arfaeinia et al. [31] detected six different parabens in raw wastewater of two Persian hospitals at median concentrations that ranged up to 674 ng/L (for methylparaben). It is worth mentioning that the average concentrations of methylparaben and propylparaben found in the current study were up to 200 times higher (Table 2). Concerning the existence

of nicotine and its metabolites in HWW, Ekpeghere et al. [20] collected samples from two Korean hospitals and determined mean concentrations of nicotine, hydroxycotinine, and cotinine equal to 29.4, 34.6, and 15.0 μg/L, respectively, which are similar or lower than those determined in the current study (Table 2). Finally, there are various studies on the presence of caffeine in HWW. In addition to coffee drinks and beverages, this compound is contained in several prescription and non-prescription medications. The concentrations of caffeine that have been reported in the literature for HWW range from some tens to some hundreds of ppbs [7,32,33].

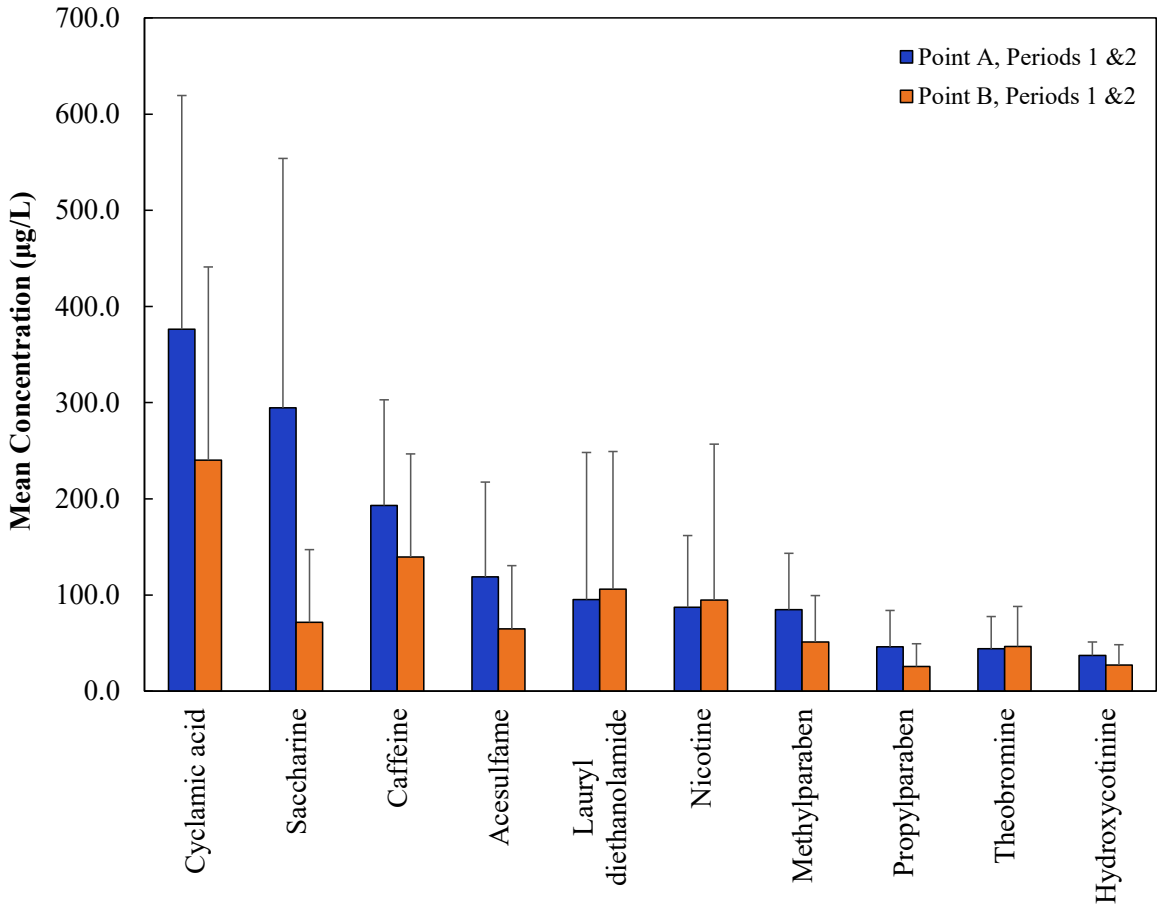

Figure 4. The 10 most abundant emerging contaminants in the HWW at Points A and B.

The occurrence of parent compounds and their associated TPs was also investigated in HWW, and the results are depicted in Figure 5.

