PRESIONES ANTROPOGÉNICAS EN EL PARQUE NATURAL DE L'ALBUFERA: CONTAMINACIÓN DEBIDA A FÁRMACOS Y PRODUCTOS PARA EL CUIDADO PERSONAL

Daniele Sadutto

Tesis Doctoral

Programa de doctorado 3154 en Química

Presiones antropogénicas en el Parque Natural de L'Albufera:
Contaminación debida a fármacos y productos para el cuidado personal

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Anthropogenic pressures in the Albufera Natural Park:
Contamination due to pharmaceuticals and personal care products

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Pressioni antropogeniche nel Parco Naturale dell'Albufera:
Contaminazione dovuta ai farmaci e ai prodotti per la cura personale

Memoria presentada para optar al título de Doctor por

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INFORMA:

Que el Licenciado *Daniele Sadutto* ha estado trabajando bajo mi dirección durante más de tres años en la elaboración de la tesis doctoral que lleva por título **"Presiones antropogénicas en el Parque Natural de L'Albufera: Contaminación debida a fármacos y productos para el cuidado personal"** por lo que autorizo su presentación para optar al Grado de Doctor.

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La tesis doctoral que lleva por título **"Presiones antropogénicas en el Parque Natural de L'Albufera: Contaminación debida a fármacos y productos para el cuidado personal"** ha sido organizada en 4 secciones que presentan 4 artículos publicados en revistas incluidas en el JCR (Web of Science) o en el SCR (scopus):

- Sadutto, D; Álvarez-Ruiz, R; Picó, Y. (2020). **Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry.** *Analytical and Bioanalytical Chemistry* **412**,113–127. [**JCR (WOS)** IF 3.637 (2019) en el área de Química Analítica 18/86 Q1 y en la de métodos de investigación bioquímicos 18/77 Q1.
- Sadutto, D; Picó, Y. (2020). **Sample Preparation to Determine Pharmaceutical and Personal Care Products in an All-Water Matrix: Solid Phase Extraction.** *Molecules* **25(21)**, 5204. [**JCR (WOS)** IF 3.267 (2019) en el área de Química (multidisplinar) 70/177 Q2 y en la de biología y biología molecular 142/297 Q2.
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Los artículos publicados han sido incluidos en la tesis el formato original de la revista. En todos ellos, Daniele Sadutto ha realizado todo el trabajo experimental, vigilando y supervisando estrechamente los experimentos, así como ha procedido al análisis de los resultados y la elaboración de los manuscritos.

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ÍNDICE

PRESENTACIÓN DE LA MEMORIA

ES

OBJETIVOS Y ESTRUCTURA

El Antropoceno es la nueva época geológica, denominada así por primera vez por Stoemer y Crutzen, durante la cual los cambios persistentes producidos por fuerzas antropogénicas contribuyeron a provocar las alteraciones biológicas y geofísicas en el medio terrestre [1-3]. La explotación de los recursos, la transformación de los paisajes y la alteración irreversible del clima (Climate Change) son solo algunos de los elementos que caracterizan la "era del hombre" [4]. Otro componente que contribuye a estas alteraciones es la contaminación, que ha incrementado dramáticamente con el tiempo y por ello debe estudiarse, para reducir los efectos del Antropoceno en los ecosistemas más sensibles.

Existen numerosos contaminantes detectados en el medio ambiente, algunos de ellos se denominan contaminantes emergentes (CE) e incluyen compuestos químicos que solo se han detectado en los últimos años gracias a técnicas analíticas nuevas y más sensibles. Los CE han sido ampliamente detectados en el agua y tal es su importancia debe realizarse un seguimiento por sus posibles efectos sobre los ecosistemas y la salud humana. Seguramente entre las clases más representativas de estos CE (de origen humano) encontramos los fármacos y productos para el cuidado personal (PPCPs), porque su producción, consumo y eliminación están en constante crecimiento [5]. Estas sustancias están presentes en diferentes compartimentos ambientales como compuestos inalterados o metabolitos [6-8] por muchas razones, debido a los desechos industriales, a los medicamentos que no se reciclan de manera correcta y a la excreción de los fármacos derivados de tratamientos terapéuticos [9].

El destino de la mayoría de los contaminantes emergentes son las matrices acuáticas, como los canales, ríos, lagos, mar, agua potable, aguas residuales, etc. que en muchos casos se comportan como distribuidores físicos de estos compuestos contribuyendo a la contaminación del ecosistema. Esto es posible gracias a la interacción vertical entre el agua y los otros compartimentos, cómo, por ejemplo, sedimentos, suelo, animales y humanos. Por esta razón, el agua puede considerarse un espejo del estado de contaminación de un área.

El principal desafío es desarrollar u optimizar técnicas analíticas que puedan mejorar la sensibilidad de detección de los PPCPs. Para ello, el paso de preparación de la muestra es fundamental y hay que tener en cuenta tres aspectos: (i) las propiedades fisicoquímicas de cada contaminante pueden afectar la estabilidad química y luego la detección, cómo pKa, polaridad, adsorción o la tendencia a ionizarse a pH ambiental; (ii) la complejidad de las matrices ambientales, las cuales contienen muchas sustancias que podrían interferir con los análisis, por lo tanto, es crucial eliminar los compuestos interferentes para aislar los analitos, y (iii) las bajas concentraciones a las que los productos farmacéuticos se pueden encontrar en las muestras ambientales (ng /L - µg / L; o ng / g - µg / g).

Por tanto, el **objetivo general** de esta tesis doctoral es evaluar el impacto antropogénico de la contaminación en el Parque Natural de L'Albufera (Valencia, España), caracterizado por una gran superficie con unas 21.000 hectáreas. Por alcanzar este objetivo se intentó establecer la presencia y la distribución de los PPCPs en diferentes matrices ambientales (sedimento, suelo, aguas residuales y superficiales), incluyendo dos evaluaciones, una sobre la distribución geográfica y otra sobre el riesgo ambiental de estos analitos. Los PPCPs, objeto de estudio, fueron seleccionados porque estos compuestos son entre los contaminantes más característicos de las grandes áreas urbanas. Finalmente, para lograr este objetivo general, fue necesario el desarrollo de nuevas metódicas analíticas, teniendo en cuenta las numerosas variables en juego en cada procedimiento.

Los **objetivos específicos** por desarrollar en esta tesis son los siguientes:

1. Optimizar los procedimientos para la extracción de los analitos a partir de dos matrices ambientales: sedimentos y aguas superficiales. A través la Extracción en Fase Sólida (SPE), y el uso de cartuchos con sorbentes a intercambio iónico y a fase inversa.

2. Aplicar los métodos propuestos a muestras del Parque Natural de L'Albufera, incluyendo distintas matrices (sedimento, suelo, aguas superficiales y residuales), con el objetivo de estudiar la presencia, la concentración y el destino de los productos farmacéuticos y para el cuidado personal seleccionados. Finalmente, para tener una visión global del estatus de contaminación de esta reserva natural, 53 puntos de muestreo fueron elegidos.

3. Evaluar la eficiencia de eliminación de las estaciones depuradoras de aguas residuales (EDAR) frente a estos compuestos. Este parámetro es relevante porque las aguas efluentes podrían usarse para regar los campos (frecuentemente en áreas áridas) o simplemente porque podrían ser reversadas en canales de riego que eventualmente desembocan en el Parque.

4. Definir la distribución geofísica de los PPCPs en el Parque, gracias al uso del *Sistema de Información Geográfica* (GIS), y realizar un análisis estadístico de la relación entre compuestos y sus concentraciones en distintas matrices, teniendo en cuenta también de las correlaciones con los parámetros ambientales.

5. Evaluar el riesgo ambiental, que ciertos PPCPs plantean a los organismos acuáticos mediante la predicción del riesgo, a través el cálculo del cociente de peligrosidad (HQ).

Para desarrollar estos objetivos se ha diseñado el siguiente **plan de trabajo**:

En primer lugar, se realizó una búsqueda bibliográfica detallada para observar los principales fármacos y productos para el cuidado personal detectados en el medio ambiente, incluyendo los más prescritos, vendidos y consumidos. Esta investigación permitió incluir, en esta tesis, los compuestos de mayor interés ambiental y sociológico.

Una vez identificados los analitos, la segunda búsqueda bibliográfica se centró en los parámetros que pueden incidir en el paso más importante para obtener datos verdaderos y precisos: *la preparación de la muestra*. Se reportaron las principales propiedades físico-químicas de cada sustancia (cómo la estructura química, pKa, log Kow y solubilidad en agua) para valorar el comportamiento de ellas en las condiciones ambientales. Sucesivamente, se estudiaron los métodos más relevantes utilizados para aislar y detectar estos compuestos a partir de matrices complejas (agua, sedimento y suelo).

Luego estas consideraciones, se desarrollaron y validaron varios métodos analíticos para determinar los compuestos en diferentes matrices ambientales. Los enfoques de extracción se basaron en el uso de la extracción sólido-líquido (SLE) y de la extracción en fase sólida (SPE). En este último caso, se testaron cartuchos caracterizados por dos mecanismos de separación distintos: por fase inversa y por intercambio iónico. Sucesivamente, la determinación de los contaminantes aislados se basó en el análisis mediante cromatografía líquida de alta resolución acoplada a espectrometría de masas de triple cuadrupolo (HPLC-QqQ-MS / MS).

Los métodos desarrollados se aplicaron a muestras de varios compartimentos ambientales del Parque Natural de L'Albufera (sedimento, suelo, aguas superficiales) y a numerosas aguas residuales (afluentes y efluentes) procedentes de diferentes EDAR, las cuales podrían liberar las aguas tratadas al Parque. Todo esto con el fin de determinar la presencia

de los PPCPs y evaluar el estado de contaminación de esta reserva natural.

Se utilizó el GIS (sistema de información geográfica) y el análisis estadístico (ANOVA, Pearson's correlation analysis, PCA, etc.) para observar la distribución geográfica de los compuestos y mostrar las diferencias estadísticamente significativas entre las concentraciones de los PPCPs y las diferentes áreas, incluyendo las correlaciones con los parámetros ambientales (tipos de agua, ubicación, usos del suelo, etc.).

Además, el posible impacto negativo de estas sustancias sobre los ecosistemas se evaluó utilizando el cociente de riesgo ecológico de aguas superficiales (RQ).

Esta tesis doctoral se estructura en **cuatro secciones**.

La **SECCIÓN 1** se caracteriza por una introducción que se centra en la importancia de la preparación de las muestras para determinar productos farmacéuticos y para el cuidado personal en ecosistemas acuáticos. Una revisión general que describe cada paso de la preparación de la muestra, incluyendo todas las variantes analíticas (métodos convencionales e innovadores) que se utilizan para detectar estos contaminantes.

La sección contiene:

• **Publicación 1:** *Sample Preparation to Determine Pharmaceutical and Personal Care Products in an All-Water Matrix: Solid Phase Extraction.*

La **SECCIÓN 2** está dedicada a las metodologías analíticas desarrolladas para determinar los PPCPs en diferentes compartimentos ambientales. Además, el apartado reporta los resultados obtenidos aplicando los métodos propuestos a las muestras recogidas en el Parque Natural de L'Albufera (Valencia, España).

La sección incluye:

• **Publicación 2**: *Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry,* en la cual se propusieron dos métodos de extracción en fase sólida para determinar, mediante el uso del HPLC-MS/MS, 32 productos farmacéuticos y para el cuidado personal en agua y sedimentos.

La **SECCIÓN 3** incluye una valoración exhaustiva de la contaminación del Parque Natural de L'Albufera por los compuestos seleccionados. Esta evaluación da un paso adelante y no es solo un ejercicio de seguimiento, sino una evaluación del transporte y destino de los contaminantes emergentes en un importante humedal costero mediterráneo que podría servir como ejemplo de lo que sucede en este tipo de ecosistemas que juegan un papel vital en el ciclo del agua.

Esta sección consta de dos publicaciones:

• **Publicación 3:** *Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment,* en el que se utilizaron los métodos propuestos en la sección anterior para determinar los PPCPs en un gran número de muestras, recogidas en 53 puntos de muestreo distribuidos por todo el Parque de L'Albufera. Se informó la presencia y distribución de los PPCPs en matrices de sedimentos, suelos, aguas superficiales, afluentes y efluentes de aguas residuales. Además, en la publicación se incluyeron: observaciones sobre la eficiencia de las EDAR, la evaluación de riesgos ambientales, la diferente distribución geofísica y un análisis estadístico acurado.

• **Publicación 4:** *Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland,* que proporciona un conjunto de datos sobre las concentraciones de los PPCPs detectadas en cada punto de muestreo y la relación estadística existente entre los contaminantes y los parámetros ambientales.

La **SECCIÓN 4** contiene un **RESUMEN** general de los resultados obtenidos y su discusión.

Finalmente, las **CONCLUSIONES** derivadas de todos los trabajos mencionados, constituyen el punto final del trabajo realizado.

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EN

AIM AND STRUCTURE

The Anthropocene is the new geological epoch, coined for the first time by Stoemer and Crutzen, during which persistent changes produced by anthropogenic forces contributed to cause biological and geophysical alterations on the terrestrial environment [1-3]. The exploitation of resources, transformation of landscapes and irreversible alteration of the climate (Climate Change) are just some elements characterizing the “age of man” [4]. Another component that contributes to these alterations is pollution, which has increased dramatically over time and must be studied to alleviate Anthropocene effects on the most sensitive ecosystems.

There are numerous contaminants detected in environment, some of them are named emerging contaminants (ECs) and including chemical compounds that have only been detected in recent years thanks to new and more sensitive analytical techniques. ECs have been recognized as new and significant water pollutants that need to be monitored for their possible effects on ecosystems and human health. The most representative classes of ECs of human origin are Pharmaceuticals and Personal Care Products (PPCPs) because their production, consumption and elimination are constantly growing [5]. These substances are present in different environmental compartments as unaltered compound or its metabolites [6-8] due to industrial waste, medicinal product not disposed in the right way, and drug excretion derived from therapeutic treatments [9].

The fate for most emerging pollutants is the aquatic matrices, such as channels, rivers, lakes, sea, drinking water, wastewater, etc. that in many cases behave as physical distri-

butors of these compounds contributing to the contamination of the ecosystem, thanks to vertical interaction between water and other compartment, such as sediment, soil, animal and humans. For this reason, water may be considered as a mirror of the pollution status of an area.

The main challenge is to develop and optimize analytical techniques that can improve the detection sensitivity for PPCPs. To do this, the *sample preparation* step is fundamental and three aspects must be taken into account: (i) the physicochemical properties of each contaminant, such as pKa, polarity, adsorption or the tendency to ionize at environmental pH, that could affect the chemical stability and then the detection; (ii) the complexity of environmental matrices containing many substances that could interfere with the analysis, therefore, remove interfering compounds is crucial to isolate analytes, and (iii) the low concentrations at which pharmaceuticals are present in environmental samples (ranging from ng/L to µg/L or from ng/g to µg/g).

Therefore, the **general objective** of this PhD thesis is to evaluate the Anthropocene impact of pollution on the Albufera Natural Park (Valencia, Spain), a big area of about 21000 ha. In order to establish the presence and distribution of PPCPs in different environmental matrices (sediment, soil, wastewater and surface water), including the evaluation of the geographic distribution and environmental risk assessment of these analytes. PPCPs were selected because these compounds are the most characteristics contaminants of big settlements and urban areas. To achieve this goal, the development of new methods was needed, considering the numerous variants in each analytical step.

The **specific objectives** to be developed in this thesis are as follows:

1. Optimize procedures for the extraction of analytes by Solid Phase Extraction (SPE), using reverse phase and ion exchange cartridges, from environmental matrices: sediment and surface water.

2. Apply the proposed methods to the Albufera Natural Park, to study the presence, concentration and fate of pharmaceuticals and personal care products in different matrices, such as sediment, soil, surface and wastewater, distributed on 53 sampling points located in this nature reserve.

3. Evaluate the wastewater treatment plant (WWTP) removal efficiency against these compounds. This parameter is relevant because the effluent waters could be used to irrigate the fields (often in arid areas) or simply because they could discharge into irrigation channels that eventually flowed into the Park.

4. Define the PPCPs geophysical distribution on the Park, thanks to use of *Geographic Information System* (GIS), and perform a statistical analysis on relationship between com-

pounds and their concentrations in distinct matrices, including the correlations with the environmental parameters.

5. Evaluate the environmental risk that certain PPCPs pose on the aquatic organisms through the risk prediction by the calculation of the hazard quotient (HQ).

To develop these objectives, the following **work plan** has been designed:

Firstly, a detailed bibliographic search was carried out to observe the main pharmaceuticals and personal care products detected in the environmental and the most prescribed, sold and consumed. This research attained the selection of the compounds of major environmental and sociological interest studied and included in this thesis.

Once identified the analytes, the second bibliographic search was focused on the parameters that could affect the most important step to obtain accurate and precise data: *the sample preparation.* For this purpose, the principal physico-chemical properties (such as chemical structure, pKa, log K_{ow} and water solubility) of each substance were reported to value their behaviour in the environment. Then, the most relevant methods used to isolate and detect these compounds from complex matrices (water, sediment and soil) were studied.

After these considerations, several analytical methods to determine the analytes in different environmental matrices were developed and validated. The extraction approaches were based on the use of solid-liquid extraction (SLE) and solid-phase extraction (SPE). In the last case, cartridges characterized by two distinct separation mechanisms: classical reversed phase and ion exchange that have been tested. Then, the determination of the isolated compounds was based on the analysis by liquid chromatography triple quadrupole tandem mass spectrometry (HPLC-QqQ-MS/MS).

The developed methods were applied to samples of several environmental compartments (sediment soil, surface water, influent and effluent wastewater) from the Albufera Natural Park and from different WWTPs that could release their effluents to the Park. To determine the presence of PPCPS and to evaluate the pollution status of this area.

The GIS (Geographic information system) and statistical analysis (by ANOVA, Pearson's correlation analysis, PCA, etc.) were used to observe the geographical distribution of compounds and to show statistically significant differences among PPCPs concentrations and the different areas, including the correlations with the environmental parameters (types of water, location, land uses, etc.).

Moreover, the possible negative environmental impacts from these substances in ecosystems was carried out using the surface-water ecological risk quotient (RQ).

This PhD thesis is structured into **4 sections**.

The **SECTION 1** was focused on importance of *sample preparation* to determine pharmaceutical and personal care products in aquatic ecosystems. A general review describes each step of sample preparation, including all analytical variants (conventional and innovative methods) used to detect these contaminants.

The section contains:

• **Publication 1:** *Sample Preparation to Determine Pharmaceutical and Personal Care Products in an All-Water Matrix: Solid Phase Extraction*

The **SECTION 2** develops and optimizes analytical methodologies to determine PPCPs in different environmental compartments (sediment, soil, surface and wastewater). Furthermore, the section contains the results obtained applying the proposed methods in the samples collected from the Albufera Natural Park (Valencia, Spain).

The section involves:

• **Publication 2**: *Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry,* in which two solid-phase extraction methods were proposed to determine 32 pharmaceuticals and personal care products in water and sediments by HPLC-MS/MS.

The **SECTION 3** includes an extensive assessment of the contamination by the selected compounds of the Albufera Natural Park. This assessment goes a step forward and it is not just a monitoring exercise but an assessment of the transport and fate of emerging contaminants in an important Mediterranean coastal wetland that could serve as an example of what happens in these types of ecosystems that play a vital role in the water cycle.

This section consists of two publications:

• **Publication 3:** *Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment,* in which the methods proposed in the previous section were used to determine PPCPs in many samples collected in 53 sampling points distributed throughout the Albufera Park. Occurrence and distribution of PPCPs in the sediment, soil, surface water, influent and effluent wastewater matrix were reported. Moreover, in the publication was included observations on WWTP efficiency, environmental risk assessment, different geophysical distribution and an accurate statistical analysis.

• **Publication 4:** *Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland* that provides dataset of previous work on PPCPs concentration detected in each sampling point and the statistical relationship of contaminants between them and with the environmental parameters.

The **SECTION 4** contains a general **SUMMARY** of the results obtained and their discussion.

Finally, the **CONCLUSIONS** derived from all the previous studies, put the finishing touch to the work.

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1 OBBIETTIVI E STRUTTURA

L'Antropocene è la nuova epoca geologica, definita così per la prima volta da Stoemer e Crutzen, durante la quale i cambiamenti persistenti prodotti dalle diverse attività dell'uomo hanno contribuito a provocare alterazioni biologiche e geofisiche sulla superficie terrestre [1-3]. Lo sfruttamento incontrollato delle risorse, la trasformazione dei paesaggi e l'alterazione irreversibile del clima (Cambio Climatico) sono solo alcuni degli elementi che caratterizzano la cosìddetta "età dell'uomo" [4]. Un altro elemento antropogenico che contribuisce a queste alterazioni è l'inquinamento, fattore aumentato notevolmente negli ultimi anni, che deve essere monitorato e studiato per poter ridurre gli effetti dell'Antropocene sugli ecosistemi più sensibili.

Esistono numerosi contaminanti che sono stati ritrovati nell'ambiente, alcuni di essi vengono denominati contaminanti emergenti (CE) e includono composti chimici che sono stati rilevati solo negli ultimi anni grazie a nuove e più sensibili tecniche analitiche. I CE sono stati riconosciuti come nuovi inquinanti problematici dell'acqua, che quindi devono essere monitorati per i loro possibili effetti sugli ecosistemi e sulla salute umana. Sicuramente tra le classi più rappresentative di questi CE (di origine umana) troviamo i farmaci e i prodotti per la cura personale (PPCPs). In quanto si è registrata una crescita costante nel tempo della loro produzione e quindi del loro consumo e della loro eliminazione [5]. Questi principi attivi si possono trovare in differenti matrici ambientali, sia nella loro forma inalterata, sia come metaboliti [6-8]. Le principali fonti di provenienza, per le quali questi composti vengono ritrovati nell'ambiente, possono essere attribuibili: agli scarti industriali, a un'ina-

deguata modalità di smaltire e/ o riciclare questi prodotti, ed infine ai prodotti d'escrezione del nostro organismo formatosi in seguito ad un trattamento terapeutico [9].

La distribuzione per la maggior parte degli inquinanti emergenti sono le matrici acquose, come canali, fiumi, laghi, mari, acqua potabile, acque reflue, ecc., che in molti casi si comportano come distributori fisici di questi composti contribuendo alla contaminazione dell'ecosistema, grazie all'interazione verticale tra l'acqua e altri compartimenti, come sedimenti, suolo, animali ed esseri umani. Per questo l'acqua può essere considerata uno specchio dello status di inquinamento di un'area.

La principale sfida è sviluppare e/o ottimizzare tecniche analitiche in grado di migliorare la sensibilità di rilevamento dei PPCPs. Per fare questo è fondamentale porre attenzione alla fase relativa alla preparazione del campione tenendo in considerazione tre aspetti: (i) le proprietà fisico-chimiche di ogni contaminante (come pKa, polarità, adsorbimento, tendenza a ionizzare a pH ambientale) che potrebbero influenzare la stabilità chimica e quindi la loro determinazione; (ii) la complessità delle matrici ambientali, le quali contengono numerose sostanze che potrebbero interferire con l'analisi, risulta quindi fondamentale rimuovere i composti interferenti per poter isolare gli analiti; (iii) infine, le basse concentrazioni alle quali i farmaci sono presenti nei campioni ambientali (ng /L - µg / L; o ng / g - µg / g).

L'**obbiettivo principale** di questa tesi di dottorato è valutare l'impatto antropogenico della contaminazione sul Parco Naturale dell'Albufera (Valencia, Spagna), una vasta aerea di circa 21000 ettari. Stabilendo la presenza e la distribuzione dei PPCPs nelle differenti matrici ambientali (sedimento, suolo, acque superficiali e residuali). Tenendo anche in considerazione la loro distribuzione geografica e la valutazione del rischio ambientale. I PPCPs oggetto di studio sono stati selezionati perché ritenuti tra i contaminanti più caratteristici delle grandi aree urbane. Infine, per poter raggiungere questo obiettivo, è stato necessario lo sviluppo di nuovi metodi, che considerassero le differenti varianti coinvolte in ogni step analitico.

Gli **obiettivi specifici** da sviluppare in questa tesi sono i seguenti:

1. Ottimizzare le procedure per l'estrazione di analiti da matrici ambientali (sedimenti e acque superficiali) mediante l'estrazione in fase solida (SPE), utilizzando cartucce con sorbenti a scambio ionico e a fase inversa.

2. Applicare i metodi proposti a campioni prelevati in 53 punti di campionamento situati nel Parco Naturale dell'Albufera. Al fine di studiare la presenza, la concentrazione e la distribuzione dei diversi farmaci e prodotti per la cura personale in diverse matrici, quali sedimento, suolo, acque reflue e superficiali.

3. Valutare l'efficienza di rimozione di questi composti da parte degli impianti di trattamen-

to delle acque reflue (Depuratori). Questo parametro è rilevante perché le acque reflue in uscita potrebbero essere utilizzate per irrigare i campi (come avviene spesso in zone aride) o semplicemente perché potrebbero essere riversate in canali di irrigazione che eventualmente sfociano nel Parco.

4. Definire la distribuzione geofisica dei PPCPs nel Parco, grazie all'utilizzo del *Sistema Informativo Geografico* (GIS), ed eseguire un'analisi statistica esaustiva che tenga in considerazione le relazioni tra i composti e le loro concentrazioni in diverse matrici, e le diverse correlazioni con i parametri ambientali.

5. Valutare e prevedere il rischio ambientale che alcuni PPCPs costituiscono per gli organismi acquatici, attraverso il calcolo del quoziente di pericolo (HQ).

Per sviluppare questi obiettivi è stato progettato il seguente **piano di lavoro**:

In primo luogo, è stata effettuata una ricerca bibliografica dettagliata per osservare i principali prodotti farmaceutici e per la cura personale rilevati nell'ambiente, includendo i più prescritti, venduti e consumati. Questa ricerca ha permesso di includere, in questa tesi, i composti di maggior interesse ambientale e sociologico.

Una volta identificati gli analiti, la seconda ricerca bibliografica si è concentrata sui parametri che potrebbero influenzare lo step più importante per ottenere dati reali e accurati: *la preparazione del campione*. Sono state riportate le principali proprietà fisico-chimiche di ciascuna sostanza (come la struttura chimica, pKa, log Kow e solubilità in acqua) per valutarne il comportamento in condizioni ambientali. Successivamente, sono stati studiati i metodi più importanti utilizzati per isolare e determinare questi composti in matrici complesse (acqua, sedimenti e suolo).

Dopo queste considerazioni, sono stati sviluppati e convalidati diversi metodi analitici per determinare i composti in diverse matrici ambientali. Gli approcci di estrazione sono stati basati sull'uso dell'estrazione solido-liquido (SLE) e dell'estrazione in fase solida (SPE). In quest'ultimo caso sono state testate cartucce caratterizzate da due diversi meccanismi di separazione: per fase inversa e per scambio ionico. Successivamente, la determinazione dei contaminanti isolati è stata basata sull'analisi mediante l'utilizzo della cromatografia liquida ad alta prestazione accoppiata ad un triplo quadrupolo (HPLC-QqQ-MS / MS).

Le metodologie sviluppate sono state applicate a campioni provenienti da vari comparti ambientali del Parco Naturale dell'Albufera (sedimenti, suolo, acque superficiali) ed a numerose acque reflue (affluenti ed effluenti) provenienti da diversi depuratori, i quali potrebbero rilasciare le loro acque trattate nel Parco. Tutto questo al fine di determinare la presenza dei PPCPs e valutare lo stato di contaminazione in questa riserva naturale.

Il GIS (sistema informativo geografico) e l'analisi statistica (ANOVA, Pearson's correlation analysis, PCA, etc.) sono stati utilizzati per osservare la distribuzione geografica dei composti e mostrare le differenze statisticamente significative tra le concentrazioni dei PPCPs e le diverse aree, includendo le correlazioni tra i contaminanti e i parametri ambientali (tipi di acqua, posizione, usi del suolo, ecc.).

Inoltre, il possibile impatto negativo di queste sostanze sugli ecosistemi è stato valutato utilizzando l'indice di rischio ecologico delle acque superficiali (RQ).

Questa tesi di dottorato è strutturata da **quattro sezioni**.

La **SEZIONE 1** è caratterizzata da un'introduzione che si focalizza sull'importanza della preparazione del campione per la determinazione dei farmaci e i prodotti per la cura personale negli ecosistemi acquatici. Una revisione generale che descrive ogni fase della preparazione del campione, comprendendo tutte le varianti analitiche (metodi convenzionali e innovativi) utilizzate per rilevare questi contaminanti.

La sezione contiene:

• **Pubblicazione 1:** *Sample Preparation to Determine Pharmaceutical and Personal Care Products in an All-Water Matrix: Solid Phase Extraction.*

La **SEZIONE 2** è dedicata alle metodologie analitiche sviluppate per determinare i PPCPs in diversi comparti ambientali. Inoltre, la sezione riporta i risultati ottenuti applicando i metodi proposti ai campioni prelevati nel Parco Naturale dell'Albufera (Valencia, Spagna).

La sezione prevede:

• **Pubblicazione 2:** *Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry,* in cui sono stati proposti due metodi di estrazione in fase solida per determinare 32 composti, farmaceutici e per il benessere, in acqua e in sedimenti, mediante l'uso di HPLC-MS / MS.

La **SEZIONE 3** include una valutazione completa della contaminazione del Parco Naturale dell'Albufera da parte dei composti selezionati. Questa valutazione consente di fare un passo avanti e non è solo un esercizio di follow-up, ma una valutazione completa del trasporto e del destino degli inquinanti emergenti in un'importante zona umida costiera del mediterraneo,la quale potrebbe servire come esempio di ciò che accade in questi tipi di ecosistemi che svolgono un ruolo vitale nel ciclo dell'acqua.

Questa sezione è composta da due pubblicazioni:

• **Pubblicazione 3:** *Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment,* in cui sono stati utilizzati i metodi proposti nella sezione precedente per determinare i PPCPs in un gran numero di campioni, raccolti in 53 punti di campionamento distribuiti in tutto il Parco dell'Albufera. È stata riportata la presenza e la distribuzione dei PPCPs in diverse matrici, come sedimenti, suoli, acque superficiali, affluenti ed effluenti delle acque reflue. Inoltre, la pubblicazione comprende osservazioni sull'efficienza dei depuratori, una valutazione dei rischi ambientali, la diversa distribuzione geofisica e una accurata analisi statistica.

• **Pubblicazione 4:** *Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland,* che fornisce una serie di dati sulle concentrazioni dei PPCPs rilevate in ogni punto di campionamento e sulla relazione statistica tra gli inquinanti e i parametri ambientali.

La **SEZIONE 4** contiene un **RIEPILOGO** generale dei risultati ottenuti e la loro discussione.

Infine, le **CONCLUSIONI** desunte da tutti i lavori menzionati, costituiscono il punto finale del lavoro svolto.

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SECCIÓN 1.
INTRODUCCIÓN

PUBLICACIÓN

01.

SAMPLE PREPARATION TO DETERMINE PHARMACEUTICAL AND PERSONAL CARE PRODUCTS IN AN ALL-WATER MATRIX: SOLID PHASE EXTRACTION

molecules

MDPI

Review

Sample Preparation to Determine Pharmaceutical and Personal Care Products in an All-Water Matrix: Solid Phase Extraction

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Abstract: Pharmaceuticals and personal care products (PPCPs) are abundantly used by people, and some of them are excreted unaltered or as metabolites through urine, with the sewage being the most important source to their release to the environment. These compounds are in almost all types of water (wastewater, surface water, groundwater, etc.) at concentrations ranging from ng/L to µg/L. The isolation and concentration of the PPCPs from water achieves the appropriate sensitivity. This step is mostly based on solid-phase extraction (SPE) but also includes other approaches (dispersive liquid-liquid microextraction (DLLME), buckypaper, SPE using multicartridges, etc.). In this review article, we aim to discuss the procedures employed to extract PPCPs from any type of water sample prior to their determination via an instrumental analytical technique. Furthermore, we put forward not only the merits of the different methods available but also a number of inconsistencies, divergences, weaknesses and disadvantages of the procedures found in literature, as well as the systems proposed to overcome them and to improve the methodology. Environmental applications of the developed techniques are also discussed. The pressing need for new analytical innovations, emerging trends and future prospects was also considered.

Keywords: pharmaceuticals and personal care products; isolation; concentration; solid-phase extraction; cartridges; disks; online; dispersive liquid-liquid microextraction; water samples

1. Introduction

The production and consumption of pharmaceutical and personal care products (PPCPs) is considered an important environmental risk [1–4]. In the last decades, the occurrence of these compounds in nature increased, as described in a number of studies [5–7]. PPCPs can be detected as the active substance, with an unaltered chemical structure, or as a metabolite or a degradation product produced by human and environmental enzymatic activity [8], weather conditions, wastewater treatments [9] and by chemical-physical properties of matrices. There are many reasons for the increasing occurrence of these compounds in different environmental compartments, e.g., their intensive use in farms and aquaculture [10–12] or their inefficient removal from wastewater treatment plants [13,14]. The latter explains why PPCPs used and excreted at home or in hospital can ultimately be released into the environment. Another important source of contamination by PPCPs is industrial waste [15], which is not always processed in the correct form. Furthermore, treated wastewaters are reused for agriculture activity, especially in arid regions [16], contributing to the spread of PPCPs in more matrices, such as soil, wild animals, vegetation, and even food crops.

These considerations on the sources of PPCPs shows the key role that the analysis of water plays to fight against contamination. In fact, water—the most affected environmental compartment—may

be considered as a mirror of the pollution status of an area, and also a scarce resource that must be preserved with optimal quality and zero pollution. In addition, water contaminants, depending on their physicochemical properties, may also (bio)accumulate in sediments and biota, consequently harming human health [17]. Therefore, it was considered a relevant vehicle to different environmental compartments.

Determining and quantifying PPCPs in different types of water provides considerable interesting information not only related to pollution status. For example, the analysis of wastewater samples, divided into influent and effluent waters, could offer information on the PPCPs consumption of a community, estimate the wastewater treatment plant efficiency and establish the most recalcitrant compounds difficult to eliminate. River, lake, and seawater samples could give us an idea of the more persistence substances. The detection in irrigation channels could identify food quality issues. In addition, drinking water is certainly another matrix that should be monitored to assess the potential risks on human and animal health for long-term use [18,19].

For an accurate analysis of PPCPs in different types of water, it is fundamental to consider all water characteristics that could influence recovery of the contaminants. The pH could affect the structure of molecule, promote ionization according to pKa, or activate a prodrug with a change of structure. Many substances were thermolabile and photosensitive, for this reason, sample temperature must always be considered. The salinity of water could increase or decrease extraction efficiency due to different ionic strengths of the media, or the formation of molecular complexes between PPCPs and multivalent metal cations present in the samples that are soluble in water [20]. Other water components have also a strong influence on the PPCPs recovery because are responsible for degradation and/or metabolism. A large range of different metabolites can be formed depending on the specific enzymatic activities, presence of fulvic and humic acids, microorganisms, etc. [21–23].

In addition to the matrix, it is also important to consider the structural variability of PPCPs, designed to interact with specific targets. The presence of distinct functional groups (such as esters, carboxylic acid, ketones, amides, etc.) or the existence of nucleophile/electrophile substituents contribute to all chemical-physical characteristics of each active substance. Influencing stability, reactivity, and solubility in water are all parameters that need to be considered before a sample's preparation for analysis. Despite the variability in the PPCPs' chemical structures, for most laboratories specialized in the analysis of these compounds, the use of multiresidue methods is very attractive because not only attains a reduction of cost and time, but also offers global patterns of contamination with only one analysis. Moreover, these methods easily facilitate an eco-friendly analysis with decreases in waste. In these multiresidue methods, the sample preparation becomes the heart of analysis that influences any other procedural steps from sample collection and storage to the specific instruments selected for final quantification (high performance liquid chromatography-mass spectrometry (HPLC-MS), gas chromatography-mass spectrometry (GC-MS), etc.). The choice of a liquid or gas chromatography (LC or GC), to analyze the final extract, is guided by the analytes' polarity. Generally, compounds with polar characteristics are more suitable for LC, and those with non-polar properties are more amenable to GC; most PPCPs are polar or moderately polar [24]. Surprisingly, some contemporary review articles either cover broader aspects of environmental analysis [25–27], or focus on a particular type of extraction process (e.g., microextraction, use of nanomaterials, magnetic, ultrasonic, etc.) [28–30] but do not cover the entire sample preparation.

Therefore, the goal of this review was to critically analyze the status of sample preparation to determine PPCPs in an all-water matrix. Each step of sample preparation, including all analytical variants (conventional and innovative methods) used to detect these contaminants were considered. Furthermore, each sample preparation method was critically analyzed, highlighting advantages and disadvantages. This review performs an examination of all studies published from January 2018 to May 2020. The search was conducted on the database Scopus (Elsevier), with two different inputs: "extraction pharmaceutical environmental"/"extraction personal care products environmental" and "extraction pharmaceutical water"/"extraction personal care products water". More than one thousand

one hundred works have been viewed. The selection criteria to choose the studies were based on (i) the presence at least of 10 PPCPs to include attractive multiresidue methods; and (ii) water compartmentation, in all variants (wastewater, rivers, irrigation channels, lakes, drinking water, seas, urban storms, swimming pools and thermal water), was chosen. In addition, some reviews outside the interval of time were also chosen.

