Supporting Information

Impacts of emerging contaminants on surrounding aquatic environment from a youth festival

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Text S1. Materials and Methods.

Chemicals and standards.

LC-MS-grade methanol and acetonitrile were obtained from J.T. Baker (Phillipsburg, PA, USA). ACS-grade formic acid and hydrochloric acid were obtained from Fluka (Buchs, Switzerland). ACS-grade ammonium acetate was purchased from Sigma-Aldrich (St. Louis, MO, USA). Analytical-grade disodium ethylenediamine tetra-acetate (Na_2EDTA) was obtained from Mallinckrodt Baker (Phillipsburg, PA, USA). Deionized (DI) water was prepared with a Milli-Q water purification system (Millipore, Bedford, MA, USA).

Thirty ECs, including analgesics, antibiotics, lipid regulators, β-blockers, antiepileptic drugs, antidepressants, caffeine, ulcer healing compounds, UV filters, and illicit drugs/controlled substances, were selected as target compounds. Most of the target ECs are frequently used in prescriptions, over-the-counter medications, human treatments, veterinary medicines, and drugs of abuse in Taiwan. These ECs are also reported in many other locations, such as Europe, the USA, Japan, Korea, and China [1-6]. Detailed physiochemical properties of the selected ECs are presented in the Table S1. Acetaminophen, acetaminophen-d_4, diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid, codeine, ampicillin, gemfibrozil, carbamazepine, fluoxetine, atenolol, caffeine, omeprazole, amphetamine, amphetamine-d_{11}, methamphetamine, methamphetamine-d_{14}, cocaine, heroin, ketamine, pseudoephedrine, cannabinol, flunitrazepam, 3,4-methylenedioxymethamphetamine (MDMA), MDMA-d_5, and gamma-hydroxybutyric acid (GHB) were obtained from Cerilliant (Round Rock, TX, USA). Sulfamethoxazole, tetracycline, erythromycin-H_2O, and clofibric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Benzophenone-3 and benzophenone-4 were obtained from Fluka (Buchs, Switzerland). $^{13}C_3$-caffeine and $^{13}C_6$-ibuprofen (1 mg/mL) were purchased from Cambridge Isotope Laboratories (Andover, MA, USA). Stock standard solutions of 1,000 mg/L were prepared in methanol and stored in amber glass bottles at −20°C for a maximum of 15 days. Working solutions were prepared by diluting the stock standard

solution in methanol.

LC-MS/MS analysis

The instrumental analysis method was optimized based on the method described by several authors and our previous study.[7-17] Chromatography was performed using an Agilent 1200 module (Agilent Technologies, Palo Alto, CA, USA). The injection volumes for method 1 and method 2 were 50 and 10 μL, respectively, and the auto-sampler was operated at 25°C. Separation in method 1 was performed on a 150 × 4.6 mm ZORBAX Eclipse XDB-C18 column with a 5 μm particle size (Agilent, Palo Alto, CA, USA) and a mobile phase consisting of 0.1% formic acid (v/v), 5 mM ammonium acetate in DI water (mobile phase A), and 0.1% formic acid (v/v) in methanol (mobile phase B) gradient. The flow rate was kept constant at 1.0 mL/min. The gradient began with a 0% mobile phase B for 0.5 min, increasing to 40% from 0.5–3.0 min, to 70% from 3.0–7.5 min, to 95% from 7.5–9.0 min, and remaining at 95% until 11 min, decreasing to 0% from 11–12 min, and remaining at 0% thereafter (Table S4). Separation in method 2 was performed using a Kinetex PFP column (Phenomenex, Torrance, CA, USA, 100 × 2.1 mm, 2.6 μm). The flow rate through the column was 300 μL/min, with gradient elution conditions initiating at 10% mobile phase B, increasing to 95% at 6 min and maintained before reverting to the original conditions at 10 min. The compositions of the mobile phase for method 2 were as follows: (A) deionized water/0.1% formic acid and (B) acetonitrile/0.1% formic acid.

Mass spectrometry was performed using an API 4000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA) with an electrospray ionization source set to operate in positive/negative mode. The conditions for the mass spectrometer were as follows: ion spray voltage at 5.0 kV; curtain gas, nebulizer gas, and turbo gas at 10, 60, and 50 L/h, respectively; heated capillary temperature at 550°C; and collisionally activated dissociation at 7 (Table S5). After selecting the precursor ions, product ions were obtained and optimized using four key parameters: declustering potential, entrance potential, collision

energy, and collision cell exit potential. Ions were acquired in MRM modes with a dwell time of 200 ms and unit mass resolution on both mass analyzers. Two MRM pairs were used to identify the target compounds (Table S6).

For all the compounds, wide linearity ranges were obtained for the quantification. The calibration curve used in this study was constructed using least-squares linear regression analysis, and subjecting them to the same SPE procedures used for the environmental water samples instead of performing standard addition method in every sample. In this study, two types of recovery experiments were performed in DI water, river water, and wastewater samples: (1) Recovery experiments for isotopically labelled standards (surrogate standards) were performed in all DI water, river water and wastewater samples; and (2) the recovery experiments for spiking 500 ng/L target analytes standards were performed only in DI water, river water and effluent samples (n=12), which did not contain extremely high levels of target analytes, and therefore, their recoveries could be estimated. The mean recoveries of isotopically labeled surrogate standards in all samples were 82±13% (acetaminophen-d_4), 87±11% (amphetamine-d_{11}), 85±12% (methamphetamine-d_{14}), 78±9.0% (MDMA-d_5), 92±8.0% ($^{13}C_6$-ibuprofen), and 89±11% ($^{13}C_3$-caffeine), respectively. The mean recoveries (spiking 500 ng/L target analytes standards) in DI water ranged from 79% to 108%, compared with 83% to 115% in river water and 69% to 128% in effluents. As spiked environmental water samples already contained target compounds, blanks (non-spiked samples) were analyzed to determine their concentrations, which were afterward subtracted from the spiked environmental water samples.

The LOQs for the wastewaters were difficult to determine because the samples already contained some the selected analytes and the matrix interference was serious. Therefore, LOQs in the water samples were defined as a signal-to-noise (S/N) ratios of 10. The results indicated that the LOQs for each compound ranged from 0.04 ng/L to 3 ng/L for DI water, from 0.04 ng/L to 10 ng/L for river water, from 1 ng/L to 10 ng/L for influent samples, and from 2

ng/L to 10 ng/L for effluent samples.

Text S2. Derivation of PNECs and risk assessment

The potential for contamination to cause undesired environmental effects can be estimated from an index of environmental risk assessment.[18-21] Usually, risk quotient (RQ) is calculated from the ratio of a measured environmental concentration (MEC) and a predicted no-effect concentration (PNECs: the concentration at which no adverse effect is suspected to occur) using the lowest value for each endpoint, as shown in Equation (a):

$$\mathrm{RQ} = \frac{\mathrm{MEC}}{\mathrm{PNECs}}$$

A commonly used risk ranking criterion was applied: RQ (risk quotients) <0.1 means minimal risk, 0.1≤ RQ <1 means median risk, and RQ ≥1 means high risk.[22]

Derivation of PNECs was based on chronic toxicity data available in the literature.[22-27] PNECs are calculated by dividing the lowest chronic no-observed-effect concentrations (NOECs) by assessment factors (AFs) chosen according to the European Technical Guidance Document.[28] PNEC values for ibuprofen and ketoprofen were based on aquatic toxicity data to marine species from the literature (mainly toxicological studies of *Daphnia magna* and *Vibrio fischeri*). PNEC value for erythromycin-H_2O was based on aquatic toxicity data from toxicological studies with *Pseudokirchneriella subcapitata*. Due to a lack of aquatic chronic toxicity data in the literature, derivation of some PNECs via the species sensitivity distribution method was not possible. Therefore, these PNEC values were estimated using the Ecological Structure Activity Relationships (ECOSAR) models from the US Environmental Protection Agency. The lowest LC50 value and assessment factor of 1000 were chosen according to the European Commission's Technical Guidance Document.[28] PNECs for the examined CECs in this study were showed in Table S12.

