Supplementary material:

Wastewater micropollutants as tracers of sewage contamination: Analysis of combined sewer overflows and stream sediments

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1. Introduction

1.1.Descriptions of compounds analysed

Selected PPCPs typically have properties favoring their use as wastewater tracers. Information on the proposed function as a wastewater marker are summarized in Table S1. Their physico-chemical properties suggest that they are relatively water-soluble and non-volatile. Additionally, these compounds are present, albeit at trace concentrations, in aquatic environment receiving wastewater effluents. The present section reviews some data present in the literature about these compounds.

Atenolol, a beta-blocker discovered in 1958, has received massive clinical attention due to its effectiveness in treating hypertension and heart diseases, and ranks 34th in the top-selling drugs in the world [1]. Atenolol was found to be present in rivers at levels exceeding 100 ng L^{-1}. This was expected due to its higher dispension (over 2300 kg/year) and its high excretion rates as an unchanged drug (50%) [2]. The removal efficiency for atenolol in wastewater treatment plants is as low as 10% [3] up to 19% [4]. This compound is resistant to biodegradation and once released into the aquatic environment, it can bind to dissolved organic matter (DOM) which enhances its transport in the environment; however it is reported to be moderately accumulated into aquatic sediments [5], persistent and ubiquitous in the aqueous environment [2].

Diclofenac is an anti-inflammatory drug developed in the 1960's, and is a highly consumed drug showing analgesic, antipyretic and anti-inflammatory properties. It tends to be relatively persistent in the environment [6] and detected pharmaceutical in the water cycle of Europe [7] and North America[8]. The concentration of diclofenac detected in sewage treatment plant (STP) effluents has been reported to reach up to 5.5 µg/L [9-11] and decreases by substantial degradation when gathered in river sediments [6]. It seems eliminated from lake waters mainly by phototransformation [12]. Regarding ecotoxicological effects, previous studies reported that 1 mg/L of diclofenac is the lowest concentration which causes an observed effect on zooplankton [13]; however, effects on microorganisms were also reported at much lower concentrations [14, 15].

The analgesic **acetaminophen** (paracetamol) is commonly used as Over-The-Counter (OTC) medications. Approximately 96% of acetaminophen is excreted as metabolites by sulfate and glucuronide conjugation. It has been found at low part per billion (or µg/L) concentration in wastewater and surface water. Previously published methods for the analysis of acetaminophen in environmental samples commonly use gas or liquid chromatography coupled to mass spectrometry [16-21]. Recently, levels of acetaminophen detected by LC-MS/MS in STPs influent in Korea were very high (75 µg/L) compared to the effluent concentrations (0.023 µg/L) [4]. It was detected eventually in the hospital

effluents with a relatively high concentration of around 16 μg/L [22]. However, it was not detected in any of the STPs effluent or receiving water samples taken during the study of Roberts and Thomas [23]. The highest reported concentration for acetaminophen was 10 mg/L in stream water [19]. Acetaminophen has a predicted no effect concentration of 9.2 μg/L and a hazard coefficient (Predicted environmental concentrations (PEC)/predicted no-effect concentration (PNEC) ratio) of 1.8, thus demonstrating some risks for producing potential adverse effects in the environment [24-26]. It was estimated that acetaminophen was neither accumulative in both DOM and sediments but slightly bioaccumulative, whereas it was highly biodegradable when discharged into the aquatic environment [5]. Results obtained by Gros et al. (2006) showed that anti-inflammatories and analgesics were the major groups detected in WWTP and among them acetaminophen, diclofenac and atenolol were the most abundant, with concentrations in high ng/L or low μg/L levels [27].

Caffeine is widely distributed in many plant species and produced in high volume around the world. Being a major human dietary component, it can be found in common food and beverage products such as coffee, tea, colas and chocolates. It is associated with theophylline in tea and with theobromine in chocolate. In pharmaceuticals, caffeine is generally used as a mild neurological, cardiac and respiratory stimulant, psychoactive drugs, and analgesic enhancer in cold, cough and headache medicines [28, 29]. Only 0.5% to 2% of ingested caffeine is excreted as such in the urine due to 98% tubular reabsorption; caffeine is metabolized in the liver to dimethylxanthines (paraxanthine (PX) is the main metabolite of caffeine, theobromine and theophylline) [30]. Discarding unconsumed caffeine-containing beverages [31] and combined sewer overflows [32] have been reported as the main sources of caffeine in surface water. Caffeine showed excellent elimination rates (>99%) throw the wastewater treatment process [4, 32], while it has high detection frequency and been reported to reach concentrations in streams of 6.0 mg/L, with a median concentration of 0.1mg/L [19]. It has nutrient-like effects on microbial community development [33], having a no effect concentration of 182 μg/L [34]. Even the short mean half-life of caffeine (1.5 days) [35], it can act as a persistent chemical in the aquatic environment [36]. Caffeine has been suggested as an anthropogenic marker for wastewater pollution entering the aquatic system [37, 38]. In correlation with caffeine, theophylline can qualitatively be used to support the specificity of caffeine for wastewater.

Theophylline is among the primary monodemethylated metabolites of caffeine in humans [39]. It can also be administered directly as drugs for different pharmaceutical applications including their use as diuretics, bronchodilators, asthma control and for relief of bronchial spasms. For the most part, theophylline enters the environment via liquid effluents and domestic wastes and originates from coffee consumption. Given that the majority of consumed caffeine is excreted as metabolites, it is pertinent to see whether measuring the metabolites would provide better predictive models than caffeine itself. By comparing the concentration of theophylline in a wastewaster treatment plant (WWTP), the influent (4.2 μg/L) and effluent STP (0.023 μg/L) shows excellent elimination rates during wastewater processing [4].

