



Targeted profiling of chlorinated transformation products and the parent micropollutants in the aquatic environment: A comparison between two coastal cities

Wen-Ling Chen, Ph.D. ^{a, b, *}, Yee Soon Ling, Ph.D. ^d, Dexter Jiunn Herng Lee ^c,
Xiao-Qian Lin ^{a, e}, Ze-Ying Chen ^f, Ho-Tang Liao, Ph.D. ^g

^a Institute of Food Safety and Health, College of Public Health, National Taiwan University, Taiwan

^b Department of Public Health, College of Public Health, National Taiwan University, Taiwan

^c Biotechnology Research Institute, University Malaysia Sabah, Malaysia

^d Water Research Unit, Faculty of Science and Nature Resources, University Malaysia Sabah, Malaysia

^e Department of Environmental Science and Engineering, Tunghai University, Taiwan

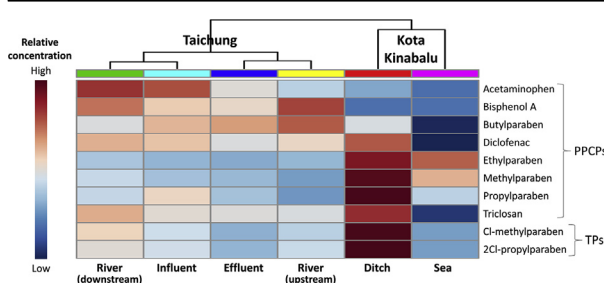
^f Institute of Environmental and Occupational Health Sciences, College of Public Health, National Taiwan University, Taiwan

^g Research Center for Environmental Changes, Academia Sinica, Taiwan

HIGHLIGHTS

- 16 chlorinated TP of 9 PPCPs in urban waters of tropical islands were studied.
- Chlorinated TP of bisphenol A, diclofenac, triclosan, and parabens were detected.
- Conventional processes in a WWTP in Taichung removed most PPCPs and chlorinated TP.
- Higher levels of chlorinated TP were detected in ditch water than seawater.
- Chlorination in the WWTP or seawater were not major sources of TP.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 2 September 2019

Received in revised form

28 October 2019

Accepted 29 October 2019

Available online 2 November 2019

Handling Editor: Klaus Kümmerer

Keywords:

Micropollutants

Chlorinated transformation products

Wastewater treatment

ABSTRACT

This study investigated chlorinated transformation products (TPs) and their parent micropollutants, aromatic pharmaceuticals and personal care products (PPCPs) in the urban water bodies of two metropolitan cities. Nine PPCPs and 16 TPs were quantitatively or semi-quantitatively determined using isotope dilution techniques and liquid chromatography-tandem mass spectrometry. TPs and most PPCPs were effectively removed by conventional wastewater treatments in a wastewater treatment plant (WWTP). Chlorinated parabens and all PPCPs (at concentrations below 1000 ng/L) were present in the waters receiving treated wastewater. By contrast, the waters receiving untreated wastewater contained higher levels of PPCPs (up to 9400 ng/L) and more species of chlorinated TPs including chlorinated parabens, triclosan, diclofenac, and bisphenol A. The very different chemical profiles between the water bodies of the two cities of similar geographical and climatic properties may be attributed to their respective uses of chemicals and policies of wastewater management. No apparent increase in the number of species or abundances of TPs was observed in either the chlorinated wastewater or the seawater rich in halogens. This is the first study to elucidate and compare the profiles of multiple TPs and

* Corresponding author. Institute of Food Safety and Health, College of Public Health, National Taiwan University, 17 Xuzhou Rd., Taipei, 100, Taiwan.

E-mail address: adelachen@ntu.edu.tw (W.-L. Chen).

Chlorination
Urban waters

their parent PPCPs in the water bodies of coastal cities from tropical islands. Our findings suggest that chlorinated derivatives of bisphenol A, diclofenac, triclosan, and parabens in the surface water originate from sources other than wastewater disinfection or marine chlorination. Although further studies are needed to identify the origins, conventional wastewater treatments may protect natural water bodies against contamination by those chlorinated substances.

© 2019 Elsevier Ltd. All rights reserved.

1. Introduction

Pharmaceuticals and personal care products (PPCPs) are present in natural water bodies due to the massive use and discharge of treated and untreated wastewater (McCance et al., 2018; Ojemaye and Petrik, 2019). The global monitoring of surface water and wastewater indicates the ubiquitous distribution of PPCPs at ng/L to µg/L levels (Focazio et al., 2008; Maruya et al., 2016; Wilkinson et al., 2019). Conventional wastewater treatment processes involving primary and secondary treatments have been proven to effectively eliminate most PPCPs from the municipal wastewater influent (Wang et al., 2019). However, some PPCPs are difficult to be degraded by wastewater treatments and the market for them is expanding, leading to increased input into the aquatic environment (Rivera-Utrilla et al., 2013; Salimi et al., 2017).

The application of tertiary treatments, such as ozonation and advanced oxidation, can be promising in removing recalcitrant PPCPs (Hofman-Caris et al., 2019; Wang et al., 2019). In Taiwan, chlorination is a tertiary treatment process in most wastewater treatment plants (WWTPs) that reduces bacterial concentrations in the effluent. Chlorination is cost-effective and can reduce the concentrations of some PPCPs with phenolic moieties (Westerhoff et al., 2005). As the reduction of concentrations indicates the removal of parent PPCPs, concerns have been raised regarding the generation of transformation products (TPs) in WWTPs (Pico and Barcelo, 2015).

Many studies have demonstrated that TPs of PPCPs can form during wastewater treatments and natural attenuation (Bagnis et al., 2018; Gworek et al., 2019; Hofman-Caris et al., 2019; Ojemaye and Petrik, 2019). The generation and occurrence of TPs in human and animal metabolism, biodegradation, hydrolysis, and photodegradation have been adequately investigated (Bagnis et al., 2018; Gworek et al., 2019; Hofman-Caris et al., 2019). However, most of those TPs are smaller molecules with simpler structures and higher polarities than their parent PPCPs (Ojemaye and Petrik, 2019).

Apart from the aforementioned TPs, laboratory studies have demonstrated that PPCPs can be transformed into halogenated TPs. A high dose of chlorine (10 mg/L) transformed acidic pharmaceuticals—including salicylic acid, naproxen, and diclofenac—into halogenated compounds through the substitution of hydrogens by chlorines or bromides on the aromatic rings (Quintana et al., 2010). At a lower dose (0.2–3 mg/L), PPCPs, such as triclosan and parabens, can be transformed into mono- and dichlorinated TPs (Chen et al., 2018; Vanderford et al., 2008). Besides in WWTPs, marine and estuarine environments with abundant halogens are favourable to the halogenation of organic contaminants (Comba et al., 2015; Li et al., 2016). These halogenated TPs have higher log K_{ow} values, indicating that they are potentially more bioaccumulative, persistent, and toxic than their parent PPCPs. However, their occurrence in the aquatic environment (either open sea or river) is rarely investigated.

Taichung is a metropolitan city that is adjacent to Taiwan Strait. Similar to most areas in West Taiwan, Taichung has tributaries of rivers of short lengths and fast flows draining into the Taiwan Strait. The tributaries receive wastewater effluents from municipal and

industrial WWTPs; all WWTPs conduct chlorination disinfection in addition to primary and secondary treatments. Instead, Kota Kinabalu is a coastal city located in Sabah, Malaysia, whose surface water bodies are some mixture of river water, seawater, and wastewater. The ditches, rivers, and seas receive direct wastewater discharges from nearby hospitals and residential and industrial sources. Taichung and Kota Kinabalu are similar in many respects. They are both highly urbanised cities with population densities of 1300–1500/km² located on an island in East Asia. Their climates are warm throughout the year (monthly average temperature above 15 °C and below 30 °C). However, Kota Kinabalu has more precipitation than Taichung (average annual rainfall 2788 mm and 1700 mm, respectively) because of the northeast monsoon between October and February. Because Taiwan and Malaysia have different policies for wastewater management and chemical control, we have the opportunity to investigate the waters that receive untreated wastewater and that receive chlorinated WWTP effluent in the urbans of high geographical, climatic, and population similarities. We hypothesized that chlorination in WWTPs and seawater can contribute to the occurrence of chlorinated TPs in the river water that receives WWTP effluent and the seawater that receives untreated wastewater, respectively. The profiles of PPCPs and the chlorinated TPs may be consequently different in these surface waters. This study compared the profiles of 16 chlorinated TPs and their parent PPCPs in the waters of these two places to elucidate the key factors affecting the occurrence of these micropollutants in the aquatic environment.