Text S3. Removal of ECs in WWTPs

The removal efficiency percentage for ECs by the wastewater treatment processes was calculated based on the influent and effluent concentration difference divided by the influent concentrations, with complete data shown in the Supporting Information (see Table S9). Fig. S4 summarizes the average removal efficiency for 26 ECs in the WWTPs. In general, the encountered ECs could be divided into three groups depending on their removal percentages: limited removal, <30%; moderate removal, 30–70%; and effective removal, >70%.

The investigated ECs were not always sufficiently removed via the conventional wastewater treatment processes applied in WWTPs in the Kenting area. Therefore, diverse removal efficiencies for 26 detected ECs (14–100%) were found throughout the treatment processes, with the exception of ketoprofen, clofibric acid, and FM2, for which there no removal was observed in the WWTPs. Most EC compounds showed moderate removal efficiencies, ranging from 32% to 67%, in good agreement with most previously reported values. For example, diclofenac was the poorest removed analgesic compound, with an average removal efficiency of 32%. The poor removal of diclofenac is probably due to the combination of degradation in wastewater together with the liberation of additional diclofenac molecules by the de-conjugation of glucoroonidated or sulfated diclofenac and/or its desorption from particles.[31]

The removal efficiency for sulfamethoxazole in our study was 38%, which is comparable with studies performed in Sweden,[32] Croatia,[33] and China.[34] In contrast, Gobel et al. [35] reported low and highly variable removal efficiency for sulfamethoxazole during secondary treatment in two Swiss WWTPs, which was interpreted to be a consequence of the re-transformation of sulfonamide metabolites during the wastewater treatment processes. The average removal efficiencies of naproxen and gemfibrozil were 45% and 61%, respectively. Their

moderate elimination rates are consistent with the results reported by several authors.[26, 34]

Eight EC compounds (acetaminophen, salicylic acid, benzophenone-3, benzophenone-4, amphetamine, cocaine, heroin, and pseudoephedrine) were found at effective eliminated rates (>70%). Both salicylic acid and benzophenone-4 were the most effectively eliminated EC compounds (>99%). Martin et al.[31] reported that the anti-inflammatory drug salicylic acid was the most effectively removed pharmaceutical compound in the WWTPs from Spain. Since this compound has a low pK_a value, it is expected to be found mainly in the aqueous phase. The removal of salicylic acid from wastewater could be explained by biodegradation instead of by sorption onto sludge. The removal efficiencies of acetaminophen, benzophenone-3, cocaine, and heroin were also quite high (83–92%) in this study. Stackelberg et al.[36] monitored a higher level of removal for acetaminophen (>98%) in the USA due to its hydrophilic characteristic (log K_{ow} <1.0). However, the removal efficiencies of ampicillin, carbamazepine, and GHB were limited, with average removal efficiencies of 18%, 27%, and 15%, respectively. Carbamazepine is a pharmaceutical compound with a high chemical stability to the point that it has been proposed as an anthropogenic marker.[37] The partial removal of carbamazepine was also observed by other authors.[26, 34]

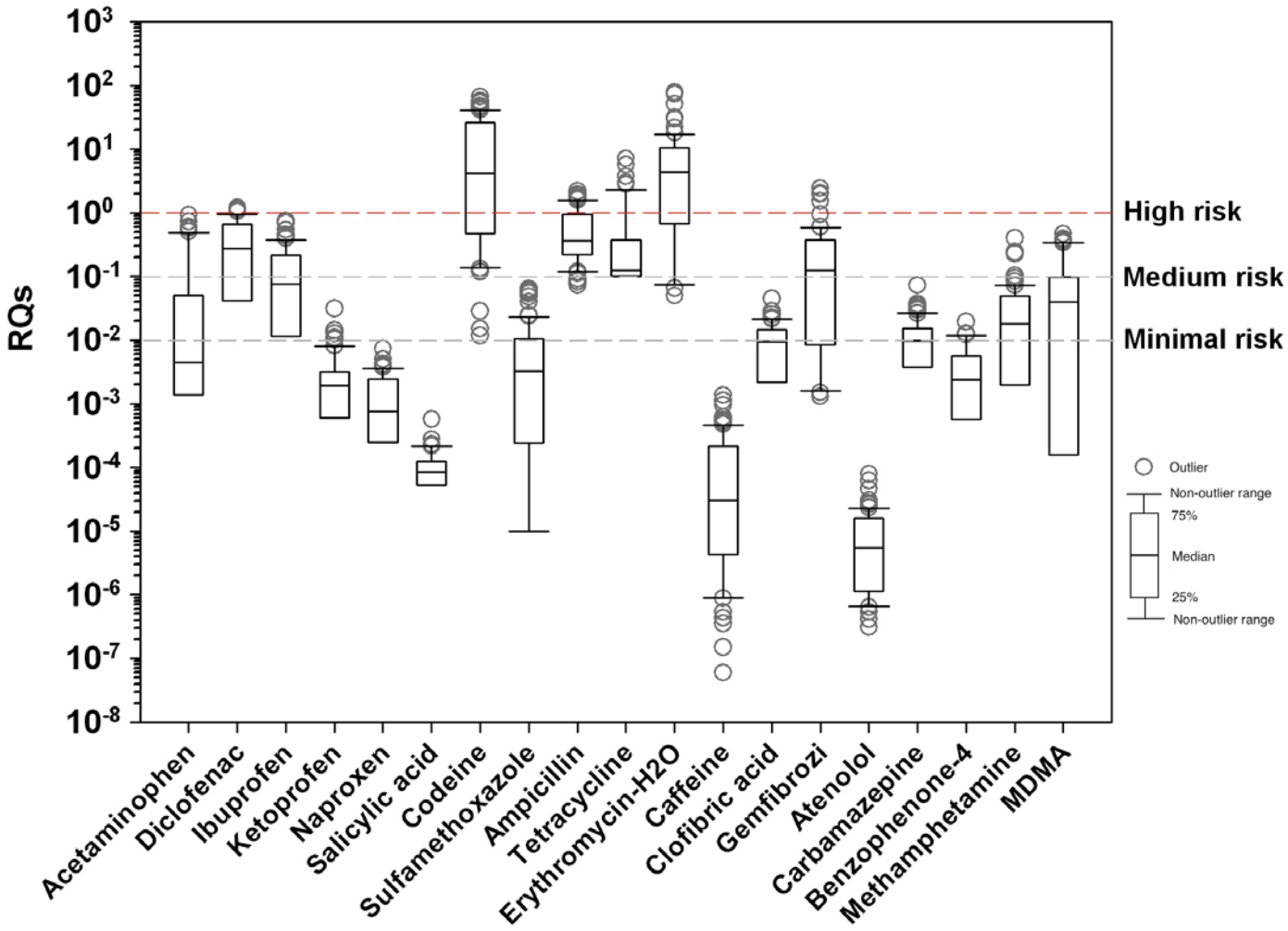

Figure S1. Boxplots for the calculated risk quotients (RQs) of the ECs detected in this study.