Galaxolide, a personal care product compound, was detected mainly in Point A, while its transformation product (galaxolidone) was present at trace concentration levels at both sampling sites. As mentioned above, caffeine and caffeine metabolites were found in all samples. It is well-known that caffeine is excreted by humans in urine [16]. The mean concentration of caffeine metabolite, theobromine, was approximately 45 μg/L at both sampling sites. Nicotine and its metabolites were also detected in all samples. About 10% of the absorbed nicotine is excreted in its original form in urine [16], however, nicotine is extensively metabolized in the liver and forms a wide variety of metabolites, including cotinine and hydroxycotinine [34]. Based on our results, hydroxycotinine was the major metabolite of nicotine, with a mean concentration of 37.4 μg/L and 27.2 μg/L for Points A and B, respectively. In addition, the mean concentration of cotinine reached almost 8 μg/L.

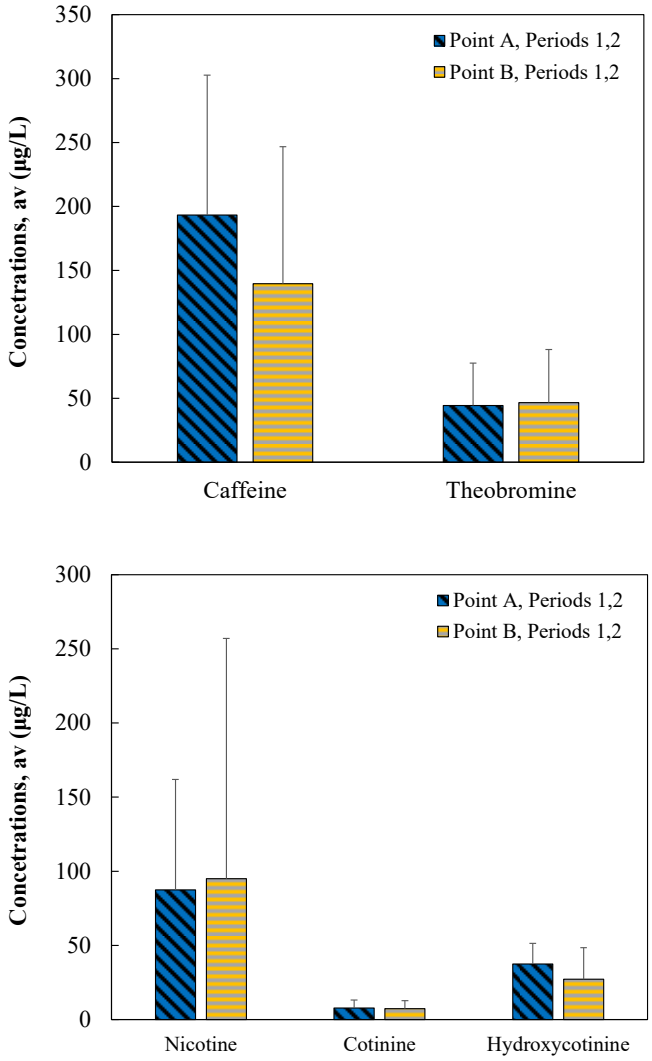

Figure 5. Average concentrations of the parent compounds and their associated transformation products in HWW samples of each sampling site (results as mean ± sd).

3.3. Comparison with Literature Data Originated from Greek Municipal Wastewater

To investigate whether hospitals act as important pollution point-sources for these contaminants, literature data were collected for the occurrence of the studied compounds in Greek municipal wastewater and compared with the findings of the current study. According to the literature, relevant data were found for the group of artificial sweeteners, caffeine, benzotriazole, and hydroxybenzothiazole (Table 3).

On the subject of artificial sweeteners, Kokotou et al. [35] analyzed eight sweeteners in influent samples collected from a Sewage Treatment Plant (STP) located in the city of Athens. Concentrations ranged between 12–25 μg/L, 6–58 μg/L, 15–46 μg/L, and 6–25 μg/L for acesulfame, cyclamic acid, saccharine, and sucralose, respectively. Except for sucralose, the levels of sweeteners detected in the present study were higher in comparison to the previous report [35] by many orders of magnitude.

Table 3. Comparison of the concentration levels of the studied emerging contaminants in Greek raw municipal wastewater with those found in HWW.