2. Methods

2.1. Samples

Wastewater samples were obtained from a domestic WWTP located in the metropolitan district of Taichung, Taiwan twice a month from December 2018 to April 2019. The average volume of water treated in this WWTP is 150 thousand cubic meters per day. The whole process of the WWTP includes primary treatment (filtration and sedimentation), secondary treatment (aeration), and chlorination. The influent (W0), primary and secondary treated wastewater (W1), and chlorinated effluent (W2) were obtained according to the hydraulic retention time provided by the WWTP. The water in the river that receives the effluent was also sampled at a site 50 m upstream of the effluent outlet (R0), at the outlet (R1), and 50 m downstream of the outlet (R2, Fig. 1).

The surface water that was receiving untreated wastewater was obtained from three ditches (D1–3) and beaches (B1–3, Fig. 2) in the coastal area of Kota Kinabalu monthly from December 2018 to February 2019. Sites D1–3 are adjacent to hospitals and the water receives untreated domestic wastewater and treated medical wastewater. Sites B1 to B3 are close to a resort, an outdoor activity centre, and a shopping mall, respectively, where the seawater receives direct discharges when people are engaged in recreational activities.

The field samplings were not performed on rainy days. When there was heavy rain (24-h accumulated rainfall ≥80 mm or 1-h rainfall ≥40 mm), the sampling was carried out three days later



Fig. 1. Sampling locations in Taichung. W0 (influent), W1 (primary and secondary treated wastewater), and W2 (chlorinated effluent) were located in the wastewater treatment plant. R0, R1, and R2 were in the river that receives the effluent at 50 m upstream of the effluent outlet, the outlet, and 50 m downstream of the outlet, respectively.

to avoid diluted samples. All the water samples were collected in amber glass bottles. The samples collected in Taichung and Kota Kinabalu were transported to the lab in Tunghai University, Taichung and University Malaysia Sabah, Kota Kinabalu, respectively, within 1 h. They were stored at 4 °C before the sample preparation in one week. The sampling, as well as sample storage and preparation, followed the identical protocol in both labs.

2.2. Analysis of aromatic PPCPs and TPs

We used the sample preparation method previously optimized for the analysis of PPCPs and TPs (Chen et al., 2018). In brief, a water sample (of 100 mL) was spiked with 100 ng of the isotopically labeled standards of the nine PPCPs, shaken, and filtered through a 0.45- μ m PVDF membrane. Solid-phase extraction (SPE) was conducted to separate nine PPCPs and 16 TPs from the wastewater and surface water matrix. A sample was passed through an Oasis HLB Vac Cartridge (6 mL, sorbent 200 mg, particle size 30 μ m; Waters Corp., Milford, MA, USA) which was pre-conditioned using 5 mL of methanol and 5 mL of Milli-Q water (resistivity 18.2 M Ω cm, Merck KGaA, Darmstadt, Germany). The cartridge was vacuum dried and then eluted with 5 mL of methanol containing 0.1% of ammonium hydroxide and 5 mL of methanol:dichloromethane (1:1, v/v) at 1 drop/s. The extract was concentrated to approximately 2 mL, filtered through a 0.20- μ m PTFE membrane, concentrated to nearly dry, and then shipped to National Taiwan University for sequential sample reconstitution (100 μ L of methanol:Milli-Q water (1:1, v/v)) and instrumental analysis.

Both analyses of the PPCPs and TPs were performed on an ultra-performance liquid chromatography device (UPLC, ACQUITY UPLC, Waters Corp.) coupled with a triple-quadrupole mass spectrometer (QQQ, Quattro Premier XE, Waters Corp.). We employed the parameters used on a UPLC-quadrupole-time of flight system (Bruker microTOF-Q, Bruker Corporation, Billerica, MA, USA) in our

previous study on the screening of TPs (Chen et al., 2018). The parameters were optimized for the semi-quantification of TPs that are without standards on the present UPLC-QQQ system, which was achieved by injecting the model water samples which were spiked with 5000 ng/L of aromatic PPCPs and chlorinated at the same doses as those in our previous study (0.2 mg/L and 0.7 mg/L). The mass chromatograms of these TPs in the model water were acquired to calibrate the retention times and ion transitions (Fig. S1) under the same chromatographic conditions of our previous study. These conditions include the column (MN Nucleoshell RP 18, 50 \times 2.0 mm i.d., particle size 2.7 μ m, Macherey-Nagel, Düren, Germany), mobile phases, and elution gradients. The mobile phases were 5 mM ammonium acetate_(aq) with 0.1% of acetic acid and acetonitrile in the positive ionisation mode and 0.005% of acetic acid_(aq) and acetonitrile in the negative ionisation mode. The flow rate was 0.5 mL/min at 40 °C.

The analytes were detected in the selected reaction monitoring mode (Table 1). All PPCPs and four TPs (of which standards were commercially available) were quantified using isotope dilution. The four TPs were methyl 3-chloro-4-hydroxybenzoate (Cl-methylparaben), methyl 3,5-dichloro-4-hydroxybenzoate (2Cl-methylparaben), ethyl 3-chloro-4-hydroxybenzoate (Cl-ethylparaben), and propyl 3-chloro-4-hydroxybenzoate (Cl-propylparaben). Two ion transitions were monitored to acquire the signals of both the most abundant product ion for quantification as well as the second abundant ion for confirmation. As for the other 12 TPs of which standards were not available, only one ion transition of each compound was monitored. They were semi-quantified by normalizing the peak area to that of the isotopically labeled PPCPs acquired from the same acquisition segment (Table 1).

2.3. Quality assurance and quality control

Reagent blanks, field blanks, duplicates, and matrix spikes were analysed with each batch of real samples. The matrix spikes were conducted by spiking 100 ng/L and 5000 ng/L of PPCPs, Cl-methylparaben, 2Cl-methylparaben, Cl-ethylparaben, and Cl-propylparaben into the R0 sample. The recovery of each of these compounds was evaluated using matrix spikes ($n = 3$) to exhibit the precision and accuracy of quantification. The concentration in R0 was deducted if a compound was detected. The limits of detection (LODs) and quantification (LOQs) were evaluated using the 100-ng/L matrix spikes ($n = 3$), which were calculated using the confirmatory and quantitative ions at S/N ratio = 3 and 10, respectively. In the case that the calculated LOQ < LOD, the LOD was reported as the LOQ (Chen et al., 2012b).

To prevent the adsorption of basic compounds onto the surface, glassware was rinsed with toluene that contained 7% of dimethyldichlorosilane and then rinsed with acetone and methanol before use. After use, it was sonicated sequentially for 15 min in tap water and Milli-Q water and then rinsed with acetone and methanol to remove potential residual contaminants. The use of plastics was avoided except for the SPE cartridges, syringe filters, and pipette tips, which were rinsed using methanol to remove the unbound monomers on the surface.

2.4. Statistics

The median concentrations and positive rates of PPCPs and TPs were calculated to describe the spatial distribution. The removal rates of PPCPs by the whole process and chlorination in the WWTP were evaluated by dividing the reduced concentration by the concentration of influent and before chlorination, respectively, for each batch of samples. The levels of mean and standard deviation were then calculated to describe the removal rates during the