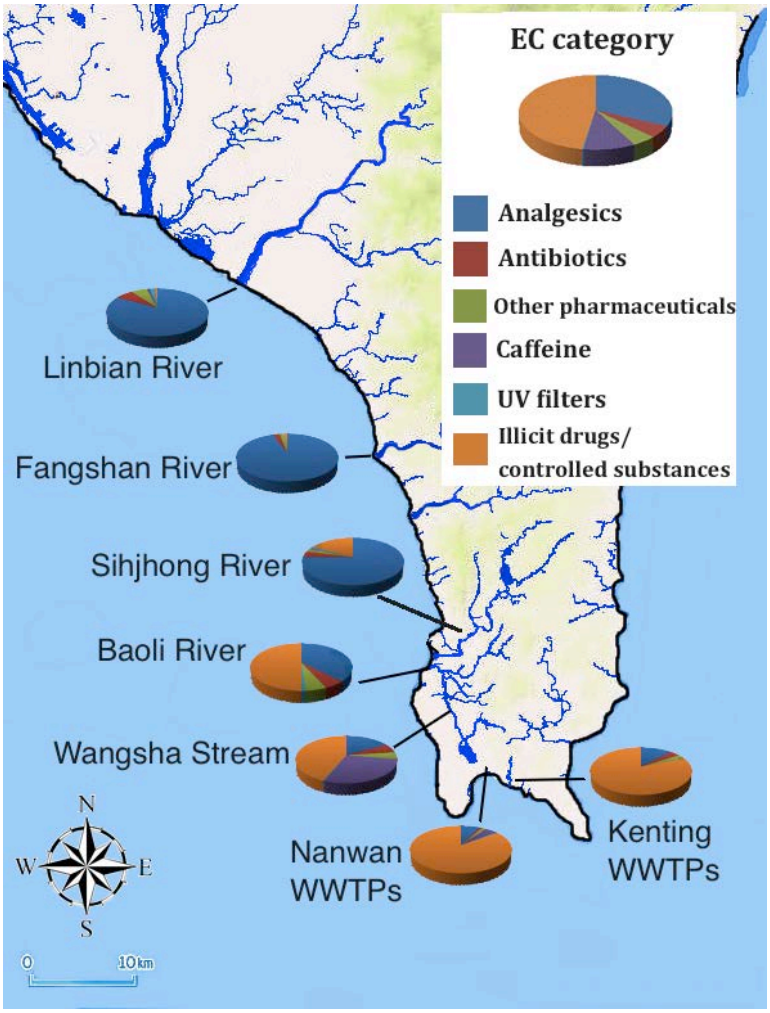

Figure S2. Mean relative contribution of detected ECs in this study

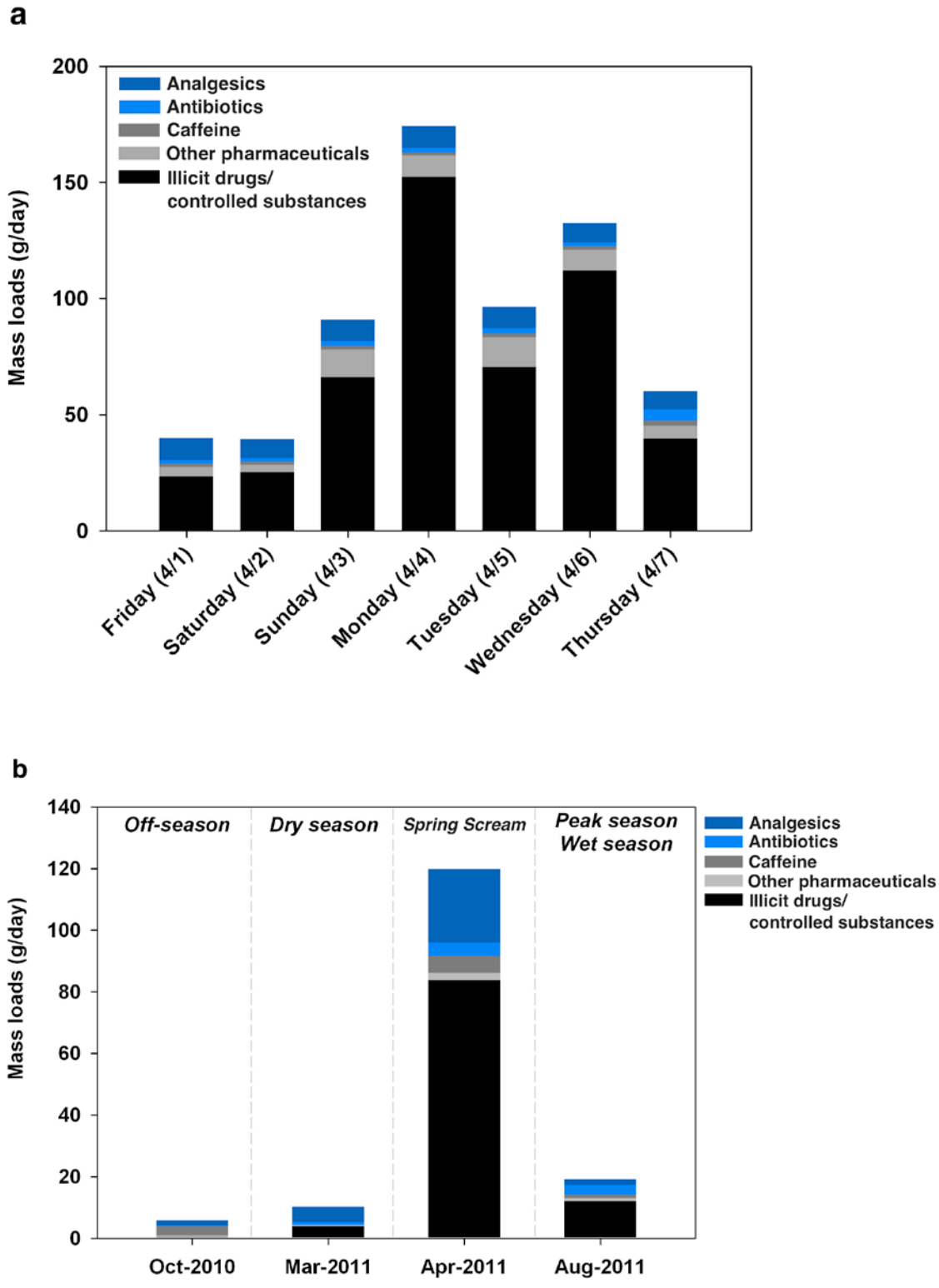

Figure S3. Estimated daily discharges from WWTP effluents into aquatic environments. (a) Spring Scream; (b) different sampling campaigns.

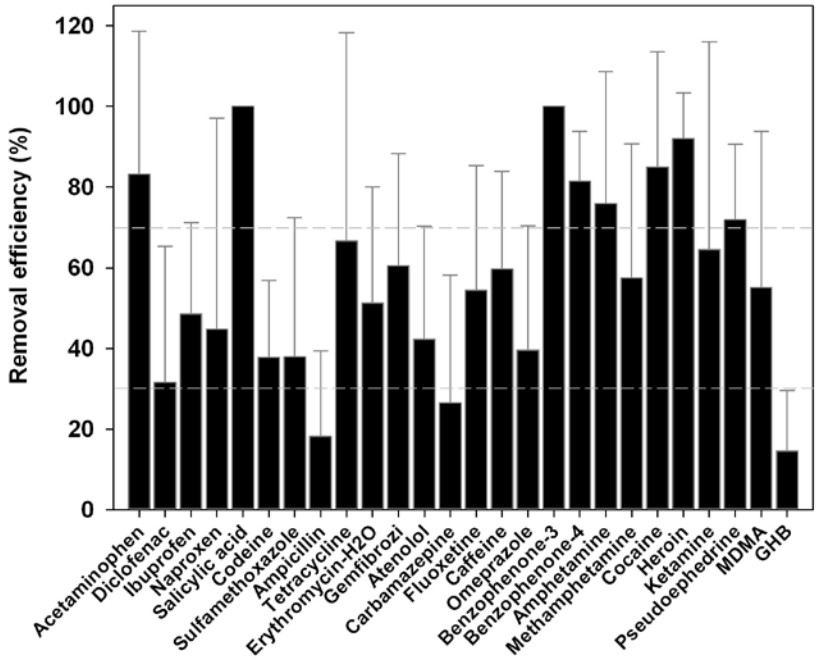

Figure S4. Average removal efficiency of the ECs in the two WWTPs.