Carbamazepine is often used to control seizures, epilepsy, bipolar disorders and pain [40]. Once ingested, 2 to 3% of this drug is excreted unchanged in the urine [41]. Carbamazepine is a persistent

contaminant commonly detected in sewage treatment effluents and surface waters, and 7% of it is removed upon sewage treatment [18, 42]. The half-lives of this pharmaceutical compound have been reported between 82 and 100, at 328 and 495 d in aqueous matrices, sediments and soils respectively [9, 35, 43, 44], thus raising concerns over its potential accumulation and persistence in aquatic environment. It has been found at low part per billion levels in wastewater and surface water [8, 9, 18, 41, 45, 46]. In U.S. rivers, average levels were 60 ng/L in water and 4.2 ng/mg in sediments [40]. Furthermore, the growth of Daphnia and midges was inhibited at 12.7 and 9.2 mg/L respectively; however, they were killed when carbamazepine was present at 17.2 mg/L and midges at 34.4 mg/L. There were no significant toxic effects to either *C. tentans* or *H. azteca* at concentrations as high as 56 mg/kg dry weight of spiked sediments [47]. Carbamazepine, acetaminophen, caffeine, diclofenac [13, 48-51] and atenolol [13, 49] were among the most studied pharmaceutical compounds in the aquatic environment according to recent reviews. Atenolol, diclofenac, acetaminophen and carbamazepine can be used as chemical indicators of human faecal contamination because they were found in surface water with 100% frequency at the sampling points located below WWTPs [2]. Acetaminophen, caffeine, theophylline and carbamazepine have been frequently observed in wastewater in the Greater Montreal Area [52].

DEET - N,N-diethyl-3-methylbenzamide is widely used as an insect repellent for humans and may be applied in agriculture; it also is the most important analytes within this group[53, 54]. Annual usage of DEET have been estimated to be approximately 1.81 million kg per year in the US [55]. Excretion of DEET may be a minor route[56]. It enters aquatic environments mainly through communal WWTP effluents [57] where it is frequently detected at concentrations ranging between 51 and 773.9 ng/L [58-62]. Although DEET is considered to be neither persistent, bioaccumulative, nor toxic [63].

Aspartame (methyl ester of a dipeptide) is a popular artificial sweetener used in diet soft drinks. It is a substance 180 to 200 times sweeter than sugar, not heat-stable and degradable over a long period of time. Aspartame was assumed to be quickly biodegraded in WWTPs [64]. In the literature, aspartame is the most controversially discussed artificial sweetener regarding health aspects causing adverse effects such as neurological disturbances [65-67] or even cancer in rats [68, 69]. Nevertheless, Health Canada, the Scientific Committee for Food of the European Community, and the Joint Expert Committee on Food Additives (JECFA) of the United Nations Food and Agriculture Organization and World Health Organization consider this substance to be safe based on toxicological and clinical studies [70]. Aspartame was not detected in wastewater and surface water samples analysed by Scheurer *et al.* [71].

Natural (**progesterone)** and synthetic (**medroxyprogesterone**) steroids have been regarded as the most important members of endocrine disrupting chemicals (EDCs) which may cause dangerous effects on aquatic organisms at a low ng/L level [72, 73]. Progesterone was detected in wastewater influent, surface water and river sediment at concentrations up to 6.1 ng/L, 2.5 ng/L and 6.82 ng/g respectively [74, 75], while medroxyprogesterone was detected in wastewater effluent at concentration up to 15 ng/L. This compound was not rapidly attenuated from an effluent-receiving engineered treatment wetland and shallow groundwater wells [76].

Table S1. Reported functions of selected test pharmaceuticals in the literature.

Compound/abbreviation	Specific functions	References
Acetaminophen/ACE	Tracer of raw or insufficiently treated wastewater/ Indicator of WWTP malfunction or CSOs	[2, 77, 78]
Aspartame/APM	Potential marker of domestic wastewater in groundwater	[64]
Atenolol/ATL	Indicator of human faecal contamination	[2]
Caffeine/CAF	Indicator of recent and cumulative wastewater contamination of natural waters (surface waters and stormwater outfalls)	[38, 52, 78-85]
Carbamazepine/CBZ	Indicator of cumulative wastewater discharges	[2, 41, 52, 78, 79, 84, 86, 87]
Diclofenac/DIC	Indicator of human faecal contamination	[2]
Medroxyprogesterone/MedP	Indicator of municipal wastewater discharges	[76]
N,N-diethyl-3-methylbenzamide /DEET	Indicator of human fecal contamination to identify human sewage contamination in water bodies	[57, 78]
Progesterone/PRO	Indicator of fecal contamination in drinking water sources	[84]
Theophylline/THEO	Indicator of human faecal contamination	[79]

[a]**NR, not reported**

1.2. Extraction methods

Most methods developed to determine WWMPs in sediments usually include an extraction protocol followed by chromatographic analysis. Various extraction techniques used in the past include : ultrasonic-assisted extraction (USE) [88, 89], pressurized liquid extraction (PLE) [90, 91] and microwave extraction (MAE) [92, 93]. Depending on effectiveness, capital cost, operating cost, simplicity of operation, and waste production, USE is a robust method for extracting organic contaminants from solid matrices comparable to other commonly used methods such as Soxhlet, PLE, and MAE [94-96]. During the USE process, cavitation bubbles that are produced may initially have extreme internal temperature and pressure, which collapse afterwards causing the extraction solvent to propagate outwards with a high velocity on a collision course with matrix particles. These collisions separate the matrix and produce smaller particles and expose more surface area to the extraction solvent [97]. Since extractions are carried out at room temperature instead of high temperatures of around 100 °C, USE reduces the risks of degrading the target compounds; while a higher precision is also reported than with using MAE methods [88]. It can be effectively applied to extract organic contaminants that differ significantly in their physico-chemical properties [95, 97]. Sample extracts obtained from solid matrices contain other components which may affect the signal of target analytes; therefore, it is necessary to introduce an additional clean-up step before chromatographic analysis [98]. Solid phase extraction (SPE) is the best method providing both cleanup and preconcentration at the same time [89].