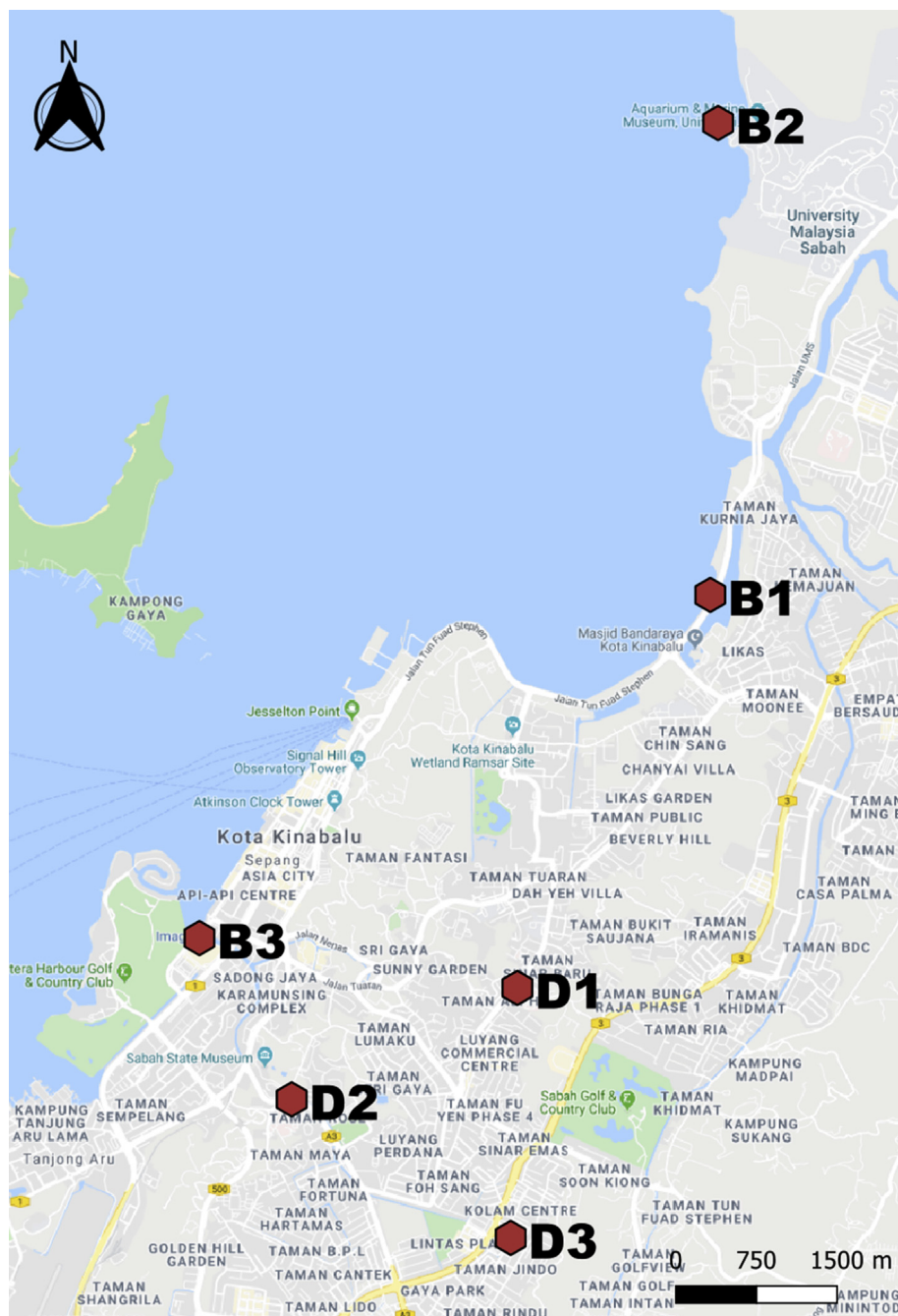


Fig. 2. Sampling locations in Kota Kinabalu. Ditch water (D1–3) was taken at the wastewater outlets in the ditches adjacent to hospitals. Seawater (B1–B3) was taken at the beaches close to a resort, an outdoor activity centre, and a shopping mall, respectively.

sampling period. Principal component analysis (PCA) on MetaboAnalyst 4.0 (Chong et al., 2018) was applied to compare the profiles of PPCPs and TP among sampling sites and times. For each PCA model, the concentrations were log-transformed, mean-centred, and divided by the standard deviation of each compound. If a PCA model discriminates the chemical profiles of different groups, the differences in concentrations between two groups and among more than two groups were analysed using Wilcoxon rank-sum test and Kruskal–Wallis test by ranks, respectively.

3. Results and discussions

3.1. Analytical method performance

The method optimized for the determination of all PPCPs, CI-methylparaben, and 2Cl-methylparaben showed satisfactory accuracy and precision with the means and standard deviations of recoveries ranged within $100\% \pm 20\%$ (82.3%–118.3%) and $<20\%$ (0.64%–17.2%), respectively (Table S1). However, the levels of

Table 1

Parameters for the quantification and semi-quantification of analytes.

	Formula	Retention time (min)	Ion transitions	Internal standard
PPCPs				
Acetaminophen	C ₈ H ₉ NO ₂	0.42	(+) 151.8 > 109.8, 151.8 > 92.7	Acetaminophen- ² D ₄
Bisphenol A	C ₁₅ H ₁₆ O ₂	2.45	(-) 227.0 > 211.0, 227.0 > 132.8	Bisphenol A- ¹³ C ₁₂
Butylparaben	C ₁₁ H ₁₄ O ₃	2.91	(-) 192.9 > 136.0, 192.9 > 91.8	Butylparaben- ¹³ C ₆
Diclofenac	C ₁₄ H ₁₁ Cl ₂ NO ₂	3.42	(-) 295.9 > 251.9, 293.9 > 249.9	Diclofenac- ² D ₄
Ethylparaben	C ₉ H ₁₀ O ₃	1.63	(-) 164.7 > 135.7, 164.7 > 91.9	Ethylparaben- ¹³ C ₆
Methylparaben	C ₈ H ₈ O ₃	1.00	(-) 150.8 > 135.7, 150.8 > 91.8	Methylparaben- ¹³ C ₆
Oxybenzone	C ₁₄ H ₁₂ O ₃	3.57	(+) 229.0 > 150.8, 229.0 > 104.7	Oxybenzone- ¹³ C ₆
Propylparaben	C ₁₀ H ₁₂ O ₃	2.30	(-) 178.8 > 135.9, 178.8 > 91.9	Propylparaben- ¹³ C ₆
Triclosan	C ₁₂ H ₇ Cl ₃ O ₂	4.17	(-) 288.8 > 35.1, 286.8 > 35.1	Triclosan- ¹³ C ₂
TPs				
2Cl-methylparaben	C ₈ H ₆ Cl ₂ O ₃	2.42	(-) 218.9 > 159.4, 218.9 > 131.4	Propylparaben- ¹³ C ₆
2Cl-acetaminophen ^a	C ₈ H ₇ Cl ₂ NO ₂	0.80	(-) 217.9 > 174.7	Methylparaben- ¹³ C ₆
Cl-methylparaben	C ₈ H ₇ ClO ₃	1.82	(-) 185.0 > 169.4, 185.0 > 125.6	Ethylparaben- ¹³ C ₆
2Cl-ethylparaben ^a	C ₉ H ₈ Cl ₂ O ₃	3.04	(-) 232.9 > 160.1	Butylparaben- ¹³ C ₆
Cl-ethylparaben ^a	C ₉ H ₉ ClO ₃	2.44	(-) 199.0 > 169.5, 199.0 > 125.8	Propylparaben- ¹³ C ₆
2Cl-propylparaben ^a	C ₁₀ H ₁₀ Cl ₂ O ₃	3.53	(-) 246.9 > 159.9	Diclofenac- ² D ₄
Cl-propylparaben ^a	C ₁₀ H ₁₁ ClO ₃	3.02	(-) 213.0 > 171.0, 213.0 > 125.9	Butylparaben- ¹³ C ₆
2Cl-butylparaben ^a	C ₁₁ H ₁₂ Cl ₂ O ₃	3.93	(-) 261.0 > 159.7	Triclosan- ¹³ C ₂
Cl-butylparaben ^a	C ₁₁ H ₁₃ ClO ₃	3.48	(-) 227.0 > 125.6	Diclofenac- ² D ₄
2Cl-triclosan ^a	C ₁₂ H ₅ Cl ₃ O ₂	4.70	(-) 354.8 > 210.0	Triclosan- ¹³ C ₂
Cl-triclosan ^a	C ₁₂ H ₆ Cl ₄ O ₂	4.38	(-) 320.9 > 320.9	Triclosan- ¹³ C ₂
3Cl-benzylamine ^a	C ₁₃ H ₁₀ Cl ₃ N	3.33	(-) 284.1 > 284.1	Diclofenac- ² D ₄
2Cl-oxybenzone ^a	C ₁₄ H ₁₀ Cl ₂ O ₃	4.36	(-) 294.9 > 278.9	Triclosan- ¹³ C ₂
Cl-diclofenac ^a	C ₁₄ H ₁₀ Cl ₃ NO ₂	3.69	(-) 328.9 > 249.8	Diclofenac- ² D ₄
3Cl-bisphenol A ^a	C ₁₅ H ₁₃ Cl ₃ O ₂	3.67	(-) 328.9 > 314.2	Diclofenac- ² D ₄
Cl-bisphenol A ^a	C ₁₅ H ₁₅ ClO ₂	4.03	(-) 261.0 > 180.8	Triclosan- ¹³ C ₂

^a Semi-quantified TPs.

quantitative bias of Cl-ethylparaben and Cl-propylparaben were approximately 40% and 30%, respectively (Table S1), because their isotopically labeled internal standards were unavailable and the substitutes acquired from the same segment (propylparaben-¹³C₆ and butylparaben-¹³C₆, respectively) had lower recoveries than these two TPs. Because of this finding, the abundance of Cl-ethylparaben and Cl-propylparaben were expressed as relative concentrations throughout this study.

The limits of detection for butylparaben, diclofenac, ethylparaben, methylparaben, propylparaben, and Cl-methylparaben were below 10 ng/L, while those of the other PPCPs and 2Cl-methylparaben ranged from 10.6 to 59.6 ng/L (Table S1). None of the PPCPs or TPs was positively detected in the blanks. The duplicates exhibited good reproducibility of semi-quantified TPs with relative percent differences of relative concentrations <15% for positive detects. For example, 2Cl-propylparaben and Cl-butylparaben were found in the duplicate influent samples taken in February 2019 with relative percent differences at 0.46% and 2.09%, respectively.