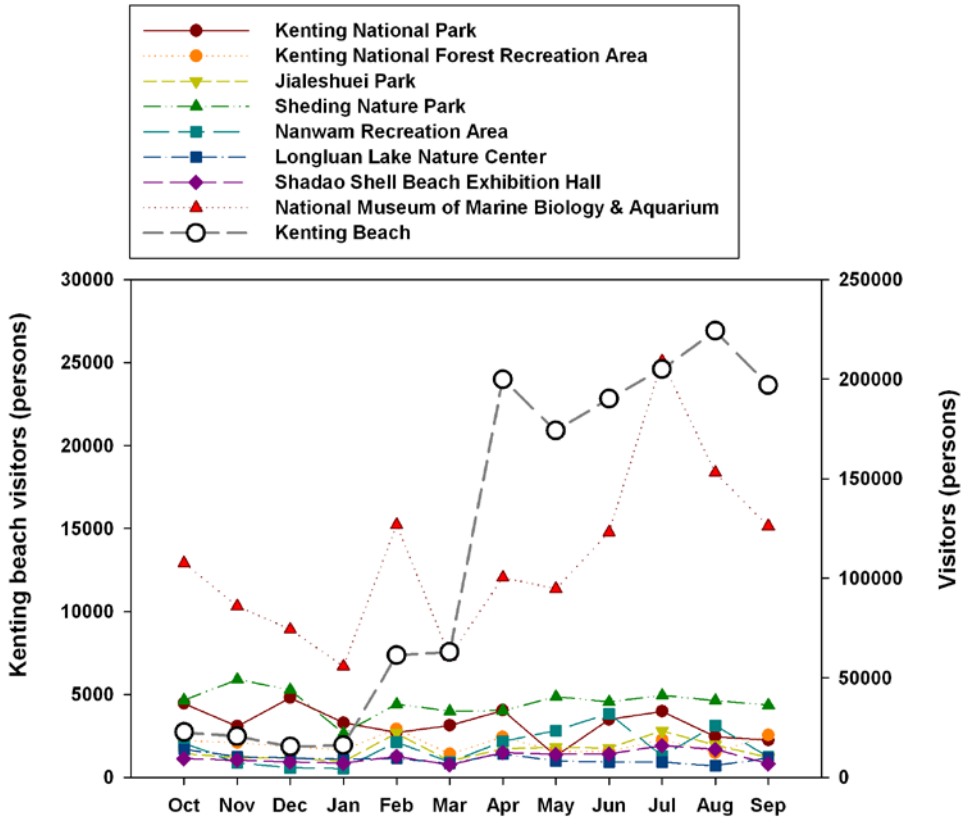

Figure S5. Number of the visitors in different location from the Kenting area between Oct 2010 and Sep 2011.

Table S1. CAS number, formula, molecular weight, $logK_{ow}$, $logK_{oc}$, melting point, vapor pressure, and solubility of the selected ECs.

Compounds	CAS No.	Formula	Molecular weight	$logK_{ow}$	$logK_{oc}$	Melting point (℃)	Vapor pressure (mmHg 25)	Solubility (g/L)
Analgesics								
Acetaminophen	103-90-2	$C_8H_9NO_2$	151.17	0.46	1.654	170	$1.94x10^{-6}$	14
Diclofenac	15307-79-6	$C_{14}H_{10}Cl_2NO_2Na$	318.14	0.7	2.661	284	$3.13x10^{-14}$	2.43[b]
Ibuprofen	15687-27-1	$C_{13}H_{18}O_2$	206.28	3.97	2.626	76	$1.86x10^{-4}$	0.021
Ketoprofen	22071-15-4	$C_{16}H_{14}O_3$	254.29	3.12	2.586	94	$1.46x10^{-6}$	0.051
Naproxen	22204-53-1	$C_{14}H_{14}O_3$	230.27	3.18	2.525	153	$1.27x10^{-6}$	0.016
Salicylic acid (The metabolite of acetylsalicylic acid)	69-72-7	$C_7H_6O_3$	138.12	2.26	1.336	158	$3.19x10^{-5}$	2.24
Codeine (opioids)	76-57-3	$C_{18}H_{21}NO_3$	299.37	1.19	2.845	280	$1.91x10^{-10}$	9
Antibiotics								
Sulfamethoxazole	723-46-6	$C_{10}H_{11}N_3O_3S$	253.28	0.89	2.412	167	$1.30x10^{-7}$	0.61
Ampicillin	69-53-4	$C_{16}H_{19}N_3O_4S$	349.41	1.35	1.926	198	$2.84x10^{-13}$	10.1
Tetracycline	60-54-8	$C_{22}H_{24}N_2O_8$	444.44	-1.3	1.644	178	$2.08x10^{-21}$	0.23
Erythromycin-H_2O	114-07-8	$C_{37}H_{67}NO_{13}$	733.95	3.06	2.754	191	$2.12x10^{-25}$	$5.17x10^{-4}$[b]
Lipid regulator								
Clofibric acid	882-09-7	$C_{10}H_{11}ClO_3$	214.65	2.57	1.64	118-119	$7.54x10^{-5}$	0.58[b]
Gemfibrozil	25812-30-0	$C_{15}H_{22}O_3$	250.34	4.77[a]	2.636	62	$3.05x10^{-5}$	$4.96x10^{-3}$[b]

Compounds	CAS No.	Formula	Molecular weight	$logK_{ow}$	$logK_{oc}$	Melting point (℃)	Vapor pressure (mmHg 25)	Solubility (g/L)
β-blockers								
Atenolol	29122-68-7	$C_{14}H_{22}N_2O_3$	266.34	0.16	1.825	147	$7.69x10^{-10}$	13.3
Antiepileptic drugs								
Carbamazepine	298-46-4	$C_{15}H_{12}N_2O$	236.28	2.45	3.123	190.2	$8.80x10^{-8}$	0.112
Antidepressants								
Fluoxetine	54910-89-3	$C_{17}H_{18}F_3NO$	309.33	4.05	4.971	105.27	$2.52x10^{-5}$	0.06[b]
Caffeine	58-08-2	$C_8H_{10}N_4O_2$	194.19	-0.07	1	238	$7.33x10^{-9}$	21.6
Ulcer healing								
Omeprazole	73590-58-6	$C_{17}H_{19}N_3O_3S$	345.42	2.23	3.163	156	$1.16x10^{-11}$	0.082[b]
UV filters								
Benzophenone-3	131-57-7	$C_{14}H_{12}O_3$	228.25	3.79	2.98	65.5	$6.62x10^{-6}$	0.069
Benzophenone-4	4065-45-6	$C_{14}H_{12}O_6S$	308.31	0.37[a]	1.825	145	$1.34x10^{-11}$	250
Illicit drugs/controlled substances*								
Amphetamine	300-62-9	$C_9H_{13}N$	135.21	1.76	2.883	11.3	$3.1x10^{-1}$	28[b]
Methamphetamine	537-46-2	$C_{10}H_{15}N$	149.24	2.07	2.951	172.5	$4.48x10^{-3}$	13.3[b]
Cocaine	50-36-2	$C_{17}H_{21}NO_4$	303.36	2.3	2.9	98	$1.29x10^{-5}$	1.8