2. Extraction and Clean-Up of PPCPs in Water

PPCPs are organic compounds, and traditionally this type of compound has been extracted by solid-phase extraction (SPE). This technique was commercialized in the late 1970s and rapidly replaced the liquid-liquid extraction that was previously used [31]. Table 1 and Figure 1 show the analytical methods applied to extract PPCPs in water. The most common were still based on SPE in all possible variants (cartridge, disk, offline, online, etc.). The classic SPE process (cartridges offline) was used in 71.3% of the studies, the online version was employed in the determination in 9.2%, and disks were utilized instead of cartridges in 3.2%.

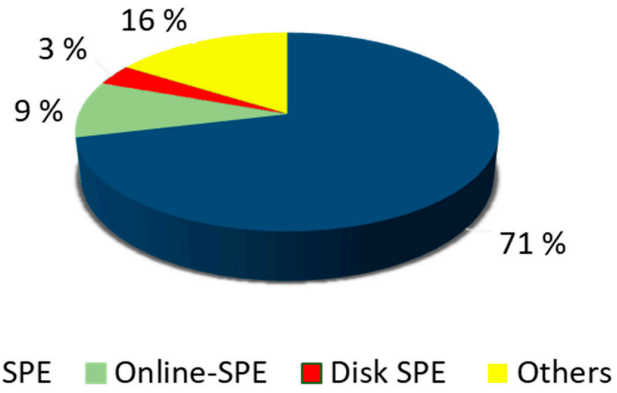

Figure 1. Pharmaceuticals and personal care products (PPCPs) extraction procedures according to the percentage of studies that applied them. SPE: solid-phase extraction.

Only 16% of the studies use other types of methods, such as direct injection, dispersive liquid-liquid extraction (DLLME) (based on liquid-liquid extraction), polyether sulfone microextraction (PES) or buckypaper devices. It is important to note here that many of the methods classified as "other" are based on the basic principles of SPE, but using new phases or formats.

2.1. SPE

This technique involved the use of a small amount of sorbent (commonly hundreds of mg) in a cartridge or syringe barrel. After activation of the sorbent, a water sample of hundreds of mL was passed through the sorbent, which retained the analytes of interest (in this case PPCPs) whereas the water was discarded. Then, the analytes retained in the sorbent were eluted using a few mL of organic solvent. This technique has some advantages, such as the minor investment in reagent and materials, and rapidity.

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Table 1. Selected applications extraction approaches to determine PPCPs in water samples.

Matrix *	No. of PPCPs	Preservation	Volume (mL)	Extraction Method	Sorbent or Cartridge	Detection	Recovery %	Reference
WW, SF	168	Na_4EDTA	50	SPE	Clearnert PEP-2	HPLC-MS/MS	0.05–127	[32]
WW, SF	168	Na_4EDTA	-	Direct injection	-	HPLC-MS/MS	0.05–127	[32]
SF	59	Na_2EDTA	1000	SPE	Oasis HLB	HPLC-MS/MS	52–137	[33]
WW, SF, DW	27	-	-	SPE	Cleanert PEP	HPLC-MS/MS	74–120	[34]
WW	55	Na_2EDTA	150	SPE	Oasis HLB	HPLC-MS/MS	9–119	[35]
SW	91	-	1000	SPE	Oasis HLB	HPLC-MS/MS	70–110	[36]
WW	12	-	7.9	DLLME	-	GC-MS/MS	91–115	[37]
WW, SW	12	-	1000	SPE	Oasis HLB	GC-MS/MS	65–115	[38]
WW, SF, DW	58	-	1.8	Online-SPE	PLRP-s	HPLC-MS/MS	70–120 (82% of total)	[39]
SW	62	-	≤20	Online-SPE	Oasis HLB	HPLC-MS/MS	81–120	[40]
SW	62	-	200	SPE	Oasis HLB	HPLC-MS/MS	81–121	[40]
WW, SW	44	Na_2EDTA	200	SPE	Oasis HLB	HPLC-MS/MS	8–239	[41]
SW	11	-	200	SPE	Strata-X	HPLC-MS/MS	40–120	[42]
SW	34	Na_2EDTA	400	SPE	Oasis HLB	HPLC-MS/MS	41–125	[43]
WW, SW	30	Na_2EDTA	250	SPE	Oasis MCX	HPLC-MS/MS	78–106	[44]
SW	10	-	500	SPE	Oasis HLB	HPLC-MS/MS	69–88	[45]
WW	11	-	-	Online-SPE	TurboFlow™ column	HPLC-MS/MS	45–150	[46]
SW	16	-	10	DLLME	-	HPLC-MS/MS	70–120	[47]
WW, SW	27	Na_2EDTA	125–500	SPE	Oasis MCX	HPLC-MS/MS	73–116	[48]
WW, SW	25 (of 41)	Na_2EDTA	120	PES microextraction	-	HPLC-MS/MS	80–119	[49]
WW, SW	25 (of 41)	Na_2EDTA	100–250	SPE	Oasis HLB	HPLC-MS/MS	71–131	[49]
WW, SW	10	-	20 uL	Online-SPE	Oasis HLB	HPLC-MS/MS	-	[50]
SW	12	-	500	SPE	Oasis HLB	HPLC-MS/MS	55–120	[51]
WW, SW	44	-	500	SPE innovative	GCHM, Oasis HLB	HPLC-MS/MS	76	[52]
WW	190	-	100	SPE innovative	Oasis HLB, Isolute ENV+, Strata-X-AW, Strata-X-CV	UPLC-Q-TOF-MS/MS	57–120	[53]
WW	52	-	100	Disk SPE	BAKERBOND C18 Polar Plus	GC-TOF-MS	-	[54]
SW	24	Na_2EDTA	1000	SPE	Chromabond HR-X	HPLC-MS/MS	52–117	[55]
SW	13	Na_2EDTA	250	SPE	Strata-X	HPLC-MS/MS	51–102	[56]
SW	32	-	200	SPE	Strata-X	HPLC-MS/MS	36–119	[57]
SW	32	-	200	SPE	Strata-X-CW	HPLC-MS/MS	25–110	[57]
SP	111	-	150	SPE	Strata-X-CW	SFC-MS/MS	77 (average)	[58]

Table 1. *Cont.*

Matrix *	No. of PPCPs	Preservation	Volume (mL)	Extraction Method	Sorbent or Cartridge	Detection	Recovery %	Reference
WW, SW	40	-	250	SPE	Oasis HLB	HPLC-MS/MS	17–146	[59]
WW	11	-	250	SPE	Oasis HLB	HPLC-MS/MS	53–124	[60]
SW	39	-	1000	SPE	Oasis HLB	HPLC-MS/MS	1–125	[61]
WW	15	-	250	SPE innovative	Strata-X, PSA, Alumina	GC-MS	19–103	[62]
SW	69	-	100	SPE	Strata X-CW	SFC-MS/MS	76	[63]
WW, SW	31	-	100–500	SPE	Chromabond HR-X	HPLC-MS/MS	32–97	[64]
SW	130	Na_2EDTA	2000	SPE innovative	Oasis WAX, Oasis HLB, Sep-Pak Plus AC 2	HPLC-MS/MS	50–150	[65]
WW, DW	28	-	1000	SPE	C18 Cartridges	HPLC-MS/MS	n.r.–293	[66]
WW, SW	10	Na_2EDTA	500	SPE	Oasis HLB	UPLC-Q-TOF-MS/MS	n.r.–128	[20]
WW, SW	23	-	500	SPE	Oasis MCX	HPLC-MS/MS	54–117	[67]
WW	52	Na_2EDTA	10	Online-SPE	Shim-pack MAYI-ODS	HPLC-MS/MS	74–104	[68]
SW	20	Na_2EDTA	100	SPE	Strata-X	HPLC-MS/MS	70–119	[69]
WW, SW	20	-	200	SPE	Strata-X-Drug B	HPLC-MS/MS	39–102	[70]
SW	61	Na_2EDTA	1000	Disk SPE	Speedisk®	HPLC-MS/MS	-	[71]
SW	61	Na_2EDTA	200	SPE	Oasis HLB	HPLC-MS/MS	-	[71]
WW	26	Na_2EDTA	500	SPE	Oasis HLB	HPLC-MS/MS	-	[72]
WW	10	-	-	SPE	Oasis HLB	HPLC-MS/MS	85–94	[73]
SW	35	Na_2EDTA	1000	SPE	Oasis HLB	HPLC-MS/MS	58–194	[74]
WW, SW	20	-	300–400	SPE	Oasis HLB Prime	GC-MS	≥40%	[75]
WW	83	Na_2EDTA	50–100	SPE	Strata-X	HPLC-MS/MS	n.r.–122	[76]
WW	59	Ascorbic acid; Na_2EDTA	1000	SPE	Oasis HLB	HPLC-MS/MS	9–143	[77]
WW	20	Sodium thiosulfate	500	Online-SPE	Oasis HLB	HPLC-MS/MS	-	[78]
WW	20	Sodium thiosulfate	-	Direct injection	-	HPLC-MS/MS	-	[78]
SW	13	-	-	Passive sampling	PES membranes	LC-DAD	-	[79]
WW	21	-	1000	SPE	Oasis HLB	LC-HRMS	40 (average)	[80]
WW, SW	103 (of 300)	Formaldehyde	250	SPE innovative	Strata-X	UPLC-Q-TOF-MS/MS	-	[81]
WW	37	-	0.5	Online-SPE	PLRPs	HPLC-MS/MS	5–132	[82]
WW	20	-	2	Direct injection	-	HPLC-MS/MS	60–124	[83]
WW	12	-	20–100	SPE	Oasis HLB	HPLC-MS/MS	77–115	[84]
WW, SW	48	-	300–400	SPE	Oasis HLB Prime	GC-MS	>40	[85]
WW	38	-	100	SPE	Oasis MCX	HPLC-MS/MS	65–134	[86]
SW	33	-	200	SPE innovative	Oasis HLB, LC18 column	HPLC-MS/MS	50–106	[87]

Table 1. *Cont.*

Matrix *	No. of PPCPs	Preservation	Volume (mL)	Extraction Method	Sorbent or Cartridge	Detection	Recovery %	Reference
SP	48	Na_4EDTA	200	SPE	Oasis MCX	HPLC-MS/MS	71–122	[88]
WW	22	NaCl	100	Online SPE	DVB/CAR/PDMS	GC-MS	6–104	[89]
WW	19	-	250	SPE	Oasis HLB	LC-TOF/MS	5–111	[90]
WW	11	-	0.9	DLLME	-	HPLC-MS/MS	n.r.–124	[91]
WW, SW	40 (of 139)	-	1000	SPE	Oasis HLB	HPLC-MS/MS	n.r.–99	[92]
WW, SW	41 (of 139)	-	1000	SPE	Bond-Elut ENV	HPLC-MS/MS	n.r.–99	[92]
SW	10 (of 28)	-	500	Buckypaper Device	-	HPLC-MS/MS	n.r.–102	[93]
SW	44	-	200	SPE	Strata-X	HPLC-MS/MS	85–100	[94]
SW	45	Na_2EDTA	1000	SPE	Strata-X	HPLC-MS/MS	38–112	[95]
WW	13	-	150–300	SPE	Oasis HLB	HPLC-MS/MS	40–115	[96]
SW	42	Na_2EDTA; ASA(DW)	50	SPE	Oasis HLB	HPLC-MS/MS	33–117	[97]
WW, SW	39 (of 80)	-	500–100	SPE	Oasis MCX; Oasis HLB	HPLC-MS/MS	31–131	[98]
SW	110 (of 1153)	Phosphate buffer	1000	Disk SPE	Glass microfiber, Empore™ SDB-XD, Empore™ AC	GC-TOF-MS/MS	-	[99]
WW	82	-	250	SPE	Oasis HLB	LC–Q-TOF-MS	66–149	[100]
SW	35	-	100–500	SPE	Oasis HLB	HPLC-MS/MS	2–132	[101]
WW, SW	10	-	50–100	SPE innovative	Oasis MCX, Oasis MAX	LC-HRMS	60–109	[102]
WW, SW	10	Sodium azide; ascorbic acid	200–1000	Disk SPE	Atlantic HLB	HPLC-MS/MS	48–122	[103]
WW, SW	10	Sodium azide ascorbic acid	200-1000	SPE	Oasis HLB	HPLC-MS/MS	1–110	[103]
WW	17	-	250	SPE	Oasis HLB	HPLC-MS/MS	<40%	[104]
SW	10	Citric acid	1000	SPE	C18	HPLC-MS/MS	97–101	[105]
WW	100	-	200	SPE	UCT XRDAH	LC-Q-TOF-MS/MS	-	[106]

* WW = Wastewater; SF = Surface water; SP = Swimming pool water. n.r. = not recovered.

2.1.1. Sorbents and Formats

There are different marketed sorbents that work principally with two distinct separation mechanisms: classical reversed phase chromatography (RP) or ion exchange chromatography (IC). Characteristics of these sorbents are summarized in Table 2. The sorbents used in RP are mostly of a polymeric nature and could be used for a large spectrum of PPCPs, including acidic, basic, and neutral compounds. RP sorbent was applied in 85% of SPE approaches (see Table 1). This is attributable to its ability to retain a wide range of different polarity compounds, a relevant characteristic for a multiresidue method that includes different chemical classes. Of these, two-thirds had a stationary phase characterized by polymeric sorbent that contained vinylpyrrolidone (Oasis® HLB, Strata®X and Cleanert® PEP). Another polymeric sorbent applied was marked by the presence of polystyrene-divinylbenzene (Isolute® ENV+, Chromabond® HR-X and Bond ElutTM ENV) that was applied to polar analytes, or the presence of octadecyl endcapped silica RP (Supelclean™ LC-18 SPE) that was used for nonpolar to moderately polar analytes from aqueous samples.

The IC sorbents were used in the so-called mixed-mode cartridges that combine the polymeric sorbent with an ionic exchanger that could be weak or strong. The IC can be of cations or anions, and this affects the target specificity. Cationic exchange sorbents (weak or strong) were designed to extract basic PPCPs, and anionic exchange sorbent (weak or strong) were to extract the acidic ones. However, weak polymeric cationic-exchangers (Oasis® MCX, Strata®X-CW or X-Drug B and UCT XTRACT® XRDAH) were the most prevalent.

Different studies applied attractive modifications to these traditional cartridges, to obtain the best recoveries for a large spectrum of compounds. Zhu et al. [52] developed, characterized and tested a hydrophilic resin based on poly(*N*-vinyl pyrrolidone-co-divinylbenzene) (NVP-co-DVB) that improved the average absolute recovery for 44 PPCPs, with respect to the use of HLB sorbents. Alternatively, Caban et al. [62] studied the modification of the columns through the application of additional sorbents on top of a polymeric HLB column to improve the SPE of 15 analytes (pharmaceuticals and estrogens) from water. PSAs (Primary and Secondary Amines) and alumina retained matrix components (e.g., humic and fulvic acids) without decreasing the analyte recovery. The solution was named triple-sorbents SPE. They were applied in order to reduce matrix effect. Similarly, Gago-Ferrero et al. [53] mixed four SPE materials simultaneously in an in-house cartridge. These materials included classical RP and ion mixed-mode sorbents (Oasis HLB, Isolute ENV+, Strata-X-AW and Strata-X-CV). Salas et al. [102] combined anionic and cationic exchange sorbents in the same cartridge to extract basic and acidic pharmaceuticals simultaneously. These minor improvements in the SPE procedure (without any relevant cost increment or enlargement of the procedure) can produce an important effect on the quantification of PPCPs, and increase the reliability and reproducibility of the results.

The format of the cartridge and the volume of samples that pass through the cartridge were other elements to take into consideration. The sorbent weight (mg), capacity (mL) and pore size (μm) can influence the efficiency of the columns. These parameters have a key role on the surface area, on which analytes interacted. The amount of sorbent ranged from 60 to 600 mg, and the most used was a quantity of 200 mg. The capacities most used were 3 and 6 mL. There is a global consensus on this point.

In SPE, the volume of water processed generally involves hundreds of milliliters. The capacity to detect lower amounts is one of the advantages of SPE. The matrix effect (ME) could be an element to take in consideration in the choice of volume because it is directly proportional to volume as well as the organic matter content of the water; in this case, clogging of the cartridge slows the process too much. For this reason, some studies chose different volumes of water (depending on its characteristics) with the same method. For example, influent wastewater samples were generally analyzed with smaller volumes compared to effluent samples [46,48].

Table 2. Mechanism, type of sorbent and target of the most used brand name of offline columns.

Brand Name	Mechanism	Sorbent	Target
Oasis HLB, HLB Prime	RP	divinylbenzene-co-*N*-vinylpyrrolidone	acidic, basic, and neutral compounds
STRATA-X	RP	styrene-divinylbenzene-co-*N*-vinylpyrrolidone	acidic, basic, and neutral compounds
Cleanert PEP	RP	divinylbenzene-co-*N*-vinylpyrrolidone-Urea	acidic, basic, and neutral compounds
Isolute ENV+	RP	polystyrene-divinylbenzene (PS-DVB)	polar compounds
Bond-Elut ENV	RP	polystyrene-divinylbenzene (PS-DVB)	polar compounds
Chromabond HR-X	RP	polystyrene-divinylbenzene (PS-DVB)	polar compounds
Oasis MCX	IC	mixed-mode CATION-exchange polymer-based	basic compounds, particularly strong bases
Oasis WAX	IC	mixed-mode ANION-exchange sorbent polymer-based	acidic compounds
Strata-X-CW	IC	mixed-mode CATION-exchange polymer-based	basic compounds, particularly strong bases
Strata-X-AW	IC	mixed-mode ANION-exchange sorbent Polymer-based	acidic compounds
Strata-X-Drug B	IC	mixed-mode strong CATION-exchange polymer-based	basic compounds, particularly strong bases
UCT XRDAH	IC	mixed-mode CATION-exchange polymer-based	basic compounds, particularly strong bases

Figure 2 compares the various volumes that were selected in the different studies. There are two ranges of volumes commonly chosen—between 200 and 250 mL (32% of the studies) and in interval ≥500 mL (42% of works). The volumes commonly used were 200, 250, 500 and 1000 mL. The latter is most commonly selected, but mainly for surface and drinking water.

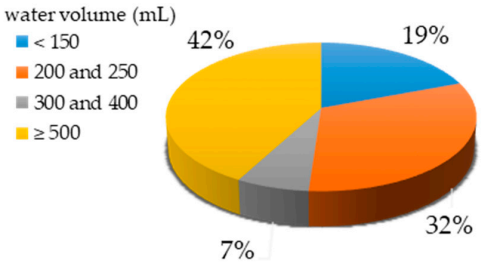

Figure 2. Percentage of studies according to water volume.

2.1.2. SPE Activation, Washing and Elution

In SPE, the first step is the conditioning of the sorbent in order to favor the interaction of the sorbent with the analytes by a mechanism namely "solvation". RF and IC sorbents are usually activated by filling the column two or three times with a solvent miscible with water (e.g., methanol, acetonitrile) followed by the solvent in which the analyte is dissolved (pure matrix, e.g., water, buffer). Methanol and water are most frequent solvents to activate cartridges. Water used for activation can be pH-adjusted or spiked with salt, counter ions or metal sequestrators (sodium acetate buffer [106], monopotassium phosphate [95], sodium dodecyl sulphate [57], etc.) to promote several types of interactions with compounds.

Once the sample passed through the sorbent, another important step is to remove the impurities retained on the SPE packing. For this reason, a wash solution strong enough to remove these impurities, but weak enough to leave the analytes of interest, is passed through the cartridge. These solutions are water, pH-adjusted water, or in a few cases methanol-water (5:95, *v*/*v*). The wash was followed by cartridges air-drying by vacuum or pressure to remove the remaining water, although in few cases, the cartridges can be dried with nitrogen instead of air [37,48,55,61,63].

The RP SPE is the mechanism more commonly used to extract contaminants from water samples, as described previously. The hydrophobic or non-polar interactions between sorbent functional groups and analytes must be destroyed with an organic solvent or solvent combination of enough non-polar character. The most used elution solvents are methanol and acetonitrile. The pH modification during elution can improve recovery if the analyte is ionizable and the eluent favors its ionic form, and basic and acidic compounds become more polar [107].

Figure 3 shows the eluents most frequently applied with HLB sorbents. Only methanol was used in more than half of methods, with acid or basic pH adjustment in 13%, and with a mix of other solvents or followed by a second elution with different solvent, for example, acetonitrile, dichloromethane and acetone, in 27%. Only 7% of the methods presented an eluent mixes (mostly acetonitrile and acetone) without methanol. In the case of weak cationic-exchange sorbents, the eluent was a basic solution with NH_4OH in methanol or acetonitrile.

It is fundamental to consider not only the elution but also all steps that follow the elution. Once the PPCPs have been eluted, the extract is evaporated under a gentle stream of nitrogen in order to concentrate the analytes. The temperature used in this evaporation step is an important parameter that could affect the molecular stability of PPCPs. However, this temperature was not always reported in the studies, even though it can be responsible for the degradation of some PPCPs. The temperature range was between 25 and 50 °C, and the average was 39 °C.

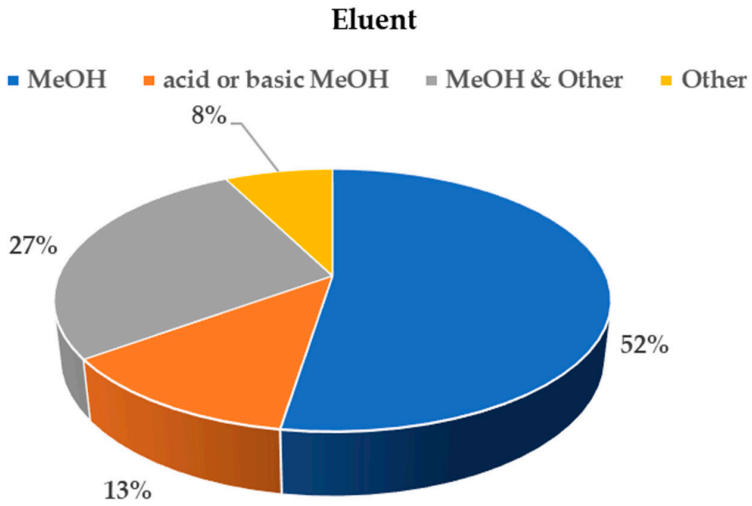

Figure 3. Percentage of studies according to the type of eluent used.

The dried extracts are reconstituted with one or more solvents. If the compounds are determined by HPLC-MS, the mixture of solvents is usually comparable in composition to the initial mobile phase. Again, the reconstituting solvent more commonly used was the methanol-water mix. The most common volumes used for reconstitution were 0.5 and 1 mL. In the case of GC analysis, the addition of a derivatization reagent was often required because PPCPs are mostly polar and/or thermolabile, and these compounds are not amenable for GC analysis without increasing the stability of analytes.

Lastly, the final extract is filtrated before the analysis. Different syringe filters were reported, such as nylon, PVDF (polyvinylidene fluoride), PTFE, RC, GHP, PP, etc. The size used were 0.20 and 0.22 µm. This procedure was an ulterior clean-up to remove the particles with a large size to optimize analysis, for example by reducing the presence of obstruction phenomena in column. For this step, it was fundamental to remember which combinations (solvent-filter) are safe and which are corrosive.

2.1.3. Water Sample Pretreatment before SPE

Regarding the characteristics of the water sample, the preservation of its integrity from the sampling point to the moment of the analysis was vital. To this end, in many cases, the water samples were spiked by preservative compounds or solutions. As described in the U.S. Library of Medicine (2017), a pharmaceutical preservative is referred to as "substances added to pharmaceutical preparations to protect them from chemical change or microbial action" [108]. In the same way, these preservatives can be added to the water sample to avoid the degradation of the PPCPs present in the sample. Preservatives can be natural or synthetic compounds and included buffers, bulking agents, chelating agents, antioxidants, antimicrobial agents, surfactants, etc. " [108,109]. The most used was EDTA—a chelating agent thanks to its four carboxyl groups and two nitrogen atoms that can form stable complexes with cations—which is able to improve the extraction efficiency of certain pharmaceuticals that also form complexes with metals, such as antibiotics, because they sequestrate the metals of the solution, liberating the PPCPs and increasing their recovery [110]. Generally, EDTA was added in the samples to a final concentration of 0.1% (1.000 g/L) or 0.05% (0.500 g/L), but it could reach a final concentration of 0.2, 2 or even 5%. Other preservatives used were antimicrobials, such as formaldehyde, NaCl, sodium azide and citric acid, and/or antioxidants, such as ascorbic acid and sodium thiosulfate. These antioxidants reduced any residual chlorine, chloramine and ozone that had been used as a disinfectant because they could react with some antibiotics [97]. Furthermore, more than half of the methods adjusted the pH of the sample to prevent degradation, ionization phenomena, or to achieve the optimum value for the extraction. For about 70% of methods, pH was adjusted between 2

and 3 units. In a few cases this adjustment was between 3.5 and 7. It was rarely adjusted by 9 and 10 units.

To ensure the proper quantification of the analytes is always very important. Therefore, samples were spiked by a solution of internal standard (IS) in more than 83% of the studies to obtain more reliable results, taking matrix effects into consideration. It was not always possible to use an isotopic reference for every compound, because the cost of the ISs are high, and are not available for some of the target analytes [57].

Another pretreatment widely used in water sample preparation was filtration, the role of which was to remove suspended substances, such as suspended particles, colloids and microorganisms from samples to prevent obstruction of the SPE cartridges or significant interferences in subsequent treatment processes [74]. In various studies, it was easy to find filters constituted of different materials, such as paper, nylon, PVDF (polyvinylidene fluoride) and cellulose membrane. The most frequently used to monitor the water pollution was a glass microfiber filter. The mesh filter range was from 0.20 to 1.60 μm; the size most commonly used was 0.45 μm. Sometimes filters with different sizes were coupled to remove particles at different levels. Centrifugation was an alternative to filtration, with the same goal but much less used [32]. In this case, the mass deposited on the bottom was removed and analysis was focused on supernatant.

2.2. Online SPE

SPE can be used offline (independently from the further chromatographic analysis) or online (directly connected to the chromatographic system). However, there are few difference in the components of the techniques between the two formats, with the exception of the valves system used to connect SPE online with the determination technique (commonly any type of HPLC-MS). In both, the main factors that affected the results of these technique were the formats and sorbents of stationary phase (cartridge) and the solvent(s) used for activation, washing and elution. Online SPE can be coupled to both, LC or GC. However, the preferred technique is online SPE liquid chromatography tandem mass spectrometry (SPE-LC-MS/MS), PPCPs and the SPE eluents are much more compatible with the mobile phase of LC than with that of GC.

To be functional, online systems require the use of 6 or 10 port valves to automate extraction and connection to the instrument. A schematic illustration of the analytical system is presented in Figure 4. The most common are home-made devices, but there are also commercial systems such as an automated sample processor [82]. These devices can be personalized and adapted to the particular analysis, for example, to obtain online cross, which allows the automatic cross-utilization of two SPE columns to speed up the analysis of pharmaceuticals in different water samples [40].

The columns for online-SPE mode were characterized by similar polymeric RP sorbents. The main differences, with offline-SPE, were the length of columns (generally 1–2 cm). OASIS HLB (2.1 × 30 mm, 10 μm) [40,50,78], MAYI-ODS (10 mm × 2.0 mm, 50 μm) [68], and PLRP columns [39,82] have been the most widely reported. However, sorbents based on alternative mechanisms, such as the so-called TurboFlow™, which mixes size exclusion chromatography with reversed sorbents, has also been reported to determine pharmaceuticals [46]. To this end, three TurboFlow™ columns (TFC) connected in series were used, i.e., Cyclone P–C18-P XL–Cyclone MAX in order to achieve a proper extraction and clean-up.

The online SPE systems present the advantage to provide automatic and efficient sample loading, clean-up, desorption, separation, and detection at the same time, to reduce the sample volume, save time and solvents, prevent sample contamination and PPCP loss, and improve the method performance. The reduction in sample volume that could decrease sensitivity is normally compensated for by the increase in sensitivity as all the analyte retained in the sorbent passes to the chromatographic column.

The disadvantage of these methods is that they are not very versatile to be adapted to different types and conditions of analysis, because sample pH, injection volume, and valve-switching time

needs to be very carefully optimized to ensure appropriate method performance for target PPCPs [39]. Once established, they are more suitable for routine analysis.

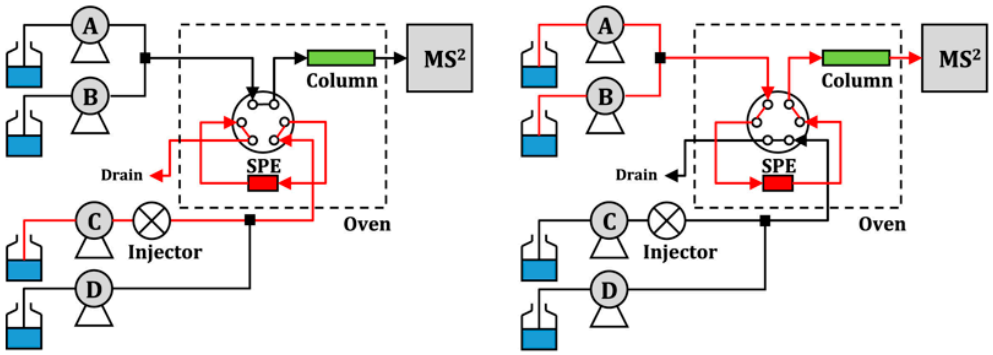

Figure 4. Configuration of the online SPE liquid chromatography tandem mass spectrometry (SPE-LC-MS/MS) system. I. separation column equilibration (pump A and B); II. sample loading and trapping (pump C); III. SPE desorption (pump A and B) and cleaning (pump D). Reproduced from [68] with permission from Elsevier. (**a**) Sample loading (Pump A, B, and C: On); (**b**) Sample analysis (Pump A, B, and D: On).

2.3. SPE Disk

The disks are a variant of cartridges that follow the same principle to retain an elute PPCPs. The disks have a higher diameter (commonly ca. 45 mm) and low height (a few millimeters). This format attempts to address several disadvantages of the cartridges, such as plugging due to the suspended particulate matter, high back-pressure that reduces flow rates, and improve retention kinetics of the analytes by using lower particle size. Generally, it was used with higher volumes of samples than SPE. The passage of the sample was much quicker (up to 100 mL/min). Moreover, the use of disks was advantageous for handling dirty samples. Only four studies used this approach (Table 1). There are disposable disks of many types of sorbents: C18, hydrophilic divinylbenzene (DVB), HLB or carbon.

Hydrophilic divinylbenzene (DVB) disks have been compared with Oasis HLB cartridges. Although the most apolar analytes (LogP ≥ 4) attained higher process efficiencies following Speedisk extraction, it could be noticed that in general, process efficiency was lower than for Oasis HLB extraction: 16 versus 59 analytes having a process efficiency >60% for Speedisk and Oasis HLB, respectively [71]. However, this study did not compare the same type of sorbent in both formats. Kafeenah et al. [103] did compare both formats using HLB sorbent. The method using disk SPE was better in terms of recovery, sensitivity, rapidness, and matrix effect, compared to the cartridge method.

The combination of different disks in order to improve recoveries has also been tested for GC-MS amenable analytes using, in sequence, a glass microfiber disk (GMF 150, 47 mm, Whatman), a styrene-divinylbenzene disk (Empore™ SDB-XD, 47 mm), and an active carbon disk (Empore™ AC, 47 mm) [99]. However, the same study recommended the use PS-2 and AC-2 Sep-Pak short cartridges for compounds analyzed by HPLC-MS.

The main disadvantages, as evidenced in the studies, are related with highest waste of samples and reagents used to active, wash and elute the sorbent.

2.4. Other Extraction Approaches

Other approaches have been reported to extract the PPCPs from water, and even though they are not as used as SPE, can be advantageous for some applications. These approaches are commonly focused on more environmentally friendly alternatives that reduce the use of materials, organic solvents and reagents; the so-called green chemistry. The simplest process is direct injection without any

pre-concentration steps [78,83]. This was possible thanks to the excellent sensitivity of the HPLC-MS/MS. Botero-Coy et al. [83] included a simple dilution with water (×5) in order to reduce the matrix complexity. The most important problem in this method is its high matrix effects.

The microextractions, both solid and liquid, are an attractive alternative to SPE. The Dispersive Liquid-liquid Microextraction (DLLME) [37,47] has benefits related to a quick, easy cleaning and highly efficient pre-concentration procedure. Moreover, the sample volume required was very small, reducing the wastes. Two solvents were used, a dispersant and an extractor. The dispersant must be soluble in water and in the extractor, and the choice was methanol. As extractor (few microliters) both, the most traditional, chloroform, and the most recently introduced ionic liquids (1-Hexyl-3-methylimidazolium hexafluorophosphate) have been reported. The most important problem of this technique to determine PPCPs is that it is more efficient for non-polar compounds. Other approaches applied were the solid phase microextraction (SPME), which is attractive, because it enables extraction and clean-up in only one step, eliminating the problems associated with extensive use of solvents and equipment, since the analytes retained in the fiber can be thermally desorbed in the GC injector [111]. Another advantage of this technique is that the adsorbed analyte can be derivatized on-fiber, to transform it into a more volatile compound in order to make it more GC-MS amenable. Recently, this on-fiber derivatization and on-line thermal desorption has been applied for the extraction of 17 mL of water sample for the simultaneous determination of 22 pharmaceuticals and personal care products, including three transformation products, in sewage [89]. The fiber used was 2-cm long, 50/30-µm thick Divinylbenzene/Carboxen/Polydimethylsiloxane (DVB/CAR/PDMS). This method has the advantage of avoiding the use of organic solvent, since analytes are directly desorbed in the GC injector. SPME fiber can also be desorbed with a few mL of organic solvent to analyze the PPCPs by HPLC-MS. As in the method reported by Mijangos et al. [49], preconcentrated pharmaceuticals and personal care products in a disposable and low cost polyethersulfone (PES) sorbent are further desorbed in methanol.

Other approaches are based on testing new phases consisted of nanomaterials as more efficient sorbents. Tomai et al. [93] performed an SPE with oxidized buckypaper (BP) for Stir-Disc. The aim was to propose an SPE extraction device which combined the properties of carbon nanotubes and magnetic stirring with the main advantages of disk SPE. The concept was the same as classic SPE, but in this case the extraction device was immersed into the aqueous sample and left under magnetic stirring to permit analyte absorption on a BP membrane.

The last approach was the use of a PASSIL sampler [79]. The acronym PASSIL describes a device constituted of two PES membranes impregnated with an ionic liquid. After passive sampling, the receiving phase was eluted from the membranes and dissolved with acetonitrile.

3. Environmental Applications

Seventy-six studies have been selected (Table 1). Nine studies proposed the application of two different methods or approaches for sample preparation. In many cases, the method was applied to various aqueous matrices. The average number of PPCPs detected for each method was forty-one. The average number of PPCPs included in the studies reviewed increased over time, which may be justified by the growing interest in using methods that include as many substances as possible in the same analysis. In the studies published in 2018, the average number of PPCPs included was 34; in 2019 the average was 38 and up to May 2020 it was 60. In the Figure 5, the different studies are classified according to the number of compounds detected. Forty-six percent of studies covered between 10 and 25 PPCPs. The second range (between 26 and 50) included 30% of studies. Fifteen percent showed a 50 < PPCPs < 100 range. Lastly, a small portion (9%) included more than 100 PPCPs. A few methods reported a contaminants list characterized by a multiclass of compounds, not only PPCPS, but pesticides, drugs, flame retardants, etc., too. For these cases, only the total number of PPCPs was considered.

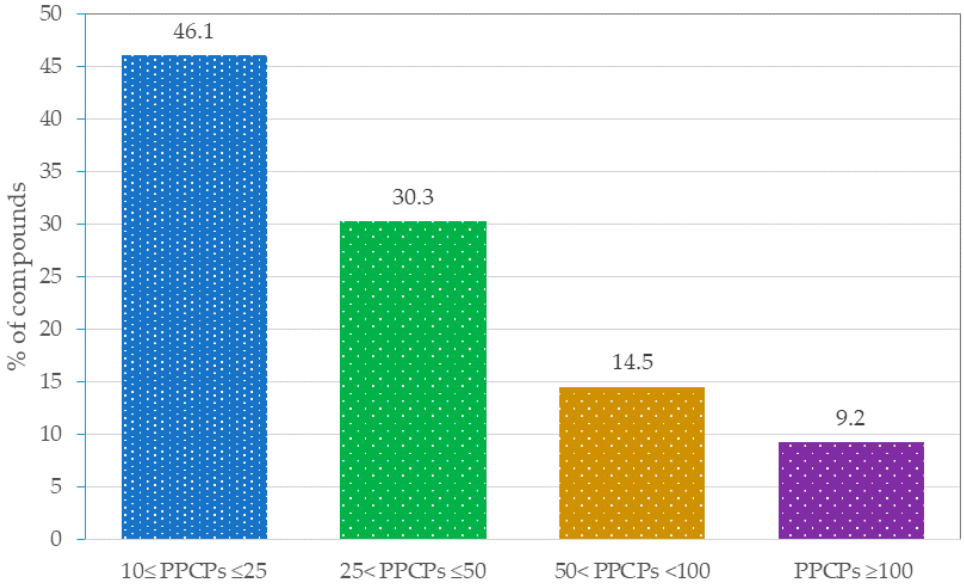

Figure 5. Percentage of studies according to the number of PPCPs analyzed.