3.2. PPCPs and TPs in Taichung, Taiwan

All nine target PPCPs were found in the wastewater and the river water of Taichung. The aromatic PPCPs were most abundant in the wastewater influent, where the median concentration of acetaminophen reached 9.2 µg/L (Table 2). The majority of the detected concentrations were below 100 ng/L, with the exceptions of acetaminophen in the influent and river water, diclofenac in the wastewater and river water, and both methylparaben and triclosan in the influent (Table 2). The considerably high abundance of acetaminophen in the wastewater reflected its high use in the population. According to the latest data (National Health Insurance Administration, Taiwan Ministry of Health and Welfare, 2019), Taiwan uses 168 tons of acetaminophen a year. To obtain the annual use of personal care products, we searched for each of them on a publicly-available database of chemical substances (Toxic and

Chemical Substances Bureau, Taiwan Environmental Protection Administration, 2019). These data indicated that diclofenac and methylparaben were also extensively used in Taiwan (5.0 and 3.0 tons annually, Table S2). Although bisphenol A was more intensely used (at 7.2 tons annually), it is primarily applied in plastics rather than in aqueous solutions or creams as methylparaben and diclofenac, which are readily mixed with wastewater. The concentrations of bisphenol A was stable and not especially high in the wastewater (60.3–78.0 ng/L), compared to acetaminophen (9200 ng/L), methylparaben (179 ng/L), and triclosan (221 ng/L) in the influent and diclofenac in all the wastewater (228–314 ng/L, Table 2). The levels of bisphenol A were within the range of that obtained in a recent survey in Taiwan (Chou et al., 2015).

The whole process (primary, secondary and chlorination treatments) in the WWTP removed almost all the acetaminophen, ethylparaben, oxybenzone, and propylparaben (removal rate >95%, Table 3) and more than half the butylparaben, methylparaben, and triclosan (73.9%, 84.0%, and 53.1%, respectively, Table 3). Less than half amount of bisphenol A and diclofenac were removed, which resulted in the discharge of 70.4 ng/L and 228 ng/L, respectively, with the effluent (Table 2). This explains the 75.1 ng/L increase of diclofenac in the river near the effluent outlet relative to the concentrations at the upstream site (Table 2). Other studies also observed that WWTPs have difficulty removing bisphenol A and diclofenac, which resulted in its constant occurrence in all effluents and contributed to the loads in surface waters (Hofman-Caris et al., 2019). Chlorination was not the predominant treatment method in the WWTP. The removal rates provided by chlorination were <30%, except for butylparaben and ethylparaben (removal rates achieved 132% and 47.1%, respectively, Table 2). Though, both these removal rates were highly variable (standard deviations: 228% and 66.6%, respectively).

Among the TPs, only 2Cl-propylparaben was found at all sampling sites at detection frequencies of 57.1–71.4% (Table 2). The relative concentration of 2Cl-propylparaben in the water after chlorination was 1.49 times higher than that before chlorination.

Table 2
Median concentrations (positive rate%) of PPCPs and TPs (ng/L) in the wastewater and the river that receives the effluent in Taichung.

	Wastewater			River		
	Influent	Before chlorination	Effluent	Upstream	Outlet	Downstream
Acetaminophen	9200 (100%)	ND (16.7%)	ND (0.00%)	262 (66.7%)	150 (100%)	132 (100%)
Bisphenol A	60.3 (66.7%)	78.0 (66.7%)	70.4 (100%)	60.3 (66.7%)	63.3 (50.0%)	62.5 (83.3%)
Butylparaben	ND (33.3%)	ND (16.7%)	ND (0.00%)	3.60 (50.0%)	ND (33.3%)	ND (0.00%)
Diclofenac	314 (100%)	261 (100%)	228 (100%)	41.9 (66.7%)	117 (100%)	101 (100%)
Ethylparaben	2.45 (50.0%)	ND (16.7%)	ND (0.00%)	ND (33.3%)	ND (33.3%)	1.40 (33.3%)
Methylparaben	179 (100%)	79.8 (100%)	25.3 (100%)	90.2 (66.7%)	32.2 (100%)	33.8 (100%)
Oxybenzone	93.4 (100%)	ND (16.7%)	ND (0.00%)	21.4 (50.0%)	ND (16.7%)	ND (16.7%)
Propylparaben	36.0 (83.3%)	ND (33.3%)	ND (16.7%)	35.6 (66.7%)	20.7 (100%)	21.7 (100%)
Triclosan	221 (100%)	72.0 (100%)	48.4 (100%)	54.2 (66.7%)	43.6 (100%)	40.0 (83.3%)
2Cl-methylparaben	152 (50.0%)	ND (0.00%)	ND (0.00%)	1.80 (42.9%)	ND (28.6%)	ND (0.00%)
2Cl-acetaminophen ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-methylparaben	5.40 (100%)	ND (0.00%)	ND (0.00%)	0.900 (42.9%)	ND (14.3%)	ND (0.00%)
2Cl-ethylparaben ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (28.6%)
Cl-ethylparaben ^a	ND (33.3%)	ND (0.00%)	ND (0.00%)	ND (28.6%)	ND (14.3%)	ND (0.00%)
2Cl-propylparaben ^a	161 (66.7%)	6.77 (71.4%)	10.1 (57.1%)	11.7 (71.4%)	8.30 (71.4%)	7.40 (71.4%)
Cl-propylparaben ^a	0.400 (33.3%)	ND (0.00%)	ND (0.00%)	ND (28.6%)	ND (14.3%)	ND (0.00%)
2Cl-butylparaben ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-butylparaben ^a	1.88 (50.0%)	ND (14.3%)	ND (0.00%)	ND (28.6%)	ND (28.6%)	ND (14.3%)
2Cl-triclosan ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (14.3%)
Cl-triclosan ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
3Cl-benzylamine ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
2Cl-oxybenzone ^a	ND (0.00%)	ND (0.00%)	ND (14.3%)	ND (0.00%)	ND (14.3%)	ND (14.3%)
Cl-diclofenac ^a	ND (0.00%)	ND (14.3%)	ND (0.00%)	ND (14.3%)	ND (0.00%)	ND (0.00%)
3Cl-bisphenol A ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (14.3%)	ND (0.00%)	ND (0.00%)
Cl-bisphenol A ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)

^a Semi-quantified by normalizing the peak areas to that of the internal standard in the same segment of the run.**Table 3**
Removal of aromatic PPCPs in the WWTP in Taichung.

	Whole process ^a	Chlorination
Acetaminophen	100% ± 0.00%	0.85% ± 1.47%
Bisphenol A	−41.7% ± 133%	−19.7% ± 86.2%
Butylparaben	73.9% ± 4.73%	132% ± 228%
Diclofenac	32.8% ± 10.9%	6.75% ± 3.85%
Ethylparaben	100% ± 0.00%	47.1% ± 66.6%
Methylparaben	84.0% ± 9.05%	22.8% ± 29.1%
Oxybenzone	100% ± 0.00%	14.2% ± 24.7%
Propylparaben	96.5% ± 1.93%	13.9% ± 13.4%
Triclosan	53.1% ± 44.8%	−6.12% ± 23.4%

^a Whole process: primary treatment (filtration and sedimentation), secondary treatment (aeration), and chlorination.

However, the highest relative concentration was detected in the influent, which decreased by 23.8 times after primary and secondary treatments (Fig. 3). Canosa et al. (2006) also discovered 2Cl-methylparaben and 2Cl-propylparaben in wastewater influent. In addition, we found the frequent occurrence of 2Cl-propylparaben in the river (>70%), with a slightly higher level at the upstream site relative to those at the other two river sites (Table 2). These results revealed that unspecified sources other than chlorinated wastewater contributed to the presence of 2Cl-propylparaben in the wastewater and river. Nevertheless, primary and secondary treatments removed almost all the 2Cl-propylparaben (95.8%), and the effluent discharge did not result in the increase in 2Cl-propylparaben levels in the receiving river (Fig. 3, Table 2). Similar trends were observed for Cl-propylparaben as well as the TPs of methylparaben and butylparaben (Fig. 3). The absence of chlorinated diclofenac and bisphenol A was also reported in other WWTPs employing primary, secondary, and chlorination treatments (Bullock et al., 2015). However, the removal of these chlorinated derivatives was not found in literature.