Compounds	CAS No.	Formula	Molecular weight	$\log K_{ow}$	$\log K_{oc}$	Melting point (℃)	Vapor pressure (mmHg 25)	Solubility (g/L)
Heroin	561-27-3	$C_{21}H_{23}NO_5$	369.42	1.58	3.42	173	$7.59x10^{-10}$	0.6
Ketamine*	6740-88-1	$C_{13}H_{16}ClNO$	237.73	2.18	3.062	92.5	$5.15x10^{-5}$	200
Pseudoephedrine	90-82-4	$C_{10}H_{15}NO$	165.24	1.13	1.856	40	$1.07x10^{-2}$	63.6
Cannabinol	521-35-7	$C_{21}H_{26}O_2$	310.44	7.23[a]	5.517	77	$7.25x10^{-8}$	$2.1x10^{-6}$
Flunitrazepam (FM2)*	1622-62-4	$C_{16}H_{12}FN_3O_3$	313.29	2.06	4.075	166-167	$5.96x10^{-9}$	0.073
3,4-methylenedioxy-N-methylamphetamine (MDMA)	42542-10-9	$C_{11}H_{15}NO_2$	193.25	2.15	2.357	150	$2.27x10^{-4}$	7.03
Gamma-hydroxybutyric acid (GHB)	591-81-1	$C_4H_8O_3$	104.11	- 0.4[a]	0	45.54	$3.69x10^{-3}$	1x103

[a] Estimated by KOWWIN v1.68 [b] Water Solubility Estimate from Log Kow

Data from EPI suite, U.S. Environmental Protection Agency.

Table S2. Description of the sampling sites.

Site	Type	Influence	Note
L1	Fresh	Rural	
L2	Fresh	Rural	
L3	Fresh	Rural	Tributary
L4	Brackish	Urban	
L5	Brackish	Urban	
FS	Brackish	Rural	Fangshan River estuary
S1	Fresh	Rural	Reservoir
S2	Fresh	Rural	
S3	Fresh	Rural	Tributary
S4	Fresh	Rural	
S5	Fresh	Rural	
S6	Brackish	Urban	Estuary
B1	Fresh	Rural	
B2	Fresh	Rural	
B3	Fresh	Suburban	Tributary
B4	Brackish	Suburban	Estuary
W1	Fresh	Rural	
W2	Fresh	Rural	
W3	Fresh	Rural	
W4	Fresh	Urban	
W5	Fresh	Urban	
W6	Fresh	Suburban	
W7	Fresh	Urban	
W8	Fresh	Suburban	
W9	Fresh	Suburban	
Nanwan WWTPs	Waste	Domestic and resort	Influents and effluents
Kenting WWTPs	Waste	Domestic and resort	Influents and effluents
K1	Brackish	Rural	River estuary
K2	Fresh	Rural/Resort	River estuary
K3	Fresh	Rural/Resort	River estuary

Table S3. Characteristics of the two investigated wastewater treatment plants (WWTPs) in the Kenting area.

WWTP	Type of wastewater	Type of treatment	Disinfection method	Flow rate (m^3/d)
Nanwan	Domestic and touristic	Primary + Secondary	-	2000
Kenting	Domestic and touristic	Primary + Secondary	Chlorination	1500

Table S4. Gradient elution program of chromatographic separation.

Method 1

Eluent	Mobile phase A: 0.1% formic acid and 5 mM ammonium acetate in DI water Mobile phase B: 0.1% formic acid in methanol Flow rate: 1.0 mL/min	
Time (min)	Mobile phase	
	A (%)	B (%)
0.0	100	0
0.5	60	40
3.0	30	70
7.5	5	95
11	5	95
12	100	0
15	100	0

Method 2

Eluent	Mobile phase A: 0.1% formic acid in DI water Mobile phase B: 0.1% formic acid in acetonitrile Flow rate: 300 μL/min	
Time (min)	Mobile phase	
	A (%)	B (%)
0.0	90	10
6.0	5	95
9.0	5	95
10	90	10
15	90	10

Table S5. HPLC-MS/MS operation parameters.

Ionization Mode	ESI Positive Mode	ESI Negative Mode
Dwell time	200 ms	200 ms
Ion spray voltage (IS)	5.0 kV	-5.0 kV
Curtain gas (CUR)	10 L/h	10 L/h
Gas 1 (GS1)	60L/h	60 L/h
Gas 2 (GS2)	50 L/h	50 L/h
Temperature (TEM)	550℃	550℃
Interface heater (IHE)	ON	ON
Collisionally activated dissociation (CAD)	7	7

Table S6. The 30 EC compounds, their MRM pairs, recoveries in deionized (DI) water and river water, wastewater, and limits of quantification (LOQ).

Chemical	LOQ (ng/L)				MRM1 (quantification)	MRM2 (confirmation)	Recovery (%) ± SD (n=12)		
	DI water	River water	Wastewater (influents)	Wastewater (effluents)			DI water	River water	Wastewater (effluents)
Analgesics									
Acetaminophen	1	5	5.5	6.5	152/110	152/93	101 ± 13	102.0 ± 5.2	105.3 ± 9.7
Diclofenac	1	2.5	2.8	4	294/250	294/214	91.3 ± 3.6	94.0 ± 5.7	83.8 ± 9.3
Ibuprofen	2	5	5.5	6.5	205/161	205/158	102.0 ± 5.2	96.0 ± 3.9	104 ± 12
Ketoprofen	3	10	10	10	252/209	–	99.8 ± 7.1	98.0 ± 8.1	89 ± 10
Naproxen	2.5	2.5	5.2	6	228/169	228/184	96.0 ± 6.3	92.0 ± 5.5	85.6 ± 9.5
Salicylic acid	2	2.5	5.5	6	136/65	136/93	99.0 ± 8.5	92.0 ± 4.4	87.7 ± 8.5
Codeine (opioids)	0.25	0.5	3	5	300/153	300/215	100.4 ±7.8	97.0 ± 9.7	101 ± 14
Antibiotics									
Sulfamethoxazole	0.5	1	3	5	254/156	254/92	106.0 ± 7.5	103.8 ± 7.0	87 ± 15
Ampicillin	1	5	5.5	5.5	350/160	350/333	99.2 ± 8.9	97 ± 10	95 ± 12
Tetracycline	2	5	5.5	7	445/154	445/410	82.5 ± 9.6	83.5 ± 9.8	69 ± 13
Erythromycin–H_2O	1	1	3	4.5	734/576	734/158	90.5 ± 8.2	92.8 ± 8.3	92 ± 12
Lipid regulator									
Clofibric acid	0.5	1	5.2	5.5	213/126	213/91	91.4 ± 7.2	90.5 ± 7.1	91 ± 13
Gemfibrozil	0.5	1	2	3.5	248/121	248/126	90.7 ± 8.5	86.1 ± 6.6	81 ± 12
β–blockers									
Atenolol	2	5	5.5	6	267/190	267/179	82.5 ± 10.6	86.1 ± 5.6	88 ± 14
Antiepileptic drugs									
Carbamazepine	1	2.5	5	5.5	237/194	237/179	90.8 ± 9.4	94.3 ± 7.6	128 ± 15
Antidepressants									
Fluoxetine	2.5	5	5.5	6.5	310/148	–	86.2 ± 8.9	90.8 ± 6.3	91 ± 10
Caffeine	0.5	0.5	2	3.2	195/138	195/110	97.4 ± 7.3	115.3 ± 8.1	112 ± 11