Different types of water were collected. The principal parameters monitored were temperature, pH, EC (electrical conductivity, μS cm^{-1}), TDS (total dissolved solids, μg L^{-1}), DO (dissolved oxygen, mg L^{-1}), TSS (total suspended solids, mg L^{-1}) and BOD (biochemical oxygen demand, mg L^{-1}). Influent and effluent wastewater samples from hospitals or wastewater treatment plants (WWTPs) were the most analyzed (46% of studies). This matrix was marked by complexity due to the presence of numerous interferents. Some studies investigated the presence of PPCPs in raw wastewater at the treatment plant, some just the effluents, and some investigated both [35]. Most of these studies also studied the efficiency of the elimination of the PPCPs in the WWTPs [35]. All these studies identified the WWTP effluents as one source of PPCPs to the environment.

In the second block of studies, different matrices were regrouped into a single group: surface water (SW). The 40% of works analyzed and studied in this group investigated a large spectrum of water sources: streams, rivers, estuaries, lakes, seas, ground water, and urban and agricultural storm waters. Drinking and tap water (DW) constituted the third group, with an occurrence of 12% in the studies selected. DW was regulated by "The Drinking Water Directive 98/83/EC" that supervises the quality of water (for human consumption). It provided a general framework and a minimum value of 48 specific parameters that must be monitored regularly [24].

Lastly, two works included other two aqueous matrices: thermal and swimming pool water (SP). Chemicals in these matrices can come from different sources, such as bathers, who continuously release organic matter mainly through sweat and urine [25].

4. Conclusions and Future Trends

The review article focused on the extraction methods for PPCPs. Although these extraction methods are clearly dominated by offline solid-phase extraction using cartridges, there are significant knowledge gaps in accurately understanding the extraction mechanisms for PPCPs, including some metabolite and/or degradation products. Many of the most recent and innovative methods are based on the combination of sorbents with different chemical-physical properties either in the same cartridge, in parallel, or even in series. These modifications are considered to be small steps, but nevertheless, they represent a great advance by improving the extraction of a group of compounds with very different polarities. Multiresidue methods able to cover more than 100 compounds are already a reality. Rapid, lower cost, and eco-friendly sample preparation techniques are urgently needed. Automated, online

preconcentration, and clean-up steps prior to the instrument analysis would be the future of the technique. Solvent-free microextraction methods are the trend of extractions such as DLLME. However, these techniques are rarely used, as they work especially well with non-polar PPCPs, but most are polar.

Most of the environmental studies carried out so far have two aspects, (i) analytical including validation of the methods that mainly improves the accuracy in the quantification and the elimination of the matrix effects, and (ii) the environmental aspect in which the whole cycle of the water is covered, including the identification of the sources of these compounds to the environment, the efficiency in the elimination, and the influence of environmental factors such as seasonality. All these studies have contributed to an important advance of knowledge about the distribution and hazards of PPCPs. A gap detected in these studies is the lack of knowledge about the mixtures of PPCPs found in the environment and on the different metabolites and/or degradation products that can be present. It is expected that, in the near future, there will be an increase in knowledge in these fields.

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SECCIÓN 2. METODOLOGÍAS ANALÍTICAS DESAROLLADAS

PUBLICACIÓN

02.

SYSTEMATIC ASSESSMENT OF EXTRACTION OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN WATER AND SEDIMENT FOLLOWED BY LIQUID CHROMATOGRAPHY–TANDEM MASS SPECTROMETRY

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RESEARCH PAPER

Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry

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Abstract

Two solid-phase extraction methods were systematically studied to determine 32 pharmaceuticals and personal care products in water and sediments by ultrahigh-performance liquid chromatography–tandem mass spectrometry. One involves HLB cartridges activated with sodium dodecyl sulfate before the passage of the sample to form an ion pair with cationic analytes, and the other uses mixed HLB–cation exchange cartridges. The accuracy of the sodium dodecyl sulfate method was good for most compounds (recoveries of 61–120% with relative standard deviation less than 23%). However, the recoveries for atorvastatin, codeine, paracetamol, flufenamic acid, and salicylic acid were approximately 50% and for omeprazole and triclocarban were even lower (from 0 to 12%). The detection limits were 1.65–25 ng L^{-1} in water and 0.33–4.00 ng g^{-1} (dry weight) in sediment. The recoveries for the mixed-mode cartridge (Strata-X-CW) method ranged from 57% to 120% with relative standard deviation less than 21%, with the exception of codeine [25% (water)], metformin [11% (sediment)], paracetamol [48% (sediment)], and salicylic acid [32% (sediment)]. The detection limits were 1.65–38.35 ng L^{-1} in water and 0.33–10 ng g^{-1} (dry weight) in sediment. Both methods followed the same pattern when applied to water. For sediments, the recoveries, which offer good performance, were not very high, although 60% of the compounds had recoveries greater 80%. The methods were applied to the analysis of surface water and sediments from the Albufera Natural Park (Spain). Twenty-seven of 32 analytes were detected in the samples analyzed.

Keywords Pharmaceuticals and personal care products · Ion pairing · Environmental matrices · High-performance liquid chromatography–tandem and mass spectrometry · Sodium dodecyl sulfate solution · Solid-phase extraction

Introduction

The environmental occurrence of pharmaceuticals and personal care products (PPCPs) has grown over the years because of their increased consumption by humans [1]. As a result, their entry into environmental compartments needs to be supervised to the point where some PPCPs were included in a "watch list" in the EU Water Framework Directive [2–8] for their adverse effects in the aquatic environment. The development of new analytical methods to establish their sources, transport, and fate in the environment is crucial.

The importance of the topic could explain the number of methods already developed to determine PPCPs although the analytical difficulties for their detection are also numerous [1, 2]. One of the constraints is the complexity of environmental matrices, such as water, sediment, and soil containing many substances that interfere with the analysis [9–17].

The more extensive methods for determining PPCPs involve solid–liquid extraction if the matrix is solid or solid-phase extraction (SPE) if the matrix is liquid followed by liquid chromatography (LC)–mass spectrometry (MS) [1, 8, 18–24]. Typically, SPE is also used as a cleanup step to isolate analytes and remove interfering compounds from the extract of the solid matrices [25–27]. However, these methods have several weaknesses that require the development of an

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appropriate workflow for the analysis. Cleanup of the extracts is needed because of the matrix effect (ME), whereby the presence of other matrix components can sometimes greatly reduce the sensitivity [2], forcing one to remove some of the large number of potentially interfering compounds [26]. The low concentrations at which pharmaceuticals are present in samples, subnanograms per liter to micrograms per liter [21, 28] or subnanograms per kilogram to micrograms per kilogram, is also an important factor [29]. Other key aspects are the physicochemical properties of emerging contaminants, such as pK_a, polarity (see Table S1), and absorption. The different properties can strongly affect determination of analytes. PPCPs can be ionized at various pH values or even at any environmental pH depending on the pK_a. Ionic compounds can interact not only with the matrix as already mentioned but also with the SPE cartridge sorbent (OH groups, amino groups, etc.) if ion-exchange materials are used or may simply be slightly retained in the case of reversed-phase sorbents in the SPE, influencing the recovery.

Generally, the cartridges most commonly used to detect many PPCPs in the same analysis are reversed phases functionalized with polymeric sorbent, both hydrophilic and lipophilic, which gives interesting retention for substances with a wide polarity range (e.g., Strata-X® and Oasis HLB®) [30–32]. Unfortunately, these do not ensure good recoveries for ionic compounds. Instead, for these compounds mixed-mode sorbents either with weak cation-exchange or weak anion-exchange for basic or acidic compounds, respectively, or the formation of ion pairs is a better choice. However, a study of the literature on the topic reveals the lack of systematic studies showing the advantages of one proposed strategy over another. Most of the reported methods are multiresidue methods devoted to extracting as many compounds as possible, including altogether acidic, basic, and neutral, and there is no information on whether acidic compounds can be extracted with acceptable recoveries with use of mixed HLB–cation exchanger cartridges or anionic ion pairings optimized initially for basic PPCPs that are commonly ionic at environmental pH and therefore are more difficult to extract. Although these modes are not the ideal ones for acidic compounds, if they could be acceptably extracted, a higher PPCP coverage with only one extraction method will be achieved. This will help to establish a universal extraction and/or cleanup method for the selected target compounds with a certain polarity range.

Previous reviews pinpointed the need for systematic studies exploiting the feasibility of different procedures to identify and quantify PPCPs with different physicochemical properties. The purpose of the present study was to determine 32 PPCPs of basic, neutral, and acidic character in surface water and sediment samples by a systematic study using two approaches suggested for the extraction of basic PPCPs ionized at environmental pH that are not well recovered with conventional HLB cartridges. This knowledge is important because it can help to develop wide-ranging multiresidue methods that might reduce costs while preserving appropriate recoveries for target analytes. Two different analytical methods for the SPE were compared: (1) ion pairing using sodium dodecyl sulfate (SDS) as a counterion and (2) mixed-mode cartridges with polymeric weak cation-exchange stationary phases (Strata-X-CW®). To our knowledge the efficiency of the extraction of acidic compounds by these sorbents designed to extract basic compounds has never been tested. Furthermore, the potential combination of mixed mode and chelating agents is also innovative. This study provides useful and systematic information to analyze PPCPs in water and sediments.

Materials and methods

Chemical and reagents

Selected PPCPs are listed in the electronic supplementary material (Text S1 and Table S1). The analytical standards were from Sigma-Aldrich (Madrid, Spain) with a purity greater than 95%. Six isotopically labeled internal standards were used. Diclofenac-d_4 and triclosan-d_3 were acquired from Toronto Chemicals Research (Toronto, Canada) and acetaminophen-d_3, atenolol-d_7, bisphenol A-d_{16}, and ibuprofen-d_3 were acquired from Sigma-Aldrich (Houston,TX, USA). The individual analytical and internal standard solutions were prepared in methanol (MeOH) at a concentration of 1 mg mL^{-1}. Stock and working individual solutions and mixtures were prepared by appropriate dilution and mixture of the standard solutions in MeOH–water (30:70 v/v) and were stored in the dark at −20 °C.

A McIlvaine–EDTA buffer (pH 4.5) was made with 100 mL of citric acid (0.1 mol L^{-1}), 62.5 mL of Na_2HPO_4 (0.2 mol L^{-1}) and 6.05 g of Na_2EDTA. Citric acid, Na_2HPO_4, and Na_2EDTA were purchased from Alfa Aesar (Karlsruhe, Germany). SDS, from VWR International (Spain), was used to prepare a 2 mmol L^{-1} SDS solution (0.576 g of SDS in 1 L of Milli-Q water) for activation of cartridges.

Ultrahigh-purity water was obtained from an Elix Milli-Q system (Millipore, Billerica, MA, USA). MeOH, dichloromethane, and ammonia solution (25%) were from VWR International (Barcelona, Spain). The mobile phase additives formic acid and ammonium fluoride were obtained from Sigma-Aldrich. The two different stationary phase cartridges tested—Strata-X (33 μm, 200 mg/6 mL, polymeric reversed phase) and Strata-X-CW (33 μm, 200 mg/6 mL, polymeric weak cation exchange)—were from Phenomenex (Torrance, CA, USA).

Samples

The surface water and sediment samples were obtained from the Albufera Natural Park (Valencia, Spain). Water samples were collected in poly(ethylene terephthalate) bottles (1 L), and sediment samples were taken at the same point as water samples with a Van Veen grab sampler. The samples were frozen at −20 °C in the laboratory to prevent degradation of contaminants, and sediments were lyophilized with a Virtis lyophilizer (SP Scientific, Gardiner, NY, USA) with a vacuum between 1 and 4 mTorr for 48 h. Lyophilized samples were also stored at −20 °C.

Before SPE, 200 mL of water samples was vacuum filtered with a 0.45-μm glass fiber filter (Advantec MFS, Dublin, CA, USA). Internal standards were added to water samples to a concentration of 500 μg L^{-1} (100 ng mL^{-1} in the final extract).

Lyophilized sediment (1 g) was weighed and spiked with 100 μL of a mixture of internal standards at 1 μg mL^{-1} (to a concentration of 100 ng g^{-1} for each internal standard in sediment). Then 5 mL of Milli-Q water, 5 mL of McIlvaine–EDTA buffer, and 5 mL of MeOH were added. The mixture was homogenized for 5 min by vortex agitation, sonicated for 10 min, and centrifuged for 6 min at 3000 rpm and 10 °C. The supernatant was separated and diluted to 250 mL with Milli-Q water for further cleanup by SPE.

Solid-phase extraction

Cartridges of two different stationary phases were tested: Phenomenex Strata-X (33 μm, polymeric reversed phase, 200 mg/6 mL) and Phenomenex Strata-X-CW (33 μm, polymeric weak cation exchange, 200 mg/6 mL). All samples were passed through both cartridges by use of a vacuum. The cartridges were activated before the passage of the sample with 6 mL of MeOH, 6 mL of Milli-Q water, and if ion pairing is form, with 6 mL of 2 mmol L^{-1} SDS solution. The analytes were eluted with 6 mL of MeOH and 3 mL of MeOH–dichloromethane (50:50 v/v) for Strata-X and with 6 mL of MeOH–NH_4OH (NH_4OH at 9.5 mol L^{-1}) (95:5 v/v) for Strata-X-CW by gravity. The eluates were evaporated to dryness with a Stuart nitrogen evaporator, and the extracts were reconstituted with 1 mL of 70:30 Milli-Q water–MeOH.

LC–MS/MS analysis

Chromatographic separation was performed with a 1260 Infinity ultrahigh-performance LC system coupled to a 6410 triple-quadrupole mass spectrometer from Agilent Technologies (Santa Clara, CA, USA) as previously reported [19, 33, 34]. The mobile phase consisted of NH_4F (2.5 mmol L^{-1}) in MeOH (solvent A) and NH_4F (2.5 mmol L^{-1}) in water (solvent B) for negative mode and MeOH (solvent A) and water (solvent B) with 0.1% formic acid in both solutions for positive mode. Other high-performance LC parameters are described in the electronic supplementary material (Text S2).

MS/MS detection was performed in multiple reaction monitoring mode. Details of the MS/MS determination are provided in the electronic supplementary material (Text S2 and Table S2). The chromatograms were acquired and processed by MassHunter (version 07.00, build 7.0.457.0) supplied by Agilent Technologies.

Method validation

The method was validated with distilled water, surface water, and sediments. A previous analysis was performed in surface water and sediments to establish if the analytes were present. As it was not always possible to find negative samples, the analyte area of the peak calculated for the blank sample was subtracted from the area obtained for spiked samples. The quantification was performed with an external standard or an internal standard depending on the compound because the cost of the internal standard is high and internal standards for some of the target analytes are not available. Alprazolam, atenolol, atorvastatin, bisphenol A, caffeine, codeine, diclofenac, ibuprofen, metformin, omeprazole, paracetamol, tramadol, and triclosan were quantified by internal standards as described in Table S2. The other analytes were quantified by external calibration curves because they have chromatographic properties completely different from those of the internal standards. In some optimization assays, all analytes were quantified by an external standard.

The parameters evaluated to validate the methods were linearity, ME, recovery, precision (as intralaboratory reproducibility), and sensitivity [as limits of detection (LODs) and limits of quantification (LOQs)].

Three calibration curves were prepared by dissolving the PPCP standards in pure solvent, one for PPCPs that were determined in negative ionization mode and two for those that were determined in positive mode (1) with H_2O–MeOH (70:30 v/v) as solvent and (2) with SDS (2 mmol L^{-1})–MeOH (70:30 v/v) as solvent. Seven points were used for the negative mode in a concentration range from 5 to 500 ng mL^{-1} (equivalent to a concentration between 20 and 2000 ng L^{-1} in water) and 14 points were used for the positive mode from 5 to 1000 ng mL^{-1} (equivalent to a concentration between 20 and 4000 ng L^{-1} in water). The internal standards were always at 100 μg mL^{-1} of each compound in the final extract. To study the ME, three matrix-matched calibration curves were prepared by spiking sample extracts with the described calibration solutions. A weighted least squares linear ($1/x^2$) regression model was used to create the calibration curves.

The ME was determined according to the following equation:

$$\text{ME}\ (\%)=\left(\frac{m_{\text{extract}}}{m_{\text{std solution}}}-1\right)\times 100, \quad (1)$$

where m_{extract} is the slope of linear equation for the spiked extract and $m_{\text{std solution}}$ is the slope of the linear calibration equation for standard solution.

Recovery tests were performed in samples (water and sediment) spiked at four levels in the final extract: 10, 25, 50, and 100 $\mu g L^{-1}$ analyzed in quadruplicate. Reproducibility of the methods was expressed as the relative standard deviation (RSD) of the samples analyzed in quadruplicate.

The LOD and LOQ were established as the minimum concentration of the analyte that can be detected in spiked samples with a signal-to-noise ratio of 3 and 10, respectively. They were estimated by our studying the response of the extract from spiked samples at the lowest concentration tested (10 ng g^{-1} and 50 $\mu g L^{-1}$).

Results and discussion

Optimization of the methods

The solvent that provides the greatest recoveries for solid–liquid extraction of the sediment was established. Milli-Q water, solvent mix_1 (McIlvaine–EDTA buffer and Milli-Q water) and solvent mix_2 (MeOH, McIlvaine–EDTA buffer, and Milli-Q water) were tested. This choice of solvents was made because the analytes' polarity is high to moderate (Table S1) so they will be soluble in polar solvents [1]. Furthermore, sediments are complex matrices, containing clays with a high capacity to retain cations (some of the analytes are ionized as a function of pH), and the literature establishes that solvents at slightly acidic pH improve extraction [19]; in addition, some drugs tend to form complexes with the inorganic cations present in the clays and therefore the use of a complexing agent is also recommended [19, 35, 36]. These tests were performed with a Strata-X sorbent.

Before we established the best extraction solvents for sediments, their influence on the SPE cleanup recovery efficiency was ascertained (Table S3). For most PPCPs, the recoveries obtained with any of the solvents tested were similar (differences were less than ±10 percentage points with any of the solvents), with RSD ranging from 1% to 25%. Milli-Q water as solvent provided the greatest recovery for several compounds, e.g. bisphenol A, diclofenac and furosemide, indicating a negative effect of the percentage of MeOH in the extract on SPE retention (Table S3). Contrarily, simvastatin, tramadol, caffeine, and etoricoxib had greater recoveries when mix_2 was added probably because of the capacity of EDTA to sequestrate cations (Table S3). The small variations in the recovery obtained with the three solvents tested indicated that any of the mixtures could provide acceptable recoveries in the subsequent SPE cleanup.

Furthermore, the effects of the evaporation step on the eluate obtained by SPE were studied. This step was characterized by the temperature of the plate, nitrogen flow, and evaporation time. All these parameters could damage the structure of compounds that are thermolabile or volatile. Therefore, we evaluated recoveries without an evaporation step. The SPE test was performed with mix_2 spiked at a high concentration (200 $\mu g L^{-1}$) and eluted with only 6 mL of MeOH. Three milliliters of the eluate was diluted to 10 mL with Milli-Q water to give H_2O–MeOH in a ratio of 70:30 (v/v), which was considered such as the final extract ready to be analyzed. Alprazolam, caffeine, codeine, enalapril, etoricoxib, lorazepam, simvastatin, tramadol, triclocarban, and triclosan exhibited higher recoveries when the evaporation step was suppressed (see Table S3). The evaporation step was not eliminated because the decrease in the recovery was less than 20 percentage pointsfor many of the compounds and this step increased the concentration factor and increased the method's sensitivity. However, it requires special care to minimize analyte losses as much as possible (strict temperature, time, and nitrogen flow control).

The best solvent to extract these compounds from sediments was studied (Table S4). The optimum results were obtained by extraction with mix_2 considering the list of compounds selected and the best possible agreement. This mixture provides greater recoveries of alprazolam, butylparaben, caffeine, clofibric acid, etoricoxib, flufenamic acid, indomethacin, lorazepam, propylparaben, and tramadol and maintains those of bezafibrate, chloramphenicol, ethylparaben, thiamphenicol, and warfarin.

Some basic analytes characterized by their high polarity and tendency to be ionized at environmental pH, such as metformin, etoricoxib, simvastatin, and omeprazole, did not provide appropriate recoveries. However, these compounds are important from an environmental point of view because even through the recoveries are low, their occurrence has been widely reported [19, 35, 37, 38].

SPE was also optimized to increase the recoveries by our studying the mixed-mode sorbent that combines an HLB-type sorbent, a weak cation exchanger, and the formation on an ion pair in the sorbent to retain cationic compounds in the conventional HLB cartridges.

The results show that both approaches increase the recoveries of these analytes (Table S5). Preliminary tests were performed with mix_2, using the two different cartridges (Strata-X and Strata-X-CW) being activated with and without SDS solution. Although the use of SDS and EDTA in electrospray ionization MS applications can be the origin of the more marked ME due to competition in the ionization processes, the results point to some benefits in extraction. The ion pairing with SDS previously adsorbed on the cartridge increases recovery of metformin from 2% to 109% and that of simvastatin from 30% to 131% with the Strata-X cartridge (SDS method).

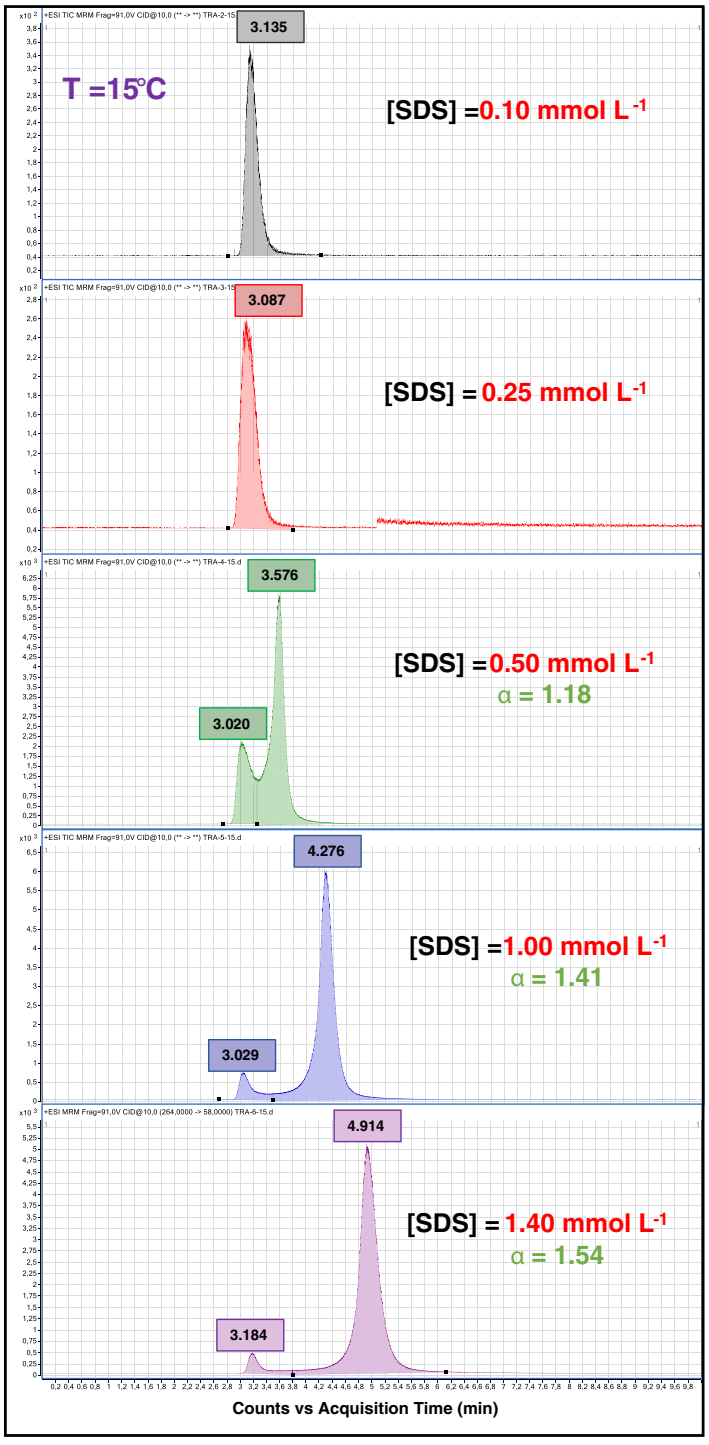

Fig. 1 Influence of sodium dodecyl sulfate (SDS) concentration (i.e., 0.10, 0.25, 0.50, 1.00, and 1.40 mmol L^{-1}) on the chromatographic separation of tramadol. The tramadol peak was split and a de novo minor species was clearly visible from the critical SDS concentration of 0.50 mmol L^{-1}

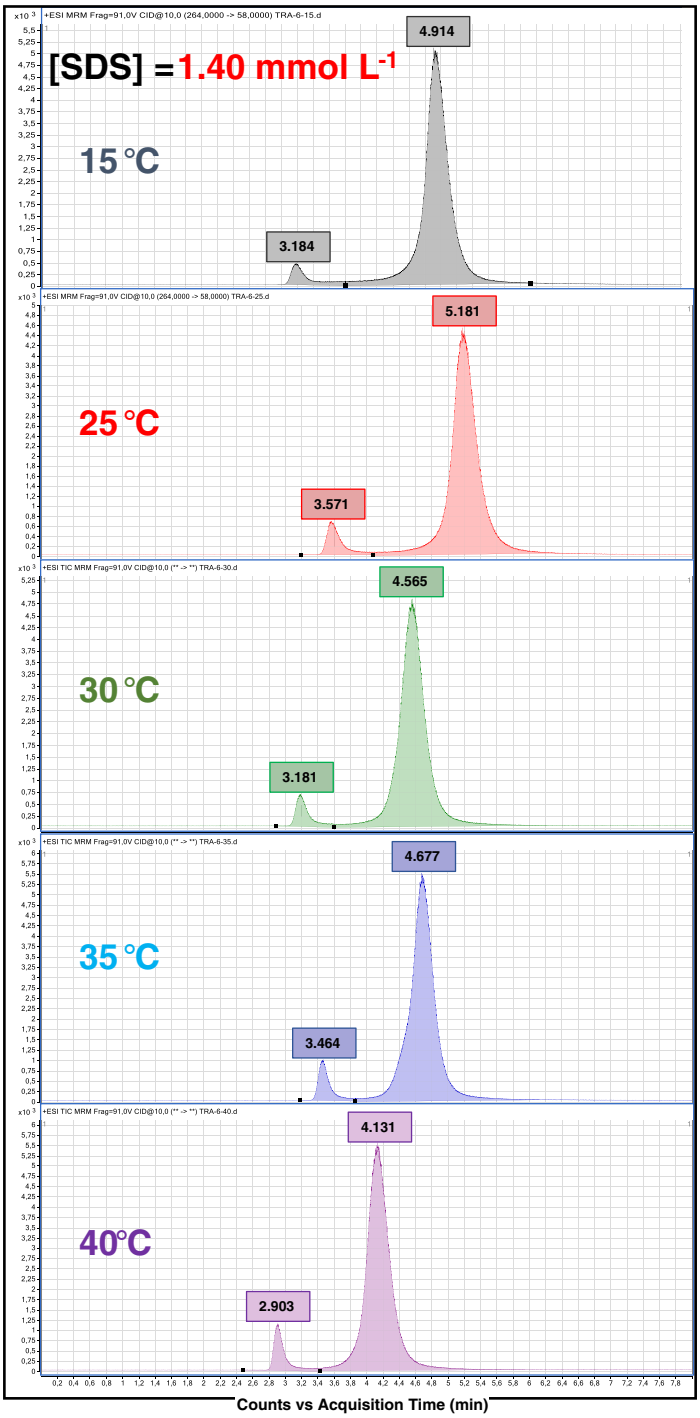

Fig. 2 Temperature-dependent chromatograms of tramadol obtained by high-performance liquid chromatography–tandem mas spectrometry. Kinetex® XB-C18 column (50 mm × 2.1-mm inner dimeter); eluent, methanol (mobile phase A) and water (mobile phase B) with 0.1% formic acid in both; flow rate, 0.2 mL min^{-1}

Table 1 Sodium dodecyl sulfate (SDS) method in water. Limit of detection (LOD), limit of quantification (LOQ), recovery, relative standard deviation (RSD), matrix effect (ME), and R^2 obtained with SDS solution and without SDS solution with Strata-X with SDS to extract pharmaceuticals and personal care products

	LOD (ng L^{-1})	LOQ (ng L^{-1})	Recovery (%) (± RSD, %) (n = 4)				ME (%)	R^2	
			50 ng L^{-1}	125 ng L^{-1}	250 ng L^{-1}	500 ng L^{-1}		With SDS	Without SDS
Alprazolam	1.65	5.00	70 (±9)	71 (±7)	71 (±3)	72 (±14)	-22	0.99	–
Atenolol	15.00	45.00	98 (±10)	71(±18)	75 (±8)	70 (±8)	-54	0.99	–
Atorvastatin	1.65	5.00	59 (±3)	64 (±20)	60 (±2)	61 (±1)	-33	0.99	–
Bezafibrate	1.65	5.00	99 (±8)	110 (±10)	104 (±6)	92 (±7)	-6	–	0.99
Bisphenol A	6.65	20.00	90 (±20)	105 (±4)	97 (±5)	112 (±16)	-4	–	0.99
Butylparaben	1.65	5.00	107 (±1)	114 (±1)	103 (±5)	96 (±11)	49	–	0.99
Caffeine	1.65	5.00	88 (±17)	90 (±2)	98 (±1)	82 (±1)	-76	0.99	–
Chloramphenicol	1.65	5.00	120 (±11)	100 (±19)	74 (±2)	107 (±1)	-41	–	0.99
Clofibric acid	11.65	35.00	119 (±6)	111 (±4)	106 (±1)	115 (±7)	-56	–	0.99
Codeine	5.00	15.00	65 (±4)	66 (±7)	62 (±2)	64 (±15)	-46	0.98	–
Diclofenac	11.65	35.00	70 (±8)	71 (±11)	90 (±4)	83 (±6)	56	–	0.99
Enalapril	1.65	5.00	104 (±7)	117 (±8)	89 (±2)	119 (±4)	55	0.99	–
Ethylparaben	1.65	5.00	77 (±17)	71 (±14)	71 (±1)	82 (±3)	-53	–	0.99
Etoricoxib	8.35	25.00	115 (±1)	113 (±15)	106 (±1)	116 (±1)	-98	0.99	–
Flufenamic acid	3.35	10.00	68 (±1)	65 (±3)	70 (±6)	72 (±9)	-11	–	0.99
Furosemide	25.00	75.00	68 (±1)	76 (±13)	79 (±4)	81 (±15)	-33	–	0.99
Ibuprofen	3.3	10.00	95 (±15)	107 (±5)	103 (±11)	107 (±16)	0	–	0.99
Indomethacin	6.65	20.00	109 (±15)	84 (±14)	72 (±21)	90 (±16)	-86	–	0.98
Lorazepam	1.65	5.00	109 (±22)	101 (±1)	113 (±1)	91 (±17)	-94	0.99	–
Metformin	1.65	5.00	110 (±13)	100 (±4)	95 (±2)	97 (±5)	-69	0.99	–
Methylparaben	5.00	15.00	77 (±7)	71 (±6)	74 (±7)	72 (±7)	-49	–	0.99
Naproxen	3.35	10.00	92 (±8)	95 (±11)	100 (±15)	117 (±7)	-25	–	0.98
Omeprazole	–	–	–	–	–	–	-82	0.98	–
Paracetamol	1.65	5.00	31 (±4)	30 (±1)	38 (±1)	36 (±15)	-86	0.98	–
Propylparaben	1.65	5.00	91 (±5)	94 (±14)	97 (±1)	86 (±5)	50	–	0.99
Salicylic acid	6.65	20.00	35 (±10)	30 (±20)	33 (±1)	39 (±4)	-52	–	0.99
Simvastatin	16.65	50.00	119 (±9)	112 (±6)	110 (±1)	119 (±8)	-95	0.99	–
Thiamphenicol	20.00	60.00	<LOQ	68 (±6)	62 (±14)	54 (±14)	-57	–	0.99
Tramadol	1.65	5.00	120 (±7)	116 (±1)	101 (±1)	109 (±3)	-97	0.99	–
Triclocarban	1.65	5.00	85 (±19)	88 (±25)	82 (±6)	86 (±9)	-31	–	0.99
Triclosan	5.00	15.00	105 (±13)	102 (±18)	102 (±7)	110 (±15)	9	–	0.99
Warfarin	1.65	5.00	118 (±4)	100 (±5)	104 (±3)	103 (±4)	61	–	0.99

The best results with SDS were obtained with the Strata-X cartridges, but good results were also obtained with Strata-X-CW cartridges, with the exception of those particular compounds that are the most problematic (e.g., indomethacin, paracetamol, omeprazole and metformin, which was not recovered) (see Table S5). The recovery reduction with Strata-X-CW (activated by SDS) was probably associated with competition between SDS and PPCP molecules for the active site of the stationary phase, reducing formation of the ion pair and so compound retention in cartridge. However, use of SDS with Strata-X-CW increased greatly the recoveries of methylparaben, propylparaben, ethylparaben, and triclosan to 86%, 87%, 102%, and 120%, respectively. Strata-X-CW, a polymeric weak cation-exchange sorbent, can retain basic analytes by several different mechanisms (weak cation exchange, π–π bonding, and hydrophobic interaction) that can increase the recoveries.

The Strata X-CW cartridge without any SDS treatment was tested with pH adjustment (pH 2.5) and without pH adjustment (pH 7.15–8.60) (WC method). The recoveries obtained were very similar at any pH value. For tramadol an increase in recovery of about 30 percentage points with acidification of the sample (Table S5). No pH adjustment was performed because the acidic pH could degrade some substances, such as

Table 2 WC method in water. Limit of detection (LOD), limit of quantification (LOQ), recovery, relative standard deviation (RSD), matrix effect (ME), and R^2 obtained with Strata X-CW without sodium dodecyl sulfate to extract pharmaceuticals and personal care products

	LOD (ng L^{-1})	LOQ (ng L^{-1})	Recovery (%) (± RSD, %) (n = 4)				ME (%)	R^2
			50 n gL^{-1}	125 ng L^{-1}	250 ng L^{-1}	500 ng L^{-1}		
Alprazolam	1.65	5.00	104 (±6)	90 (±10)	98 (±11)	96 (±16)	-8	0.99
Atenolol	15.00	45.00	65 (±2)	72 (±16)	71 (±6)	65 (± 16)	-51	0.99
Atorvastatin	1.65	5.00	70 (±4)	81 (±25)	75 (±1)	71 (±19)	20	0.99
Bezafibrate	1.65	5.00	86 (±3)	96 (±3)	92 (±6)	96 (±2)	-10	0.99
Bisphenol A	3.35	10.00	112 (±11)	93 (±11)	90 (±5)	82 (±17)	-13	0.99
Butylparaben	1.65	5.00	102 (±6)	108 (±6)	86 (±5)	71 (±4)	-79	0.99
Caffeine	1.65	5.00	82 (±1)	106 (±3)	102 (±12)	90 (±10)	-76	0.99
Chloramphenicol	5.00	15.00	102 (±20)	120 (±20)	82 (±2)	103 (±13)	-28	0.99
Clofibric acid	13.35	40.00	120 (±13)	109 (±13)	104 (±2)	101 (±6)	-40	0.99
Codeine	5.00	15.00	27 (±1)	28 (±15)	28 (±11)	25 (±12)	-72	0.99
Diclofenac	8.35	25.00	70 (±15)	73 (±15)	76 (±4)	81 (±7)	28	0.99
Enalapril	1.65	5.00	85 (±2)	74 (±20)	79 (±6)	110 (±12)	65	0.99
Ethylparaben	1.65	5.00	105 (±1)	93 (±17)	83 (±4)	86 (±4)	-33	0.99
Etoricoxib	8.35	25.00	108 (±4)	97 (±4)	93 (±1)	91 (±14)	-35	0.98
Flufenamic acid	1.65	5.00	75 (±3)	76 (±3)	78 (±6)	83 (±13)	0	0.99
Furosemide	21.65	65.00	91 (±20)	94 (±25)	94 (±4)	100 (±7)	-56	0.99
Ibuprofen	3.30	10.00	106 (±10)	115 (±3)	100 (±8)	101 (±6)	3	0.99
Indomethacin	6.65	20.00	64 (±3)	65 (±3)	62 (±21)	64 (±6)	-27	0.98
Lorazepam	5.00	15.00	70 (±15)	78 (±9)	92 (±9)	91 (±17)	-91	0.98
Metformin	1.65	5.00	72 (±6)	75 (±11)	71 (±20)	73 (±11)	-4	0.98
Methylparaben	5.00	15.00	61 (±1)	64 (±1)	70 (±7)	61 (±10)	-27	0.99
Naproxen	5.00	15.00	107 (±2)	103 (±2)	102 (±15)	110 (±5)	-25	0.98
Omeprazole	3.35	10.00	98 (±2)	90 (±14)	98 (±2)	96 (±16)	-40	0.99
Paracetamol	6.65	20.00	62 (±6)	65 (±3)	66 (±2)	65 (±7)	-90	0.99
Propylparaben	1.65	5.00	72 (±1)	82 (±1)	82 (±1)	82 (±15)	25	0.99
Salicylic acid	1.65	5.00	34 (±8)	35 (±15)	35 (±2)	32 (±2)	-36	0.99
Simvastatin	38.35	115.00	103 (±3)	93 (±9)	84 (±1)	90 (±12)	-87	0.99
Thiamphenicol	13.35	40.00	<LOQ	70 (±1)	83 (±14)	82 (±1)	-49	0.99
Tramadol	1.65	5.00	101 (±1)	93 (±6)	97 (±7)	98 (±17)	-7	0.99
Triclocarban	1.65	5.00	34 (±12)	35 (±12)	35 (±6)	32 (±8)	-14	0.99
Triclosan	5.00	15.00	80 (±20)	106 (±27)	85 (±7)	84 (±13)	3	0.99
Warfarin	1.65	5.00	73 (±7)	84 (±7)	81 (±3)	90 (±8)	41	0.99

omeprazole (with a decrease in recovery of 47 percentage points). This is a prodrug that under acidic conditions is activated, acting as a proton pump inhibitor in the active sulfenamide form, which attacks H^+,K^+-ATPase [39]. Ibuprofen and simvastatin showed a recovery decrease of 20 and 25 percentage points, respectively.