3.3. PPCPs and TPs in Kota Kinabalu, Sabah, Malaysia

In the surface water in the coastal area of Kota Kinabalu, acetaminophen, bisphenol A, butylparaben, and oxybenzone were absent or scarcely detected (Table 4). The concentrations of the ubiquitously-detected PPCPs, including diclofenac, ethylparaben, methylparaben, and propylparaben, were generally more than ten times higher near the wastewater outlet than in the seawater. Triclosan was detected at thousands ng/L near the wastewater outlet but was absent in the seawater. Triclosan in seawater is more vulnerable to photodegradation than in freshwater (Aranami and Readman, 2007). Kota Kinabalu is located along the equatorial belt where the sea is exposed to direct sun radiation. The dilution by seawater along with photodegradation in seawater may explain the absence of triclosan. The highest concentrations of these PPCPs were detected at Site D1 (Table 4), which has a width of 1.5 m and a water depth of 2 m in general and maintains at 30 ± 5 cm on consecutive sunny days. The water in this shallow ditch was mainly composed of the sewage discharge adjacent to a hospital. Hospitals are one of the most frequently listed emission sources of pharmaceuticals (Cizmas et al., 2015; der Beek et al., 2016). The concentrations of diclofenac in the wastewater outlet adjacent to hospitals (medians 84.7–1030 ng/L) were comparable to previous reports (<50–2100 ng/L in hospital wastewater effluents) (Carraro et al., 2016; Chen et al., 2012a; Gomez et al., 2006; Kosma et al., 2010). Literature exhibits considerable variation on acetaminophen concentrations (<100–29000 ng/L) (Carraro et al., 2016; Chen et al., 2012a; Gomez et al., 2006; Kosma et al., 2010). In Kota Kinabalu, acetaminophen was only detected in one sample at 270 ng/L. The absence of acetaminophen in most of the ditch water receiving hospital wastewater is probably because acetaminophen is an over-the-counter drug sold directly to the consumer rather than prescribed and applied in the hospital (Sim et al., 2011). The other PPCPs were rarely studied or not detected (such as triclosan by Kosma et al., 2010) in hospital wastewaters in literature.

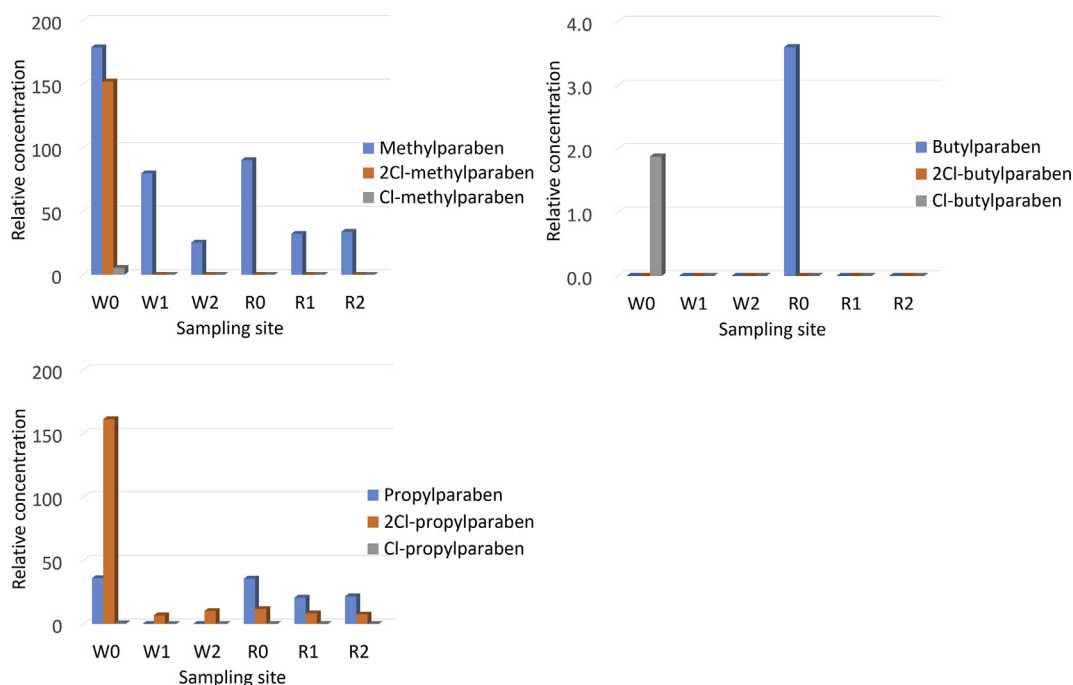


Fig. 3. Relative concentrations of TPs and their parent PPCPs in the WWTP in Taichung. W0: influent; W1: primary and secondary treated wastewater; W2: chlorinated effluent; R0: 50 m upstream of the effluent outlet in the river that receives the effluent; R1: at the outlet; R2: 50 m downstream of the outlet.

Table 4

Median concentrations (%detection frequency) of PPCPs and TPs (ng/L) in the surface water in Kota Kinabalu.

	Seawater			Wastewater outlet		
	B1	B2	B3	D1	D2	D3
Acetaminophen	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (33.3%)	ND (0.00%)
Bisphenol A	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Butylparaben	ND (0.00%)	ND (0.00%)	ND (33.3%)	ND (0.00%)	71.1 (66.7%)	ND (0.00%)
Diclofenac	ND (0.00%)	10.2 (66.7%)	42.7 (100%)	1030 (100%)	544 (100%)	84.7 (100%)
Ethylparaben	115 (100%)	153 (100%)	228 (100%)	1810 (100%)	1110 (100%)	503 (100%)
Methylparaben	467 (100%)	225 (100%)	1030 (100%)	9400 (100%)	5540 (100%)	1810 (100%)
Oxybenzone	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Propylparaben	28.8 (66.7%)	25.0 (66.7%)	314 (100%)	4810 (100%)	2600 (100%)	369 (66.7%)
Triclosan	ND (0.00%)	ND (0.00%)	ND (0.00%)	2560 (100%)	1010 (100%)	2030 (100%)
2Cl-methylparaben	2180 (33.3%)	948 (33.3%)	645 (33.3%)	13400 (33.3%)	2220 (66.7%)	ND (0.00%)
2Cl-acetaminophen ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-methylparaben	ND (0.00%)	ND (0.00%)	ND (0.00%)	186 (100%)	267 (66.7%)	77.1 (66.7%)
2Cl-ethylparaben ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-ethylparaben ^a	19.8 (33.3%)	ND (0.00%)	86.0 (33.3%)	576 (33.3%)	19.0 (33.3%)	ND (0.00%)
2Cl-propylparaben ^a	39.6 (33.3%)	13.5 (33.3%)	77.8 (66.7%)	1430 (100%)	308 (100%)	299 (100%)
Cl-propylparaben ^a	2.20 (33.3%)	ND (0.00%)	ND (0.00%)	2480 (100%)	2150 (66.7%)	ND (0.00%)
2Cl-butylparaben ^a	174 (33.3%)	200 (33.3%)	ND (0.00%)	1380 (33.3%)	ND (0.00%)	772 (33.3%)
Cl-butylparaben ^a	22.8 (33.3%)	ND (0.00%)	ND (0.00%)	67.2 (66.7%)	ND (0.00%)	35.2 (33.3%)
2Cl-triclosan ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-triclosan ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	372 (66.7%)
3Cl-benzylalanine ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
2Cl-oxybenzone ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
Cl-diclofenac ^a	177 (33.3%)	ND (0.00%)	91.3 (66.7%)	ND (0.00%)	ND (0.00%)	ND (0.00%)
3Cl-bisphenol A ^a	104 (33.3%)	ND (0.00%)	295 (33.3%)	386 (33.3%)	ND (0.00%)	ND (0.00%)
Cl-bisphenol A ^a	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)	ND (0.00%)

^a Semi-quantified by normalizing the peak areas to that of the internal standard in the same segment of the run.

Acetaminophen and diclofenac ranked top 10 and 24, respectively, among the most used drugs in Malaysia (Pharmaceutical Services Division, Ministry of Health Malaysia, 2017), at the amounts of 8.21 and 3.96 DDD/1000 population/day, respectively, equivalent to 272 and 4.4 tons/year (WHO Collaborating Centre for Drug Statistics, 2019) (Table S2). Although the statistical data echoed the considerable discharge of diclofenac (up to 1030 g/L), they could not explain the absence of acetaminophen in the

seawater. However, because Sabah is remote (i.e. far from the administrative centre of Malaysia), nationwide statistics may not represent the actual trend of pharmaceutical use in Kota Kinabalu. Therefore, a detailed search on the local drug use is necessary in order to understand the commutation of drugs in wastewater. Unfortunately, data on the amount other PPCPs used are unavailable.

The profiles of PPCPs and TPs were different between seawater

and ditch water taken at the beaches and wastewater outlets, respectively (Fig. 4). The first principal component, which explained 69.3% total variance, was mainly composed of diclofenac, ethylparaben, methylparaben, propylparaben, triclosan, Cl-methylparaben, 2Cl-propylparaben, and Cl-propylparaben (loadings >0.30, Fig. 4). The concentrations of these eight compounds in the ditch water were significantly higher than those in the seawater ($p < 0.05$), probably attributing to the dilution of seawater. Eight of the TPs—2Cl-methylparaben, Cl-ethylparaben, 2Cl-propylparaben, Cl-propylparaben, 2Cl-butylparaben, Cl-butylparaben, Cl-triclosan, and 3Cl-bisphenol A—were detected in both the ditch water and seawater samples, whereas Cl-methylparaben was only present in the ditch, and Cl-diclofenac was only present in the sea (Table 4, Fig. 5). Among the sampling sites, the highest concentrations of all PPCPs and all TPs, except for Cl-methylparaben, diclofenac, and triclosan, were observed at Site D1 (surrounded by housing area and a hospital adjacent to the sampling site). The relative concentrations of TPs did not depend on that of the parent PPCPs or the halogen abundance of the water.