Ulcer healing									
Omeprazole	1	1	2	3.5	346/197	346/179	79.4 ± 4.6	83.4 ± 4.5	83 ± 10
UV filters									
Benzophenone–3	2.5	5	5.5	6.5	226/211	–	95.3 ± 5.7	102.0 ± 9.7	90.8 ± 8.3
Benzophenone–4	2	1	4	5.5	306/291	306/211	101.2 ± 7.5	99.5 ± 9.4	89.3 ± 9.2
Illicit drugs/controlled substances*									
Amphetamine	0.05	0.07	1	2	136/119	136/91	107.2 ± 9.1	105.3 ± 6.7	95.8 ± 9.4
Methamphetamine	0.5	2	3	5	150/119	150/91	106.0 ± 5.1	106.3 ± 3.3	102.0 ± 9.7
Cocaine	0.05	0.05	1	2.5	304/182	304/82	104.0 ± 9.5	104.2 ± 2.2	106.7 ± 9.3
Heroin	0.04	0.04	1	2.5	370/268	370/210	108.0 ± 9.4	109.4 ± 5.0	82 ± 10
Ketamine*	0.25	0.25	2.5	3.5	238/219	238/125	103.0 ± 8.1	97.6 ± 7.5	103 ± 11
Pseudoephedrine	0.25	0.5	1	3	166/148	166/133	95.5 ± 4.5	97.7 ± 3.5	108.2 ± 9.4
Cannabinol	0.25	1	2	3.5	309/279	309/171	97.2 ± 6.3	97.4 ± 5.7	94 ± 12
Flunitrazepam*	1	1	2	3.5	314/267	314/239	100.5 ± 7.2	103.8 ± 5.3	88 ± 14
3,4–Methylenedioxymethamphetamine (MDMA)	0.05	0.05	2	3	194/163	194/104	101.0 ± 8.2	107.3 ± 6.5	98 ± 13
Gamma–Hydroxybutyric acid	0.5	1	2	2.5	103/85	103/57	95.7 ± 6.7	109.0 ± 7.2	83 ± 12

Table S7. Summary of EC concentrations in river waters in this study (ng/L).

Chemicals	Concentration of ECs (ng/L)																	
	Linbian River n=5			Sihchong River n=6			Baoli River n=4			Wangsha Stream n=9			Kenting area n=3			Fangshan river n=1		
	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max
Analgesics																		
Acetaminophen	33	<5	101	52	10.4	537	33	<5	147	38	<5	510	17	<5	37.7	50	<5	350
Diclofenac	17	<2.5	5	0	<2.5	0	8	<2.5	16.4	44	<2.5	92.7	67	7.15	23.9	13	<2.5	6.6
Ibuprofen	22	<5	52	10	<5	11.5	50	<5	222	68	23.9	440	67	113	523	25	<5	159
Ketoprofen	56	<10	487	5	<10	16.4	25	<10	34.3	47	<10	222	67	23.4	61.3	38	<10	79.3
Naproxen	11	<2.5	12.8	0	<2.5	0	25	<2.5	8.2	32	<2.5	74.3	67	28.4	64.3	13	<2.5	31.5
Salicylic acid	17	<2.5	34	24	<2.5	13	58	3	7.4	38	<2.5	12.8	17	<2.5	4	25	<2.5	9.9
Codeine (opioids)	44	<0.5	1623	52	0.7	863	50	11.8	2747	79	52.9	1690	83	37.1	1640	63	5	1393
Antibiotics																		
Sulfamethoxazole	61	26.3	967	29	<1	18.4	42	<1	58.3	44	<1	197.7	50	1.7	227	25	<1	268
Ampicillin	61	8.5	163	67	13.1	46	100	15.6	76	100	24.9	96.3	83	10.25	62	25	<5	45.7
Tetracycline	50	<5	21.1	38	<5	15.8	42	<5	33.3	21	<5	30.7	17	<5	47	38	<5	11.2
Erythromycin–H_2O	28	<1	627	5	<1	1.6	50	<1	303	44	<1	247.7	50	25.4	296	13	<1	10.7
Caffeine	61	6.2	236	62	4.3	130	50	4.55	533	71	179	2153	83	88.4	1237	25	<0.5	637
Other pharmaceuticals																		
Clofibric acid	44	<1	28.4	19	<1	3.7	25	<1	20.4	50	<1	22.5	67	7.6	17.6	25	<1	9.2
Gemfibrozil	33	<1	55	33	<1	16.5	25	<1	105	68	8.45	1513	50	1.5	328	25	<1	175
Atenolol	22	<5	51	29	<5	32.4	42	<5	54.7	62	10.9	175	50	8.15	87.3	25	<5	117

Chemicals	Concentration of ECs (ng/L)																	
	Linbian River n=5			Sihchong River n=6			Baoli River n=4			Wangsha Stream n=9			Kenting area n=3			Fangshan river n=1		
	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max	%	Median	Max
Carbamazepine	72	4.1	183	71	5.4	40.3	67	5.7	38	53	7	81.3	33	<2.5	48.3	50	<2.5	44.7
Fluoxetine	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5
Omeprazole	11	<1	1.3	10	<1	1.3	17	<1	2.9	18	<1	7	0	<1	<1	0	<1	<1
UV filters																		
Benzophenone–3	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5	0	<5	<5
Benzophenone–4	6	<1	8.4	10	<1	10.5	8	<1	11.6	35	<1	30.6	50	2.35	57.3	25	<1	3.6
Illicit drugs/controlled substances*																		
Amphetamine	28	<0.07	1.9	14	<0.07	0.2	8	<0.07	3.3	6	<0.07	90.3	33	<0.07	11.2	13	<0.07	0.3
Methamphetamine	6	<2	4.5	0	<2	0	0	<2	0	32	<2	917	50	2.7	10.2	25	<2	5.3
Cocaine	0	<0.05	<0.05	0	<0.05	<0.05	0	<0.05	<0.05	0	<0.05	<0.05	0	<0.05	<0.05	0	<0.05	<0.05
Heroin	0	<0.04	<0.04	0	<0.04	<0.04	0	<0.04	<0.04	0	<0.04	<0.04	0	<0.04	<0.04	0	<0.04	<0.04
Ketamine*	33	<0.25	226	10	<0.25	413	42	<0.25	917	62	29.6	9000	67	286	9533	25	<0.25	850
Pseudoephedrine	44	<0.5	817	38	<0.5	247	50	1.75	3,293	79	33.2	3733	83	89.9	2193	25	<0.5	1907
Cannabinol	0	<1	0	0	<1	0	0	<1	0	0	<1	0	0	<1	0	0	<1	0
FM2*	22	<1	14.5	0	<1	0	25	<1	22.1	21	<1	11.8	33	<1	5	13	<1	1.4
MDMA	11	<0.05	5.6	0	<0.05	0	17	<0.05	14.9	21	<0.05	667	33	<0.05	1023	13	<0.05	165
GHB	28	<1	6.7	24	<1	2.8	17	<1	3.5	12	<1	6	0	<1	0	25	<1	2.7

%: Detection frequency.

n: amount of sampling sites.

Table S8. The detection frequency and concentration rank of ECs in river waters.