Good recoveries were obtained for the acidic compounds with the mixed-mode cartridge (recommended for basic compounds that form cations) and with the use of a solution of SDS, which is negatively charged. As shown in Table S5, the recovery range for the acidic compounds for the WC method was from 48% to 101% (except for indomethacin and triclocarban) and for the SDS method was from 45% to 117% without exceptions.

The use of SDS changed the chromatographic behavior of some analytes because of the formation of an ion pair that for etoricoxib, enalapril, metformin, and tramadol has a longer retention time than the non-ion-pairing analyte. Because of this, we studied the chromatographic behavior of one of these compounds—tramadol.

As an example, the effect of SDS concentration on the retention time of tramadol was evaluated. Six mixtures containing different SDS concentration (i.e., 0.10, 0.25, 0.50, 1.00, and 1.40 mmol L^{-1}) were prepared. The aqueous solutions of SDS were mixed with MeOH in a ratio of 70:30 (v/v) (to maintain the same ratio of MeOH to H_2O as in the final extract). In addition, a blank methanolic solution was prepared without

Table 3 Sodium dodecyl sulfate (SDS) method in sediment. Limit of detection (LOD), limit of quantification (LOQ), recovery, relative standard deviation (RSD), matrix effect (ME), and R^2 with SDS solution and without SDS solution obtained with Strata-X with SDS to extract pharmaceuticals and personal care products

	LOD (ng g^{-1}), dry weight.	LOQ (ng g^{-1}), dry weight	Recovery (%) (± RSD, %) (n = 4)				ME (%)	R^2	
			10 ng g^{-1}	25 ng g^{-1}	50 ng g^{-1}	100 ng g^{-1}		With SDS	Without SDS
Alprazolam	1.33	4.00	53 (±10)	55 (±12)	52 (±12)	102 (±7)	-9	0.99	–
Atenolol	6.33	19.00	60 (±19)	74 (±5)	70 (±9)	87 (±16)	-15	0.99	–
Atorvastatin	0.33	1.00	42 (±5)	42 (±13)	40 (±18)	41 (±9)	24	0.99	–
Bezafibrate	0.33	1.00	79 (±10)	91 (±5)	88 (±3)	98 (±10)	-86	–	0.99
Bisphenol A	0.67	2.00	92 (±12)	98 (±3)	95(±6)	105 (±20)	-61	–	0.99
Butylparaben	0.33	1.00	90 (±5)	99 (±4)	84 (±2)	88 (±10)	-15	–	0.99
Caffeine	0.33	1.00	62 (±5)	67 (±6)	67 (±3)	84 (±8)	-26	0.99	–
Chloramphenicol	1.00	3.00	107 (±4)	96 (±1)	81 (±1)	81 (±9)	-88	–	0.99
Clofibric acid	2.33	7.00	105 (±10)	106 (±21)	112 (±5)	100 (±4)	24	–	0.99
Codeine	3.00	9.00	45 (±18)	47 (±2)	47 (±1)	52 (±19)	-11	0.98	–
Diclofenac	3.00	9.00	75 (±25)	66 (±4)	65 (±14)	95 (±8)	-72	–	0.99
Enalapril	0.33	1.00	79 (±3)	82 (±17)	88 (±1)	86 (±8)	8	0.99	–
Ethylparaben	0.33	1.00	81(±6)	81 (±5)	83 (±10)	85 (±14)	-69	–	0.99
Etoricoxib	2.00	6.00	95 (±3)	90 (±20)	91 (±4)	93 (±13)	16	0.99	–
Flufenamic acid	1.33	4.00	42 (±3)	43 (±4)	43 (±4)	41 (±14)	-74	–	0.99
Furosemide	3.33	10.00	<LOQ	78 (±3)	80 (±1)	79 (±8)	-89	–	0.99
Ibuprofen	0.66	2.00	98 (±9)	87 (±3)	90 (±3)	84 (±1)	-55	–	0.99
Indomethacin	1.33	4.00	74 (±25)	74 (±11)	76 (±6)	74 (±1)	-86	–	0.98
Lorazepam	0.33	1.00	94 (±3)	100 (±23)	93 (±7)	88 (±13)	2	0.99	–
Metformin	6.67	20.00	32 (±5)	29 (±5)	30 (±1)	33 (±9)	-6	0.99	–
Methylparaben	1.33	4.00	95 (±3)	105 (±27)	100 (±3)	92 (±6)	-63	–	0.99
Naproxen	1.33	4.00	102 (±3)	105 (±6)	109 (±4)	102 (±13)	-60	–	0.98
Omeprazole	–	–	–	–	–	–	–	0.98	–
Paracetamol	2.67	8.00	38 (±2)	39 (±12)	39 (±8)	38 (±11)	-27	0.98	–
Propylparaben	0.33	1.00	106 (±8)	108 (±10)	94 (±5)	96 (±9)	-8	–	0.99
Salicylic acid	0.33	1.00	42 (±6)	42 (±1)	40 (±3)	44 (±2)	-52	–	0.99
Simvastatin	4.00	12.00	66 (±26)	64 (±22)	68 (±19)	61 (±15)	70	0.99	–
Thiamphenicol	4.00	12.00	<LOQ	59 (±6)	60 (±19)	61 (±15)	-50	–	0.99
Tramadol	0.67	2.00	65 (±8)	66 (±5)	69 (±1)	70 (±17)	-2	0.99	–
Triclocarban	1.67	5.00	15 (±22)	13 (±17)	14 (±7)	12 (±7)	-74	–	0.99
Triclosan	1.33	4.00	120 (±18)	117 (±16)	115 (±5)	120 (±16)	-81	–	0.99
Warfarin	0.33	1.00	93 (±6)	95 (±14)	92 (±3)	95 (±11)	-60	–	0.99

SDS. Under the same chromatographic conditions (flow rate, mobile phase, temperature, etc.) only one peak was observed for an SDS concentration lower than 0.25 mmol L^{-1}. Above the critical SDS concentration of 0.50 mmol L^{-1} the peak was split, showing an additional minor compound was clearly visible. Furthermore, the separation factor (α) representing the separation between the two peaks progressively increased as the SDS concentration changed (Fig. 1).

To evaluate the effects of temperature on retention and resolution of the two peaks pertinent to tramadol, the column temperature was changed from 15 to 40 °C in steps of 5 °C (Fig. 2). As shown in Fig. 2, no distortion of the chromatographic profile from an on-column dynamic process was observed. This excludes the possibility of a relationship between the two species by interconversion or association phenomena. As expected, the retention decreased as the temperature increased.

There are several potential explanations for the peak duplication. Tramadol is a chiral compound with two stereogenic centers. It is assumed that the peak pertinent to the minor species is the diastereomer of tramadol since the MS transitions are the same. The peak duplication can also be due to the coexistence of tramadol and the tramadol–SDS complex (SDS can interact with the amino group of tramadol without change

Table 4 WC method in sediment. Limit of detection (LOD), limit of quantification (LOQ), recovery, relative standard deviation (RSD), matrix effect (ME), and R^2 obtained with Strata-X-CW without sodium dodecyl sulfate to extract pharmaceuticals and personal care products

	LOD (ng g^{-1}), dry weight	LOQ (ng g^{-1}), dry weight	Recovery (%) (± RSD, %) (n = 4)				ME (%)	R^2
			10 ng g^{-1}	25 ng g^{-1}	50 ng g^{-1}	100 ng g^{-1}		
Alprazolam	0.33	1.00	77 (±10)	78 (±9)	74 (±2)	114 (±7)	2	0.99
Atenolol	3.00	9.00	95 (±9)	70 (±5)	82 (±8)	90 (±16)	-11	0.99
Atorvastatin	0.33	1.00	91 (±8)	92 (±6)	90 (±7)	94 (±9)	7	0.99
Bezafibrate	0.33	1.00	89 (±26)	101 (±2)	76 (±19)	80 (±18)	21	0.99
Bisphenol A	0.67	2.00	106 (±21)	92 (±20)	88 (±1)	95 (±8)	-6	0.99
Butylparaben	0.33	1.00	73 (±3)	79 (±1)	75 (±12)	73 (±17)	21	0.99
Caffeine	0.33	1.00	98 (±9)	118(±6)	115 (±6)	120 (±8)	-6	0.99
Chloramphenicol	0.67	2.00	104 (±19)	106 (±20)	85 (±20)	78 (±15)	-9	0.99
Clofibric acid	2.33	7.00	87 (±14)	101 (±3)	77 (±11)	92 (±19)	4	0.99
Codeine	1.67	5.00	76 (±3)	74 (±7)	76 (±4)	77 (±8)	-27	0.99
Diclofenac	2.33	7.00	115 (±18)	120 (±7)	118 (±15)	120 (±8)	-1	0.99
Enalapril	0.67	2.00	78 (±13)	81 (±5)	60 (±1)	62 (±3)	18	0.99
Ethylparaben	0.33	1.00	62 (±4)	62 (±5)	70 (±10)	81 (±10)	18	0.99
Etoricoxib	1.67	5.00	88 (±1)	100 (±6)	105 (±1)	101 (±8)	-3	0.98
Flufenamic acid	1.33	4.00	83 (±2)	81 (±6)	76 (±5)	78 (±6)	8	0.99
Furosemide	5.00	15.00	<LOQ	87 (±1)	82 (±5)	73 (±3)	-4	0.99
Ibuprofen	0.66	2.00	106 (±15)	100 (±8)	109 (±11)	103 (±20)	24	0.99
Indomethacin	4.00	12.00	67 (±8)	74 (±8)	79 (±3)	72 (±3)	15	0.98
Lorazepam	0.33	1.00	81 (±16)	82 (±2)	83 (±16)	82 (±1)	19	0.98
Metformin	1.33	4.00	12 (±11)	10 (±12)	10 (±18)	11 (±5)	1	0.98
Methylparaben	1.67	5.00	82 (±1)	88 (±6)	93 (±11)	91 (±15)	5	0.99
Naproxen	1.33	4.00	<LOQ	75 (±11)	89 (±25)	93 (±21)	-1	0.98
Omeprazole	6.67	20.00	79 (±5)	76 (±1)	72 (±2)	98 (±5)	70	0.99
Paracetamol	1.67	5.00	42 (±5)	41 (±2)	45 (±3)	48 (±11)	-20	0.99
Propylparaben	0.33	1.00	82 (±5)	80 (±5)	76 (±19)	86 (±19)	30	0.99
Salicylic acid	0.33	1.00	37 (±1)	39 (±11)	38 (±3)	40 (±6)	-10	0.99
Simvastatin	10.00	30.00	<LOQ	53 (±9)	51 (±1)	57 (±14)	25	0.99
Thiamphenicol	2.67	8.00	71 (±18)	69 (±18)	70 (±20)	70 (±9)	-15	0.99
Tramadol	0.33	1.00	81 (±14)	73(±7)	75 (±7)	85 (±6)	3	0.99
Triclocarban	1.67	5.00	9 (±17)	8 (±19)	8 (±2)	7 (±7)	-3	0.99
Triclosan	1.00	3.00	75 (±23)	72 (±10)	78 (±13)	81 (±19)	24	0.99
Warfarin	0.33	1.00	96 (±2)	107 (±1)	86 (±12)	98 (±20)	49	0.99

of the chiral positions). This feature was not exploited in the determination of this compound in the environmental samples because of the low environmental concentrations. Further study is needed to establish the species involved in this phenomenon and the exact mechanism of peak duplication.

Validation of the analytical procedure

Tables 1, 2, 3 and 4 report LODs, LOQs, recoveries with their RSDs, the ME as a percentage, and correlation coefficients (R^2). The linearity of compounds determined in positive ionization mode was prepared in solvent H_2O-MeOH (without SDS) and in solvent with SDS to obtain correct quantification of those compounds that form an ion pair with SDS with retention time different from that of the nonpairing analyte. R^2 was always greater 0.998, showing proper behavior in any of the solvents as well as in the matrix extracts.

The LOQs obtained for water samples with SDS were 75 ng L^{-1} or less (Table 1). The most common and lowest value was 5 ng L^{-1} (47% of the compounds). The least sensitive compound was furosemide (LOQ 75 ng L^{-1}). Omeprazole was not recovered. In the WC method (Table 2), the LOQs were 65 ng L^{-1} or less, with the exception of simvastatin (115 ng L^{-1}). The lowest and most common value was also 5 ng L^{-1} (44% of the compounds).

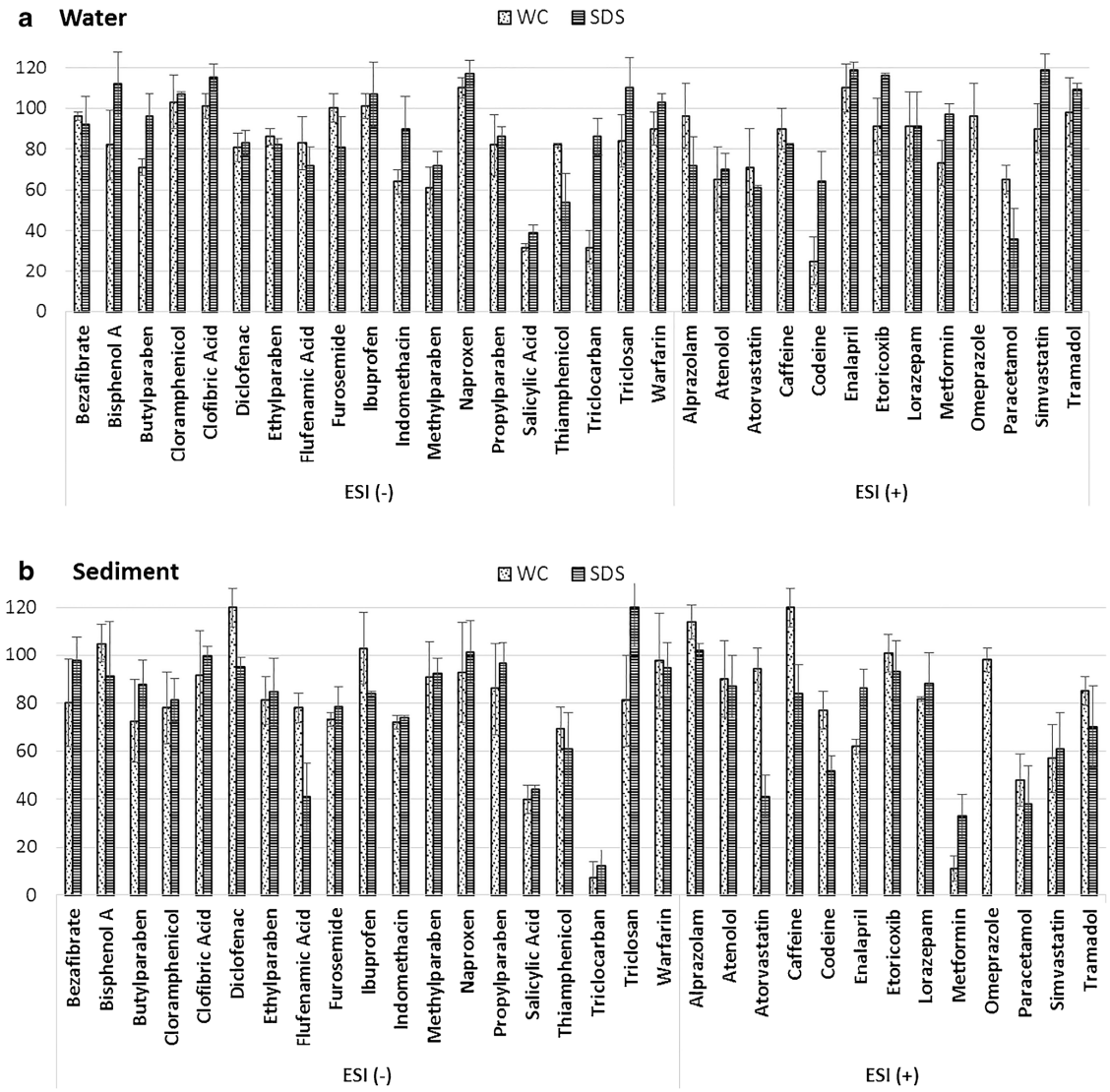

Fig. 3 Comparison of the absolute recoveries (bars) and relative standard deviations (error bars) obtained with cartridges of a polymeric weak cation-exchange phase (WC) and a polymeric reversed phase activated with sodium dodecyl sulfate (SDS) solution in **a** water and **b** sediment. The compounds are grouped according to the use of positive electrospray ionization mode [ESI (+)] and negative electrospray ionization mode [ESI (-)]

In sediment, the LOQs for the SDS method (Table 3) were 20 ng g^{-1} or less, and the lowest sensitivity was obtained for metformin (20 ng g^{-1}). The lowest LOQ was 1 ng g^{-1} (31% of the compounds). For the WC method (Table 4), the LOQs were 30 ng g^{-1} or less. The least sensitive compound was simvastatin (LOQ 30 ng g^{-1}). The lowest LOQ was also 1 ng g^{-1} (34% of the compounds). These results demonstrated that both methods perform similarly.

In addition to Tables 1, 2, 3 and 4, a graphical comparison of the recoveries (at 500 ng L^{-1} and 100 ng g^{-1}) and the RSDs for the two methods (WC method and SDS method) for water and sediment is shown in Fig. 3. The list of compounds was divided according to the ionization source used (negative or positive electrospray ionization). The recoveries were different depending on the compound and on the matrix. Atorvastatin, caffeine, and omeprazole produce greater yields with the WC method. This increase of recovery is more evident in sediment matrix.

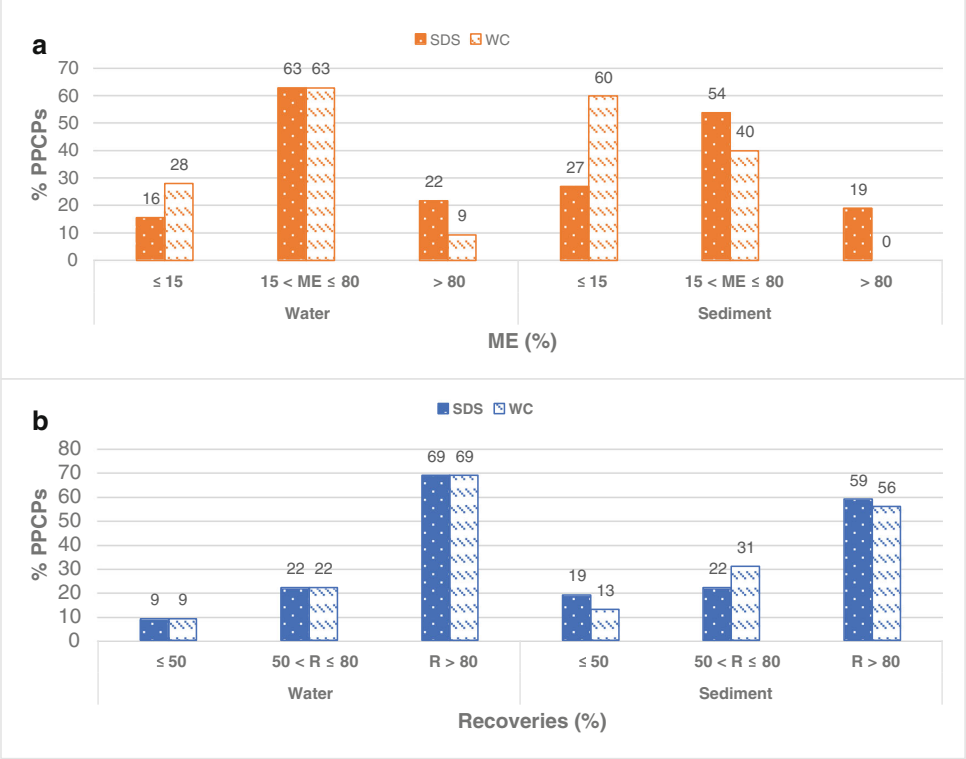

Fig. 4 Percentage of compounds distributed according to **a** the matrix effect (ME) and **b** the recoveries in water and sediments. The ME of selected pharmaceuticals and personal care products (PPCPs) is represented by three ranges in water and sediment for the sodium dodecyl sulfate (SDS) method and the WC method. The distribution of the recoveries for the selected PPCPs is represented by three ranges in water and sediment for the SDS method and the WC method

Atorvastatin and caffeine exhibited an increase in recovery of 53 and 26 percentage points, respectively, whereas omeprazole was not recovered by the SDS method. Instead, the recovery of indomethacin, triclosan, bisphenol A, and triclocarban increased by 26, 26, 30, and 54 percentage points, respectively, with the SDS method (in water). This method achieved outstanding performance for many PPCPs, such as bisphenol A, chloramphenicol, clofibric acid, diclofenac, naproxen, warfarin, and tramadol. The RSDs were less than 21% for all the compounds in all methods. Figure 4 classifies the compounds according to the ME and the recovery for water and sediments. This figure can help to observe the general trend of these methods. THe SDS method provided greater recoveries for more PPCPs but also exhibits a greater ME for many of them. For both matrices and methods, recovery greater than 80% was obtained for three fifths of the substances. The recovery was less than 50% for only three contaminants in water and only six contaminants in sediment.

According to our results, both methods have advantages and disadvantages and provide different results in each matrix, and the optimum method to determine each compound in the two different matrices can be different depending on the compound (Table S6). For example, the WC method is better for furosemide, thiamphenicol, alprazolam, atorvastatin, and omeprazole in water and for diclofenac, ibuprofen, atorvastatin, caffeine, and omeprazole in sediment. In contrast, the SDS method is better for bisphenol, indomethacin, tramadol, triclocarban, and triclosan in water and for bezafibrate, enalapril, metformin, simvastatin, and triclosan in sediment.

Application to real samples

These methods were applied to the determination of PPCPs in surface water and sediment samples from the Albufera Natural Park (Valencia, Spain) to establish whether the results obtained in method validation with spiked samples are reproduced in nonspiked samples. We detected 27 substances in sediment and 26 in water among the 32 compounds. Atenolol, omeprazole, paracetamol, and simvastatin were detected only in sediments, and alprazolam, indomethacin, and codeine were detected only in water. Atorvastatin, caffeine, clofibric acid, chloramphenicol, diclofenac, etoricoxib, ethylparaben, flufenamic acid, furosemide, ibuprofen, lorazepam,

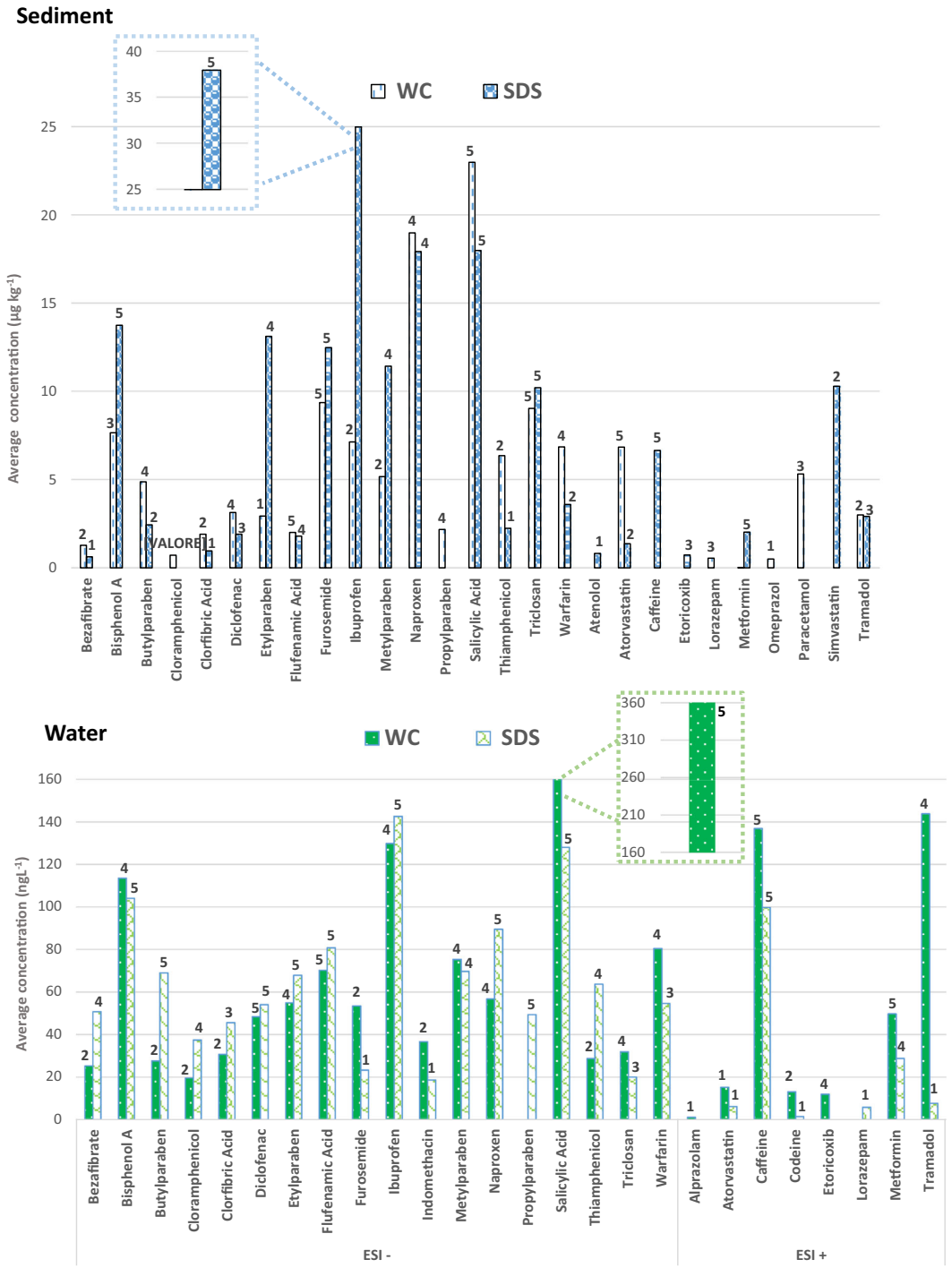

Fig. 5 Average concentrations of pharmaceuticals and personal care products in sediment and surface water samples (n = 5) from the Albufera Natural Park. The number on the bars means: number of occurrences. The analysis was conducted by the WC method and the sodium dodecyl sulfate (SDS) method

metformin, methylparaben, naproxen, propylparaben, salicylic acid, thiamphenicol, tramadol, triclosan, and warfarin were detected in both matrices. Enalapril and triclocarban were not detected.

The average concentrations are displayed in Fig. 5 with compounds occurrence (*n*) for all samples. The compounds detected at the highest concentration in sediment were naproxen, salicylic acid, and ibuprofen, at 42, 32, and 24 ng/g for the WC method and at 41, 23, and 71 ng/g for SDS method. In water, salicylic acid at 971 ng L^{-1} (by the WC method) and ibuprofen at 452 ng L^{-1} (by the SDS method) had the average concentrations. Although the results showed small differences, there was close agreement, particularly for the surface water samples.

Because of these two methods we were able to detect relevant contaminants in environmental samples of surface water and sediments.

Conclusions

This systematic evaluation of two analytical procedures (SDS method and WC method) to detect PPCPs in water and sediment demonstrated that these methods are advantageous for basic and/or neutral pharmaceuticals that are highly to moderately polar and with tendency to ionize and can provide proper validation parameters for the acidic ones. This finding is highly interesting to enlarge the scope of the methods and to improve their analytical performance.

To our knowledge, this is the first comprehensive study that shows good recoveries for acidic compounds with the mixed-mode HLB–weak cation exchanger cartridge (recommended for basic compounds generally). They were recovered with values greater than or equal to 70% for about 80% of the acidic compounds. Second, the use of SDS solution to active conventional Strata-X cartridges increased the recoveries of many PPCPs, such as metformin, simvastatin, naproxen, triclosan, tramadol, and etoricoxib. Only omeprazole was not recovered by the SDS method. In this way, these multiresidue methods might reduce costs while preserving appropriate recoveries for target analytes with a large polarity range.

Summarizing, this study pinpointed that it is necessary to improve analytical procedures for sample preparation, such as extraction, to obtain the best recoveries for the growing number of PPCPs frequently detected in environmental samples. This would allow close monitoring of contaminants in different environmental compartments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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ANNEX

Analytical and Bioanalytical Chemistry

Electronic Supplementary Material

Systematic assessment of extraction of pharmaceuticals and personal care products in water and sediment followed by liquid chromatography–tandem mass spectrometry

Daniele Sadutto, Rodrigo Álvarez-Ruiz, Yolanda Picó

Text S1. Compounds included in the method

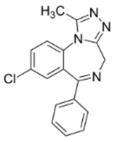
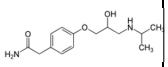
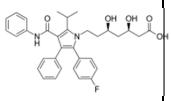
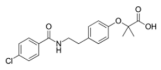
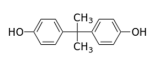
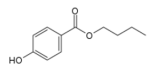
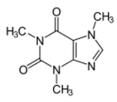
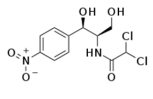
Alprazolam, atenolol, atorvastatin, bezafibrate, bisphenol A (BPA), butylparaben (butyl 4-hydroxybenzoate), caffeine, chloramphenicol, clofibric acid, codeine, diclofenac sodium, enalapril, etoricoxib, ethylparaben (etyl 4-hydroxybenzoate), flufenamic acid, furosemide, ibuprofen, indomethacin, lorazepam, metformin, methylparaben (methyl 4-hydroxybenzoate), omeprazole, paracetamol, propylparaben (propyl 4-hydroxybenzoate), salicylic acid, simvastatin, thiamphenicol, tramadol, triclocarban, triclosan and warfarin were purchased from Sigma-Aldrich (Texas, USA).

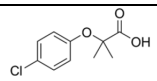
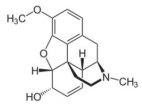
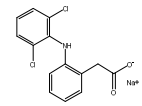
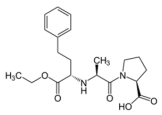
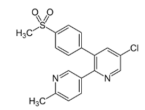
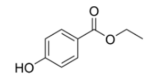
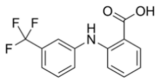
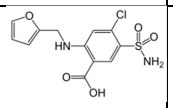
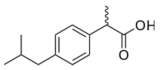
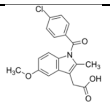
Text S2. HPLC and MS/MS parameters

HPLC separations were obtained by using Kinetex® XB-C18 column (1.7 µm, 100 Å, 50 x 2.10 mm), purchased from Phenomenex (Torrance, CA, USA) and maintained at temperature of 25°C. Working in gradient mode: started with a 30% of A and ended with a 95% of A in 12 min that was maintained for 8 min. And then, the system was stabilized 15 min more to arrive to the initial conditions. The flow rate was of 0.2 mL min^{-1}. The injection volume was of 5 µL.

The MS/MS system parameters were as follows: drying gas (nitrogen) flow of 11 $minL^{-1}$, vaporizer temperature of 300 °C and nebulizer pressure of 15 psi. The internal source voltage was held at 4000 V.