3.4. Comparisons of chemical profiles

Although some studies on wastewater and natural waters have observed seasonal variations in the occurrence of micropollutants because of greater photochemical and biological degradation in summer, concentration effects in dry seasons, or flushes into the rivers in rainy seasons (Borrull et al., 2019; Nam et al., 2014; Padhye et al., 2014; Pal et al., 2014), no significant temporal trend in the occurrence of PPCPs or TPs was observed in Taichung or Kota Kinabalu in the time frame of this study (Fig. S2 and S3, respectively). This is consistent with a previous observation of micropollutants in the surface water of North Taiwan (Chen et al., 2014). Taiwan and Malaysia both have oceanic and tropical climates that are characterised by warm temperatures and high levels of precipitation throughout the year. Although the temporally stable trend that is observed in this study is different from those in many previous reports, it is typical in the islands of the tropical region.

Despite the many similarities between Taichung and Kota

Kinabalu, their profiles of chlorinated TPs and their parent PPCPs in the surface water are very different (Fig. 6). The first principal component, which explained 52.7% total variance, was mainly composed of diclofenac, ethylparaben, methylparaben, propylparaben, triclosan, and 2Cl-propylparaben (loadings < -0.30, Fig. 6). The river that receives treated wastewater in Taichung contained only the detectable TPs of parabens and all target PPCPs at median concentrations ranging from 1.40 to 262 ng/L (Table 3). By contrast, the surface water bodies that receive untreated wastewater in Kota Kinabalu contained the chlorinated TPs of parabens, triclosan, diclofenac, and bisphenol A; only diclofenac, ethylparaben, methylparaben, propylparaben, and triclosan were detectable at more than one site at median concentrations from 10.2 to 9400 ng/L (Table 4). Higher concentrations of 2Cl-propylparaben, methylparaben, ethylparaben, and propylparaben were detected in the water of Kota Kinabalu than Taichung, while the opposite was observed in acetaminophen and bisphenol A ($p < 0.05$).

The outcomes regarding the comparisons of different water bodies suggest that the TPs may not be generated from disinfection in WWTPs or halogenation in the sea. Active ingredients of PPCPs are also used in manufacturing industries. The manufacturing processes involving contacts between aromatic PPCPs and halogenated reagents, such as paper bleaching, can be an origin of chlorinated micropollutants (Fukazawa et al., 2002). Previous reports have indicated the occurrence of chlorinated derivatives of bisphenol A, diclofenac, and parabens in wastewater, drinking water, and swimming pools (Bullock et al., 2015; Fan et al., 2013; Li et al., 2015). However, only 3Cl-bisphenol A (at <10 ng/L, Yang et al., 2014) and chlorinated parabens (up to 28 ng/L, Terasaki et al., 2012) were reported to present in river water among natural waters, to the best of our knowledge. The profiles of PPCPs and their chlorinated derivatives in the natural surface waters elaborated by this study are the consequence of multiple-source contamination. The higher concentrations of chlorinated derivatives would indicate more exposure to persistent, bioaccumulative, and toxic compounds among aquatic species (Haman et al., 2015; Pan et al., 2019). Although this study did not specify the source of each chlorinated derivative, the decreases in the levels of chlorinated derivatives in

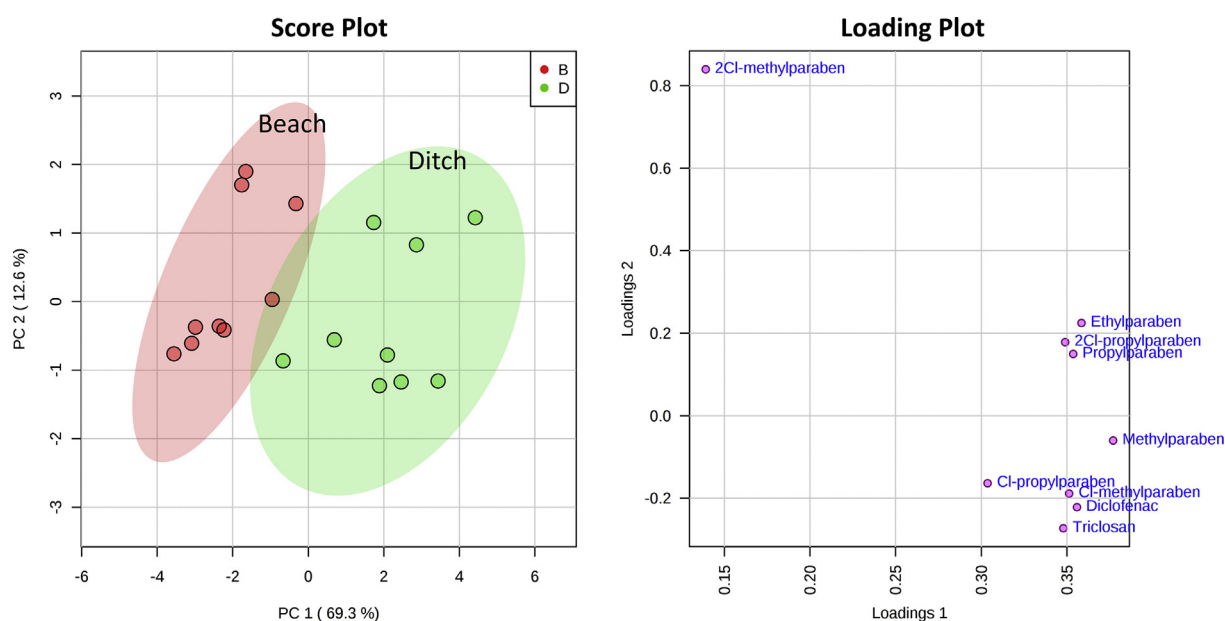


Fig. 4. The score plot and loading plot of principal component analysis model for the comparison of chemical profiles between seawater taken at the beaches (B) and ditch water taken at the wastewater outlets (D) in Kota Kinabalu.