Compounds	Concentrations (μg/L)	References
Artificial Sweeteners		
Acesulfame	18.3–279	This study
	11.9–25.3	Kokotou et al. [35]
Cyclamic acid	29.3–782	This study
	6.04–57.8	Kokotou et al. [35]
Saccharine	6.53–787	This study
	15.0–46.0	Kokotou et al. [35]
Sucralose	n.d.–24.2	This study
	6.25–25.4	Kokotou et al. [35]
Coffee and tobacco-related compounds		
Caffeine	36.0–433	This study
	n.d.–96.6	Kosma et al. [36]
	45.9–92.0	Ofrydopoulou et al. [37]
	0.860–6.68	Stamatis et al. [38]
	0.100–5.40	Papageorgiou et al. [39]
	n.d.–222	Papageorgiou et al. [32]
Industrial Chemicals		
2-Hydroxybenzothiazole (2-OH-BTH)	n.d.–7.71	This study
	0.256–0.958	Stasinakis et al. [19]
Benzotriazole (BTR)	n.d.–15.6	This study
	0.516–2.63	Stasinakis et al. [19]

As regards coffee and tobacco-related compounds, caffeine has been investigated in many studies. Kosma et al. [36] detected caffeine in more than 80% of the collected samples from eight Greek STPs and the highest concentration reached 97 μg/L. Papageorgiou et al. [32] found caffeine in raw wastewater of four STPs and reported concentrations up to 222 μg/L. In a recent study by Ofrydopoulou et al. [37], caffeine was also monitored in two Greek STPs in the region of Thessaloniki and it was detected in all samples with a maximum concentration of 92 μg/L. Other studies reported lower concentrations of caffeine [38,39]. Stamatis et al. [38] detected caffeine in all analyzed samples collected from the STP of Agrinio with mean and maximum concentration levels of 3 μg/L and 7 μg/L, respectively. Papageorgiou et al. [39] also detected caffeine in the influents of Volos STP, and they reported mean and maximum concentration of 4 μg/L and 6 μg/L, respectively. Compared to previous Greek findings, the measured caffeine levels in this study are noticeably higher. Specifically, our results showed that its concentrations ranged between 36 and 433 μg/L.

Concerning industrial chemicals, Stasinakis et al. [19] studied the occurrence and fate of benzotriazoles and benzothiazoles in raw wastewater from an STP located in Athens. Concentrations in wastewater influents were below 3 μg/L for 2-hydroxybenzothiazole and benzotriazole. The determined levels of these substances in the present study are similar to those previously reported [19].

It is worth mentioning that the concentration levels of emerging pollutants reported above for Greek municipal wastewater are, in most cases, in agreement with previously published studies conducted in other areas (Europe, USA, Asia, etc.) [40–46].

4. Conclusions

The occurrence of different groups of emerging contaminants as well as their metabolites were investigated in a Greek General Hospital. Twenty-seven compounds were detected at least once during both sampling periods. The most predominant compounds were from the coffee and tobacco-related group (5 out 5 with 100% FoA), followed by artificial sweeteners (3 out 4 with 100% FoA), personal care products (2 out of 6 with 100% FoA), and industrial chemicals, (5 out of 12 with 100% FoA). However, artificial sweeteners added the most to the total concentration of emerging contaminants followed by coffee and tobacco-related compounds. On the other hand, industrial chemicals contributed similarly to the group of personal care products in both examined points for Periods 1 and 2. Considering all sampling campaigns, the observed concentrations were higher in Point A compared to Point B and for Period 1 compared to Period 2. The three highest mean concentrations were recorded for cyclamic acid (377 μg/L, Point A), saccharine (295 μg/L, Point A), and caffeine (193 μg/L, Point A). The findings of the current article indicate that, in addition to pharmaceuticals, hospitals are a significant source for other groups of emerging pollutants, such as artificial sweeteners, parabens, and stimulants.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/w15050936/s1, Figure S1: Extracted Ion Chromatograms for the detected compounds: (a) artificial sweeteners by LC-ESI(-)-QToF-MS, (b) personal care products by LC-ESI(+)-QToF-MS, (c) personal care products by LC-ESI(-)-QToF MS, (d) coffee and tobacco-related compounds by LC-ESI(+)-QToF-MS, and (e) industrial chemicals by LC-ESI(+)-QToF-MS, Figure S2: % Frequency of appearance (% FoA) of the detected ECs in Building A (Point A) and entire hospital (Point B) of the two studied periods, Table S1: CAS number, chemical formula, molecular weight, pKa, and log Kow values of 27 detected and quantified emerging contaminants, Table S2: Information on the samples collected in this study (dates, sampling points), Table S3: The gradient elution program of LC-HRMS analysis, Table S4: UHPLC-ESI-QToF MS identification data for the detected compounds, Table S5: Performance of method applied for the analyses of emerging contaminants, Table S6: Results of wide-scope target screening in HWW (μg/L) at both sampling sites.

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