2. Methods and materials

2.1. Chemicals and reagents

High purity (> 97%) analytical standards of caffeine, carbamazepine, theophylline, acetaminophen, atenolol, aspartame, progesterone, medroxyprogesterone, diclofenac and N,N-diethyl-3-methylbenzamide were provided by Sigma-Aldrich Canada (Oakville, ON, Canada). Some of the important parameters of the compounds are summarized in Table S2. The surrogate (carbamazepine-d_{10}; 98%) and internal standard ($[^{13}C_3]$-atrazine; 99%, $[^{13}C_3]$-caffeine; 99%, $[^{13}C_2]$-acetaminophen; 99%, progesterone-d_9; 98% and diclofenac-d_4; 98%) were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA).

Selected compounds have low vapor pressure and medium to high water solubility. They remain stable under normal operating conditions and variable time of storage [99]. Individual stock standard solutions were prepared by dissolving each compound in methanol at a concentration of 1000 mg/L for the analytes and at 1 mg/L for the isotopically-labeled standards. A standard mixture solution containing all the analytes was prepared weekly in methanol at a concentration of 50 mg/L.

All organic solvents and water used were HPLC grade and obtained from Fisher Scientific (Whitby, ON, Canada) and all the other reagents were of analytical grade. The SPE with the following adsorbents was evaluated: Strata C18-E, 52 μm, 500 mg/6 cc (silica-based, reversed phase absorbent with a hydrocarbon and aromatic functional group) and Oasis HLB, 30 μm, 60 mg/3 cc (lipophilic divinylbenzene + hydrophilic N-vinyl pyrrolidone) [100]. The adsorbents were obtained respectively from Phenomenex (Torrance, California, USA) and Waters (Milford, MA, USA). Polypropylene syringe filters (hydrophobic, 0.22 μm, 30 mm diameter) were obtained from Sterlitech (Kent, WA, USA).

2.2. Apparatus

Liquid chromatography with mass spectrometric detection was performed using a thermostated autosampler (CTC HTS PAL analytics AG, Switzerland) fitted with a cooled sample holder at 10 °C, a 100 μL syringe, a 25-μL loop, six-port switching valves, an additional solvent reservoir and an Accela 1250 quaternary pump from Thermo Fisher Scientific (San Jose, CA, USA). Chromatographic separation was carried out in a reversed phase Hypersil GOLD C18 UPLC column (50 x 2.1 mm, 1.9 μm) from Thermo Fisher Scientific, preceded by a security guard column (0.2 μm, 2.1 mm) of the same packing material from the same manufacturer. It was used to prevent particles from clogging the column and to prolong column life. Polyetheretherketone (PEEK) capillary tubing (1/16 in O.D x 0.005 in I.D., Thermo Scientific) was used to minimize the void volume of the system. Mass spectrometry was performed on a Thermo Scientific TSQ Quantum Ultra AM Mass Spectrometer equipped with an atmospheric pressure chemical ionisation (APCI) interface. Analytical instrument control, data acquisition and treatment were performed by Thermo Fisher Scientific Xcalibur 1.2 software (Waltham, MA, USA).

2.3.Preparation and spiking of sediment samples

The frozen sediment samples were lyophilized and sieved through an 80-μm screen in order to optimize the mechanism of sorption of analytes to solids and then stored in a closed flask at -20 °C. To optimize the extraction procedure, fractions of the sample (1 and 0.1 g of stream and CSO sediments respectively) were placed in different 15-mL conical polypropylene centrifuge tubes, covered with acetone (800 µL) and spiked with a mixture of standards (10 and 100 ng/g for stream and CSO sediments respectively). The samples were shaken at 100 rpm in a refrigerated incubator shaker Innova 4230 (New Brunswick Scientific Edison, NJ. USA) and allowed to equilibrate overnight in the dark before extraction, in order to obtain a dry and homogenous material.

2.4.UHPLC–APCI–MS/MS

A sample of 20 µL was injected through a 25-µL sample loop. Compounds were separated and measured by ultra-high performance liquid chromatography (UHPLC) using a Hypersil GOLD C18 UPLC column (50 x 2.1 mm, 1.9 µm). The analytical column was previously chosen and analysis was successfully done in our laboratory for the majority of the studied compounds [52, 101]. The column temperature was set to 45°C. We used a binary gradient of mobile phases A (H_2O) and B (acetonitrile) both contained 0.1% formic acid and operated at a constant flow rate of 0.4 mL/min. An HPLC gradient program was applied as follow: hold at 5% (B) over 0.7 min, increased from 5% to 30% (B) over 0.1 min, increased from 30 % to 35 % (B) over 1 min then increased linearly to 95 % over 0.1 min and hold on for 0.6 min and then decreased to 5 % (B). The composition was held at 5 % (B) for a further 1.7 min for re-equilibration, giving 4.5 min of total run time for each sample (Figure S1).