Table S1 PPCPs selected in this study, their category therapy, IUPAC name, CAS number, chemical structure, pKa and log Kow

Compound name	Category Therapy	IUPAC Name	N° CAS	Chemical structure	pKa	Log Kow
Alprazolam	Anxiolytic	8-Chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3a][1,4]benzodiazepine	28981-97-7		18.30	2.12
Atenolol	Antihypertensive	[RS]-4-[2-Hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide	29122-68-7		9.60	0.16
Atorvastatin	Lipid regulator	(3R,5R)-7-[2-(4-Fluorophenyl)-4-[(Z)-hydroxy(phenylimino)methyl]-5-isopropyl-3-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid	134523-00-5		4.30	6.36
Bezafibrate	Lipid regulator	2-(4-[2-[(4-Chlorobenzoyl)amino]-ethyl]-phenoxy)-2-methylpropanoic acid	41859-67-0		3.83	3.99
Bisphenol A	Plastic additive	4,4'-(2,2-Propanediyl)diphenol	80-05-7		9.60	3.32
Butylparaben	Preservative	Butyl 4-hydroxybenzoate	94-26-8		8.47	3.57
Caffeine	CNS stimulant	1,3,7-Trimethyl-3,7-dihydro-1H-purine-2,6-dione	58-08-2		10.40 at 40 °C	-0.07
Chloramphenicol	Antibiotic	2,2-Dichloro-N-[(1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl)-2-propanyl]acetamide	56-75-7		7.49	0.92

Clofibric Acid	Lipid regulator	2-(4-Chlorophenoxy)-2-methylpropanoic acid	882-09-7		3.18	2.84
Codeine	Analgesic	(5β,6β,9α,13α,14α)-3-Methoxy-17-methyl-7,8-didehydro-4,5-epoxymorphinan-6-ol	76-57-3		8.21	1.19
Diclofenac Sodium	Analgesic	2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid	15307-79-6		4.15	4.51
Enalapril	Antihypertensive	N-[(2S)-1-Ethoxy-1-oxo-4-phenyl-2-butanyl]alanyl-L-proline	75847-73-3		2.97	0.07
Etoricoxib	Analgesic	5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine	202409-33-4		19.69	2.91
Ethylparaben	Preservative	2-Ethoxybenzoic acid	5026-62-0		8.34	2.47
Flufenamic Acid	Analgesic	2-((3-(Trifluoromethyl)phenyl)amino)benzoic acid	530-78-9		3.88	5.25
Furosemide	Antihypertensive	4-Chloro-2-[(2-furylmethyl)amino]-5-sulfamoylbenzoic acid	54-31-9		3.90	2.03
Ibuprofen	Analgesic	2-(4-Isobutylphenyl)propanoic acid	15687-27-1		4.91	3.97
Indomethacin	Antibiotic	[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	53-86-1		4.50	4.27

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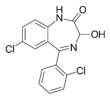
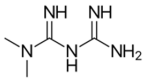
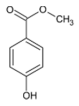
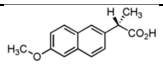
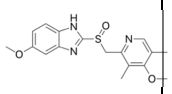
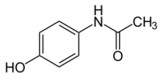
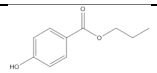
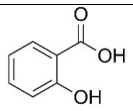
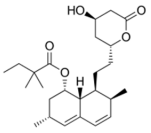
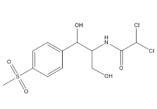
Lorazepam	Anxiolytic	7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one	846-49-1		13.00	2.40
Metformin	Antidiabetic	N,N-Dimethylimidodicarbonimidic diamide	657-24-9		12.4	-2.64
Methylparaben	Preservative	Methyl 4-hydroxybenzoate	99-76-3		8.40	1.96
Naproxen	Analgesic	2-(6-Methoxy-2-naphthyl)propanoic acid	26159-34-2		4.15	3.18
Omeprazole	Gastrointestinal	5-methoxy-2-(((4-methoxy-3,5-dimethylpyridin- 2-pyridinyl)methyl)sulfinyl)-1H-benzoimidazole	73590-58-6		9.29	2.23
Paracetamol	Analgesic	N-(4-Hydroxyphenyl)acetamide	103-90-2		9.38	0.46
Propylparaben	Preservative	Propyl 4-hydroxybenzoate	94-13-3		8.05	3.04
Salicylic Acid	Analgesic	2-hydroxybenzoic acid	69-72-7		2.97	2.26
Simvastatin	Lipid regulator	(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-Hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-1-naphthalenyl 2,2-dimethylbutanoate	79902-63-9		14.91	4.68
Thiamphenicol	Antibiotic	2,2-dichloro-N-[(1R,2R)-1,3-dihydroxy-1-(4-methanesulfonylphenyl)propan-2-yl]acetamide	15318-45-3		7.65	-0.33

5

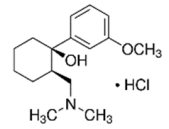
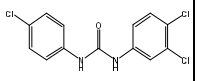
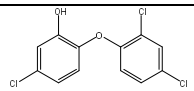
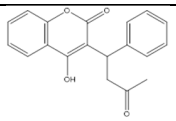
Tramadol hydrochloride	Analgesic	(±)-cis-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol hydrochloride	36282-47-0	
Triclocarban	Antibacterial	N-(4-Chlorophenyl)-N'-(3,4-dichlorophenyl)carbamimidic acid	101-20-2	
Triclosan	Antibacterial	5-Chloro-2-(2,4-dichlorophenoxy)phenol	3380-34-5	
Warfarin	Anticoagulant	4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one	81-81-2	

Table S2 MS/MS retention time and transitions used to determine these compounds

	Negative mode	IS*	RT (min)	SRM1	Frag (V)	SRM2-SRM3	$CE_1/CE_2/C_3$ (V)	Ratio % (±SD) (SRM1-SRM2)
1	**Bezafibrate**	/	13.3	360 > 274	106	360 >154	10/22	19.9 (± 2.1)
2	**Bisphenol A**	BPA-d16	14.2	227 > 212	138	227 >133	14/25	50.0 (±4.7)
3	**Butylparaben**	/	14.8	193 > 137	122	193 > 92	10/10	62.0 (±2.6)
4	**Cloramphenicol**	/	3.4	321 > 176	128	321 >152	10/10	16.8 (±2.9)
5	**Clorfibric Acid**	/	5.4	213 > 127	76	213 > 35	1/33	2.5 (±1.1)
6	**Diclofenac**	Dif-d4	14.4	294 > 250	88	294 >178	10/22	9.1 (±4.3)
7	**Ethylparaben**	/	9.4	165 > 137	103	165 > 92	22/10	6.3 (±0.7)
8	**Flufenamic Acid**	/	15.5	280 > 176	106	280 >263	10/30	15.10 ±0.13
9	**Furosemide**	/	2.9	329 > 285	110	-	12	/
10	**Ibuprofen**	Ibu-d3	14.8	205 > 161	68	-	2	/
11	**Indomethacin**	/	14.7	356 > 297	98	356 >282	10/22	75.9 (±6)
12	**Methylparaben**	/	4.2	151 > 136	93	151 > 92 151 > 91	18/10/10	9.2 (±1.4)
13	**Naproxen**	/	12.0	229 > 185	76	229 >170	6/15	15.6 (±3.8)
14	**Propylparaben**	/	13.7	179 > 137	112	179 > 92	22/10	5.0 (±1.1)
15	**Salicylic Acid**	/	1.1	137 > 93	86	-	10	/
16	**Thiamphenicol**	/	1.3	354 > 290	128	354 > 64	10/74	43.9 (±4.0)
17	**Triclocarban**	/	16.3	313 > 160	86	313 >126	10/10	6.4 (±0.4)
18	**Triclosan**	Tcl-d3	16.4	287 > 35	98	289 > 35	10/10	110.3 (±20.3)
19	**Warfarin**	/	13.6	307 > 161	136	307 >117	10/30	21.5 (±1.7)

Positive mode		IS*	RT (min)	SRM1	Frag (V)	SRM2-SRM3	$CE_1/CE_2/C_3$ (V)	Ratio % (±SD) (SRM1-SRM2)
20	**Alprazolam**	Ate-d7	14.3	309 > 281	80	309 >205	10/50	1.7 (±0.1)
21	**Atenolol**	Ate-d7	0.8	267 > 91	91	267 > 77	57/77	100.2 (±2.1)
22	**Atorvastatin**	Ate-d7	15.8	559 > 440	167	559 >250	14/46	60.6 (±2.6)
23	**Caffeine**	Ate-d7	1.6	195 > 138	109	195 >110	18/22	25.2 (±0.9)
24	**Codeine**	Acm-d3	0.8	300 > 215	161	300 >119	25/30	0.9 (±0.1)
25	**Enalapril**	/	8.7	377 > 234	114	377 >117 377 > 91	10/34/50	85.6 (±13.9)
26	**Etoricoxib**	/	4.5	359 > 280	181	359 >279	30/46	75.4 (±1.4)
27	**Lorazepam**	/	14.4	321 > 275	45	321 >193	16/60	8.9 (±0.5)
28	**Metformin**	Acm-d3	0.7	130 > 71	86	130 > 60	22/10	82.2 (±1.0)
29	**Omeprazole**	Ate-d7	5.2	346 > 198	101	346 >180 346 >136	10/22/30	30.1 (±1.3)
30	**Paracetamol**	Acm-d3	1.1	152 > 110	88	152 > 92	14/25	9.4 (±0.2)
31	**Simvastatin**	/	17.2	419 > 225	96	419 >199	10/10	54.8 (±2.6)
32	**Tramadol**	Ate-d7	1.7	264 > 58	91	-	10	/

*IS: Internal Standard used to quantify. Compound reported is the deuterated of reference. BPA-d16: *Bisphenol A-d16*; Dif-d4: *Diclofenac-d4*; Ibu-d3: *Ibuprofen-d3*; Tcl-d3: *Triclosan-d3*; Ate-d7: *Atenolol-d7*; Acm-d3: *Acetaminophen-d3.*

/ : Internal Standard was not used to quantify, but it was used in External Standard.

Table S3 Absolute recoveries (% Rec) and relative standard deviation (± RSD) obtained by SLE (without sediment) followed by conventional Strata X SPE clean-up. The analysis were carried out in quadruplicate

	Mix_2		Mix_1		MillQ-water		Mix_2 W. Ev.	
	% Rec.	± RSD	% Rec.	± RSD	% Rec.	± RSD	% Rec.	± RSD
Alprazolam	74	20	69	17	69	6	80	16
Atenolol	16	10	28	5	5	21	13	16
Atorvastatin	81	3	80	1	80	1	80	21
Bezafibrate	95	6	84	5	91	9	61	22
Bisphenol A	114	12	110	2	122	4	72	22
Butylparaben	117	5	107	10	120	1	60	21
Caffeine	58	21	35	21	34	12	65	21
Cloramphenicol	103	2	96	11	92	10	71	19
Clorfibric Acid	81	4	92	2	85	4	75	14
Codeine	37	24	32	22	32	19	42	17
Diclofenac	105	7	77	6	118	11	66	21
Enalapril	82	12	103	12	87	2	107	12
Etoricoxib	57	14	25	16	25	19	63	2
Ethylparaben	83	7	77	13	78	3	80	6
Flufenamic Acid	60	4	58	2	61	18	59	17
Furosemide	88	8	73	3	102	1	76	12
Ibuprofen	104	10	95	14	94	12	75	22
Indomethacin	89	8	75	11	82	11	48	3
Lorazepam	71	22	42	25	26	1	79	17
Metformin	2	8	1	8	2	9	0	0
Methylparaben	75	10	68	4	72	2	69	15
Naproxen	82	4	77	2	72	6	59	25
Omeprazole	9	2	9	6	0	0	15	7
Paracetamol	40	22	46	18	54	1	24	19
Propylparaben	93	9	78	2	83	2	68	24
Salicylic Acid	82	3	74	3	70	6	68	23
Simvastatin	30	11	5	1	0	0	35	6
Thiamphenicol	90	1	84	20	89	4	46	12
Tramadol	56	20	48	12	18	13	62	15
Triclocarban	31	15	26	25	26	25	40	3
Triclosan	33	9	29	12	35	11	39	3
Warfarin	77	6	70	1	77	7	61	22

Mix_2 MeOH, McIlvaine-EDTA buffer and MilliQ-water.
Mix_1 McIlvaine-EDTA buffer and MilliQ-water.
Mix_2 W. Ev. Without evaporation step.

Table S4 Recovery (% Rec) and relative standard deviation (± RSD) obtained by SLE (with sediment) followed by conventional Strata X SPE clean-up. The analysis were carried out in quadruplicate

	Mix_2		Mix_1		MillQ-water	
	% Rec.	± RSD	% Rec.	± RSD	% Rec.	± RSD
Alprazolam	67	1	38	12	27	1
Atenolol	10	2	22	11	0	0
Atorvastatin	32	10	36	14	25	3
Bezafibrate	89	1	89	2	83	1
Bisphenol A	98	4	31	4	16	13
Butylparaben	85	7	50	1	41	1
Caffeine	53	4	27	18	6	9
Cloramphenicol	74	2	89	1	87	1
Clorfibric Acid	84	8	70	1	65	4
Codeina	17	5	12	10	4	4
Diclofenac	66	6	56	3	62	6
Enalapril	72	1	107	12	91	1
Etoricoxib	47	5	19	7	18	1
Etylparaben	68	6	66	2	60	3
Flufenamic Acid	50	12	30	1	34	1
Furosemide	57	8	68	1	54	7
Ibuprofen	59	8	85	13	61	5
Indomethacin	69	8	33	1	37	1
Lorazepam	60	2	38	10	20	1
Metformin	2	1	0	0	0	0
Methylparaben	40	1	74	1	68	1
Naproxen	91	1	60	11	65	3
Omeprazole	0	0	2	0	3	9
Paracetamol	16	3	26	11	26	11
Propylparaben	87	3	69	7	53	1
Salicylic Acid	18	2	68	1	63	1
Simvastatin	21	5	2	7	0	0
Thiamphenicol	69	5	62	2	76	7
Tramadol	45	1	34	13	13	1
Triclocarban	10	15	0	0	0	0
Triclosan	19	14	13	10	21	7
Warfarin	76	3	58	1	71	1

Mix_2 MeOH, McIlvaine-EDTA buffer and MilliQ-water.
Mix_1 McIlvaine-EDTA buffer and MilliQ-water.

Table S5 Recovery pre-test were performed with only Mix_2 by two different cartridges Strata-X-CW and Strata-X, without and with SDS to extract PPCPs. It contains the percentage recovery and relative standard deviations (±RSD)

	%Strata-X-CW rec. *(WC method)* (±RSD)	%Strata-X-CW rec. (±RSD) [pH =2.5]*	%Strata-X rec. with SDS *(SDS method)* (±RSD)	% Strata-X-CW rec. with SDS (±RSD)
Alprazolam	94 ± 3	81 ± 3	63 ± 25	55 ± 1
Atenolol	73 ± 3	79 ± 12	115 ± 9	105 ± 11
Atorvastatin	119 ± 8	93 ± 0	55 ± 18	73 ± 7
Bezafibrate	81 ± 1	79 ± 1	61 ± 1	85 ± 4
Bisphenol A	88 ± 25	100 ± 16	101 ± 9	94 ± 15
Butylparaben	80 ± 3	71 ± 6	92 ± 1	94 ± 5
Caffeine	102 ± 7	94 ± 2	92 ± 7	69 ± 9
Cloramphenicol	93 ± 1	93 ± 7	72 ± 5	98 ± 15
Clorfibric Acid	79 ± 13	67 ± 8	75 ± 17	82 ± 4
Codeina	74 ± 9	76 ± 3	116 ± 17	92 ± 0
Diclofenac	87 ± 15	77 ± 6	55 ± 11	70 ± 3
Enalapril	89 ± 4	115 ± 3	113 ± 20	75 ± 3
Etoricoxib	93 ± 5	89 ± 2	117 ± 18	77 ± 1
Etylparaben	72 ± 7	67 ± 0	90 ± 4	102 ± 6
Flufenamic Acid	78 ± 5	68 ± 1	70 ± 1	77 ± 4
Furosemide	94 ± 0	80 ± 13	69 ± 3	102 ± 6
Ibuprofen	101 ± 25	81 ± 15	87 ± 5	113 ± 2
Indomethacin	25 ± 5	47 ± 25	50 ± 3	20 ± 25
Lorazepam	96 ± 2	93 ± 9	115 ± 12	90 ± 8
Metformin	74 ± 7	5 ± 17	109 ± 21	0
Methylparaben	59 ± 9	51 ± 4	91 ± 3	86 ± 3
Omeprazole	63 ± 9	16 ± 1	0	18 ± 10
Paracetamol	94 ± 21	24 ± 9	68 ± 17	5 ± 5
Propylparaben	67 ± 1	67 ± 6	94 ± 1	87 ± 3
Salicylic Acid	63 ± 8	63 ± 6	74 ± 9	42 ± 8
Simvastatin	85 ± 15	60 ± 18	131 ± 25	45 ± 10
Thiamphenicol	93 ± 15	72 ± 25	45 ± 25	69 ± 5
Tramadol	67 ± 15	97 ± 7	104 ± 23	73 ± 0
Triclocarban	37 ± 20	34 ± 21	117 ± 4	83 ± 8
Triclosan	48 ± 4	34 ± 24	107 ± 0	120 ± 4
Warfarin	72 ± 4	71 ± 7	51 ± 3	63 ±5

* Adjustment of pH sample (pH=2.5) was performed before SPE procedure.
** Naproxen was not reported because it was not available at time of analysis.

Table S6 The best conditions to determine each PPCPs by WC and SDS method in two different matrices. The symbol " ↑ " identifies the method with best result in the matrix. The symbol " = " identifies the similar result in the matrix

	WATER		SEDIMENT	
	WC	*SDS*	*WC*	*SDS*
Alprazolam	↑		↑	
Atenolol	=	=	=	=
Atorvastatin	↑		↑	
Bezafibrate	=	=		↑
Bisphenol A		↑	↑	
Butylparaben		↑		↑
Caffeine	=	=	↑	
Clofibric Acid		↑	=	=
Cloramphenicol	=	=	=	=
Codeine		↑	↑	
Diclofenac	=	=	↑	
Enalapril		↑		↑
Etoricoxib		↑	=	=
Ethylparaben	=	=	=	=
Flufenamic Acid	↑	=	↑	
Furosemide	↑		=	=
Ibuprofen	=	=	↑	
Indomethacin		↑	=	=
Lorazepam	=	=	=	=
Metformin		↑		↑
Methylparaben		↑	=	=
Naproxen		↑		↑
Omeprazole	↑		↑	
Paracetamol	↑		=	=
Propylparaben	=	=		↑
Salicylic Acid	=	=	=	=
Simvastatin		↑		↑
Thiamphenicol	↑		=	=
Tramadol		↑	=	=
Triclocarban		↑	=	=
Triclosan		↑		↑
Warfarin		↑	=	=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SECCIÓN 3. EVALUACIÓN DE LA CONTAMINACIÓN DEL PARQUE NATURAL DE L'ALBUFERA

PUBLICACIÓN

03.

PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN A MEDITERRANEAN COASTAL WETLAND: IMPACT OF ANTHROPOGENIC AND SPATIAL FACTORS AND ENVIRONMENTAL RISK ASSESSMENT

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Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment☆

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ABSTRACT

The present study focused on the occurrence, distribution and risk assessment of 32 pharmaceuticals and personal care products (PPCPs) in water and sediment, as well as the surrounding soil of the irrigation channels and lake of a Mediterranean coastal wetland, the Albufera Natural Park (Valencia, Spain). Moreover, the influent and effluent of ten wastewater treatment plants (WWTPs) that treat wastewater from Valencia and the surrounding areas were also studied. BPA, caffeine, diclofenac, ethyl paraben, methyl paraben, metformin, tramadol and salicylic acid were the predominant PPCPs detected in the channels and the lake, and are in good agreement with those detected in the effluent. Furthermore, 22 PPCPs were detected in >47% of the sediment samples. Of them, BPA, ethyl paraben, furosemide, ibuprofen and salicylic acid were at higher concentrations. In contrast, only seven PPCPs were detected in >44% of the soil samples. Spatial variation showed that the concentration of many PPCPs was higher in the northern area of the park, whereas the ibuprofen concentrations were higher in the south. Differences were also observed according to the type of water used for irrigation and the land uses of the area. A risk assessment based on the hazardous quotient (HQ) indicated that caffeine is a compound of concern, and tramadol at the highest concentration showed a moderate risk for the organisms assessed. Considering the mixture of the PPCPs found at each sampling point, the green algae are at risk, particularly in those points located near the city of Valencia (the most important nearby human settlement). These results indicate the need for further studies.

1. Introduction

The Anthropocene is the name proposed by Stoemer and Crutzen (Liz-Rejane Issberner, 2018; Steffen et al., 2011) for the new geological epoch during which persistent changes produced by anthropogenic forces in the surface environments of Earth are occurring (Falkenmark et al., 2003; Liz-Rejane Issberner, 2018; Steffen et al., 2011). Regarding water bodies in the Anthropocene, global change and pollution constitute the prevalent binomial that must be studied jointly to alleviate Anthropocene effects on the most sensitive ecosystems. The most representative classes of emerging contaminants of human origin are pharmaceutical compounds (PCs) and personal care products (PCPs) (Blasco and DelValls, 2008; Paíga et al., 2016; Pico et al., 2019). A number of studies on the presence of these compounds in the environment have been recently published, showing their widespread occurrence worldwide (Álvarez-Ruiz and Picó, 2020; Andreu et al., 2016; Carmona et al., 2017; Puckowski et al., 2016). In fact, the EU Water Framework Directive has already placed amoxicillin and ciprofloxacin on the "watchlist" due to their adverse effects in the aquatic environment (Bonnefille et al., 2018; Miller et al., 2018; Zenker et al., 2014). However, there is still very little information on how the added impact from global change currently is affecting the occurrence of pharmaceuticals and personal care products (PPCPs) in the environment.

In this sense, global and regional analyses have identified the Mediterranean Basin as an area shaped by human activity, particularly affected by climate change, as well as sensitive and highly

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0269-7491/

vulnerable to the effects of anthropic contamination. To illustrate the extent to which chemical pollution affects this area, it is sufficient to say that 101 "hot spots" of pollution have been identified in the Mediterranean, generally located in coastal wetlands and estuaries near most important ports, large cities and industrial districts (Airoldi et al., 2007). This basin has a major worldwide interest because it borders three continents: Europe, Africa and Asia, and could be considered as a model for explaining behaviour in other areas with a Mediterranean climate, such as the coastal areas of the western United States, the western Cape in South Africa, central Chile, southwestern Australia and the coastal areas of South Australia. Furthermore, for other parts of the world that are not as affected, this study could consider a future forecast to anticipate future measures. Global change is gradually increasing until it inexorably affects the entire planet.

Within this area, wetlands, especially coastal wetlands, are particularly affected and can be considered as ecosystems threatened by all types of anthropic activities (Ciężkowski et al., 2019). Few studies have been undertaken at a local scale to assess the different temporal and spatial scenarios of PPCP risk to the aquatic environment (Chaves et al., 2020; Desbiolles et al., 2018; Palma et al., 2020; Vazquez-Roig et al., 2011). Vazquez-Roig et al. (2011) presented nine years ago the first evidence of significant PPCP contamination in the Albufera Natural Park in Spain. Desbiolles et al. (2018) reported an inventory of previous studies on the PPCPs detected in the sewage and surface waters flowing into the Mediterranean Sea. Čelić et al. (2019) established the occurrence, distribution, and fate of a large number of multiple-class PPCPs in the vulnerable area of the Ebro River Delta (Catalonia, northeastern Spain) and proposed a list of ecologically relevant PPCPs as markers of wastewater contamination. A few more studies have correlated the dynamics and environmental risk of PPCPs with different temporal and hydrological patterns (Chaves et al., 2020; Palma et al., 2020). These studies are relevant to establish the effectiveness of some of the practices used to mitigate the negative effects on coastal wetlands, to estimate their risk and to preserve the biodiversity of coastal wetlands. However, these studies only examined the relationship between the occurrence of PPCPs and wastewater treatment plants.

Considering all the above information, comprehensive monitoring was performed in this study involving the collection of wastewater, surface water, sediment and soil in order to (i) analyse the occurrence and spatial distribution of PPCPs in a Mediterranean coastal wetland (the Albufera Natural Park) affected by several land uses and increasing water scarcity; (ii) assess anthropic effects in different areas of the coastal wetland through the concentration of PPCPs; (iii) compare these results with those from a previous study made nine years ago; and (iii) estimate the environmental risks from PPCPs to the aquatic biota. These contaminants are of special concern in Mediterranean coastal wetlands because the effluent from wastewater treatment plants are used to supply ecological flow. This assessment involves mapping using geographic information systems (GIS) to establish the spatial distribution and statistical analysis of the different variables. The results will add to our knowledge concerning the behaviour of PPCPs in regard to global climate change and will help identify those PPCPs that deserve priority consideration in European water policies.

2. Materials and methods

2.1. Chemicals and reagents

This study included a list of 32 PPCPs that were selected for their high consumption and environmental occurrence recorded in previously published articles (Carmona et al., 2014; Kuster et al., 2008; Tran et al., 2018; Zhang et al., 2017). PPCPs and isotopically labelled internal standards with a purity greater than 95% (see supplementary material **Text S1** and Table S1 for their structure and properties) were purchased from Sigma-Aldrich (Madrid, Spain) and from Toronto Chemicals Research (Toronto, Canada). Ammonium hydroxide (NH_4OH) (25%), sodium dodecyl sulfate (SDS), dichloromethane (DCM) and methanol (MeOH) were obtained from VWR International (Barcelona, Spain), and citric acid, Na_2HPO_4, and Na_2EDTA were obtained from Alfa Aesar (Karlsruhe, Germany). Ultrapure water was obtained from a Milli-Q water purification system. McIlvaine–EDTA buffer (pH 4.5) was prepared as described in a previous study (Álvarez-Ruiz and Picó, 2019; Carmona et al., 2017; Sadutto et al., 2020).

2.2. Description of the study area

The study area is in Albufera Natural Park (ANP), located 10 km south of Valencia, Spain. This park, with an area of 21,120 ha, was declared a nature reserve in 1986 (Pascual-Aguilar et al., 2015; Pico et al., 2012), and was included in the Ramsar international list of protected wetlands in 1989 and in the Natura 2000 Network. The park consists of a shallow (ca. 1 m deep) and highly eutrophic coastal lagoon (2100 ha, 8 km in diameter) surrounded mainly by rice fields that occupy the primitive marshland (14,000 ha), and is separated from the Mediterranean Sea by a string of sand (mostly dunes). The rest of the natural park is characterized by citrus and vegetable orchards. The lake is connected to the sea through three channels called "golas" by the locals (Pujol, Perellonet and Perelló), in which the water flow is regulated by sluice gates. The sampling points are shown in Fig. 1 (see Table S2 for the type of sample taken at each point, water classification and land use; **Interactive Link S1** for the virtual map; and Fig. S1 for some pictures of the different areas of the natural park). The Turia River to the north, the Jucar River and its tributary Magro River to the southwest, and a network of sixty-three channels and ditches bring water to the Albufera. There is also a groundwater contribution through several springs. The anthropogenic pressures (Usaquén Perilla et al., 2012) were characterized by (i) the proximity to Valencia (metropolitan area with 1.2 million inhabitants) and the industrial belt in the north, and (ii) the agricultural pressures in the south. At present, ANP is affected by these pressures, together with the scarce amount of surface fresh water that reaches Albufera due to overexploitation. The irrigation channels mostly conduct part of the treated wastewater from the surrounding cities (to maintain the ecological flow) and the excess irrigation water from agriculture and farming activity (Pascual-Aguilar et al., 2015).

The effluent from ten wastewater treatment plants (WWTPs) that was discharged into irrigation channels that eventually flowed into the Park were sampled: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart-Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perelló (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS) (see locations in Fig. 1 and their most important characteristics in Table S3).

Furthermore, a total of 84 grab samples—19 sediment, 32 water and 33 soil samples—at 43 sampling points were collected between December 2016 and February 2017. The differences in the matrices are due to a couple of reasons: sometimes the irrigation channels were dry or had very low water volume, or there was no sediment because many of these channels had been covered with concrete and not enough sediment had accumulated yet (it should be noted that they are periodically cleaned). Soil samples were not always collected because some irrigation channels were located in urbanized and paved areas (see Table S2 for detailed information).

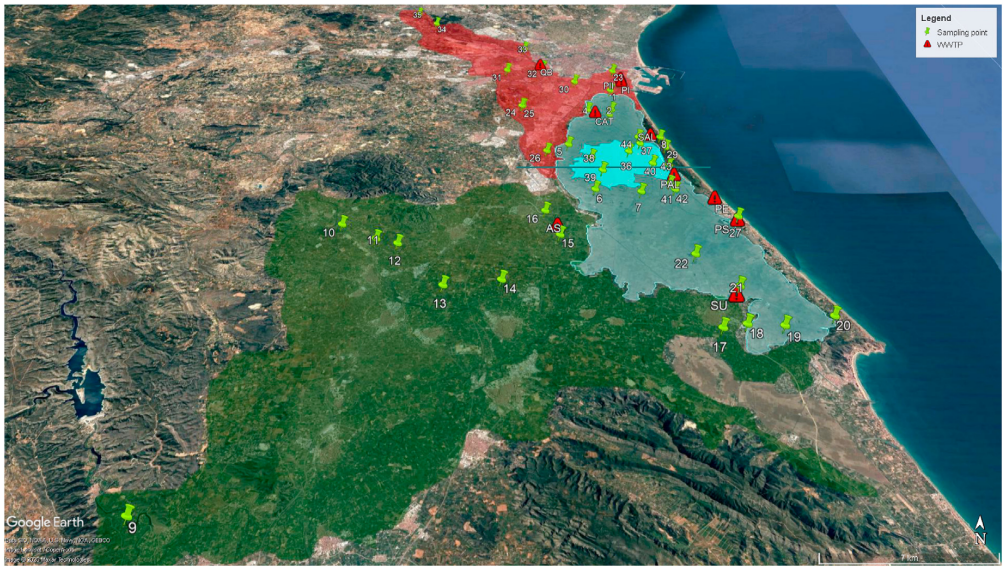


Fig. 1. Map showing sampling sites in the Albufera Natural Park, Valencia, Spain. Red transparent area: orchards; green transparent area: citrus; blue transparent area: rice fields and blue solid area: Albufera Lake. Dark blue line in the lake divide North and South areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Water samples were collected in the middle of rivers and channels at a depth of approximately 30–40 cm at 29 different points (Fig. 1) distributed homogeneously in the park (samples from 22 irrigation channels, one from ground water, four from river water and two from the "golas"). All additional information about the collection and pretreatment of the samples is described in **Text S2**.

The following water quality properties were assessed: temperature, pH, total soluble salts, dissolved O_2 and redox potential. These parameters were monitored in the field using a portable Multiparameter Eutech Instrument CyberScan PCD 650 (Thermo Fisher Scientific, Basel, Switzerland) (Table S4 shows maximum, minimum and average values). Standard laboratory methods were used to assess the main physical and chemical properties of the sediment and soil in these areas (see Tables S5 and S6 for minimum, maximum and average values).

2.3. Extraction and determination of PPCPs

The extraction and determination of all analytes were performed as described in previous work by Sadutto et al. (2020). Solid phase extraction (SPE) was carried out using two different cartridges to ensure the proper recovery of all the analytes: Strata-X (33 μm, 200 mg/6 mL, polymeric reversed-phase) and Strata-X-CW (33 μm, 200 mg/6 mL, mixed mode polymeric weak cation exchange) were obtained from Phenomenex (Torrance, CA, USA). Very briefly, sediment samples were extracted with a mixture of methanol and McIlvaine buffer (pH = 4.6) and filtered, and then, the extract was diluted to 200 mL with water. These extracts (200–250 mL of water) were used for the SPE. Analytes were eluted, evaporated and redissolved to 1 mL with mobile phase before injection. Instrumental analysis was performed by ultra-high-performance liquid chromatography (1260 Infinity UHPLC system) coupled to mass spectrometry with a triple quadrupole mass detector (6410 QqQ-MS) from Agilent Technologies (Santa Clara, CA, USA). The ionization technique used was electrospray ionization (ESI).

2.4. Method validation and quality control

The analytical method validation was also reported in the previous work by Sadutto et al. (2020). LODs ranged from 1.65 to 25 ngL^{-1} in water, from 0.33 to 4.00 ng g^{-1} dry weight (d.w.) in sediment and soil, and LOQs from 3.65 to 75 ng L^{-1} for water (surface and wastewater) and from 1.00 to 12.00 ng g^{-1} d.w. for sediment and soil. Recoveries were evaluated using 1 g of soil or sediment or 250 mL of water spiked to obtain a final concentration of 10 ng mL^{-1} in the extract (10 ng g^{-1} in soil or sediment, or 40 ng L^{-1} in water). The range of recoveries in each type of sample was 59–121% for soil and sediment, 94–106% for surface water and 54–108% in wastewater.

Strict quality control was established to ensure that no false positives or negatives were obtained. Analytical, procedural and field targets were performed regularly to avoid false positives following the protocol widely described elsewhere (Carmona et al., 2014; Ccanccapa et al., 2016). Each batch contained two different linearities, one vial of each analytical, procedural and field blank, three control samples and approximately 80 vials of samples (each sample was analysed in triplicate).

2.5. Statistical analysis

The statistical package IBM SPSS version 26.0 was used to show statistically significant differences among PPCP concentrations in different areas and correlations with the environmental parameters (types of water, location, land uses, etc.) in the three matrices selected (water, soil and sediment). Analysis of variance (ANOVA) and Tukey's multiple range test at $\alpha = 0.05$ were performed to compare differences in the concentrations of PPCPs between the north and south areas, and between different types of water and soil uses. The main criterion to divide ANP (into the north and south areas) was to draw a line through the middle point between the two opposite points that define the park.

Bivariate correlation analysis was applied at the 95 and 99%

significance levels among the pharmaceutical and water, soil and sediment characteristics to assess positive relationships between the water quality and PPCP levels. Pearson's correlation analysis was used, except for those variables that did not show a normal distribution of values. Therefore, Spearman Rho correlation analysis was applied. The r2 and standard deviation of residuals (Sy.x) were included. Multiple stepwise linear correlation analysis, discriminant analysis and categorical PCA were used to more accurately establish the weight and dependence among variables recognizing possible behavioural patterns.

2.6. Geographic information system (GIS)

All data obtained from the concentrations of the PPCPs at the different sampling points and the different matrices were integrated into the GIS environment to include a point layer with the location and analytical values. This information was integrated using ARCGIS (V.10.6) to explain in part the spatial representativeness of the anthropogenic pressures in the ANP.

2.7. Environmental risk assessment (ERA)

An environmental risk assessment (ERA) of the possible negative environmental impacts from these substances in ecosystems was carried out using the surface-water ecological risk quotient (RQ) calculated for three trophic levels (algae, *Daphnia magna* and fish). PPCP toxicity to aquatic organisms was calculated using the Ecological Structure Activity Relationships Program (ECOSAR™) as described in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA) (Committee for Medicinal Products for Human Use (CHMP), June 01, 2006; Whomsley et al., 2019) and is a QSAR tool to predict a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity. The PNEC (predicted no-effect concentration) was determined by applying an AF (assessment factor) of 10 to take into account the intraspecies variability and laboratory data for field-impact extrapolation (since the interspecies variability was already taken into account using the three trophic levels).

The RQ was calculated using the following equation:

$$RQ = EC/PNEC \quad \text{Eq. (1)}$$

where EC is the mean or maximum concentration of PPCPs detected in the water samples.

A search of the scientific literature was also carried out to collect data on reference doses (RfD), PNEC and other values, and to compare them to the ChV calculated theoretically by ECOSAR.

3. Results and discussion

3.1. Occurrence and distribution of PPCPs in the different environmental compartments of Albufera Natural Park

3.1.1. Wastewater

Regarding the 32 selected PPCPs, only thiamphenicol and clofibric acid were not found in the influent water (see Table S7), which is in agreement with what has been reported for most wastewater in Spain and other parts of the world (Martín et al., 2011; Wu et al., 2016). In fact, the occurrence of these compounds in influent water in Europe, America and Asia has been reported rarely and always at low concentrations (<107 ng L^{-1}) (Kuster et al., 2008; Tran et al., 2018; Zhang et al., 2017). The number of compounds found in each influent ranged from 24 to 29. Twenty-one compounds (alprazolam, atenolol, atorvastatin, bezafibrate, BPA, caffeine, codeine, diclofenac, ethylparaben, etoricoxib, flufenamic acid, ibuprofen, lorazepam, metformin, methylparaben, naproxen, paracetamol, propylparaben, salicylic acid, simvastatin and tramadol) were detected in the ten influents. Of these, caffeine, ibuprofen, naproxen, paracetamol and simvastatin were detected at the highest concentrations (median values > 1000 ng L^{-1}), which was also in agreement with those commonly reported in Europe, America and Asia (Čelić et al., 2019; Tran et al., 2018). These concentrations are justified because of their intensive use. Paracetamol (analgesic), ibuprofen and naproxen (anti-inflammatory) are widely used with and without a prescription. Treatment with statins (simvastatin) is one of the most frequent ways to reduce cholesterol levels (Oesterle et al., 2017). Caffeine is present in a variety of common beverages (coffee, tea, and coke and other soft drinks) and in pharmaceutical drugs such as stimulants, pain relievers, diuretics, cold medicine and weight-control products. The SU_{WWTP} showed the highest concentration (57,600 ng L^{-1} ibuprofen). Enalapril (median 167 ng L^{-1}), triclosan (median 102 ng L^{-1}) and furosemide (median 310 ng L^{-1}) were also at high concentrations and occurred in at least 80% of the influents.

Fig. 2 presents the percent average removal efficiency of the 30 PPCPs that were detected in effluent from the WWTPs. Three different trends were observed: *high* removal (% > 90%), *medium* removal (50% ≤ %≤ 90%), and *low* removal (0 ≤ % < 50%, even sometimes negative values). WWTPs were highly effective in removing 13 PPCPs from the water phase—butylparaben, caffeine, chloramphenicol, enalapril, ethylparaben, ibuprofen, indomethacin, metformin, naproxen, omeprazole, paracetamol, propylparaben and simvastatin. Consistently high removal efficiencies for these compounds have also been reported in other studies (Carmona et al., 2014; Rivera-Jaimes et al., 2018). Eight compounds were removed with medium efficiency: atorvastatin, BPA, codeine, furosemide, methylparaben, salicylic acid, triclosan and warfarin. Finally, nine compounds had a low WWTP removal performance: alprazolam, atenolol, bezafibrate, diclofenac, etoricoxib, flufenamic acid, lorazepam, tramadol and triclocarban. The negative removal of some of these PPCPs could be explained by chemical reactions that are able to form the product within the WWTPs from desorption of particulate matter (sludge) during wastewater treatment (Carmona et al., 2014) or by small differences between the sampling of the influent and effluent, and the residence time in the WWTP.

Many PPCPs detected in the influent were also detected in the effluent samples (only chloramphenicol, enalapril and indomethacin were not found) (see Table S8). Furthermore, three compounds, ibuprofen, simvastatin and butylparaben, were only sporadically detected. The number of PPCPs in each effluent sample ranged from 19 to 24. Effluent samples showed diclofenac, flufenamic acid, furosemide, salicylic acid and tramadol from at least eight WWTPs, with median concentrations >100 ngL^{-1}. The highest peak was observed in PII_{WTTP} for tramadol (1291 ngL^{-1}). Tramadol showed the highest concentration in almost all effluent samples. Only three WWTPs demonstrated positive efficiency in the removal of tramadol; in two of them, a chlorination procedure was applied. This reflects the general problem for WWTPs, where tramadol was not efficiently removed (Monteil et al., 2020; Plhalova, 2020; Romanucci, 2019), and agrees with the proposed solutions based on oxidative advanced treatments (Antonopoulou et al., 2020). Furthermore, seven compounds—atenolol, BPA, caffeine, codeine, etoricoxib, metformin and paracetamol—were present in all effluents at median concentrations >10 ng L^{-1} and <100 ng L^{-1}, even though high removal efficiencies were reported for some PPCPs, such as caffeine and paracetamol. The concentrations in both influents and effluents of the WWTPs, as well as the calculated removal efficiency, are in agreement with those

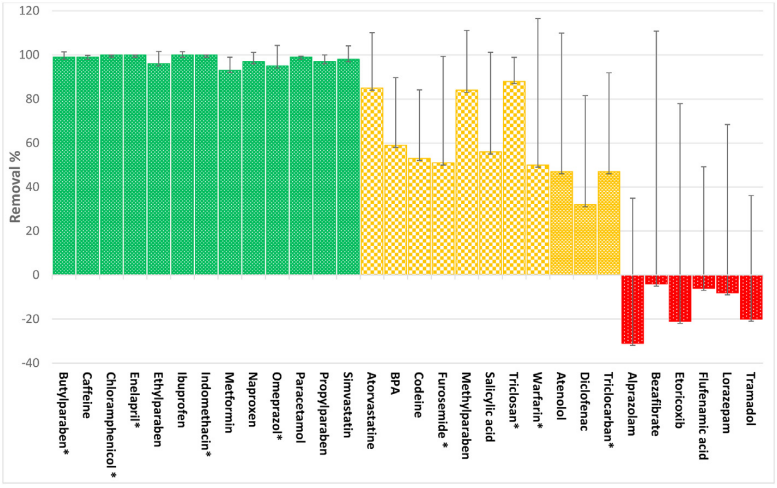


Fig. 2. Average removal efficiency (%) of PPCPs in the WWTPs.
* The average was calculated considering only WWTP that showed the compound in influent or influent and effluent samples.

previously published in the scientific literature (Carmona et al., 2014; Čelić et al., 2019; Monteil et al., 2020; Romanucci, 2019; Tran et al., 2018). Our results agree with those already reported in the literature, by showing that the removal of these contaminants was not completed in the WWTPs and that there is a continuous release of these compounds to the environment.