Rank[a]	Chemicals	%	Rank[b]	Chemicals	Concentration (ng/L)	
					Max	Median
1	Ampicillin	79	1	Ketamine	9,533	<0.25
2	Codeine	63	2	Pseudoephedrine	3,733	3.1
3	Caffeine	62	3	Codeine	2,747	20.8
4	Carbamazepine	61	4	Caffeine	2,153	24.3
5	Pseudoephedrine	57	5	Gemfibrozil	1,513	<1
6	Gemfibrozil	44	6	MDMA	1,023	<0.05
7	Sulfamethoxazole	42	7	Sulfamethoxazole	967	<1
8	Ibuprofen	41	8	Methamphetamine	917	<2
8	Atenolol	41	9	Erythromycin-H_2O	627	<1
10	Ketamine	40	10	Acetaminophen	537	<5
11	Acetaminophen	39	11	Ibuprofen	523	<5
12	Clofibric acid	38	12	Ketoprofen	487	<10
13	Ketoprofen	37	13	Carbamazepine	183	4.6
14	Tetracycline	33	14	Atenolol	175	<5
15	Salicylic acid	31	15	Ampicillin	163	16.7
15	Erythromycin-H_2O	31	16	Diclofenac	92.7	<2.5
17	Diclofenac	24	17	Amphetamine	90.3	<0.07
18	Naproxen	21	18	Naproxen	74.3	<2.5
18	Benzophenone-4	21	19	Benzophenone-4	57.3	<1
20	GHB	18	20	Tetracycline	47	<5
21	Methamphetamine	17	21	Salicylic acid	34	<2.5

21	FM2	17	22	Clofibric acid	28.4	<1
23	Amphetamine	14	23	FM2	22.1	<1
23	MDMA	14	24	Omeprazole	7	<1
25	Omeprazole	12	25	GHB	6.7	<1
26	Heroin	0	-	Cocaine	<0.05	<0.05
26	Cocaine	0	-	Heroin	<0.04	<0.04
26	Fluoxetine	0	-	Fluoxetine	<5	<5
26	Benzophenone-3	0	-	Benzophenone-3	<5	<5
26	Cannabinol	0	-	Cannabinol	<1	<1

[a] Rank by detection frequency; [b] Rank by maximum concentration

Table S9. Summary of EC concentrations in wastewaters in two WWTPs (ng/L).

Chemicals	Nanwan WWTPs							
	Influent (n=11)				Effluent (n=11)			
	Frequency	Median	Max	Min	Frequency	Median	Max	Min
Analgesics								
Acetaminophen	100	5,200	6,700	137	71	151	8,433	<5.5
Diclofenac	100	65.7	105	42.7	100	105	113	58.7
Ibuprofen	100	1,083	1,500	430	100	620	917	250
Ketoprofen	0	<10	<10	<10	43	<10	49	<10
Naproxen	14	<5.2	84.7	<5.2	100	35	79.7	15.9
Salicylic acid	43	<5.5	9.5	<5.5	0	<5.5	<5.5	<5.5
Codeine (opioids)	100	3,180	3,967	2,207	100	2,227	2,837	1,777
Antibiotics								
Sulfamethoxazole	100	477	1,280	122	100	353	493	143
Ampicillin	100	128	141	75.7	100	122	162	104
Tetracycline	71	207	507	<5.5	43	<5.5	637	<5.5
Erythromycin–H_2O	86	246	587	<3	100	151	1463	130
Caffeine	71	4,233	5,567	<2	71	2,500	3,367	<2
Other pharmaceuticals								
Clofibric acid	0	<5.2	<5.2	<5.2	0	<5.2	<5.2	<5.2
Gemfibrozil	100	943	2,400	377	100	367	600	189
Atenolol	100	235	623	190	100	133	460	100
Carbamazepine	100	31.4	87	28.7	86	66	77.3	<5

Fluoxetine	86	6.1	21.9	<5.5	100	5.5	11.7	<5.5
Omeprazole	100	122	164	109	86	80.7	138	<2
Personal care products								
Benzophenone–3	0	<5.5	<5.5	<5.5	0	<5.5	<5.5	<5.5
Benzophenone–4	0	<4	<4	<4	14	<4	14.7	<4
Illicit drugs								
Amphetamine	100	40.7	83.7	5.2	100	6.6	20.1	3.6
Methamphetamine	100	164	557	90.3	100	119	148	60.7
Cocaine	86	14.1	51.7	<1	86	2.9	7.4	<1
Heroin	0	<1	<1	<1	29	<1	3.1	<1
Ketamine	100	18,633	138,000	8,033	100	14,733	39,333	4,300
Pseudoephedrine	100	22,300	44,667	12,133	100	10,133	29,500	3,030
Cannabinol	0	<2	<2	<2	0	<2	<2	<2
FM2	71	21.9	28.8	<2	100	27.9	36	24.3
MDMA	86	207	413	<2	86	130	1267	<2
GHB	86	3.9	5.5	<2	100	2.9	3.5	2.1

Table S9. (Continued).

Chemicals	Kenting WWTPs							
	Influent (n=11)				Effluent (n=11)			
	Frequency	Median	Max	Min	Frequency	Median	Max	Min
Analgesics								
Acetaminophen	100	2,043	4,700	1,963	43	<5.5	327	<5.5
Diclofenac	100	68.3	77	38.7	86	25.9	36	<2.8
Ibuprofen	100	563	790	291	86	337	420	<5
Ketoprofen	0	<10	<10	<10	86	32.1	49	<10
Naproxen	43	<5.2	6.8	<5.2	86	38.7	52	<5.2
Salicylic acid	29	<5.5	9.5	<5.5	0	<5.5	<5.5	<5.5
Codeine (opioids)	100	2,277	2,473	2,103	100	1,123	1,403	703
Antibiotics								
Sulfamethoxazole	100	210	259	82.3	86	115	209	<3
Ampicillin	100	89.7	105	63	100	57.7	81	22.3
Tetracycline	14	<5.5	207	<5.5	29	<5.5	108	<5.5
Erythromycin–H_2O	100	114	281	86.3	86	48	54	<3
Caffeine	100	9,500	13,633	3,533	100	2,110	6,167	5.4
Other pharmaceuticals								
Clofibric acid	0	<5.2	<5.2	<5.2	86	6.7	12.3	<5.2
Gemfibrozil	100	443	517	373	86	174	211	<2
Atenolol	100	177	226	121	100	106	114	10.1
Carbamazepine	100	38.7	49.7	27.5	100	26.9	32.3	6

Fluoxetine	100	10.3	18	5.7	86	<5.5	5.6	<5.5
Omeprazole	100	72.3	78.7	61.3	86	47	59.3	<2
UV filters								
Benzophenone–3	57	5.8	13.3	<5.5	0	<5.5	<5.5	<5.5
Benzophenone–4	57	28.7	62	<4	57	13.3	29.7	<4
Illicit drugs/controlled substances*								
Amphetamine	100	32.6	53	25.3	86	4	7	<1
Methamphetamine	100	81.3	106	61.7	86	14.9	20	<3
Cocaine	100	9.3	17.6	1.3	43	<1	1.1	<1
Heroin	29	<1	17.2	<1	29	<1	2.8	<1
Ketamine*	100	84,666	92,667	44,333	86	4,800	9,867	<2.5
Pseudoephedrine	100	11,200	13,233	9,233	100	2,200	3,133	68.7
Cannabinol	0	<2	<2	<2	0	<2	<2	<2
FM2*	0	<2	<2	<2	0	<2	<2	<2
MDMA	100	403	940	89.7	71	154	983	<2
GHB	57	<2	3.4	<2	100	3.2	4.8	<2

n: amount of samples.

Table S10. Global comparison of EC concentrations in the aquatic environments in the present study (ng/L).