The APCI probe with a corona discharge used pneumatic nebulization to vaporize the solvents and analytes. The vaporizer was operated at a temperature of 450 °C with the heated capillary temperature set at 350 °C. Samples were ionized by reacting with solvent reactant ions produced by the corona discharge (3 µA) in the chemical ionization (CI) mode. The pressures were 45 and 5 arbitrary units for the nitrogen sheath gas and the auxiliary gas respectively. Mass spectrometry detection was performed under the time-scheduled selected reaction monitoring (SRM) conditions shown in Table S3, by using APCI interface operating in the positive ion (PI) mode. The parent ions $[M + H]^+$ monitored under the optimized MS conditions are listed in Table S4. Collision induced dissociation (CID) was performed by introducing argon at 1.5 mTorr in the Q2 chamber. Collision offset energy was appropriately optimized for each compound transition. The daughter scan width was set at 1.0 amu, and the total scan time was 0.02 s. Compounds were identified on the basis of their relative retention time, which is the ratio of the retention time of the analyte to that of the internal standard. Quantification was performed using internal standard method. The peak areas of analytes were normalized to those of the internal standard.

2.5.Method performance

   2.5.1.   Extraction and SPE conditions

Our preliminary choice of evaluated extraction solvents and extract pH was based on other previous studies (see Table 1). In preliminary tests with the help of the Strata C-18E absorbent, the extraction procedure was optimized for extraction solvents, extraction time, and extraction temperature using samples of treated stream sediments spiked with analytes. Different extraction organic solvents and aqueous buffers (water, water with 0.1% formic acid, methanol, acetone, 2-propanol, acetonitrile, dimethyl sulfoxide, water/methanol (9:1, v/v, pH 11 and 5:5, v/v, pH 4), water with 0.1% formic acid /methanol (5:5 and 4:6, v/v), water/acetone (2.5:7.5, v/v), water mixture contains 0.1% formic acid /acetone (6:4, v/v) and methanol/acetone (5:5 and 6:4, v/v)) and different time (20, 30 and 45 min) and temperature of sonication (30 and 50 °C) were applied. Once the optimal extraction conditions were found, multiple sequential extractions (up to 6 cycles) of the same sediment samples were conducted to ensure quantitative extraction during USE. The extracts were collected individually and analyzed.

In order to ascertain the extraction recovery of analytes at different pH values, extract samples diluted with 10 mL of UPW and were spiked with the analytes at a concentration of 1 µg/L and adjusted to the desired pH values (non-adjusted, 4, 7 and 11) using formic acid (95%) and NaOH (0.5 M). With the use of SPE cartridge (Strata C-18E), the extraction recovery rates of the analytes in interest were identified.

Prior to the SPE extraction, conditioning, washing and elution procedures were implemented on the selected cartridges (Strata C-18E and Oasis HLB). We tried different volumes and ratios of mixture washing buffers (0, 5 and 10 mL of water/methanol (100:0 and 95:5, v/v)), different volumes of the loading solution (10 and 250 mL) and different volumes and proportions of elution solvents (methanol followed by 0.5 M formic acid–methanol mixture, 1:0, 1:1 and 2:1 ratios with 5, 2 and 1.5 mL as total volume respectively).

In order to compare the SPE step with Strata C-18E and Oasis HLB cartridges, ultra-pure water (UPW) samples (n=3) with 10 mL volume and adjusted pH to7 were spiked with analytes at concentration of 1 µg/L. SPE recovery was checked through comparing the samples spiked before and after SPE. To confirm the results obtained, we repeated the same test with the extract sediment samples instead of water and compared the shape of the chromatographic peaks of each compound.

Extraction efficiency was evaluated an absolute recovery determined in relation to a non-enriched standard solution and calculated as follows: 6 replicate sediment samples for the extraction method were prepared. Three samples were added with mixture of standards after extraction (BL) and the other 3 samples were added with a mixture of standards before extraction (ADD). The recoveries were determined by comparing the measured concentrations in BL with the measured concentrations in ADD using the following Eq. (1):

$$\text{Absolute recovery} = \frac{\text{ADD}}{\text{BL}} * 100 \hspace{4cm} (1)$$

In order to distinguish between the extraction efficiency of WWMPs sorbed to the sediments and the recovery of the clean-up method, the following experiment was performed: first, 3 sediment samples were spiked with 100 µL of the non-deuterated standard solution at 0.1 mg/L. Second, 3 sample extracts were spiked prior to the clean-up step. Finally, 3 samples were spiked after the clean-up step. The differences in mean recoveries between these three sets of samples were then used for the calculation of the recoveries for each step. Carbamazepine-d_{10} was added as a surrogate standard, at concentration levels of 5 and 50 ng/g for stream and CSO sediments respectively, to all samples (before the extraction step, prior to cleanup or after cleanup) to correct for losses during sample extraction or cleanup [102]. Relative recoveries (relative to the recovery of Carbamazepine-d_{10}) were then calculated using the following Eq. (2):

$$\text{Relative recovery} = \frac{\text{Absolute recovery of the analyte}}{\text{Absolute recovery of the surrogate standard}} \qquad (2)$$

2.5.2. Analytical parameters: calibration, validation and matrix effects

To optimize the gradient separation and the conditions in the MS–MS detector, we tested water different pH values (2.65, 6 and 8) and two organic solvents (methanol and acetonitrile). The full-scan mass spectra and the MS/MS spectra of the selected compounds were obtained from the direct injection of a 2 mg/L standard of each compound at a flow-rate of 0.4 mL/min using both ionization modes (positive and negative). The highest intensity was selected for further study. Optimisation of the compound-dependent parameters such as the collision energy and tube lens for individual analytes were adjusted by syringe pump infusion, as described above. Mass spectrometer parameters were also optimized by continuous infusion of standards in order to find the best method to detect all compounds with the best possible signal for the compound of interest. Fragmentation voltage and collision energy were tested in order to select the transitions in the selective reaction monitoring (SRM) mode.