3.1.2. Surface water

Only omeprazole and simvastatin were not detected in the surface water samples (see Table S9). The other PPCPs were detected in at least one sample. Bisphenol A (BPA) (additive) and caffeine (stimulant) were found in 100% of the samples, with concentrations ranging from 12 to 205 ng L^{-1} and from 11 to 668 ng L^{-1}, respectively. BPA is used in containers for food, beverages and personal-care products and in many other fields (Notardonato et al., 2019). Due to its adverse health effects, BPA concentration is regulated by different institutions, such as the FDA (Food and Drug Administration) and EFSA (European Food Safety Authority) (Baluka and Rumbeiha, 2016). Other PPCPs detected with a relevant average concentration (≥50 ng L^{-1}) and occurrence (≥50%) were diclofenac, methyl paraben, metformin, tramadol and salicylic acid. Tramadol, an opioid used for the treatment of moderate or severe pain (Baluka and Rumbeiha, 2016; Beretta et al., 2014), had the highest concentration of the compounds that were studied (up to 1264 ng L^{-1}). The presence of tramadol in the environment has been recently reported in different studies (Baluka and Rumbeiha, 2016; Golovko et al., 2020; Juksu et al., 2019; Kroll et al., 2016; Liu et al., 2021; Sodré et al., 2018). Furthermore, metformin, caffeine and salicylic acid also showed high maximum concentrations of 375, 668 and 858 ng L^{-1}, respectively. Atorvastatin, ethyl paraben, etoricoxib, flufenamic acid, paracetamol, propylparaben, triclocarban, triclosan and warfarin were detected at low concentrations (average < 50 ng L^{-1}), but had high occurrence among the samples (>50%).

The other PPCPs occurred at very low frequencies ≤ 50%. Of these, atenolol, butylparaben, clofibric acid, furosemide, ibuprofen and naproxen were found at high concentrations in the samples (maximum concentration in the samples in which they were detected > 71 ng L^{-1}). This can be an indicator of the periodic release of nontreated water at some points, which would explain why these compounds that should have been eliminated in the WWTPs appeared at high concentrations. In contrast, alprazolam, chloramphenicol, enalapril, indomethacin, lorazepam and thiamphenicol occurred at very low frequencies.

3.1.3. Sediment

Twenty-two PPCPs were frequently detected (> 47.4% of total samples) (see Table S10). Five of these PPCPs (BPA, ethyl paraben, furosemide, ibuprofen and salicylic acid) were detected at mean concentrations > 10 ng g^{-1}. BPA, furosemide, ibuprofen and salicylic acid have low water solubility. However, ethylparaben is water soluble and can be formed in situ by degradation of other parabens present in the water. The compounds with the highest concentrations in sediment were furosemide (48 ng g^{-1}) and ibuprofen (100 ng g^{-1}), and each had a high occurrence. The other fifteen compounds—atenolol, atorvastatin, butylparaben, caffeine, clofibric acid, diclofenac, etoricoxib, methylparaben, paracetamol, propylparaben, simvastatin, thiamphenicol, tramadol, triclocarban and warfarin—were at mean concentrations <10 ng g^{-1} but were frequently detected (> 42% of the samples). Atenolol, caffeine, methylparaben and thiamphenicol are very soluble in water (see Table S1). However, the presence of these compounds in sediment has been widely reported in other studies (Álvarez-Ruiz and Picó, 2019; Beretta et al., 2014; Golovko et al., 2020; Juksu et al., 2019; Liu et al., 2021; Sodré et al., 2018), which suggests that mechanisms other than hydrophobic interactions, such as ionic retention in clays, must be involved in the retention and accumulation of these compounds.

3.1.4. Soil

Seven compounds were frequently detected in soil (approximately 40% of the samples): BPA, caffeine, diclofenac, salicylic acid, propylparaben, atenolol and methylparaben, with maximum peaks of 22 and 26 ng g^{-1}. BPA was the most detected PPCP (31 samples, at a mean concentration of 6 ng g^{-1}). The highest concentrations in a single sample were tramadol (60 ng g^{-1}), lorazepam (62 ng g^{-1}), alprazolam (67 ng g^{-1}) and ibuprofen (76 ng g^{-1}). Alprazolam and lorazepam are benzodiazepines that are generally used to treat conditions such as anxiety and insomnia (Kroll et al., 2016). Most

PPCPs were detected at a nonrelevant occurrence (between one and six samples, with the exception of triclosan) and at a concentration < 7 ng g^{-1} (see Table S11). Their absence or very low concentration could be explained because soil contamination is not as direct as in the case of water and sediment. The contaminants reach soil through irrigation water and the use of organic amendments.

3.1.5. Pollution status of Albufera Natural Park (2008–2017)

The level of PPCPs in the Albufera Natural Park found in this study could be compared to the results obtained in a previous study by our research group performed nine years ago (Vazquez-Roig et al., 2011). In the 2008 study, five of the PPCPs selected for this study (codeine, clofibric acid, diclofenac, ibuprofen and paracetamol) were monitored at 20 sampling points.

Clofibric acid, paracetamol and diclofenac showed higher abundances in the water samples in the current study (increases of 23, 32 and 48%). Codeine had no relevant increase. Only ibuprofen was more abundant in 2008 than in 2017. The concentrations were higher in the earlier study, except for clofibric acid.

Sediment showed a higher occurrence of codeine and paracetamol with 56 and 16 percentage points, respectively, in 2008. However, the paracetamol concentration was lower, 0.66 ng g^{-1} versus 3.00 ng g^{-1}. The other PPCPs were more frequently detected (from 55 to 89%) in this study. Diclofenac showed an 89% occurrence, while it was not found in the previous study.

Finally, in the 2008 soil samples, only paracetamol (21%) was found. In contrast, codeine, paracetamol, ibuprofen and diclofenac were detected in 2017 in 9, 27, 39 and 45% of the samples, respectively. Therefore, clofibric acid showed the same behaviour in all sample types.

3.2. Assessing anthropic influences on the presence of the PPCPs

The concentrations were higher at the points closest to the WWTPs in the northern part near the city of Valencia, especially near the Turia River (Fig. 3). Higher concentrations of PPCPs in locations near WWTPs have been widely reported recently, especially in the Ebro Delta (Čelić et al., 2019), the Amazon Estuary and its mangroves in Brazil (Chaves et al., 2020), the Nakivubo wetlands and Lake Victoria (Kampala, Uganda) (Dalahmeh et al., 2020) and the Al-Hassa irrigation network and its shallow lakes (Saudi Arabia) (Picó et al., 2020). Based on ANOVA, there were also significant differences according to location (north or south) for atenolol, BPA, caffeine, clofibric acid, flufenamic acid, furosemide, ibuprofen and tramadol (Fig. 4A). The concentrations of all these PPCPs were significantly higher in the northern zone of the park (except for ibuprofen, the concentration of which was higher in the south). This can be explained by the fact that there is 14 times more population in the northern area of the park than in the southern area (1,280,000 vs 91,000). The direct relationship between PPCP concentrations and population density in coastal wetlands has also been reported in other studies (Chaves et al., 2020; Picó et al., 2020). The higher concentration of ibuprofen in the south might be due to the untreated sewage discharge from small towns and districts (since the WWTPs have a high elimination rate for this compound). The contribution of sewage discharge from small towns and districts to global contamination, especially in estuaries, has already been reported (Chaves et al., 2020; Rivera-Jaimes et al., 2018).

Regarding the source of water (Fig. 4B), water that was used to irrigate orchards showed significantly higher concentrations of atenolol and caffeine, together with water used to irrigate rice, which had flufenamic acid and tramadol. Atenolol, bisphenol A, butylparaben, chlofibric acid, etoricoxib, furosemide, naproxen, propylparaben and triclocarban showed significantly lower concentrations in the lake than in the other types of water. Concentrations of thirteen compounds were significantly affected by differences in land use (see Fig. 4C). Although some PPCPs are moderately persistent in aquatic ecosystems, fast and extensive degradation can occur within the organic-rich reducing environment of wetland sediment, as has been reported (Čelić et al., 2019; Tran et al., 2018). The water from the lake also showed significant differences in bisphenol A, butylparaben, naproxen, etoricoxib and warfarin from water used for citrus-crop irrigation. Concentrations of caffeine and naproxen were also significantly higher in the sediment in the irrigation channels that irrigate orchards, and tramadol was also at higher concentrations in the sediment of the channels that irrigate orchards and rice. Dalahmeh et al. (2020) pointed out that in the Nakivubo wetlands (Kampala, Uganda), the total PPCP concentrations decreased by a factor of 2–6 between the WWTP effluent samples and the samples collected from the channels due to dilution and sorption in the channel sediment, and by a factor of 1–3 between the channels and wetlands due to sorption in sediment and the uptake by plants in the wetland.

Bezafibrate, bisphenol A, enalapril, propylparaben and salicylic acid did not correlate with the quality characteristics of the water samples. The pH is the water characteristic that shows more relationships with most of the pharmaceuticals in this study. The relationship is inversed, which means that the higher the pH is, the lower the concentration of pharmaceuticals. This can be explained because many PPCP properties, such as solubility, polarity, acid dissociation constants (pKa values), and the distribution coefficient (K_D), are pH dependent. In addition, the salinization process appears to influence the dynamics of pharmaceuticals. This phenomenon is mainly due to marine intrusion into the groundwater promoted by the overexploitation of the aquifers. This was reflected in the strong relationships observed for pharmaceuticals with electric conductivity, resistivity, Mg and K. These relationships vary and correlate positively or negatively depending on the physicochemical properties of the PPCPs (salinity could decrease or increase water solubility). The highly significant positive relationship of enalapril and metformin with the nitrate content, and indomethacin with nitrites, must be highlighted. This could be explained by the connection that exists between these compounds and their actions in human and other mammalian metabolisms (Oliveira-Paula et al., 2019; Straub et al., 2019); an activity that could also be present in environmental interactions. This may need further study. These observations are confirmed by the stepwise linear regression models, but the PCA only explains 40.01% of the total variance in the best case (see Tables S12 - S13 and Fig. S2 - S3). PCA showed that pharmaceuticals form three groups with intense interactions (e.g., salicylic acid, paracetamol, caffeine and ibuprofen form a solid group).

Concentrations in sediment are commonly higher than those in soil. The north and south areas showed apparent differences (Fig. S4 shows PPCP levels in the soil and sediment at each point). Significant differences were also observed among the pharmaceutical levels in the northern and southern zones of the study area. In particular, caffeine, ibuprofen (as in the case of water), salicylic acid, and simvastatin were at higher concentrations in the south, and methyl- and propyl-parabens and triclocarban were higher in the north (Fig. S5A). This could reflect worse wastewater depuration in the south and a high use of personal care products and other goods associated with the urban lifestyle of Valencia in the north. The levels of PPCPs in the sediment of the orchard crop irrigation channels and those of the lake showed strong significant differences among them and with the other sources of water (Fig. S5B).

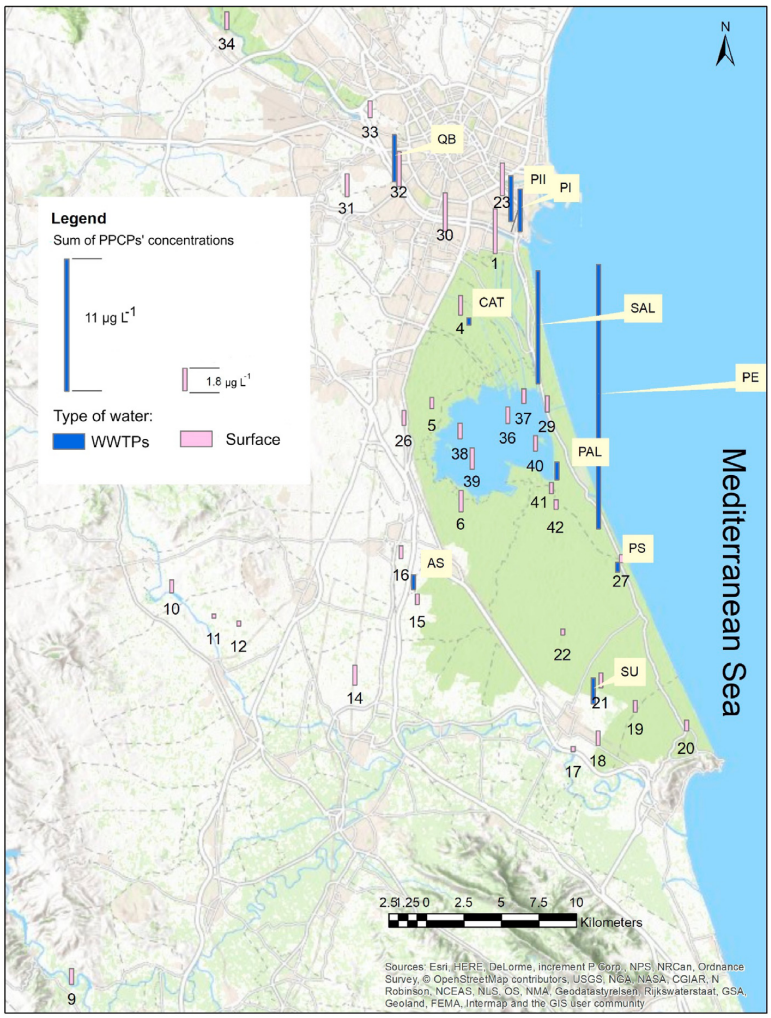
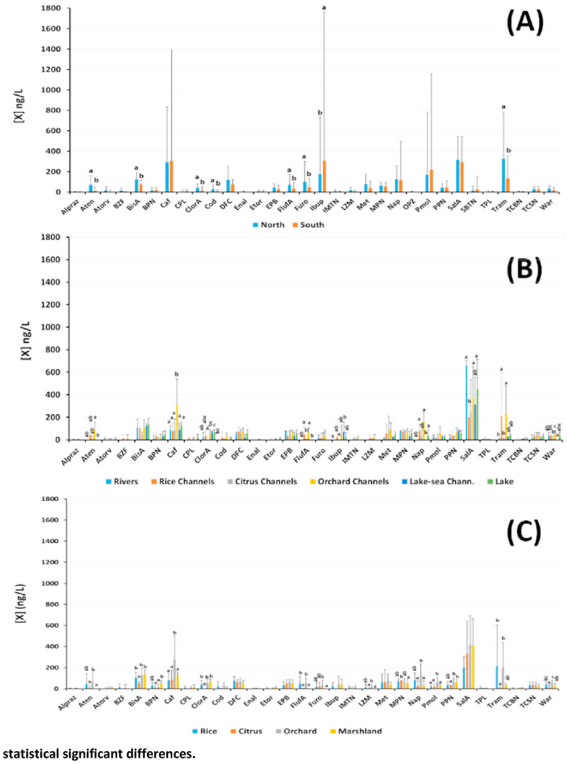


Fig. 3. Sum of the concentrations of target PPCPs in the effluents of the WWTPs and in the water of the Albufera Natural Park, Valencia, Spain.

These differences were mainly observed in atenolol, caffeine, clofibric acid, flufenamic acid, ibuprofen, methyl and propyl paraben, salicylic acid, thiamphenicol, tramadol, triclocarban, triclosan and warfarin. Orchard and citrus crops presented the highest significant differences from the other land uses (Fig. S5C). The dynamics of PPCPs in the sediment in the study area are strongly influenced mainly by the electric conductivity, calcium carbonate and pH. Particulate fractions (silt, clay, and total sand) to which the chemicals can be associated are important in the behaviour of some pharmaceuticals. For example, caffeine, ibuprofen, propylparaben or salicylic acid are probably affected by their fixation in these fractions. This was also confirmed by the linear regression models (Tables S14 and S15) and the PCA (67.71% of variance explained in this case) (Fig. S6-S7). Most of the studies remarked on a linear relationship between organic matter and PPCPs in sediment; in contrast, in our study, only bisphenol A was found (Čelić et al., 2019; Golovko et al., 2020; Wu et al., 2016). However, many studies, including some previous studies (Čelić et al., 2019), also concluded that logKow might not be the only indicator to assess PPCP sorption onto sediments. Local hydrodynamics, pH, biological activity and salinity have also been suggested as sediment characteristics that would be able to change predictable sorption trends (Castro, 2019). In fact (Chaves et al., 2020), reported a lack of significant correlations ($p > 0.05$) between TOC amount and PPCP concentrations, even considering molecules with higher Kow and Koc values only.

Parabens, alprazolam and metformin had higher concentrations in the northern zone soil, while atenolol, etoricoxib and tramadol had the highest concentrations in the southern zone (Fig. S8A). Depending on the type of water used for soil irrigation, PPCP concentrations showed significant differences mainly between the zones irrigated by lake water and those of the citrus areas. Diclofenac, methylparaben, simvastatin, ibuprofen, paracetamol and alprazolam were at higher concentrations in the citrus areas (Fig. S8B). Regarding land use, the concentrations of atenolol, bisphenol A, etoricoxib, methylparaben, ibuprofen, salicylic acid and simvastatin (Fig. S8C) showed significant differences between



statistical significant differences.

Fig. 4. Average levels of pharmaceuticals in waters according to (A) north and south area of the Natural Park, (B) type of water, and (C) land use. Different letters in the bars indicate statistical significant differences.

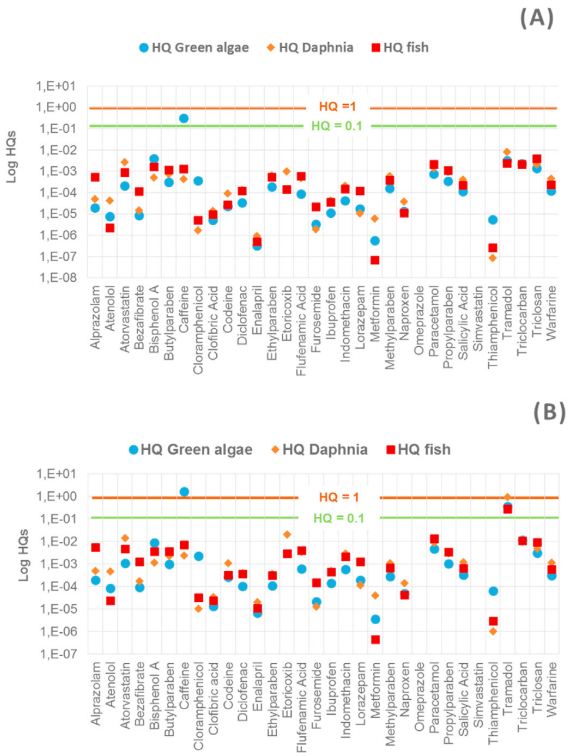


Fig. 5. HQs for the different PPCPs at (A) mean and (B) maximum concentrations.

marshland zones close to the lake and orchard soil. This is in agreement with other studies that demonstrated that soil irrigated with different water sources showed diverse detection frequencies and concentrations of PPCPs (Ma et al., 2018).

Nine pharmaceuticals showed statistical relationships with soil characteristics (Tables S16 and S17 and Fig. S9). These interactions are mainly focused on parameters related to salinity (electric conductivity, Na, K, etc.). Organic matter and carbonates showed a more significant influence on PPCP type and concentration than that found in sediment. This is confirmed by the models and the PCA (40.91% variance explained). From the PCA, regarding the interaction of pharmaceuticals, three groups were clearly observed (Fig. S10), although the percentage of variance explained was limited (30.54%). These results are also in agreement with a number of papers that showed the strong influence of soil properties on PPCP dynamics (Xu et al., 2021).

3.3. Environmental risk assessment

The data used to calculate individual HQ values for selected PPCPs using Eq. (1) are shown in Table S18, together with the data reported in the literature. There are only a few empirical studies, most values were modelled, and many of them used theoretical values using QSAR estimation. Toxicity reported using ECOSAR is mostly of the same order of magnitude as the values reported in the literature. The most important differences depend on the security or assessment factors used. The ECOSAR values were considered to perform the risk assessment because they were calculated in the same way for all compounds. As shown in Fig. 5, at the mean concentration, moderate risk ($0.1 \leq HQ \leq 1$) was registered only for caffeine in algae. Algae has been widely reported as the most sensitive organism (Bi et al., 2018; Välitalo et al., 2017). The other contaminants presented values $\ll 0.1$; therefore, adverse effects of individual PPCPs on aquatic organisms are not expected. Fig. 5 also shows that at the maximum concentration, the risk of caffeine to algae became high ($HQ > 1$), and tramadol showed a moderate risk for the three trophic levels of algae, daphnia and fish ($1 < HQ < 0.1$).

However, each sample presented a mixture of several PPCPs, and, therefore, the risk for the entire mixture of ECs in surface water was evaluated. The HQ of the mixture was calculated by summing the EC/PNEC ratios of each component. Considering the mixture, water is safe for *Daphnia* and fish (even though two points provide values > 0.1 for fish), but not for green algae. The risk of each point to algae is reported in Fig. 6, and it is particularly interesting that the two points nearest the city of Valencia (23 and 30) showed a high-risk quotient > 1 for these organisms. Fortunately, this assessment shows that the water quality of the ANP regarding the presence of the PPCPs that were studied is still appropriate to ensure the development of the biota, but the water quality also shows that it is at the limit and that further monitoring of these parameters is required to ensure the future viability of the park. Future work could extend the number of detected compounds.

4. Conclusions

This study highlights how the presence of anthropogenic

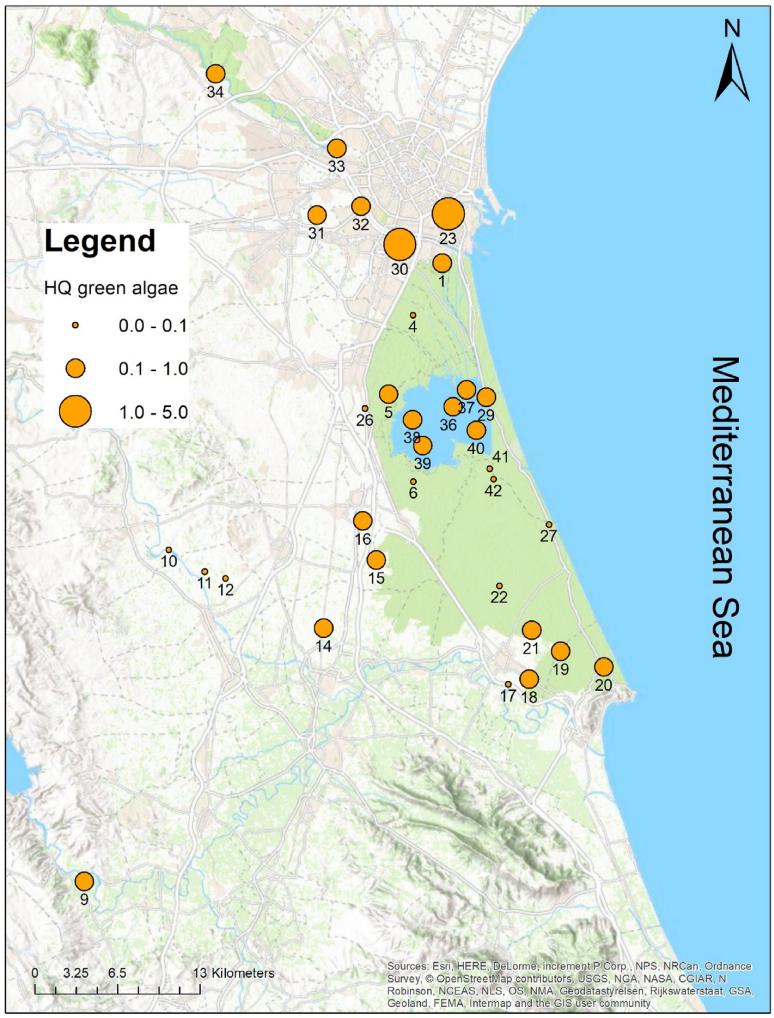


Fig. 6. ΣHQs at each sampling points.

pressures can contribute to an alteration of ecosystems, such as those in the Albufera Natural Park in Spain, where many PPCPs were found at levels of few ng L^{-1} in water and few ng g^{-1} in soil and sediment. The spatial distribution of these compounds showed significant differences between the northern and southern parts of the park, and between the types of water and land used. A comparison of the spatial pollution from 2009 to this study (2017) showed a relevant increase in the frequency of these contaminants.

The statistical analysis performed, as well as the spatial distribution, indicated that the presence of some compounds was related to the characteristics of the location. Furthermore, there are interesting differences observed according to the type of water used for irrigation and land uses, probably related to the agricultural practices.

The environmental risk assessment for the individual emerging contaminants indicates that caffeine is the only PPCP that may pose a significant risk, and that at higher concentrations, tramadol may also be of concern. However, when examining the risk that exists in each water sample due to the sum of the PPCPs, it becomes clear that the water, although still of acceptable quality for most organisms, can affect the most sensitive ones. These results indicate the importance of examining the mixture of contaminants to properly assess the potential environmental risk.

These data showed the importance of improving wastewater treatments and developing new barriers to reduce or completely eliminate the discharges of PPCPs to these sensitive environments to protect biodiversity. The study offers an accurate overview of the current basal state of the Albufera Natural Park.

Author contributions

Daniele Sadutto: Conceptualization, Methodology, Formal analysis, Validation, Investigation, Writing – original draft and Editing, Visualization; Vicente Andreu: Methodology, Formal analysis, Writing-Reviewing and Editing; Timo Ilo: Formal analysis and Methodology. Jarkko Akkanen: Methodology, Writing-

Reviewing and Editing; Yolanda Picó: Conceptualization, Methodology, Formal analysis, Validation, Writing-Reviewing and Editing, Visualization, Supervision and Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2020.116353.

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ANNEX

Supplementary material

Pharmaceuticals and personal care products in Mediterranean coastal wetlands: Impact of anthropogenic and spatial factors on environmental risk assessment

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INDEX OF THE SUPPLEMENTARY MATERIAL

Text S1. List of Analytical Standards and Isotopically Labelled Internal Standards of Pharmaceuticals and Personal Care Products

Alprazolam, atenolol, atorvastatin, bezafibrate, bisphenol A (BPA), butylparaben (butyl 4-hydroxybenzoate), caffeine, chloramphenicol, clofibric acid, codeine, diclofenac sodium, enalapril, etoricoxib, ethylparaben (ethyl 4-hydroxybenzoate), flufenamic acid, furosemide, ibuprofen, indomethacin, lorazepam, metformin, methylparaben (methyl 4-hydroxybenzoate), omeprazole, paracetamol, propylparaben (propyl 4-hydroxybenzoate), salicylic acid, simvastatin, thiamphenicol, tramadol, triclocarban, triclosan and warfarin were present in our list. The internal standards included in the method were: bisphenol A-d16 (BPA-d16), diclofenac-d4 (Dif-d4), ibuprofen-d3 (Ibu-d3), triclosan-d3 (Tcl-d3), atenolol-d7 (Ate-d7) and acetaminophen-d3 (Acm-d3).

Text S2. Collection and pre-treatment samples

Composite samples were taken using the WWTP autosamplers that were of different brands but all of them were time proportional and consisted of 24 bottles of 1 L each taken samples at regular intervals of 1 h for 24 h. Influent and effluents wastewater were taken one day with exception of PI, PII and CAT that were collected two different days to avoid rain effect from November 2016 to January 2017. They were provided by WWTPs staff.

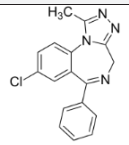
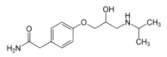
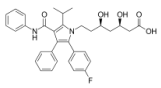
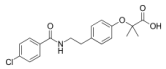
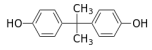
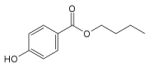
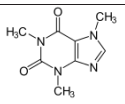
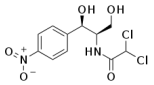
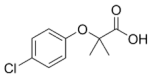
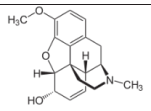
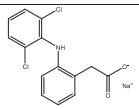
All equipment including samplers and bottles were precleaned by rinsing with methanol, purified water and water from the sampling sites prior to use.

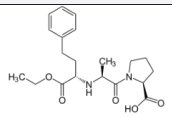
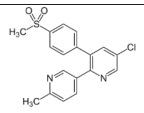
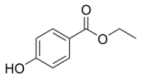
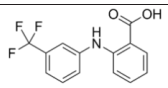
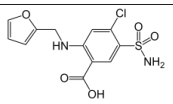
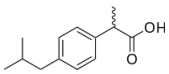
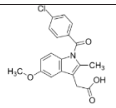
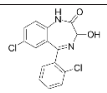
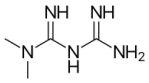
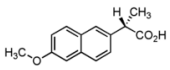
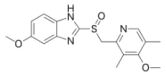
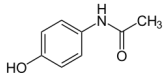
The water samples were taken by either, hand or suspension (using a stick holding a wide-mouth bottle) depending on the accessibility of each sampling point. Furthermore, samples from the lake were taken on-board the vessel of Valencia city council and the natural park management that perform periodical monitoring of other parameters of the lake. All samples were collected in 1L polypropylene bottles (2 bottles per sampling point).

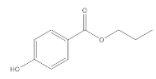
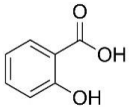
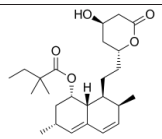
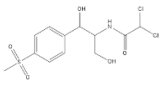
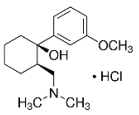
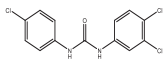
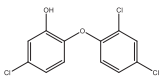
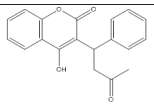
The sediment samples were taken with a Van Veen grab sampler (0.5 L capacity) at up to 15 cm depth and collected on plastic trays and then, transferred and wrapped into an aluminium foil that was put inside an aluminium box. Furthermore, the samples were lyophilized to eliminate water by a Virtis lyophilizer (SP Scientific, Gardiner, NY, USA) with a vacuum between 1 and 4 mTorr for seventy-two hours in order to reduce the water content to less than 0.1 %

Soil (ca. 1 kg) samples were taken at intervals of 2 m within a plot of 16 m^2, and five or more samples were collected from each plot and mixed to represent a single, composite sample. A stainless-steel shovel was used for sampling. Composite samples were sealed in clean polyethylene bags and then were spread out on polypropylene trays in a layer approximately 1 cm thick and air dried in the dark at 20 °C to a moisture content of approximately 3% water. Both types of samples were sieved to <2 mm. All samples were transported in a cooler with ice packs, than once in the laboratory were kept frozen at -20°C up to the analysis to prevent degradation of contaminants. Before SPE procedure, water and wastewater samples were vacuum filtered with 0.45 µm glass fiber filter (ADVANTEC MFS, Dublin, USA).

Table S1- PPCPs selected in this study, their category therapy, chemical structure, pKa, log Kow and water solubility.

Compound name	Chemical structure	pKa	Log Kow	Water solubility (mg/mL)
Alprazolam Anxiolytic		18.30 ¥	2.12 §	3.24x 10^{-2} ¥
Atenolol Antihypertensive		9.60 ¥	0.16 §	13.30 ¥
Atorvastatin Lipid regulator		4.46 ¥	6.36 §	6.30 x 10^{-4} ¥
Bezafibrate Lipid regulator		3.83 ¥	3.99 ¥	1.55 x 10^{-3} ¥
Bisphenol A Plastic additive		9.60 §	3.32 §	8.65 x 10^{-2} ¥
Butylparaben Preservative		8.47 §	3.57 §	4.66 x 10^{-1} ¥
Caffeine CNS stimulant		10.40 at 40 °C §	-0.07 §	11.00 ¥
Chloramphenicol Antibiotic		7.49 ¥	1.14 §	2.50 ¥
Clofibric Acid Lipid regulator		3.18 §	2.84 §	/
Codeine Analgesic		8.21 ¥	1.19 §	5.77 x 10^{-1} ¥
Diclofenac Sodium Analgesic		4.15 ¥	4.51 ¥	4.47 x 10^{-3} ¥

Compound name	Chemical structure	pKa	Log Kow	Water solubility (mg/mL)
Enalapril Antihypertensive		2.97 §	0.07 §	16.40 §
Etoricoxib Analgesic		19.69 ¥	2.91 §	3.28×10^{-3} ¥
Ethylparaben Preservative		8.34 §	2.47 §	2.49 ¥
Flufenamic Acid Analgesic		3.88 ¥	5.25 ¥	9.09×10^{-3} §
Furosemide Antihypertensive		3.90 §	2.03 §	7.31×10^{-2} §
Ibuprofen Analgesic		4.91 §	3.97 §	2.10×10^{-2} §
Indomethacin Antibiotic		4.50 §	4.27 §	9.37×10^{-4} §
Lorazepam Anxiolytic		13.00 §	2.40 ¥	8.00×10^{-2} §
Metformin Antidiabetic		12.4 §	-2.64 §	1.38 ¥
Methylparaben Preservative		8.40 §	1.96 §	3.69 ¥
Naproxen Analgesic		4.15 §	3.18 §	1.59×10^{-2} §
Omeprazole Gastrointestinal		9.29 §	3.40 §	3.59×10^{-1} §
Paracetamol Analgesic		9.38 §	0.46 §	4.15 ¥

Compound name	Chemical structure	pKa	Log Kow	Water solubility (mg/mL)
Propylparaben Preservative		8.50 §	3.04 §	9.60×10^{-1} ¥
Salicylic Acid Analgesic		2.97 §	2.26 §	2.24×10^{-3} §
Simvastatin Lipid regulator		14.91 ¥	4.68 §	1.22×10^{-2} ¥
Thiamphenicol Antibiotic		7.65 ¥	0.33 ¥	2.27 ¥
Tramadol hydrochloride Analgesic		9.41 §	3.01 §	7.50×10^{-1} ¥
Triclocarban Antibacterial		12.70 §	4.34 §	2.90×10^{-3} ¥
Triclosan Antibacterial		7.90 §	4.76 §	6.05×10^{-3} ¥
Warfarin Anticoagulant		5.00 ¥	2.70 §	1.70×10^{-2} ¥

¥ DrugBank *(https://go.drugbank.com)*

§ PubChem (https://pubchem.ncbi.nlm.nih.gov)

*Unless indicated otherwise, all parameters were reported at environmental conditions of 25 °C

Table S2 – Matrix sample taken and analysed at each point (represented by "✓" symbol), point coordinates, soils used and type of water

Sample point	Soil	Water	Sediment	Coordinate (DMS)		Soil use	Source water	North/South orientation
				Latitude	Longitude			
P1	✓	✓		39°25'12.00"N	0°21'15.49"O	rice field	irrigation channel (Rice)	N
P2	✓			39°23'37.90"N	0°21'19.24"O	rice field	/	N
P3	✓			39°23'14.23"N	0°21'28.37"O	rice field	/	N
P4	✓	✓		39°23'34.47"N	0°22'29.96"O	rice field	irrigation channel (Rice)	N
P5	✓	✓	✓	39°20'58.83"N	0°23'31.80"O	rice field	irrigation channel (Rice)	N
P6	✓	✓		39°18'6.69"N	0°22'29.06"O	rice field	irrigation channel (Rice)	S
P7	✓			39°18'1.02"N	0°20'32.02"O	rice field	/	S
P8	✓			39°21'35.32"N	0°19'14.05"O	marshland	/	N
P9	✓	✓	✓	39° 4'57.51"N	0°36'27.42"O	orange trees	River (Jucar effluent)	S
P10	✓	✓	✓	39°15'51.86"N	0°32'52.15"O	orange trees	River (Magro effluent)	S
P11	✓	✓		39°15'9.30"N	0°31'21.40"O	orange trees	irrigation channel (citrus)	S
P12	✓	✓		39°14'56.09"N	0°30'27.77"O	orange trees	irrigation channel (citrus)	S
P13	✓			39°12'59.46"N	0°28'27.44"O	orange trees	/	S
P14	✓	✓		39°13'17.71"N	0°26'17.57"O	orange trees	irrigation channel (citrus)	S
P15	✓	✓	✓	39°15'32.09"N	0°24'3.31"O	orange trees	irrigation channel (citrus)	S
P16	✓	✓	✓	39°16'48.98"N	0°24'38.10"O	orange trees	irrigation channel (citrus)	S
P17	✓	✓	✓	39°11'26.45"N	0°18'27.39"O	orange trees	irrigation channel (citrus)	S
P18		✓	✓	39°11'36.74"N	0°17'33.67"O	rice field	irrigation channel (Rice)	S
P19		✓		39°11'34.92"N	0°16'15.72"O	rice field	irrigation channel (Rice)	S
P20	✓	✓		39°12'1.02"N	0°14'23.05"O	rice field (abandoned)	irrigation channel (Rice)	S
P21		✓		39°13'13.26"N	0°17'27.44"O	rice field	irrigation channel (Rice)	S
P22		✓		39°14'41.37"N	0°18'49.78"O	rice field	irrigation channel (Rice)	S
P23	✓	✓	✓	39°26'53.97"N	0°21'0.05"O	Orchard	River (ground water)	N
P24	✓			39°23'49.22"N	0°25'44.36"O	Orchard	/	N
P25	✓			39°23'50.27"N	0°25'41.31"O	orange trees	/	N
P26	✓	✓	✓	39°20'30.68"N	0°24'31.83"O	orange trees	irrigation channel (citrus)	N
P27		✓		39°16'42.03"N	0°16'43.23"O	asphalt road	Lake-See channel	S
P29	✓	✓		39°20'53.33"N	0°19'4.57"O	pastureland	Lake-See channel	N
P30	✓	✓	✓	39°25'53.99"N	0°23'3.17"O	orchard	irrigation channel	N
P31	✓	✓		0°23'3.17"O	0°26'34.52"O	orchard	irrigation channel	N
P32	✓	✓		39°27'8.79"N	0°24'42.45"O	orchard	irrigation channel (WTTP)	N
P33	✓	✓	✓	39°28'58.52"N	0°25'41.41"O	orchard	irrigation channel	N

Sample point	*Soil*	*Water*	*Sediment*	*Coordinate (DMS)*		*Soil use*	*Source water*	*North/South orientation*
				Latitude	*Longitude*			
P34	✔	✔	✔	39°31'29.12"N	0°30'53.45"O	orchard	River (Turia river)	N
P35	✔		✔	39°32'33.89"N	0°32'3.94"O	orchard	River (Turia river)	N
P36		✔	✔	39°20'34.04"N	0°20'48.09"O	lake	Albufera lake	N
P37		✔	✔	39°21'7.59"N	0°20'13.62"O	lake	Albufera lake	N
P38		✔	✔	39°20'8.48"N	0°22'30.97"O	lake	Albufera lake	N
P39		✔	✔	39°19'18.04"N	0°22'5.00"O	lake	Albufera lake	S
P40		✔	✔	39°19'47.98"N	0°19'48.53"O	lake	Albufera lake	S
P41	✔	✔	✔	39°18'31.57"N	0°19'14.45"O	rice field	irrigation channel (Rice)	S
P42	✔	✔		39°18'11.20"N	0°19'4.54"O	rice field	irrigation channel (Rice)	S
P43	✔			39°19'41.31"N	0°19'6.65"O	rice field	/	S
P44	✔			39°21'34.48"N	0°20'15.27"O	rice field	/	N

Interactive link S1. Online map of sampling points (the Albufera Natural Park)

Google Maps

Fig. S1. Photos of the characteristics area of the Albufera Natural Park

(A) **Lake and marsh**

Point 37 (39°21'7.59"N ; 0°20'13.62"O)

Point 38 (39°20'8.48"N ; 0°22'30.97"O)

Point 29 (39°20'53.33"N ; 0°19'4.57"O)

Point 29 (39°20'53.33"N ; 0°19'4.57"O)

(B) **Rice Fields**

Point 6 (39°18'6.69"N 0°22'29.06"O)

Point 6 (39°18'6.69"N 0°22'29.06"O)

(c) Orange orchards

Point 26 (39°20'30.68"N ; 0°24'31.83"O)

Point 25 (39°23'50.27"N ; 0°25'41.31"O)

Point 15 (39°15'32.09"N ; 0°24'3.31"O)

Point 17 (39°11'26.45"N ; 0°18'27.39"O)

Table S3– Water treatments conducted and flow by WWTPs were reported. Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS).