Compounds	Asia							Europe			America
	Southern Taiwan		Northern Taiwan		Japan	Korea	China	UK	Italy	Spain	USA
	River water	WWTPs	River water	WWTPs							
Acetaminophen	ND–537	ND–8,433	8.3–9,170[a]	ND–30,967[c]	ND–263	ND–73[e]		ND–2,382[m]		ND–872[s]	ND–10,000[w]
Diclofenac	ND–92.7	ND–113	ND–56.5[a]	3–437[c]	ND–220	0.87–30[f]	17.6–150[h]	ND–261[m]	247[δ]	ND–148[s]	ND–177.1*
Ibuprofen	ND–523	ND–1,500	ND–4,350[a]	ND–17,933[c]	ND–77	1.2–51[f]	17.5–685[h]	ND–100[m]	31,323[δ]	ND–541[s]	ND–1,000[w]
Ketoprofen	ND–487	ND–49	ND–45[a]	ND–503[c]	ND–820	ND–41[g]	ND–31.4[h]	ND–14[m]	239[δ]	ND–	
Naproxen	ND–74.3	ND–84.7	ND–1,050[a]	ND–,	38–230	5.3–100[f]	20.9–125[h]	ND–146[m]	2027[δ]	ND–109[s]	ND–135.2[x]
Salicylic acid	ND–34	ND–9.5				ND–148[g]	66–14,736[h]	ND–302[m]			
Codeine	ND–2,747	703–3,967	ND–57[b]	26–67[b]				ND–815[m]	110–300[p]	ND–52[t]	ND–1,000[w]
Sulfamethoxazole	ND–967	ND–1,280		ND–1,760[c]	ND–160	ND–36[e]	ND–940[j]	ND–4[m]	1.8–11.4[q]		ND–520[w]
Ampicillin	ND–163	22.3–162		ND–650[c]							
Tetracycline	ND–47	ND–637	25–455[a]	ND–1,007[c]			ND–320[k]				ND–110[w]
Erythromycin–H_2O	ND–627	ND–1,463		141–1,537[c]		ND–4.8[e]	ND–121[j]	ND–351[m]	9.7–30.5[q]	ND–42[s]	ND–1,700[w]
Caffeine	ND–2,153	ND–13,633		ND–23,345[c]	ND–3,500	38–250[f]		437[n]	39,813[δ]		ND–6,000[w]
Clofibric acid	ND–28.4	ND–12.3	66.9–279[a]	ND–2,593[c]	ND–110	ND–35[g]	7.6–18.3[h]	ND–164[m]	127[#]	ND–6.1[s]	3.2–26.7[x]
Gemfibrozil	ND–1,513	ND–2,400		ND–1,378[c]		0.25–13[f]	14.9–31.2[h]		970[δ]	ND–212[s]	ND–790[w]
Atenolol	ND–175	10.1–623		ND–2,260[d]	ND–930	2.4–150[f]	ND–20[l]				
Carbamazepine	ND–183	ND–87		ND–10,933[d]	ND–86	8.4–68[f]	15.6–43.1[h]	ND–684[m]	81.5–348[r]	ND–54[s]	42.9–113.7[x]
Benzophenone–3	ND	ND–13.3						ND–44[m]	ND-306[Φ]	ND-295[θ]	
Benzophenone–4	ND–57.3	ND–62						ND–371[m]	ND-1548[Φ]		

Amphetamine	ND–90.3	ND–83.7					ND–21[m] ND–4.3[n]	ND–14.7[r]	ND–3.4[t] 1.6–11.8[u]	ND[z]
Methamphetamine	ND–917	ND–557	ND–405[b]	ND–296[b]			ND[n]	3.5–16.2[r]	ND–0.7[v] 0.3–0.7[u]	ND–570[y] ND–62.6[z]
Cocaine	ND	ND–51.7	ND–0.7[b]	0.5–1.2[b]			14[n]	ND–421[r]	ND–11.6[u] ND–59.2[v]	
Heroin	ND	ND–17.2					ND[n]		ND[t, u, v]	
Ketamine	ND–9,533	ND–13,8000	50–341[b]	147–343[b]			51[n]		ND–415[t]	
Pseudoephedrine	ND–3,733	68.7–4,4667					ND–16.5[n]		0.7–145[u]	ND–3300[y]
MDMA	ND–1,023	ND–1,267					ND–24.8[n]	4.4–14.2[r]	ND–3.4[u] ND–11.8[v]	ND–96[y]
GHB	ND–6.7	ND–5.5								
References	This study		(8); (10); (15-16)	(4)	(2); (38); (39)	(21); (40-42)	(3); (43)	(44-46); (55-57)	(47-50); (58)	(5); (51-54)

ND: not detected. [2-5, 8, 10, 15, 16, 21, 38-58]

[a] Data from Lin et al. (15); [b] Data from Lin et al. (8); [c] Data from Lin et al. (16); [d] Data from Lin et al. (10); [e] Data from Yoon et al. (2); [f] Data from Kim et al. (38); [g] Data from Sim et al. (39); [h] Data from Zhao et al. (21); [j] Data from Li et al. (40); [k] Data from Luo et al. (41); [l] Data from Chen et al. (42); [m] Data from Kasprzyk–Hordern et al. (3); [n] Data from Baker and Kasprzyk–Hordern (43); [p] Data from Repice et al. (44); [q] Data from Zuccato et al. (45); [r] Data from Castiglioni et al. (46); [s] Data from da Silva et al. (47); [t] Data from Vazquez–Roig et al. (48); [u] Data from Vazquez–Roig et al. (49); [v] Data from Postigo et al. (50); [w] Data from Kolpin et al. (5); [x] Data from Zhang et al. (51); [y] Data from Jones–Lepp et al. (52); [z] Data from Bartelt–Hunt et al. (53); * Data from Spongberg and Witter (54). [Φ] Data from Gago Ferrero et al. (55); [δ] Data from Loos et al. (56); [#] Data from Loos et al. (57). [θ] Data from Diaz-Cruz et al. (58).

Table S11. PCA loadings of the three principal components (PCs).

Total variance explained	PC1	PC2	PC3
	30.9%	23.4%	11.8%
Acetaminophen	**0.680**	0.014	0.530
Diclofenac	0.350	**0.753**	0.207
Ibuprofen	**0.751**	0.305	0.377
Ketoprofen	–0.085	**0.530**	–0.028
Naproxen	0.010	**0.639**	–0.066
Salicylic acid	0.053	–0.139	–0.034
Codeine	**0.650**	0.470	0.290
Sulfamethoxazole	**0.873**	0.194	0.113
Ampicillin	0.378	**0.669**	0.233
Tetracycline	0.328	0.129	**0.812**
Erythromycin–H_2O	0.410	**0.710**	0.452
Caffeine	**0.711**	0.171	0.061
Clofibric acid	–0.060	–0.061	–0.029
Gemfibrozil	**0.804**	0.091	0.242
Atenolol	**0.569**	0.412	0.144
Carbamazepine	0.039	**0.547**	0.051
Benzophenone–4	–0.067	**0.728**	0.236
Amphetamine	**0.514**	0.026	0.108
Methamphetamine	**0.607**	0.273	0.134
Ketamine	**0.682**	0.034	0.041
Pseudoephedrine	**0.777**	0.138	0.449
FM2	0.186	**0.740**	0.431
MDMA	**0.636**	0.265	0.059

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

Table S12. Predicted no-effect concentrations (PNECs) for the ECs examined in this study.

Substance	PNEC (ng/L)	Reference
Acetaminophen	9200	(19)
Diclofenac	100	(11)
Ibuprofen	2000	(21)
Ketoprofen	15600	(16)
Naproxen	20000	(11)
Salicylic acid	60000	(11)
Codeine	60	(10)
Sulfamethoxazole	27	(13)
Ampicillin	75	(20)
Tetracycline	90	(20)
Erythromycin-H_2O	40	(15)
Caffeine	10^7	(20)
Clofibric acid	1000	(11)
Gemfibrozil	1000	(21)
Carbamazepine	2500	(11)
Methamphetamine	2300	(10)

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