The analytical method was validated for each type of matrix through the estimation of the recovery, linearity, repeatability, reproducibility, sensitivity and matrix effects. Method trueness and precision were evaluated by recovery studies which were calculated as the percentage of agreement between the method results and the nominal amount of compound added in sediment extracts. Linearity was studied using standard solutions and matrix-matched calibrations by analyzing in triplicate six concentration levels, between 0 and 100 µg/L in the final extract. Experimental data fitted a linear mode, y = a + bx in the concentration range studied (0, 1, 5, 10, 20 and 30 µg/L for stream sediment and 0, 5, 10, 20, 60 and 100 µg/L for CSO sediment). Calibration curves were built with the response ratio (area of the analyte standard divided by area of the internal standard) as a function of the analyte concentration. [$^{13}C_3$]-caffeine was used as an internal standard to improve quantitation of caffeine, theophylline and aspartame. [$^{13}C_2$]-acetaminophen was used as internal standard to normalize acetaminophen and atenolol peak area variations. Diclofenac-d_4 was used as internal standard for diclofenac, carbamazepine, carbamazepine-d_{10} and N,N-diethyl-3-methylbenzamide, while progesterone-d_9 was used for progesterone and medroxyprogesterone. Because unspiked sample extracts already contained some of the compounds, a calibration curve was constructed by subtracting the level concentration for these

analytes in this matrix from the spiked concentration. This procedure was also carried out for the quantitative determination of the analyte recoveries in real samples. The precision of the method was determined by the repeated intra-day (n = 5) and inter-day (3 different operating days) analysis of a spiked sample extracts at concentrations levels of 10, 20 and 30 µg/L for stream sediments and 100 µg/L for CSO sediments. The precision of the method was expressed as the relative standard deviation (RSD) of replicate measurements. Precision was deemed acceptable when RSDs were lower than 15%. Limit of detection (LOD) was defined as 3.707 times the standard deviation (n = 5) of analyte measurements in stream and CSO sediment extracts at 1 and 5 µg/L respectively [52, 103].

Matrix effect (ME) can affect reproducibility and efficiency of the developed method. This phenomenon was evaluated at 10, 20 and 30 µg/L for stream sediment extracts and 20, 60 and 100 µg/L for CSO sediment extracts, by comparing the MS/MS response of known amounts of standards spiked in mobile phase with those measured in sediment extracts. ME was calculated as the following Eq. (3):

$$\text{ME \%} = \left(\frac{S1 - S2}{S2}\right) * 100 \qquad\qquad (3)$$

where S_1 = slope of the curve obtained by injection of the analytical solutions of pharmaceuticals prepared in the extract obtained after the SPE step and S_2 = slope of the curve obtained by injection of pharmaceuticals prepared with the initial mobile phase condition. ME=0 means no matrix interference while ME>0 and ME<0 represent signal suppression and enhancement, respectively. Matrix effects were considered low for a range of signal suppression/enhancement −20% < C% < +20%, medium for the ranges −50% < C% <−20% or +20% < C% < +50% and high for the ranges C% <−50% or C% > +50% [104].

Table S2. Physicochemical properties of selected test pharmaceuticals [105].

| Compound	Molecular weight (g)	LogK$_{ow}$[a]	pKa[b]	LogS (mg/L)[c]
ACE	151.17	0.46	9.3	4.15
APM	294.30	0.07	4.5–6.0	10,000
ATL	266.34	0.16	9.6	4.11
CAF	194.19	-0.07	10.0	4.33
CBZ	236.27	2.7	13.9	1.25
DIC	296.16	4.51	4.14	0.37
MedP	344.50	3.50	–	–
DEET	191.26	2.18	–	912
PRO	314.4	3.87	–	8.81
THEO	180.16	-0.02	8.81	3.87
PX	180.17	-0.63	8.5	-1.30

[a]LogK$_{ow}$, octanol-water partition coefficient; [b]pKa, acid constant; [c]LogS, solubility at a temperature of 20–25 °C

Table S3. Details of the selected reaction monitoring (SRM) parameters of selected compounds in APCI–MS/MS under positive ionization mode.

Compound	Precursor ion (m/z)	Product ion (m/z)	Collision Energy (eV)	Tube lens (V)
ACE	152.10	110.14	13	67
APM	295.10	120.20	27	90
ATL	267.16	190.10	16	90
CAF	195.10	138.10	17	70
CBZ	237.10	194.10	18	67
DIC	296.02	215.10	20	66
MedP	345.16	123.10	22	127
DEET	192.15	119.10	16	111
PRO	315.15	109.10	26	100
THEO/PX	181.10	124.10	19	67

Table S4. MS parameters.