PI	PII	CAT	QB	SU	PE	PS	PAL	SAL	AS
Pre-treatment	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***	***Pre-treatment***
- Coarse screen - sieving - degritting - degreasing	- Coarse screen - sieving - degritting - degreasing	- Coarse screen	- Coarse screen -Fine screen - sieving - tank homogenization - degritting - degreasing	- Coarse screen - sieving -degritting - degreasing	- Coarse screen - sieving - degritting - degreasing	- Fine screen - sieving - degritting -degreasing	- sieving - degritting - degreasing	- Fine screen - sieving - degritting - degreasing	- Coarse screen - Fine screen - sieving - tank homogenization - degritting - degreasing
PRIMARY TREATMENT	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***	***PRIMARY TREATMENT***
-physical-chemical -decanting	-physical-chemical -decanting	/	-physical-chemical -decanting	/	/	/	/	/	-decanting
SECONDARY TREATMENT	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***	***SECONDARY TREATMENT***
-activated sludge	--activated sludge -nitrogen removal - phosphorus removal	-extended aeration	-activated sludge -nitrogen removal -phosphorus removal	-extended aeration -nitrogen removal -phosphorus removal	-extended aeration -nitrogen removal -phosphorus removal	-extended aeration -nitrogen removal -phosphorus removal	-extended aeration -nitrogen removal -phosphorus removal	-extended aeration -nitrogen removal -phosphorus removal	-activated sludge -nitrogen removal -phosphorus removal
TERTIARY TREATMENT	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***	***TERTIARY TREATMENT***
-coagulation -flocculation -filtration	-coagulation -flocculation -filtration	/	-coagulation -flocculation -filtration	-coagulation -flocculation -filtration	/	-coagulation -flocculation	/	/	/
DISINFECTION	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***	***DISINFECTION***
UV	UV	chlorination	-UV -chlorination	UV	UV	chlorination	UV	UV	chlorination

PI	PII	CAT	QB	SU	PE	PS	PAL	SAL	AS
Flow (m^3/ day)									
124800	200000	75	60000	18150	3600	8200	456	2800	34100

*All data has been taken by EPSAR (Entitat de sanejament d'aigües): http://www.epsar.gva.es/

**The effluent flow is the same as influent flow

Table S4- Minimum, maximum, average and standard deviation values of pH, temperature, conductivity, total dissolved solids, resistivity, NaCl and dissolved oxygen in the water samples.

Parameter	Min	Max	Average	% SD
pH	7.11	8.6	7.84	0.37
T (ºC)	9.20	17.4	13.08	2.20
Conductivity (EC) (mS/cm)	0.83	2.78	1.68	0.46
Total Dissolved solids (TDS) (mg/L)	348	1446	827	263.40
Resistivity (Ω/m)	346	1430	668	228.92
NaCl (‰)	399	1400	811	245.42
Dissolved oxygen DO%	41.8	101.4	80.5	15.30
Dissolved oxygen (DO) (mg/L)	4.22	10.79	8.20	1.62

Table S5-Minimum, maximum, average and standard deviation values of organic matter, carbonates, lime, clay and sand, pH, electric conductivity and cationic exchange capacity of the sediment samples

Parameter	Min	Max	Average	% SD
Organic matter (%)	0.81	7.41	3.81	2.17
CO_3^{2-} (%)	15.80	76.21	44.27	17.72
Lime+ clay (%)	1.83	43.84	15.92	13.36
Sand (%)	55.63	98.10	84.10	13.81
pH	6.95	7.71	7.37	0.22
Electric Conductivity (dS/m)	1.35	5.48	3.25	1.53
Cationic exchange capacity (mg/kg)	2.59	24.71	14.35	7.65

Table S6. Minimum, maximum, average and standard deviation values of organic matter, carbonates, sodium, potassium, magnesium and calcium, pH, electric conductivity and cationic exchange capacity of the soil samples

Parameter	Min	Max	Average	% SD
pH	7.06	8.70	7.77	0.38
Electric Conductivity (dS/m)	0.36	7.92	2.48	2.57
CO_3^{2-} (%)	4.44	47.76	30.92	11.12
Organic matter (%)	0.69	10.09	4.30	2.53
Na (mg/kg)	0.03	4.26	1.00	1.31
K (mg/kg)	0.06	1.77	0.81	0.41
Mg (mg/kg)	0.25	8.42	4.02	2.32
Ca (mg/kg)	0.13	24.08	14.22	5.90
Cationic exchange capacity (mg/kg)	1.01	32.80	20.02	7.50

Table S7 – Minimum (C_{min}) and maximum concentration (C_{max}), mean concentration (C_{mean}) occurrence, median and standard deviation (%SD) in influents of WWTPs

Compound	C_{min} (ng L^{-1})	C_{max} (ng L^{-1})	C_{mean} (ng L^{-1})	Median	% SD	% Occurrence
Alprazolam	1	7	3	3	2	100
Atenolol	23	286	146	147	87	100
Atorvastatin	27	274	121	76	84	100
Bezafibrate	0	32	13	4	14	100
BPA	66	2155	483	175	659	100
Butylparaben	2	23	10	7	7	90
Caffeine	2462	18066	7805	6870	4546	100
Chloramphenicol	1	2	2	2	1	20
Clofibric acid	/	/	/	/	/	0
Codeine	7	93	53	59	31	100
Diclofenac	68	353	262	313	108	100
Enelapril	64	510	227	167	165	80
Ethylparaben	1	89	40	34	36	100
Etoricoxib	6	36	14	11	9	100
Flufenamic acid	26	415	126	91	114	100
Furosemide	177	927	412	310	263	90
Ibuprofen	2565	57600	12930	8241	15944	100
Indomethacin	0	6	3	1	2	60
Lorazepam	14	92	34	30	22	100
Metformin	48	333	230	246	95	100
Methylparaben	31	783	308	185	270	100
Naproxen	570	3115	2035	2050	885	100
Omeprazole	0	158	29	0	62	30
Paracetamol	2833	6084	4576	4937	1226	100
Propylparaben	40	500	240	239	125	100
Salicylic acid	212	1993	1030	935	653	100
Simvastatin	186	2061	1371	1626	630	100
Thiamphenicol	/	/	/	/	/	0
Tramadol	138	1050	490	417	277	100
Triclocarban	0	2	1	1	0	90
Triclosan	50	359	129	102	97	90
Warfarin	0	1	0	0	0	50

*/ = not detected

Table S8 – Minimum (C_{min}) and maximum concentration (C_{max}), mean concentration (C_{mean}) occurrence, median and standard deviation (%SD) in effluents of WWTPs

Compound	C_{min} (ng L^{-1})	C_{max} (ng L^{-1})	C_{mean} (ng L^{-1})	Median	% SD	% Occurrence
Alprazolam	0	8	4	4	3	90
Atenolol	4	169	58	25	58	100
Atorvastatine	0	147	28	0	52	40
Bezafibrate	0	32	8	2	11	100
BPA	10	221	89	77	72	100
Butylparaben	0	0.4	0	0	0	20
Caffeine	9	455	91	38	135	100
Chloramphenicol	/	/	/	/	/	0
Clofibric acid	/	/	/	/	/	0
Codeine	1	75	26	19	25	100
Diclofenac	0	572	207	164	193	90
Enelapril	/	/	/	/	/	0
Ethylparaben	0	4	1	0	1	70
Etoricoxib	2	28	15	16	10	100
Flufenamic acid	0	328	139	116	113	100
Furosemide	0	727	229	100	270	80
Ibuprofen	0	365	37	0	115	10
Indomethacin	/	/	/	/	/	0
Lorazepam	0	60	32	32	21	90
Metformin	1	51	17	13	15	100
Methylparaben	0	35	18	19	12	90
Naproxen	0	318	72	25	109	60
Omeprazole	0	24	7	0	10	40
Paracetamol	11	70	32	31	18	100
Propylparaben	1	8	4	5	2	100
Salicylic acid	83	580	262	257	144	100
Simvastatin	0	163	16	0	51	10
Thiamphenicol	/	/	/	/	/	0
Tramadol	2	1291	608	523	438	100
Triclocarban	0	1	0	0	0	80
Triclosan	0	26	12	11	11	70
Warfarin	0	1	0	0	0	50

*/ = not detected

Table S9 – Minimum (C_{min}) and maximum concentration (C_{max}), mean concentration (C_{mean}), occurrence, median and standard deviation (%SD) in water samples

Compound	C_{min} (ng L^{-1})	C_{max} (ng L^{-1})	C_{mean} (ng L^{-1})	% Occurrence	Median	% SD
Alprazolam	0	10	1	18	0	2
Atenolol	0	320	29	24	0	71
Atorvastatin	0	21	4	44	0	8
Bezafibrate	0	79	7	19	0	21
Bisphenol A	12	205	89	100	81	57
Butylparaben	0	71	23	45	0	29
Caffeine	11	668	123	100	103	143
Chloramphenicol	0	50	8	18	0	18
Clofibric Acid	0	80	32	50	0	39
Codeine	0	154	13	36	0	31
Diclofenac	0	169	56	88	66	35
Enalapril	0	8	0.38	6	0	2
Ethylparaben	0	82	42	67	70	35
Etoricoxib	0	25	4	73	2	6
Flufenamic Acid	0	195	28	55	1	51
Furosemide	0	115	17	24	0	36
Ibuprofen	0	217	18	30	0	50
Indomethacin	0	56	4	15	0	14
Lorazepam	0	88	8	36	0	2
Metformin	0	375	58	97	25	82
Methylparaben	0	107	61	88	75	26
Naproxen	0	225	60	45	0	80
Omeprazole	/	/	/	/	/	0
Paracetamol	0	168	27	85	25	32
Propylparaben	0	135	44	88	33	32
Salicylic Acid	0	858	286	91	249	256
Simvastatin	/	/	/	/	/	/
Thiamphenicol	0	35	3	21	0	8
Tramadol	0	1264	110	94	18	258
Triclocarban	0	15	3	61	1	6
Triclosan	0	72	31	73	44	25
Warfarin	0	70	28	58	45	30

*/ = not detected

Table S10 – Minimum (C_{min}) and maximum concentration (C_{max}), mean concentration (C_{mean}), occurrence, median and standard deviation (%SD) in sediment samples.

Compound	C_{min} (ng g^{-1})	C_{max} (ng g^{-1})	C_{mean} (ng g^{-1})	Median	% SD	% Occurrence
Alprazolam	0	0	0	0	0	0
Atenolol	0	16	3	3	4	68
Atorvastatin	0	21	5	0	9	47
Bezafibrate	0	3	1	0	1	21
Bisphenol A	0	21	12	14	8	84
Butylparaben	0	7	4	6	3	63
Caffeine	4	10	7	7	2	100
Chloramphenicol	0	4	0.21	0	1	5
Clofibric Acid	0	5	3	4	2	68
Codeine	0	1	0.11	0	0	11
Diclofenac	0	10	5	5	3	89
Enalapril	0	0	0	0	0	0
Ethylparaben	0	18	12	15	7	74
Etoricoxib	0	6	1	1	1	74
Flufenamic Acid	2	3	2	2	0	100
Furosemide	9	48	14	10	9	100
Ibuprofen	0	100	30	24	26	95
Indomethacin	/	/	/	/	/	0
Lorazepam	/	/	/	/	/	0
Metformin	1	5	2	1	1	100
Methylparaben	0	19	10	13	8	63
Naproxen	0	31	4	0	7	47
Omeprazole	0	1	0.05	0	0	5
Paracetamol	0	33	3	1	8	42
Propylparaben	0	12	5	4	4	79
Salicylic Acid	15	32	22	21	4	100
Simvastatin	0	29	8	4	9	53
Thiamphenicol	0	14	5	1	6	58
Tramadol	0	13	1	0	3	47
Triclocarban	0	15	4	0	5	42
Triclosan	7	18	10	8	3	100
Warfarin	8	9	9	9	0	100

*/ = not detected

Table S11 – Minimum (C_{min}) and maximum concentration (C_{max}), mean concentration (C_{mean}), occurrence, median and standard deviation (%SD) in soil samples.

Compound	C_{min} (ng g^{-1})	C_{max} (ng g^{-1})	C_{mean} (ng g^{-1})	% Occurrence	Median	% SD
Alprazolam	0	67	4	6	0	16
Atenolol	0	21	4	39	0	8
Atorvastatin	/	/	/	0	/	/
Bezafibrate	/	/	/	0	/	/
Bisphenol A	0	15	6	97	4	4
Butylparaben	/	/	/	0	/	/
Caffeine	0	26	11	85	4	11
Chloramphenicol	0	1	0.03	3	0	0
Clofibric Acid	/	/	/	0	/	/
Codeine	0	7	0.45	9	0	2
Diclofenac	0	3	1	45	0	1
Enalapril	/	/	/	0	/	/
Ethylparaben	0	3	0.48	18	0	1
Etoricoxib	0	51	2	6	0	9
Flufenamic Acid	0	1	0.03	3	0	0
Furosemide	/	/	/	0	/	/
Ibuprofen	0	76	4	39	0	13
Indomethacin	0	1	0.03	3	0	0
Lorazepam	0	62	6	12	0	18
Metformin	0	48	7	18	0	17
Methylparaben	0	4	1	39	0	1
Naproxen	0	1	0.18	18	0	0
Omeprazole	0	4	0.52	12	0	1
Paracetamol	0	31	7	27	0	13
Propylparaben	0	22	2	42	0	5
Salicylic Acid	0	20	3	45	0	5
Simvastatin	0	1	0.03	3	0	0
Thiamphenicol	0	3	3	3	0	1
Tramadol	0	60	13	30	0	25
Triclocarban	0	2	0.1	6	0	0
Triclosan	0	5	1	24	0	1
Warfarin	0	1	0.03	3	0	0

*/ = not detected

Table S12: Multiple stepwise linear regression models for pharmaceuticals and intrinsic characteristics of waters.

Compound	Model	R^2	Significance
Alprazolam	23.809 – 2.923 [pH]	0.199	0.009
Atenolol	654.166 -79.554 [pH]	0.171	0.017
Caffeine	345.114 – 127.108 [EC]	0.168	0.018
Codeine	315.857 – 38.520 [pH)	0.210	0.007
Enalapril	0.025 + 1.356 [$NO_3^=$]	0.520	0.000
Indomethacin	3.407 + 8.161 [NO_2^-]	0.224	0.005
Lorazepam	210.880 – 25.801 [pH]	0.227	0.005
Metformin	16.399 + 1.939 [$NO_3^=$]	0.482	0.000
Naproxen	171.409 – 1987 [Mg]	0.231	0.005
Paracetamol	70.301 – 24.679 [pH]	0.127	0.042
Salicylic Acid	688.917 – 215.024 [EC]	0.162	0.020
Thiamphenicol	-9.068 + 1.512 [K]	0.542	0.000
Triclocarban	-3.706 + 0.011 [Res]	0.194	0.010
Tramadol	2816.282 – 344.503 {pH]	0.241	0.004

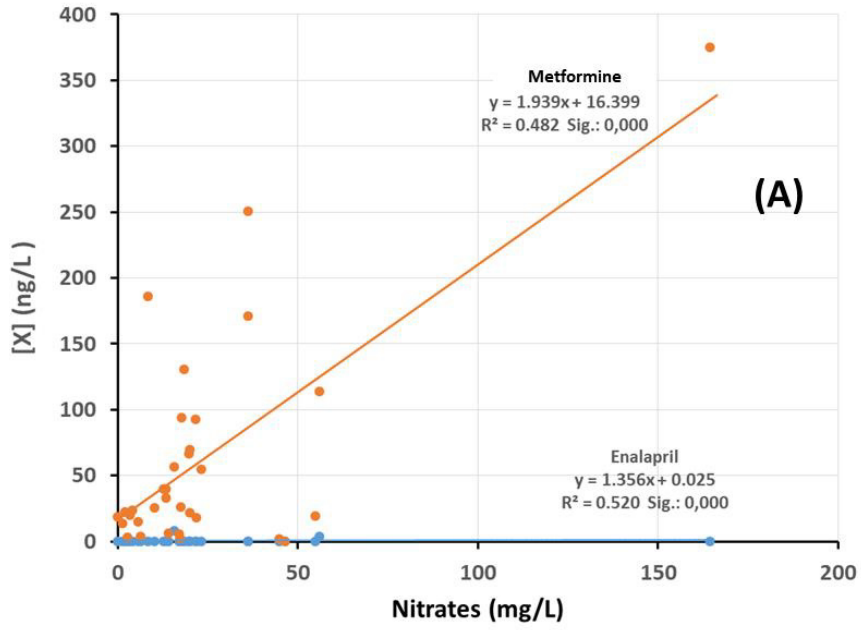
EC: Electric conductivity. **$NO_3^=$**: Nitrates. **NO_2^-**: Nitrites. **Mg**: Magnesium. **K**: Potassium. **Res**: Resistivity.

Table S13: Multiple stepwise linear regression models for pharmaceuticals in waters.

Compound	Model	R^2	Sig.
Alprazolam	-0.214 +0.007 [Tram] + 0.013 [Fluf A]	0.920	0.000
Atenolol	1.232 +3.395 [LZM]	0.914	0.000
Atorvastatin	0.080 + 0.010 [Sal A]	0.125	0.043
Benzafibrate	2.230 + 0.291 [Aten] – 0.320 [Caf]	0.849	0.000
Bisphenol A	51.369 + 1.330 [Clor A]	0.820	0.000
Butylparaben	7.639 + 0.961 [CPL] + 2.480 [TCBN]	0.518	0.000
Caffeine	5.218 + 3.762 [Pmol] + 2.053 [LZM]	0.845	0.000
Chloramphenicol	0.256 + 0.316 [BPN]	0.902	0.000
Codeine	6.090 + 0.124 [Tram] + 0.165 [Aten] – 4.422 [Alpraz] – 0.120 [DFC]	0.959	0.000
Diclofenac	52.974 + 0.088 [Tram]	0.412	0.000
Etoricoxib	-1.129 + 0.079 [Clor A] + 0.027 [Tram] – 0.139 [Fluf A] + 0.187 [War]	0.600	0.000
Ethylparaben	14.399 + 0.501 [MPN]	0.142	0.031
Flufenamic Acid	-3.924 + 16.925 [Alpraz] 0.354 [War] + 0.133 [Ibup]	0.900	0.000
Furosemide	8.302 + 0.169 [Nap]	0.137	0.034
Ibuprofen	-11.425 + 0.580 [Clor A] + 0.206 [Nap]	0.355	0.001
Indomethacin	-4.767 – 7.384 [Alpraz] + 0.088 [Tram] + 0.080 [Ibup] + 0.138 [TCSN]	0.644	0.000
Lorazepam	-0.033 + 0.181 [Aten] + 0.027 [Tram]	0.939	0.000
Metformin	44.328 + 0.555 [Aten]	0.228	0.005
Methylparaben	39.319 + 0.257 [EPB] + 0.254 [DFC]	0.257	0.012
Naproxen	15.003 + 0.345 [Aten] + 0.240 [Caf] + 1.736 [IMTN]	0.555	0.000
Paracetamol	5.366 + 0.208 [Caf] – 0.033 [Tram]	0.834	0.000
Propylparaben	51.300 + 0.414 [Clor A] – 0.314 [DFC]	0.430	0.000
Salicylic Acid	195.189 + 4.586 [Pmol]	0.0.327	0.001
Thiamphenicol	0.811 + 0.140 [Cod]	0.260	0.002
Tramadol	3.412 + 3.464 [Cod] + 72.325 [Alpraz] – 4.197 [BZF] + 0.933 [Aten]	0.985	0.000
Triclocarban	-0.225 + 0.068 [Clor A] + 0.062 [BPN]	0.376	0.001
Triclosan	30.523 + 0.672 [IMTN]	0.150	0.026
Warfarin	23.998 + 0.333 [Fluf A]	0.325	0.001

Alpraz: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Benzafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **CPL**: Chloramphenicol. **ClorA**: Clorfibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **FlufA**: Flufenamic Acid. **Ibup**: Ibuprofen. **IMTN**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: Naproxen. **Pmol**: Paracetamol. **PPN**: Propylparaben. **Tram**: Tramadol. **TCSN**: Triclosan. **War**: Warfarin.

Fig. S2. Examples of significant correlations in water between PPCPs and (A) nitrates and (B) pH



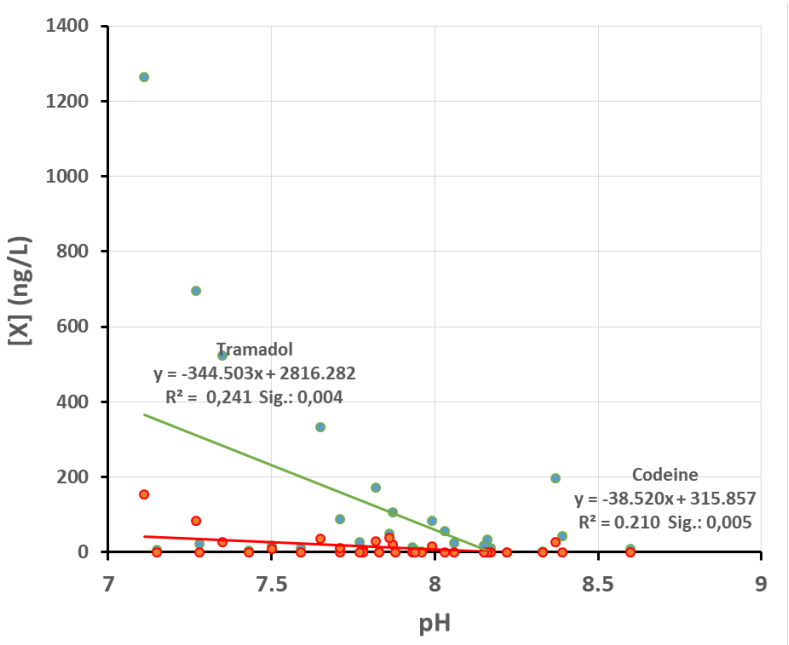


Fig. S3. PCA of the studied data for pharmaceuticals and water characteristics.

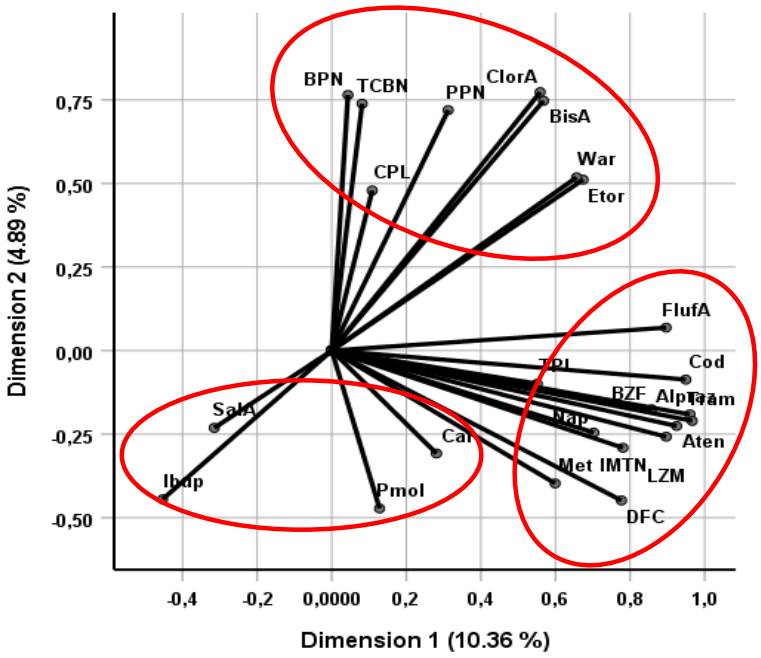


Fig. S4. Sum of the concentrations of target PPCPs in sediment and soil of the Albufera Natural Park, Valencia, Spain

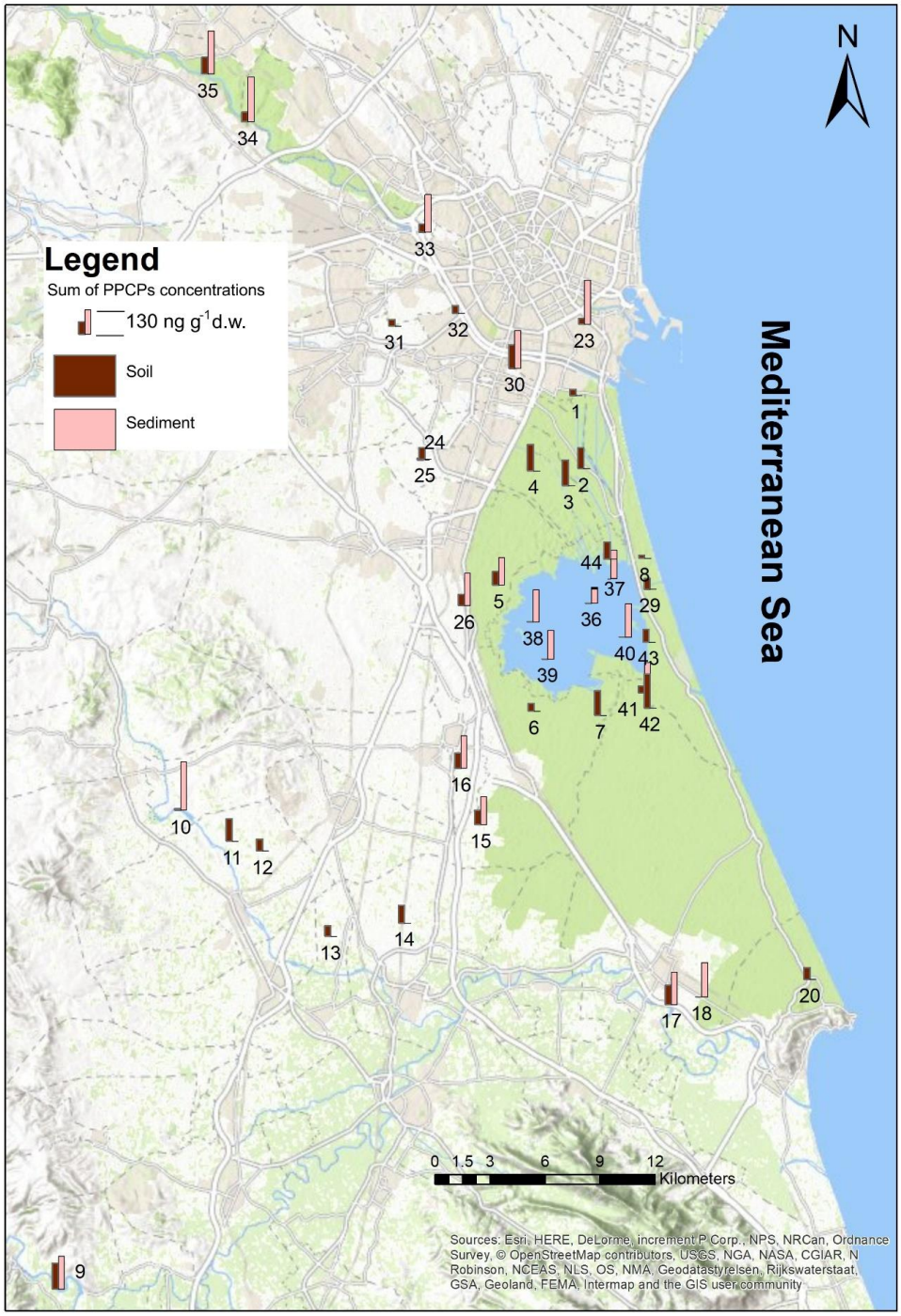
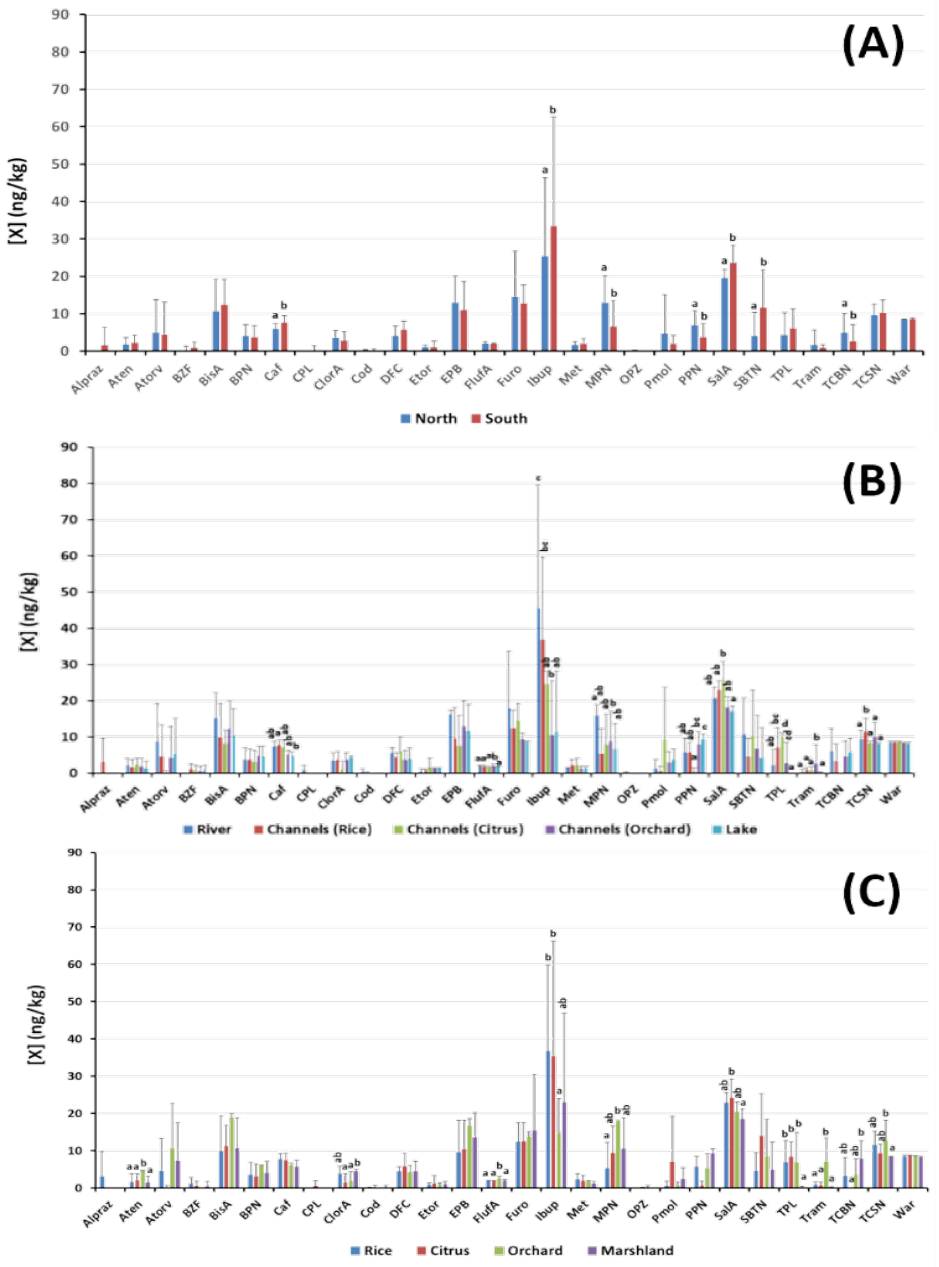


Fig. S5. Average levels of pharmaceuticals in sediments according to (A) north and south area of the Natural Park, (B) type of water, and (C) land use. Different letters in the bars indicate statistical significant differences.



***Alpraz**: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Benzofibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffeine. **CPL**: Chloramphenicol. **ClorA**: Clorfibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **EPB**: Ethylparaben. **FlufA**: Flufenamic Acid. **Furo**: Furosemide. **Ibup**: Ibuprofen. **IMNT**: indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: naproxen. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic Acid. **TPL**: Thiamphenicol. **Tram**: Tramadol. **TCBN**: Triclocarban. **TCSN**: Triclosan. **War**: Warfarin.*

Table S14: Multiple stepwise linear regression models for pharmaceuticals and intrinsic characteristics of sediments.