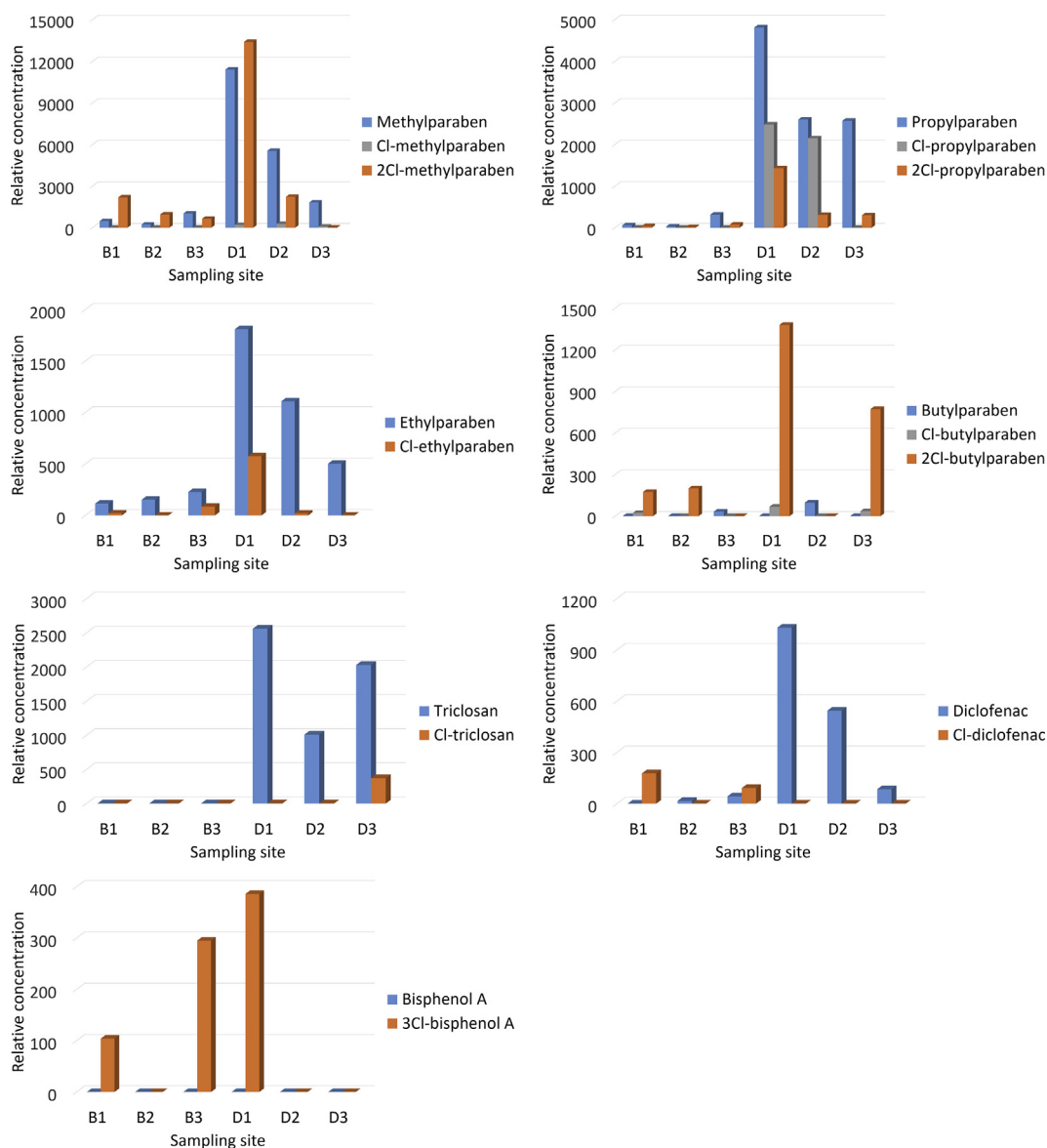


Fig. 5. Relative concentrations of TPs and their parent PPCPs in the surface water in Kota Kinabalu. B1–3: seawater taken at the beaches close to a resort, an outdoor activity centre, and a shopping mall; D1–3 ditch water taken at the outlets of wastewater.

the WWTP demonstrated that the prevention of their contamination can still be achieved by applying conventional wastewater treatments.

4. Conclusion

This is the first study to quantitatively and semi-quantitatively investigate multiple chlorinated TPs of nine aromatic micropollutants in the aquatic environment. The simultaneous analysis of multiple TPs and micropollutants facilitated the examination of their relationship in real world. Chlorinated derivatives of bisphenol A, diclofenac, triclosan, and parabens were detected in the surface water of coastal cities from tropical islands. The comparisons of the profiles of these substances in urban water bodies—specifically, wastewater, surface water receiving treated

wastewater, surface water receiving untreated surface water, freshwater, and seawater—suggest that chlorination in WWTPs or seawater may not be responsible for the generation of the chlorinated TPs. Although the earlier hypothesis was overruled by analytical results and the sources of those chlorinated derivatives were not specified, this study sheds light on water resource conservation by demonstrating that conventional processes in WWTPs can reduce the input of some chlorinated substances into natural water bodies.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

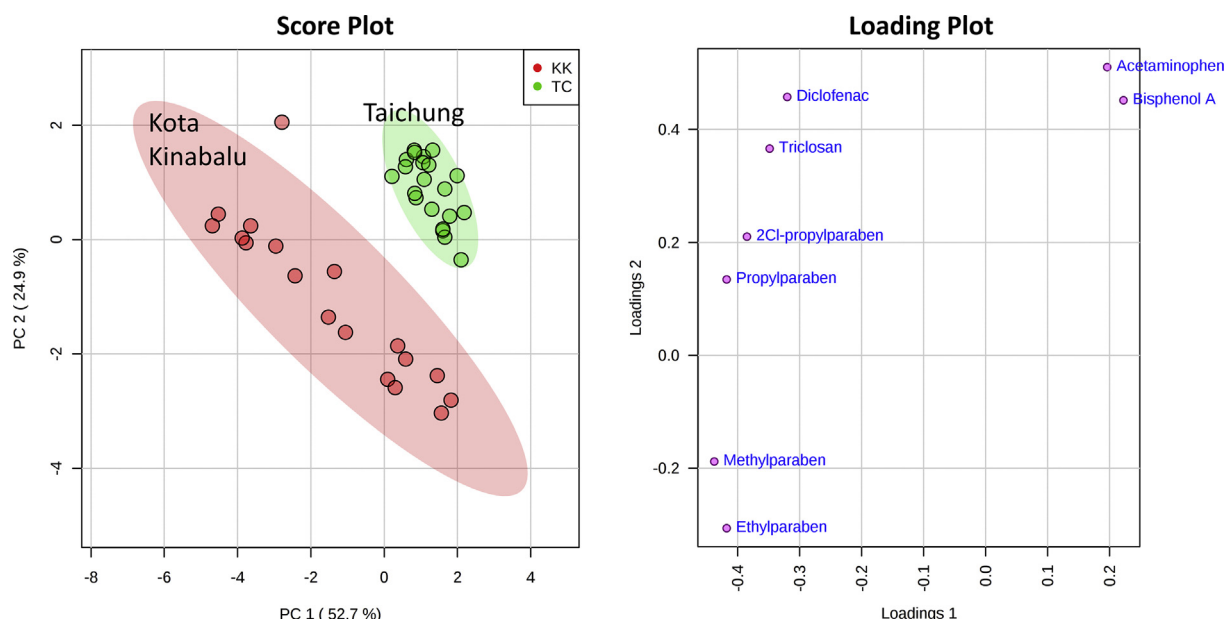


Fig. 6. The score plot and loading plot of principal component analysis model for the comparison of chemical profiles between Kota Kinabalu (KK) and Taichung (TC).

Acknowledgement

This study was supported by the Taiwan Ministry of Science and Technology (MOST 105-2218-E-029-001-MY3).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.chemosphere.2019.125268>.