Ionization mode	APCI$^+$
Discharge current	3 μA
Vaporizer temperature	450 °C
Capillary temperature	350 °C
Sheath gas pressure	45 arb units
Aux. gas pressure	5 arb units
Collision gaz pressure	1.5 mTorr
Scan time	0.02 s
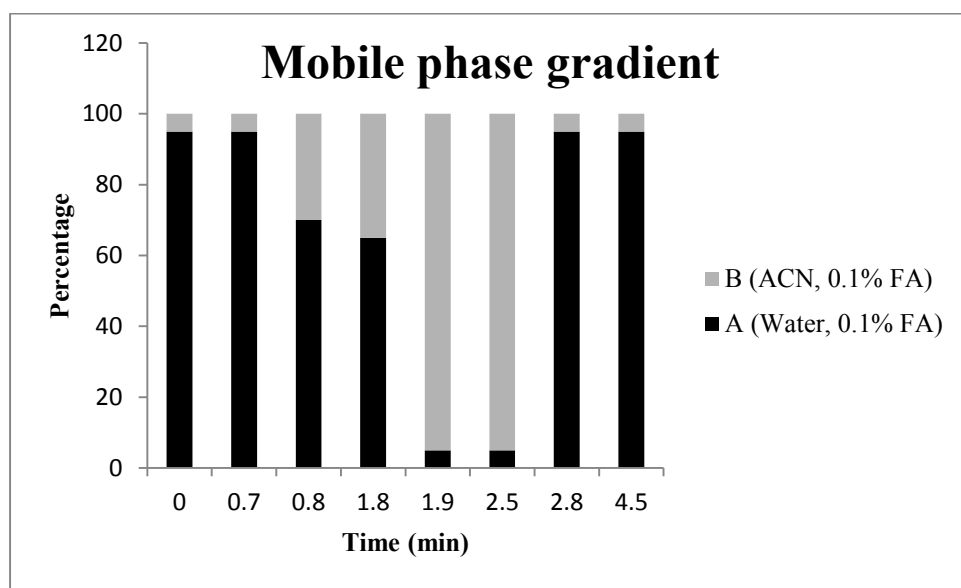
Figure S1. Binary gradient of mobile phase A (water/0.1% Formic acid) and mobile phase B (acetonitrile/0.1% Formic acid) by using LC Pump Accela 1250.

3. Results and discussion

3.1. Optimization of UHPLC–APCI–SRM/MS analysis and quantification

Other studies have previously studied the product ions of selected compounds using positive ESI or APCI. Transitions are in agreement with those reported for caffeine, carbamazepine, medroxyprogesterone, progesterone, diclofenac, atenolol, acetaminophen, and aspartame [1, 52, 91, 101, 106, 107]. The monitoring of theophylline using positive ion conditions is unusual, as the compound is acidic in nature [108]. The intensities of pseudo molecular ion peaks were higher in positive mode than negative mode, therefore (+) APCI was chosen for further study.

The most commonly used chromatography phase is C18, regardless of the compounds to be determined [109]. Good chromatographic separation and MS efficiency were achieved by using Hypersil GOLD C18 UPLC column (1.9 μm, 50 x 2.1 mm, i.d.) preceded by a guard column (0.2 μm, 2 x 2 mm, i.d.) maintained at 45 °C. It provided sharp peaks and short retention times in previous studies [52, 101]. A

chromatographic column based on 1.9 μm material reduced the analysis time. It is commonly accepted that the presence of the acid facilitates the protonation of analytes with basic functional groups in positive-ion mode [110]. Formic acid improved the sensitivity of APCI (+) sources which were selected for all standards. Therefore, the best conditions for obtaining a good separation and symmetric peaks were found with acidic water (0.1% formic acid) and acetonitrile (0.1% formic acid). Sample chromatography gradients are shown in Figure S1 and allowed sufficient chromatographic separation of all analytes. The interference of paraxanthine (PX, the primary metabolite of caffeine in humans) to theophylline is overlooked for many LC/MS/MS methods including our own - theophylline and paraxanthine are isobaric and have the same MS/MS transition.

3.2. Optimization of extraction and SPE steps

The extraction efficiency of different solvents for different periods and temperatures of sonication was tested using spiked stream sediments. We used a Strata C-18E absorbent cartridge. Three solvents (methanol/water (1/9,v/v, pH 11), acetone and water with formic acid 0.1%) were chosen because they provided satisfactory extraction efficiencies in the range of 70−120% for all compounds excepted for atenolol, caffeine and aspartame. Acetaminophen was extracted in the first three cycles while atenolol and aspartame were extracted in the first and last cycles. The remaining compounds (caffeine, carbamazepine, theophylline, DEET, diclofenac, progesterone and medroxyprogesterone) were progressively extracted throughout the cycles. In the last cycle, we used water with formic acid 0.1% to enhance the recovery of aspartame which has good stability at pH values between 3.4 and 5 [111].

We observed a slight increase in extraction efficiency when the extraction time was extended from 20 to 30, and 45 min. Recoveries of some compounds (e.g., aspartame, caffeine and atenolol) declined. Other extraction parameter that affected extraction efficiency is the ultrasonic extraction temperature. Increasing the temperature from 30 to 50 °C generated relatively low recoveries for all compounds. Therefore, a sonication of 20 min at 30 °C was set for sample treatment.

The choice of extract pH prior to SPE is a key point in solid-phase extraction, especially when we have compounds with different physicochemical properties. Extraction efficiencies for clean-up with SPE were also determined with a procedure similar to that described for extraction. The optimum pH was determined for the recovery of the selected compounds prior to the SPE of extract samples. The lowest recovery for theophylline/paraxanthine was found at pH 11, which is why we rejected the SPE method at pH 11. The highest intensity and sharp peak for theophylline/paraxanthine and best recovery for caffeine occurred at pH 7. The recovery for carbamazepine at pH 4 was very close to its recovery at pH 7 whereas the recovery for diclofenac was highest at pH 4 but remains above 70% at pH 7. In the light of these results, the optimum pH for the simultaneous extraction of all selected compounds was chosen as pH 7. Similar results have been shown in other studies: the recoveries for basic and neutral pharmaceuticals with acidification of the purification extract was between 5% and 20% lower than those obtained without acidification, whereas recoveries for acidic compounds were very similar [91]. The effect of pH on the SPE efficiency was also studied by Gómez *et al.* [22] by increasing the pH value of the sample from 2 to 4 and 7. The results showed that the extraction recoveries for many of target

compounds (e. g. carbamazepine, atenolol, acetaminophen and diclofenac) from spiking hospital effluent wastewater samples was higher at pH 7 and ranged from 88.1 to 114%. Weigel *et al.* [112] obtained good recoveries, ranging from 97 to 102%, for caffeine, carbamazepine and DEET with Oasis HLB sorbent and sample pH at 7. Acetaminophen showed low recovery in the same conditions [112]. Similar recoveries were obtained for acetaminophen (20−40%) when the Oasis HLB sorbent was used and the sample pH prior to SPE was 2 and 7. The influence of sample pH on the extraction efficiency of diclofenac, carbamazepine and caffeine was significant. The best recoveries for these compounds were obtained under acid conditions when the pH sample prior to SPE was 2 [113]. Pichon *et al.* [114] showed that the removal of humic and fulvic acid interferences from water samples was performed at neutral SPE pH by using polymeric sorbents for the simultaneous extraction of polar acidic, neutral and basic components. The co-extracted interferences directly affect the quantitation of analytes. The effect of signal suppression decreased with increasing SPE pH up to 8.5 [114].

We compared the SPE recovery rates achieved in UPW without the sediment matrix by Strata C-18E and Oasis HLB cartridges. The SPE recovery rates for acetaminophen and atenolol were very low with Strata C-18E cartridge, (respectively; 15.21 and 0.27%) while Oasis HLB showed a good retention for all analytes. Recoveries were greater than 90%, with the exception for aspartame and progesterone, which showed recoveries of 61.1% and 75.2% respectively. Moreover, the use of an Oasis HLB cartridge has produced a peak for acetaminophen with symmetrical (Gaussian) shape and straight line spikes in which no broadening occurred (Figure S2). Therefore, the Oasis HLB cartridge (at pH 7) was selected for all compounds. Several papers reported on the evaluation of a number of stationary phases for solid phase extraction (SPE) of the selected WWMPs [16, 17, 91, 112, 113, 115], however in many situations, the optimal SPE material is variable and highly dependent on target analytes and experimental conditions. For example, for diclofenac, some authors indicated that C18 silica sorbents give results superior than polymeric sorbents [16, 100], while other reported higher recoveries with the polymeric Oasis HLB cartridges [116, 117]. The comparison of different types of polymeric SPE sorbents (Bakerbond SDB-1, Lichrolut EN, Isolute Env+, Chromabond HR-P, Chromabond EASY, Abselut Nexus and Oasis HLB) demonstrated that the best performance was achieved using Oasis HLB giving highest recoveries for all tested compounds (caffeine, 97%; DEET, 100%; carbamazepine, 101% and diclofenac,102%) except for acetaminophen (14%) [112]. Another study compared Oasis HLB and Oasis MCX sorbents and showed that acetaminophen, carbamazepine and caffeine were more efficiently recovered when Oasis HLB sorbent was used, while the recovery for diclofenac was best using an Oasis MCX sorbent [113].

The choice of elution solvent and volume is dependent of the target compounds and the SPE material. The most common elution solvents of Oasis HLB are regarded as methanol, ethyl acetate and acetone [112, 113, 118, 119]. In our study, the best recoveries for selected analytes were obtained with elution by 1 mL of methanol and 1 mL of acidified methanol (with 0.5 M formic acid), successively.
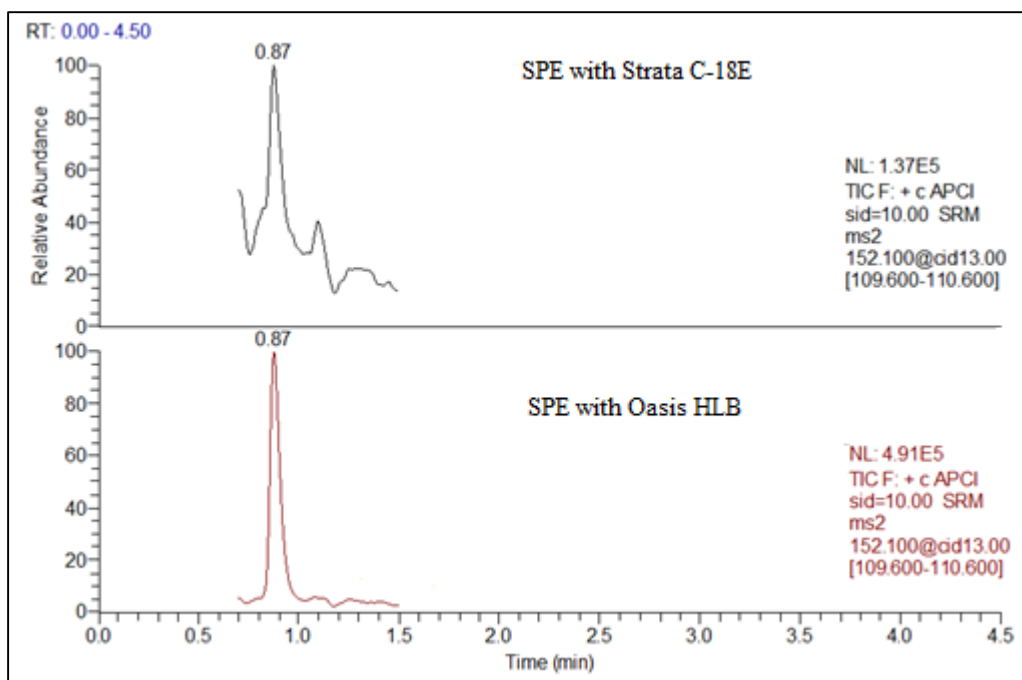
Figure S2. Shape and intensity of peak for acetaminophen after extraction from stream sediment and purification with Strata C-18E (top) and Oasis HLB (bottom).