References

- Aranami, K., Readman, J.W., 2007. Photolytic degradation of triclosan in freshwater and seawater. *Chemosphere* 66 (6), 1052–1056.
- Bagnis, S., Fitzsimons, M.F., Snape, J., Tappin, A., Comber, S., 2018. Processes of distribution of pharmaceuticals in surface freshwaters: implications for risk assessment. *Environ. Chem. Lett.* 16 (4), 1193–1216.
- Borrull, J., Colom, A., Fabregas, J., Pocurull, E., Borrull, F., 2019. A simple, fast method for the analysis of 20 contaminants of emerging concern in river water using large-volume direct injection liquid chromatography-tandem mass spectrometry. *Anal. Bioanal. Chem.* 411 (8), 1601–1610.
- Bullock, D.N., Nelson, E.D., Carr, S.A., Wissman, C.R., Armstrong, J.L., Schlenk, D., Larive, C.K., 2015. Occurrence of halogenated transformation products of selected pharmaceuticals and personal care products in secondary and tertiary treated wastewaters from southern California. *Environ. Sci. Technol.* 49 (4), 2044–2051.
- Canosa, P., Rodriguez, I., Rubi, E., Negreira, N., Cela, R., 2006. Formation of halogenated by-products of parabens in chlorinated water. *Anal. Chim.* 575 (1), 106–113.
- Carraro, E., Bonetta, S., Bertino, C., Lorenzi, E., Bonetta, S., Gilli, G., 2016. Hospital effluents management: chemical, physical, microbiological risks and legislation in different countries. *J. Environ. Manag.* 168, 185–199.
- Chen, W.-L., Cheng, J.-Y., Lin, X.-Q., 2018. Systematic screening and identification of the chlorinated transformation products of aromatic pharmaceuticals and personal care products using high-resolution mass spectrometry. *Sci. Total Environ.* 637–638, 253–263.
- Chen, W.-L., Gwo, J.-C., Wang, G.-S., Chen, C.-Y., 2014. Distribution of feminizing compounds in the aquatic environment and bioaccumulation in wild tilapia tissues. *Environ. Sci. Pollut. Res.* 21 (19), 11349–11360.
- Chen, H., Li, X.J., Zhu, S.C., 2012a. Occurrence and distribution of selected pharmaceuticals and personal care products in aquatic environments: a comparative study of regions in China with different urbanization levels. *Environ. Sci. Pollut. Res.* 19 (6), 2381–2389.
- Chen, W.-L., Wang, G.-S., Gwo, J.-C., Chen, C.-Y., 2012b. Ultra-high performance liquid chromatography/tandem mass spectrometry determination of feminizing chemicals in river water, sediment and tissue pretreated using disk-type solid-phase extraction and matrix solid-phase dispersion. *Talanta* 89, 237–245.
- Chong, J., Soufan, O., Li, C., Caraus, I., Li, S.Z., Bourque, G., Wishart, D.S., Xia, J.G., 2018. MetaboAnalyst 4.0: towards more transparent and integrative metabolomics analysis. *Nucleic Acids Res.* 46 (W1), W486–W494.
- Chou, P.H., Lin, Y.L., Liu, T.C., Chen, K.Y., 2015. Exploring potential contributors to endocrine disrupting activities in Taiwan's surface waters using yeast assays and chemical analysis. *Chemosphere* 138, 814–820.
- Cizmas, L., Sharma, V.K., Gray, C.M., McDonald, T.J., 2015. Pharmaceuticals and personal care products in waters: occurrence, toxicity, and risk. *Environ. Chem. Lett.* 13 (4), 381–394.
- Comba, P., Kersch, M., Krause, T., Scholer, H.F., 2015. Iron-catalysed oxidation and halogenation of organic matter in nature. *Environ. Chem.* 12 (4), 381–395.
- der Beek, T.A., Weber, F.A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Kuster, A., 2016. Pharmaceuticals in the environment-global occurrences and perspectives. *Environ. Toxicol. Chem.* 35 (4), 823–835.
- Fan, Z.L., Hu, J.Y., An, W., Yang, M., 2013. Detection and occurrence of chlorinated byproducts of bisphenol a, nonylphenol, and estrogens in drinking water of China: comparison to the parent compounds. *Environ. Sci. Technol.* 47 (19), 10841–10850.
- Focazio, M.J., Kolpin, D.W., Barnes, K.K., Furlong, E.T., Meyer, M.T., Zaugg, S.D., Barber, L.B., Thurman, M.E., 2008. A national reconnaissance for pharmaceuticals and other organic wastewater contaminants in the United States - II) Untreated drinking water sources. *Sci. Total Environ.* 402 (2–3), 201–216.
- Fukazawa, H., Watanabe, M., Shiraishi, F., Shiraishi, H., Shiozawa, T., Matsushita, H., Terao, Y., 2002. Formation of chlorinated derivatives of bisphenol A in waste paper recycling plants and their estrogenic activities. *J. Health Sci.* 48 (3), 242–249.
- Gomez, M.J., Petrovic, M., Fernandez-Alba, A.R., Barcelo, D., 2006. Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography-tandem mass spectrometry analysis in hospital effluent wastewaters. *J. Chromatogr. A* 1114 (2), 224–233.
- Gworek, B., Kijenska, M., Zaborowska, M., Wrzosek, J., Tokarz, L., Chmielewski, J., 2019. Pharmaceuticals in aquatic environment. fate and behavior, ecotoxicology and risk assessment - a review. *Acta Pol. Pharm.* 76 (3), 397–407.
- Haman, C., Dauchy, X., Rosin, C., Munoz, J.F., 2015. Occurrence, fate and behavior of parabens in aquatic environments: a review. *Water Res.* 68, 1–11.
- Hofman-Caris, R., ter Laak, T., Huiting, H., Tolamp, H., de Man, A., van Diepenbeek, P., Hofman, J., 2019. Origin, fate and control of pharmaceuticals in the urban water cycle: a case study. *Water* 11 (5), 16.
- Kosma, C.I., Lambropoulou, D.A., Albanis, T.A., 2010. Occurrence and removal of PPCPs in municipal and hospital wastewaters in Greece. *J. Hazard Mater.* 179 (1–3), 804–817.
- Li, W.H., Shi, Y.L., Gao, L.H., Liu, J.M., Cai, Y.Q., 2015. Occurrence and human exposure of parabens and their chlorinated derivatives in swimming pools. *Environ. Sci. Pollut. Res.* 22 (22), 17987–17997.
- Li, Y.J., Qiao, X.L., Zhang, Y.N., Zhou, C.Z., Xie, H.J., Chen, J.W., 2016. Effects of halide ions on photodegradation of sulfonamide antibiotics: formation of halogenated intermediates. *Water Res.* 102, 405–412.
- Maruya, K.A., Dodder, N.G., Sengupta, A., Smith, D.J., Lyons, J.M., Heil, A.T., Drewes, J.E., 2016. Multimedia screening of contaminants of emerging concern (CECs) in coastal urban watersheds in southern California (USA). *Environ. Toxicol. Chem.* 35 (8), 1986–1994.
- McCance, W., Jones, O.A.H., Edwards, M., Surapaneni, A., Chadalavada, S., Currell, M.,

2018. Contaminants of Emerging Concern as novel groundwater tracers for delineating wastewater impacts in urban and peri-urban areas. *Water Res.* 146, 118–133.
- Nam, S.-W., Jo, B.-I., Yoon, Y., Zoh, K.-D., 2014. Occurrence and removal of selected micropollutants in a water treatment plant. *Chemosphere* 95, 156–165.
- National Health Insurance Administration, Taiwan Ministry of Health and Welfare, 2019. Drug use analysis 2018. https://www.nhi.gov.tw/Content_List.aspx?n=5AA7CAFF61CB16D&topn=3FC7D09599D25979. (Accessed 25 October 2019).
- Ojemaye, C.Y., Petrik, L., 2019. Pharmaceuticals in the marine environment: a review. *Environ. Rev.* 27 (2), 151–165.
- Padhye, L.P., Yao, H., Kung'u, F.T., Huang, C.-H., 2014. Year-long evaluation on the occurrence and fate of pharmaceuticals, personal care products, and endocrine disrupting chemicals in an urban drinking water treatment plant. *Water Res.* 51, 266–276.
- Pal, A., He, Y.L., Jekel, M., Reinhard, M., Gin, K.Y.H., 2014. Emerging contaminants of public health significance as water quality indicator compounds in the urban water cycle. *Environ. Int.* 71, 46–62.
- Pan, L., Zhang, X.R., Yang, M.T., Han, J.R., Jiang, J.Y., Li, W.X., Yang, B., Li, X.Y., 2019. Effects of dechlorination conditions on the developmental toxicity of a chlorinated saline primary sewage effluent: excessive dechlorination is better than not enough. *Sci. Total Environ.* 692, 117–126.
- Pharmaceutical Services Division, Ministry of Health Malaysia, 2017. Malaysian statistics on medicines 2011–2014. <https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/malaysian-statistics-medicines-2011-2014.pdf>. (Accessed 27 October 2019).
- Pico, Y., Barcelo, D., 2015. Transformation products of emerging contaminants in the environment and high-resolution mass spectrometry: a new horizon. *Anal. Bioanal. Chem.* 407 (21), 6257–6273.
- Quintana, J.B., Rodil, R., Lopez-Mahia, P., Muniategui-Lorenzo, S., Prada-Rodriguez, D., 2010. Investigating the chlorination of acidic pharmaceuticals and by-product formation aided by an experimental design methodology. *Water Res.* 44 (1), 243–255.
- Rivera-Utrilla, J., Sanchez-Polo, M., Ferro-Garcia, M.A., Prados-Joya, G., Ocampo-Perez, R., 2013. Pharmaceuticals as emerging contaminants and their removal from water. A review. *Chemosphere* 93 (7), 1268–1287.
- Salimi, M., Esrafil, A., Gholami, M., Jafari, A.J., Kalantary, R.R., Farzadkia, M., Kermani, M., Sobhi, H.R., 2017. Contaminants of emerging concern: a review of new approach in AOP technologies. *Environ. Monit. Assess.* 189 (8), 22.
- Sim, W.J., Lee, J.W., Lee, E.S., Shin, S.K., Hwang, S.R., Oh, J.E., 2011. Occurrence and distribution of pharmaceuticals in wastewater from households, livestock farms, hospitals and pharmaceutical manufactures. *Chemosphere* 82 (2), 179–186.
- Terasaki, M., Takemura, Y., Makino, M., 2012. Paraben-chlorinated derivatives in river waters. *Environ. Chem. Lett.* 10 (4), 401–406.
- Toxic and Chemical Substances Bureau, Taiwan Environmental Protection Administration, 2019. Chemical substance registration information public inquiry platform. <https://tcscachemreg.epa.gov.tw/Epareg/OpenData/content/FirstExistingPage.aspx>. (Accessed 25 October 2019).
- Vanderford, B.J., Mawhinney, D.B., Rosario-Ortiz, F.L., Snyder, S.A., 2008. Real-time detection and identification of aqueous chlorine transformation products using QTOF MS. *Anal. Chem.* 80 (11), 4193–4199.
- Wang, Y.J., Gao, W., Wang, Y.W., Jiang, G.B., 2019. Suspect screening analysis of the occurrence and removal of micropollutants by GC-QTOF MS during wastewater treatment processes. *J. Hazard Mater.* 376, 153–159.
- Westerhoff, P., Yoon, Y., Snyder, S., Wert, E., 2005. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environ. Sci. Technol.* 39 (17), 6649–6663.
- WHO Collaborating Centre for Drug Statistics, 2019. ATC/DDD index 2019. https://www.whocc.no/atc_ddd_index/. (Accessed 25 October 2019).
- Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., 2019. A novel method to characterise levels of pharmaceutical pollution in large-scale aquatic monitoring campaigns. *Appl. Sci.* 9 (7), 1368.
- Yang, Y.J., Lu, L.B., Zhang, J., Yang, Y., Wu, Y.N., Shao, B., 2014. Simultaneous determination of seven bisphenols in environmental water and solid samples by liquid chromatography-electrospray tandem mass spectrometry. *J. Chromatogr. A* 1328, 26–34.