3.3. Matrix effects

Internal standards have been used to further correct for residual matrix effects and compensate for signal suppression/enhancement. At the concentrations studied, the matrix effects were low for all analytes, demonstrating the effectiveness of the sample pre-treatment. Among the compounds analyzed in APCI positive mode, diclofenac (pKa = 4.14), a weak proton acceptor, was particularly sensitive to matrix effects. Matrix effects ranged from -18% and 18% as shown in Figure S3. Wick *et al.* [120] studied matrix effects in different sample matrices (activated sludge, raw and treated wastewater, and surface water) using ESI and APCI. Similarly to our results, APCI was generally less susceptible to ion suppression than ESI but partially susceptible to ion enhancement of up to a factor of 10. In addition, Zhao and Metcalfe [121] observed a signal enhancement in wastewater extracts analyzed for neutral pharmaceuticals (e. g. caffeine and carbamazepine) as a result of interferences from the sample matrix.
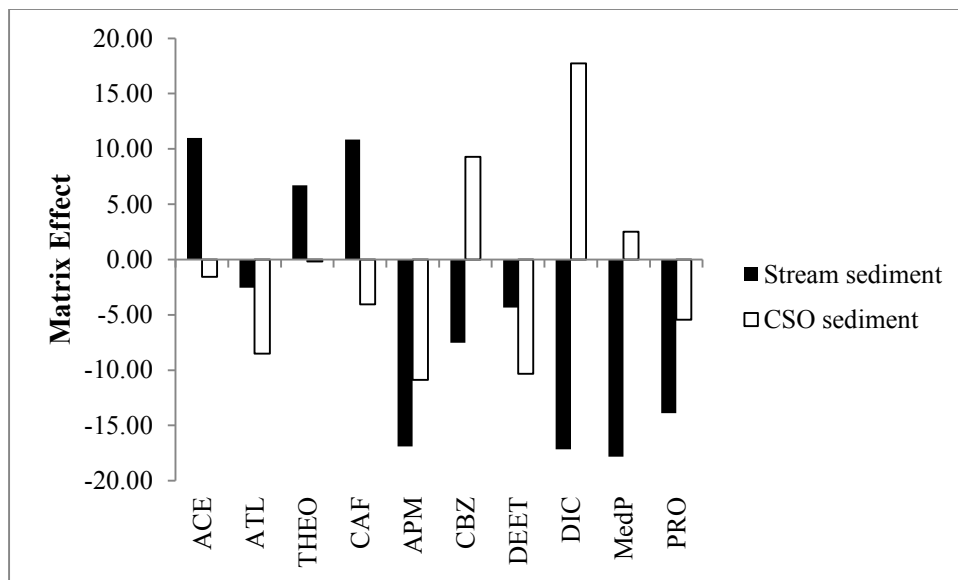
Figure S3. Percentage of matrix effect (ME) for the technique using ultrasonication-assisted extraction and LC-APCI-MS/MS for the determination of WWMPs in stream and CSO sediments.

3.4.Method applicability in sediment samples and comparison with water samples

Table S5. Classification of WWMPs depending on their average dynamic ranges in sediment (S) and water (w) under dry (DW) and wet weather (WW) conditions.

	The highest range ⟶		The lowest range	
C (S, DW)	THEO	ACE	CAF	CBZ
US1 (S, DW)	ACE	CAF	THEO	CBZ
US2 (S, DW)	ACE	CAF	THEO	CBZ
US3 (S, DW)	ACE	CAF	THEO	CBZ
Canal (S, DW)	ACE	THEO	CAF	CBZ
SA (W, DW1)	CAF	ACE	THEO	CBZ
SB (W, DW2)	THEO	ACE	CAF	CBZ
OA (W, WW1)	ACE	CAF	THEO	CBZ
OB (W, WW2)	CAF	THEO	CBZ	ACE
US1 (W, DW)	ACE	THEO	CAF	CBZ
US1 (W, WW)	CAF	ACE	THEO	CBZ
US2 (W, DW)	ACE	CAF	THEO	CBZ
US2 (W, WW)	ACE	CAF	CBZ	THEO
US3 (W, DW)	THEO	CAF	CBZ	ACE
US3 (W, WW)	THEO	CAF	CBZ	ACE
Canal (W, DW)	CAF	CBZ	THEO	ACE
Canal (W, WW)	CAF	CBZ	THEO	ACE

C (CSO); S (sediment); W (water); DW (dry weather); WW (wet weather); C, SA, SB and OA (high degree of human fecal contamination); OB, US$_1$, US$_2$ and US$_3$ (medium degree of human fecal contamination); Canal (low degree of human fecal contamination); Data about SA and SB (samples collected in the two sewersheds A (SA) and B (SB), immediately upstream of the CSO outfall during dry weather conditions), the two CSO outfalls (OA and OB), and canal were presented in Madoux-Humery *et al.* [79] and Guérineau *et al.* (2013)

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