Compound	Model	R^2	Significance
Alprazolam	55.186 – 7.371 [pH]	0.201	0.004
Bisphenol A	6.014 + 1.451 [OM]	0.166	0.011
Caffeine	-16.847 + 0.247 [S_t] + 0.183 [S_{ac}]	0.387	0.000
Clofibric Acid	1.053 + 0.048 [$CO_3^=$]	0.144	0.019
Etoricoxib	0.060 + 0.308 [EC]	0.147	0.017
Flufenamic Acid	2.269 – 0.080 [EC]	0.159	0.013
Furosemide	22.357 – 0.198 [$CO_3^=$]	0.146	0.018
Ibuprofen	40.968 – 0.709 [S_{ac}]	0.134	0.024
Methylparaben	11.163 – 2.939 [EC]	0.336	0.000
Omeprazole	0.175 – 0.036 [EC]	0.118	0.035
Paracetamol	- 81.869 + 11.544 [pH]	0.121	0.032
Propylparaben	-38.972 + 0.590 [S_{ac}] +0.414 [S_t]	0.408	0.000
Salicylic Acid	17.115 - 0.102 [$CO_3^=$] + 0.108 [S_t]	0.460	0.000
Simvastatin	114.329 – 14.407 [pH]	0.119	0.034
Thiamphenicol	13.512 – 0.187 [$CO_3^=$]	0.344	0.000
Warfarin	8.767 – 0.071 [EC]	0.166	0.011

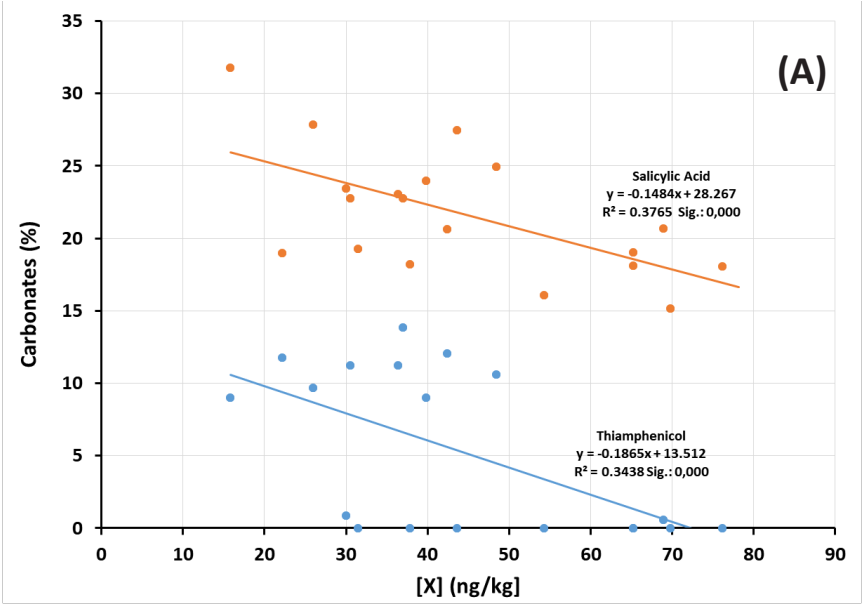
$CO_3^=$: Carbonates. **EC**: Electric Conductivity. **OM**: Organic Matter. **S_{ac}**: Silt + Cay. **S_t**: Total sand.

Table S15: Multiple stepwise linear regression models for pharmaceuticals in sediments.

Compound	Model	R^2	Sig.
Alprazolam	32.119 + 0.172 [Atorv] + 0.440 [SalA] – 4.897 [War]	0.494	0.000
Atenolol	-1.720 + 0.314 [TCSN]+ 0.618 [Etor]	0.385	0.000
Atorvastatin	1.573 + 1.791 [TCBN] – 0.674 [PPN]	0.667	0.000
Benzofibrate	-2.393 + 0.361 [Caf] + 0.148 [BPN]	0.390	0.000
Bisphenol A	-108.513 + 0.328 [[MPN] + 13.212 [War] + 0.344 [EPB]	0.482	0.000
Butylparaben	2.738 – 1.025 [etor] + 2.910 [FlufA] + 1.087 [BZF] – 0.258 [SalA] + 0.684 [Met]	0.587	0.000
Caffeine	0.650 +0.239 [SalA] + 2.209 [Cod] + 0.477 [BZF] + 0.059 [BisA] – 0.269 [Etor]	0.859	0.000
Chloramphenicol	-0.041 + 2.001 [Cod] – 0.048 [Furo] + 0.048 [TCSN] +0.014 [SBTN]	0.854	0.000
Clofibric Acid	8.975 – 0.178 [SalA] – 0.126 [SBTN] + 2.158 [Cod] – 0.671 [Met]	0.693	0.000
Codeine	-0.394 + 0.314 [CPL] + 0.018 [Furo] – 0.016 [TPL] + 0.047 [Caf]	0.899	0.000
Diclofenac	-0.402 + 0.180 [SalA] – 0.103 [Pmol] + 0.699 [BZF] + 0.689 [Met]	0.519	0.000
Etoricoxib	2.812 – 0.188 [BPN] + 0.106 [Aten] – 0.229 [Caf] + 0.051 [SBTN]	0.551	0.000
Ethylparaben	4.803 + 0.465 [BisA] + 0.372 [Atorv]	0.345	0.001
Flufenamic Acid	1.474 + 0.075 [Tram] + 0.028 [TCBN] + 0.036 [TCSN] – 0.024 [Alpraz]	0.883	0.000
Furosemide	6.129 + 30.706 [Cod] – 10.564 [CPL] + 2.090 [Aten] – 0.947 [BPN] + 1.006 [DFC] – 0.244 [BisA] + 1.256 [Met]	0.912	0.000
Ibuprofen	17.129 + 61.965 [OPZ] + 1.705 [TPL]	0.279	0.003
Metformin	-15.145 + 2.049 [War] – 1.550 [ClorA]	0.379	0.000
Methylparaben	6.459 + 0.452 [BisA] – 1.939 [Etor]	0.310	0.002
Omeprazole	-0.080 + 0.002 [Ibup] + 0.007 [[BisA]	0.244	0.008
Paracetamol	9.587 – 1.285 [DFC]	0.210	0.004
Propylparaben	7.289 – 0.382 [TPL] – 0.115 [SBTN] + 0.245 [TCBN]	0.800	0.000
Salicylic Acid	16.515 + 1.044 [Caf] – 0.998 [ClorA] + 0.420 [Alpraz] + 0.429 [DFC] – 0.330 [BPN]	0.851	0.000
Simvastatin	9.921 + 3.134 [Etor] + 5.831 [CPL] – 1.982 [ClorA]	0.551	0.000
Thiamphenicol	6.633 – 0.735 [PPN] + 0.505 [TCSN] – 0.801 [ClorA]	0.769	0.000
Tramadol	-12.372 + 7.267 [FlufA] – 0.307 [ClorA]	0.747	0.000
Triclocarban	-1.019 + 0.320 [Ator] + 0.617 [PPN]	0.820	0.000
Triclosan	-5.311 + 3.349 [FlufA] + 2.820 [CPL] + 0.678 [TPL] + 0.641 [PPN] + 0.091 [BisA]	0.811	0.000
Warfarin	7.864 + 0.086 [Met] + 0.068 [Caf] + 0.055 [Aten] – 0.017 [TCBN]	0.755	0.000

Alpraz: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Benzofibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffeine. **CPL**: Chloramphenicol. **ClorA**: Clorfibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **EPB**: Ethylparaben. **FlufA**: Flufenamic Acid. **Furo**: Furosemide. **Ibup**: Ibuprofen. **Met**: Metformin. **MPN**: Methylparaben. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic Acid. **Tram**: Tramadol. **TCBN**: Triclocarban. TCSN: Triclosan. **War**: Warfarin.

Fig. S6. Examples of significant correlations in sediment between PPCPs and (A) nitrates and (B) pH



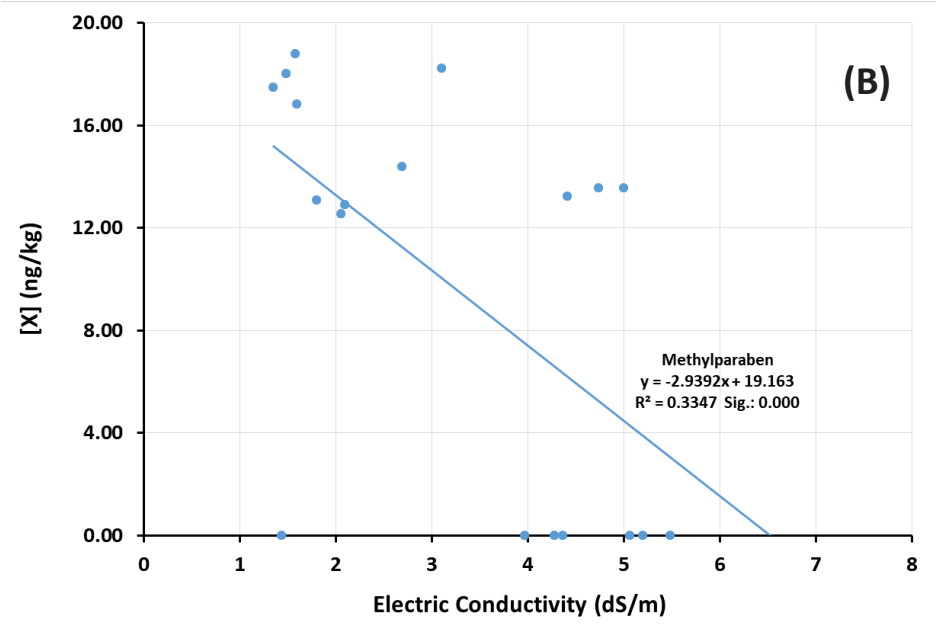


Fig. S7. PCA of the studied data for pharmaceuticals and water characteristics.

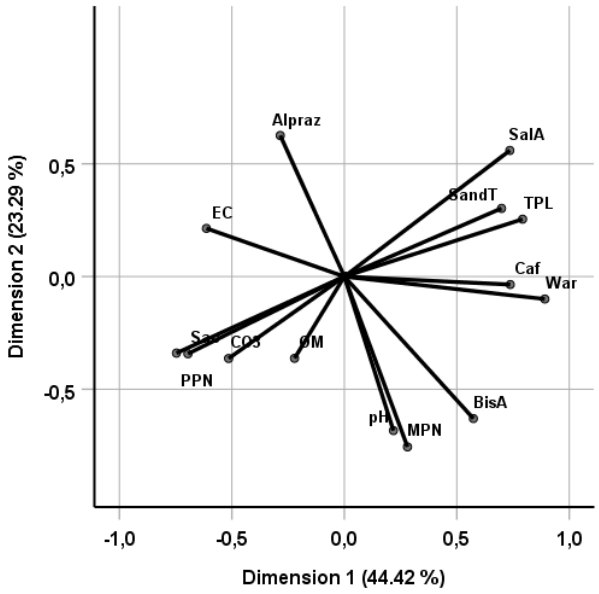
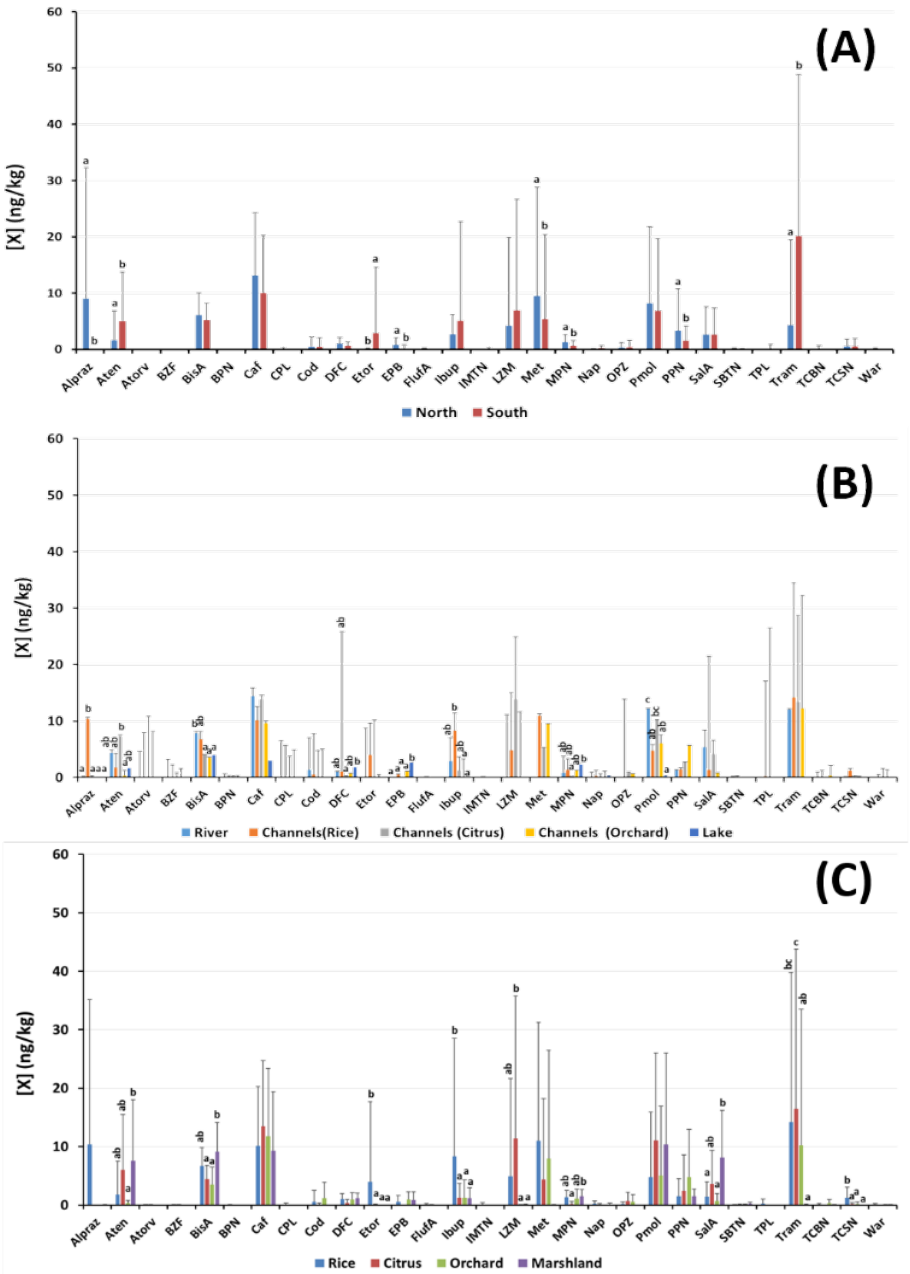


Fig. S8. Average levels of pharmaceuticals in soils according to (A) north and south area of the Natural Park, (B) type of water, and (C) land use. Different letters in the bars indicate statistical significant differences.



***Alpraz**: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Benzafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffein. **CPL**: Chloramphenicol. **ClorA**: Clorfibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **EPB:** Ethylparaben. **FlufA**: Flufenamic Acid. **Furo**: Furosemide. **Ibup**: Ibuprofen. **IMNT**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: Naproxen. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic Acid. **TPL**: Thiamphenicol. **Tram**: Tramadol. **TCBN**: Triclocarban. **TCSN**: Triclosan. **War**: Warfarin.*

Table S16: Multiple stepwise linear regression models for pharmaceuticals and intrinsic characteristics of soils.

Compound	Model	R^2	Signnificance
Alprazolam	-1.556 + 5.623 [Na]	0.204	0.000
Atenolol	7.466 – 0.931 [OM]	0.097	0.011
Bisphenol A	1.545 + 0.131 [$CO_3^=$]	0.177	0.000
Ibuprofen	-6.826 + 3.692 [Mg] – 3.949 [Na]	0.190	0.000
Methylparaben	0.012 +0.213 [OM]	0.197	0.000
Naproxen	0.362 – 0.267 [K]	0.133	0.000
Propylparaben	7.687 – 0.172 [$CO_3^=$]	0.124	0.004
Thiamphenicol	0.024 + 0.539 [Na] – 0.191 [EC]	0.269	0.000
Triclosan	0.665 + 0.061 [CEC]	0.129	0.003

CEC: Cation ExchangeCapacity. **$CO_3^=$**: Carbonates. **EC**: Electric Conductivity. **K**: Potasium. **Mg**: magnesium. **Na**: Sodium. **OM**: Organic Matter.

Table S17: Multiple stepwise linear regression models for PPCPs in soils.

Compound	Model	R^2	Sig.
Alprazolam	-0.274 + 5.416 [DFC]	0.094	0.012
Atenolol	1.581 + 82.790 [Atorv]	0.351	0.000
Atorvastatin	0.023 + 0.004 [Aten] – 0.018 [DFC]	0.440	0.000
Benzofibrate	0.006 + 0.145 [CPL]	0.527	0.000
Bisphenol A	6.292 – 0.093 [Pmol]	0.124	0.004
Butylparaben	-0.017 + 0.192 [Atorv] + 0.013 [TCSN] + 0.056 [Nap] + 0.002 [Aten]	0.520	0.000
Caffeine	11.702 – 0.184[Met] + 0.150 [LZM] + 0.222 [Pmol] – 0.109 [Tram]	0.372	0.000
Chloramphenicol	-0.045 + 0.889 [War] + 0.432 [FlufA] + 0.801 [BZF]	0.932	0.000
Codeine	0.248 + 2.273 [TPL]	0.486	0.000
Diclofenac	0.722 + 1.275 [TCBN] + 0.018 [Alpraz] – 4.387 [Atorv]	0.356	0.000
Ethylparaben	0.226 + 4.385 [War]	0.199	0.000
Flufenamic Acid	0.016 + 0.714 [CPL]	0.836	0.000
Indomethacin	-0.014 + 0.325 [Nap]	0.256	0.000
Lorazepam	-1.093 + 0.593 [Caf]	0.124	0.004
Metformin	14.508 – 0.634 [Caf]	0.156	0.001
Naproxen	0.096 + 0.810 [IMTN]+ 2.985 [BPN]	0.461	0.000
Omeprazole	0.170 + 0.083 [Sal A]	0.141	0.002
Paracetamol	9.670 – 1.154 [BisA] + 0.369 [Caf]	0.211	0.001
Salicylic Acid	0.852 + 17.745 [SBTN] + 1.965 [OPZ]	0.0.332	0.000
Simvastatin	0.032 + 0.009 [Sal A]	0.146	0.002
Thiamphenicol	-0.006 + 0.214 [Cod]	0.486	0.000
Triclocarban	-0.055 + 0.979 [War] + 0.108 [DFC]	0.286	0.001
Triclosan	0.363 + 3.308 [CPL] + 12.210 [BPN]	0.377	0.000
Warfarin	0.022 + 0.538 [CPL] + 0.001 [Ibup] + 0.011 [EPB] + 0.011 [DFC]	0.918	0.000

Alpraz: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Benzofibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **CPL**: Chloramphenicol. **ClorA**: Clorfibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Eto**r: Etoricoxib. **FlufA**: Flufenamic Acid. **Ibup**: Ibuprofen. **IMTN**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: Naproxen. **Pmo**l: Paracetamol. **PPN**: Propylparaben. **Tram**: Tramadol. **TCSN**: Triclosan. **War**: Warfarin.

Fig. S9. Examples of significant correlations in soil between PPCPs and (A) nitrates and (B) pH

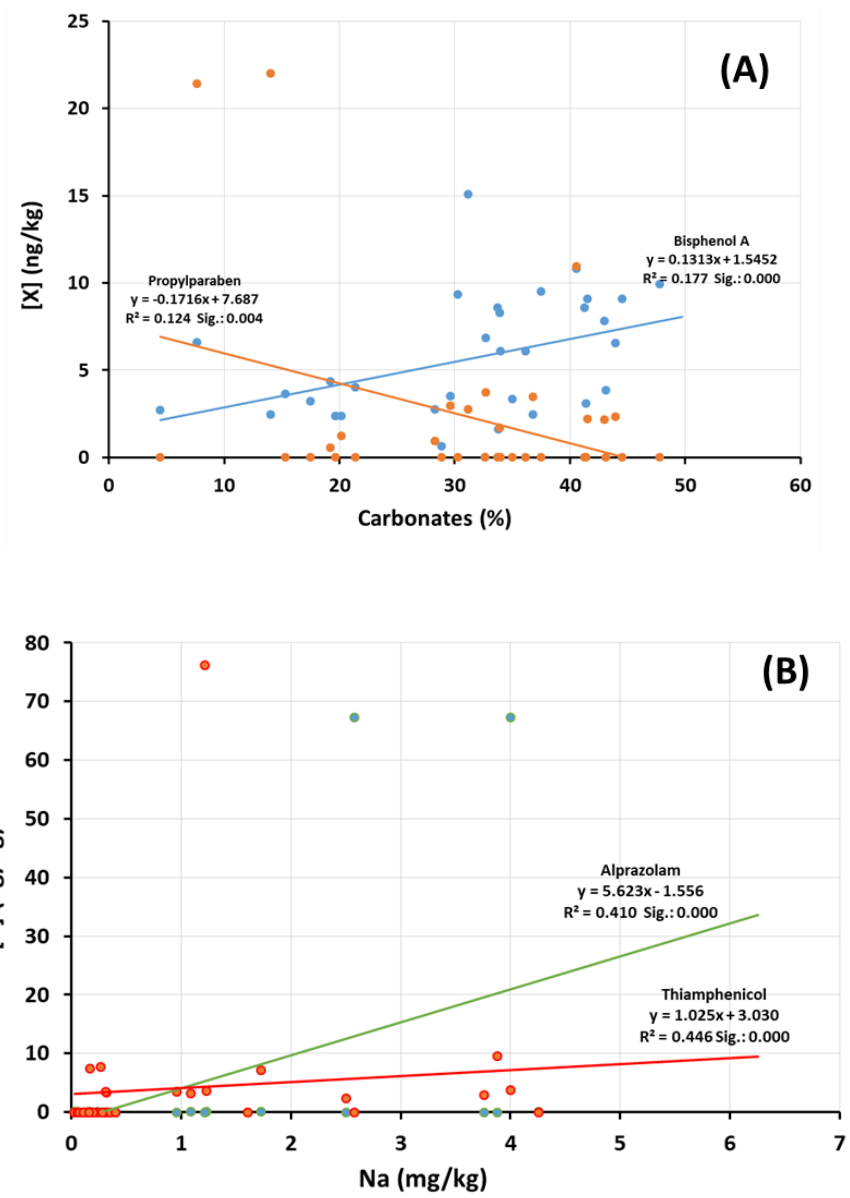


Fig. S10. PCA of the studied data for pharmaceuticals and sediment characteristics.

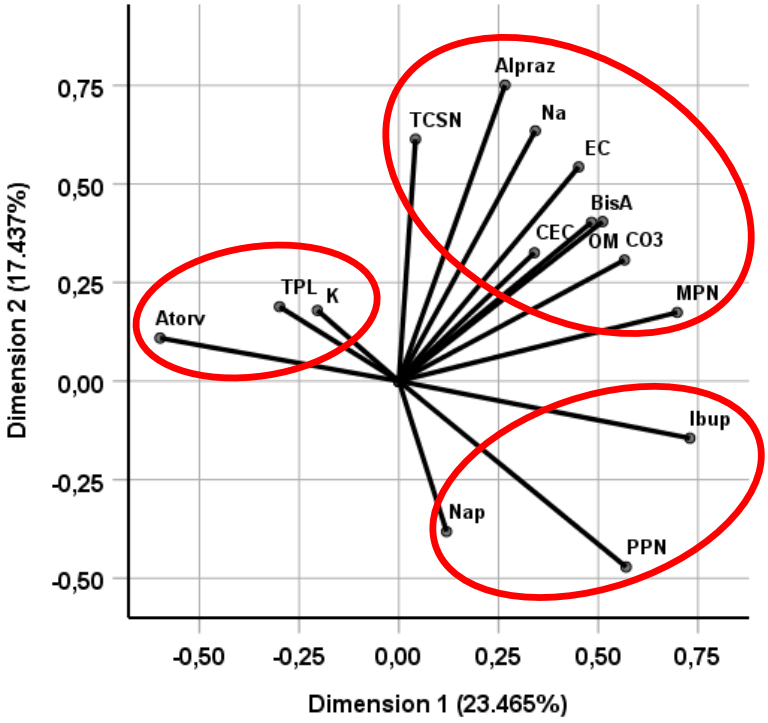


Table S18. Mean and maximum concentrations of PPCPs in The Albufera, Ecosar (ChV) values and other concentrations of interest found in the scientific literature

Contaminant	Concentrations in The Albufera ($\mu g\ L^{-1}$)		Bibliography values	ECOSAR values			*Reference*
	C_{mean}	C_{max}	PNEC (ug/L)	ChV Green Algae (mg/L)	ChV Daphnid (mg/L)	ChV Fish (mg/L)	
Alprazolam	0.001	0.01	0.892	0.503	0.2	0.018	*(Pereira et al., 2020)*
Atenolol	0.029	0.32	451	38	6.75	131	*(Astrazeneca.com, 2017)*
Atorvastatin	0.004	0.021	14	0.188	0.015	0.045	*(Vestel et al., 2016)*
Bezafibrate	0.007	0.079	1.30	8.4	4.62	0.618	*(Pereira et al., 2020)*
Bisphenol A	0.089	0.205	0.06	0.227	1.77	0.55	*(Wright-Walters et al., 2011)*
Butylparaben	0.023	0.071	/	0.724	0.307	0.199	-
Caffeine	0.123	0.668	87	0.004	2.8	0.914	*(ECHA, 2020)*
Chloramphenicol	0.008	0.05	1.6	0.217	47.6	15.5	*(Tran et al., 2019)*
Clofibric Acid	0.032	0.08	4.20	60.5	22.9	33	*(Ferrari et al., 2003)*
Codeine	0.013	0.154	0.06	5.73	1.43	4.79	*(Jiang et al., 2014)*
Diclofenac	0.056	0.169	0.05	16.4	4.22	4.58	*(Loos et al., 2018)*
Enalapril	0.00038	0.008	346	11.9	4	7.5	*(Carlsson et al., 2006)*
Ethylparaben	0.042	0.025	750	2.24	0.673	0.783	*(Kang et al., 2019)*
Etoricoxib	0.004	0.082	75	/	/	/	*(Vestel et al., 2016)*
Flufenamic Acid	0.028	0.195	/	3.24	0.573	0.475	-
Furosemide	0.017	0.115	1.56	52.4	90.4	7.86	*(Christensen et al., 2009)*
Ibuprofen	0.018	0.217	0.0002	15.6	4.31	4.94	*(Pereira et al., 2020)*
Indomethacin	0.004	0.056	43	0.946	0.185	0.257	*(Gheorghe et al., 2016)*
Lorazepam	0.008	0.088	6.07	4.64	7.58	0.673	*(Pereira et al., 2020)*
Metformin	0.058	0.375	1030	1040	93.7	8360	*(Vestel et al., 2016)*
Methylparaben	0.061	0.107	130	3.89	0.986	1.54	*(Terasaki et al., 2015)*
Naproxen	0.06	0.225	4.2	45.3	15.7	52.2	*(Center, 2020)*

Contaminant	Concentrations in The Albufera (µg L^{-1})		Bibliography values	ECOSAR values			*Reference*
	C_{mean}	C_{max}	PNEC (ug/L)	ChV Green Algae (mg/L)	ChV Daphnid (mg/L)	ChV Fish (mg/L)	
Omeprazole	0	0	83	0.204	0.056	0.058	*(Center, 2020)*
Paracetamol	0.027	0.168	0.01	0.352	0.189	0.124	*(Gómez-Canela et al., 2019)*
Propylparaben	0.044	0.135	0.16	1.28	0.456	0.396	*(Kang et al., 2019)*
Salicylic Acid	0.286	0.858	11.2	25.5	7.06	13	*(Claessens et al., 2013)*
Simvastatin	0	0	0.0032	0.209	0.308	0.029	*(Pereira et al., 2020)*
Thiamphenicol	0.003	0.035	10	5.36	339	118	*(Targets, 2018)*
Tramadol	0.11	13	0.1	0.347	0.135	0.445	*(Guruge et al., 2019)*
Triclocarban	0.003	0.015	0.025	0.013	0.015	0.014	*(Musee, 2018)*
Triclosan	0.031	0.072	53	0.227	0.146	0.076	*(Capdevielle et al., 2008)*
Warfarin	0.028	0.07	1.2	2.29	0.603	1.17	*(Commission, 2009)*

*PNEC = Predicted no-effect concentration;

Table S19. Sum of hazardous quotients (HQ) at each sampling point of the Albufera Natural Park

	ΣHQ		
Sampling point	Green algae	Daphnia	Fish
1	0.4	0.0	0.1
4	0.1	0.0	0.0
5	0.2	0.0	0.0
6	0.1	0.0	0.0
9	0.3	0.0	0.0
10	0.1	0.0	0.0
11	0.0	0.0	0.0
12	0.0	0.0	0.0
14	0.7	0.0	0.0
15	0.2	0.0	0.0
16	0.4	0.0	0.0
17	0.1	0.0	0.0
18	0.3	0.0	0.0
19	0.3	0.0	0.0
20	0.3	0.0	0.0
21	0.6	0.0	0.0
22	0.1	0.0	0.0
23	1.7	0.0	0.0
26	0.1	0.0	0.0
27	0.1	0.0	0.0
29	0.4	0.0	0.0
30	1.4	0.0	0.0
31	0.3	0.0	0.0
32	0.7	0.0	0.1
33	0.4	0.0	0.0
34	0.2	0.0	0.0
36	0.5	0.0	0.0
37	0.2	0.0	0.0
38	0.4	0.0	0.0
39	0.3	0.0	0.0
40	0.3	0.0	0.0
41	0.0	0.0	0.0
42	0.1	0.0	0.0

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DATASET OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN A MEDITERRANEAN COASTAL WETLAND

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Data Article

Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland

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ABSTRACT

The dataset provides information on Pharmaceutical and Personal Care Products (PPCPs) detected in the Albufera Natural Park (Valencia, Spain), a typical Mediterranean coastal wetland. These PPCPs constitute an important group of organic pollutants highly representative of the human impact.
The concentrations values measured in soil, sediment and water and the statistical relationship of contaminants between them and with the environmental parameters could help to understand their fate in different compartments. The data also reported the occurrence and removal efficiency (%) for each contaminant in ten wastewater treatment plants (WWTPs), located in the surrounding area. This dataset could provide an idea on the effectiveness of WWTP treatments and the capacity of released PPCPs to affect the ecosystem.
The extraction of analytes was based on solid-phase extraction (SPE) for water and solvent extraction followed by the previous SPE as clean-up for soil and sediment. Determination was carried out by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) with a triple-quadrupole.

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The present dataset was analyzed within the article entitled: "*Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment*" [1].

Specifications Table

Subject	Pollution
Specific subject area	Pharmaceuticals and personal care products occurrence and fate in Mediterranean coastal wetlands.
Type of data	Table
How data were acquired	Raw data were acquired via HPLC-MS/MS. The instrument was an Infinity 1260 UHPLC system, coupled to mass spectrometry with a triple-quadrupole mass detector 6410 (QqQ-MS) from Agilent Technologies (Santa Clara, CA, USA). The ionization technique used was electrospray ionization (ESI).
Data format	Raw Analyzed Filtered
Parameters for data collection	The mobile phase consisted of 2.5 mmol L^{-1} NH_4F in methanol (A) and 2.5 mmol L^{-1} NH_4F in water (B) for negative mode and methanol and water with 0.1% formic acid in both solutions for positive mode. The other parameters are described in literature [2].
Description of data collection	Data were obtained analysing environmental samples (soil, sediment and water) collected in 44 sampling points of the Albufera Natural Park and in ten wastewater treatment plants (WWTPs), located in the surrounding area. The final value concentrations were achieved by HPLC-MS/MS analysis.
Data source location	Institution: University of Valencia, Research Center on Desertification (CIDE) City: Valencia Country: Spain Latitude and longitude (and GPS coordinates, if possible) for collected samples/data: All coordinates are specified in related research article [1]. Moreover, the virtual map of sampling points was reported in the interactive link: https://www.google.com/maps/d/viewer?mid=1ITmoW9a9uCVfqVZ08v25oNgMxjUFAMxn&ll=39.41350461328517%2C-0.41794440579224323&z=11
Data accessibility	Pico, Yolanda; Sadutto, Daniele; Andreu, Vicente; Ilo, Timo; Akkanen, Jarkko (2021), "Details on the Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland", Mendeley Data, V1, http://dx.doi.org/10.17632/zy2zg7dhgv.1
Related research article	Daniele Sadutto, Vicente Andreu, Timo Ilo, Jarkko Akkanen, Yolanda Picó. *Pharmaceuticals and personal care products in a Mediterranean coastal wetland: Impact of anthropogenic and spatial factors and environmental risk assessment*, Environmental Pollution, 2021, 271: p. 116353. https://doi.org/10.1016/j.envpol.2020.116353

Value of the Data

- The contaminants monitoring of a Natural Park (Albufera) is needed to value the environmental risk and how it is related with anthropogenic pressures. In addition, statistical correlations show a relationship between studied PPCPs and the different matrices.
- National and international authorities, wastewater treatment plant managers and researchers can estimate removal, occurrence, transport and fate of PPCPs.
- The data of PPCPs occurrence in sediment, soil and water samples could serve as a knowledge base that allows the establishment of monitoring programs for the compounds that appear

with a higher frequency and establish a better assessment of the risks that exist for this natural space.
- The concentrations on each sampling point may help to understand the geophysical distribution of these contaminants and can be compared with other studies.

1. Data Description

The presented data were collected in the Albufera Natural Park (Valencia, Spain), which is included in the list of international wetlands (RAMSAR) (since 1990), in the Natura 2000 network as a Special Protection Area for Birds (SPA) under the Birds Directive, and is considered a Site of Community Importance (SCI) under Habitats Directive. This area of about 21000 hectares (ha) included a coastal lagoon fed by streams, rivers and irrigation channels, a sandy shoreline belt, rice paddies, vegetables and orange orchards in its most external part, where 43 sampling points and ten wastewater treatment plants (WWTPs), that discharged into irrigation channels that eventually end up in the park, were monitored. Strong anthropic pressure has already been noted in the area due to the proximity of Valencia city and its metropolitan area [3]. The occurrence of 32 pharmaceutical and personal care products (PPCPs) was investigated from November 2016 to February 2017. Detailed information of each sampling site is provided in the related article. Tables 1–2 shows the concentration of PPCPs in influent (i) and effluent (e) wastewater samples with relative date of collection. While, the removal efficiency (%) for each compound was reported in Table 3. The occurrence of (32) water, (19) sediment and (33) soil samples was described in Tables 4–6. The data presented in Tables 1–2 and 4–6 are the average value of three method's replicates for each sample to check reproducibility. In the public repository (Mendeley Data) [4] have been published the additional tables (named table S. "n°"), that contain the results of each individual extraction as well as the average (Tables S1-S5) and the linearity (R^2), LOD, LOQ and matrix effect (ME) for each contaminant (Table S6-S7). The Statistical correlations between the studied PPCPs in soils, sediment and water were described in Tables 7–9. At last, statistical correlations between contaminants and intrinsic characteristics of all matrices were schematized in Tables 10–12. The intrinsic characteristics considered were temperature, pH, total soluble salts, dissolved O_2 and redox potential in water, organic matter, carbonates, lime, clay and sand, pH, electric conductivity and cationic exchange capacity in sediments and organic matter, carbonates, sodium, potassium, magnesium and calcium, pH, electric conductivity and cationic exchange capacity in soil.

2. Experimental Design, Materials and Methods

The water characteristics were in situ measured using a portable Multiparameter Eutech Instrument CyberScan PCD 650 (Thermo Fisher Scientific, Basel, Switzerland). The soil and sediment characteristics were established in the laboratory using standard procedures. Organic matter was determined by oxidation with dichromate [5]. Carbonate was determined using the Bernard calcimeter [6] method and cationic exchanger capacity was calculated measuring sodium, potassium, magnesium and calcium by extraction with 1 M ammonium acetate solution and inductively coupled plasma optical emission spectroscopy) (ICP-OES) following the method of Rhoades [7]. Electric conductivity and pH were determined in the soil saturation extract with a pH-meter according to Richards [8] and finally, % of lime, clay and sand were established using an hydrometer according to the Bouyoucos [9] method. The waste and surface waters (200 mL) were vacuum filtered by a 0.6-µm glass fiber filter (GA-55, 90 mm - Advantec MFS, Dublin, CA, USA) and stored at -20°C until the analysis. The sediments were lyophilized with a Virtis lyophilizer (SP Scientific, Gardiner, NY, USA) and the soil samples were sieved, and air-dried in the dark at 20°C to reduce the moisture content. The samples of water, soil and sediment were spiked with labeled internal standards to quantify the PPCPs present in the all

Table 1
Concentration of PPCPs (ng L^{-1}) in the influents (i) of the WWTPs*.

Compound	iAS 25/11/2016	iCAT 22/11/2016	iCAT 13/01/2017	iPAL 14/12/2016	iSAL 13/01/2017	iPE 13/01/2017	iPI 22/11/2016	iPI 13/01/2017	iPII 22/11/2016	iPII 13/01/2017	iPS 25/11/2016	iQB 14/12/2016	iSU 25/11/2016
Alprazolam	2.30	n.d.**	2.42	4.03	1.43	3.01	3.82	4.34	4.23	4.01	2.33	7.12	1.91
Atenolol	132	5.63	63.5	113	22.9	162	236	335	154	244	82.0	257	174
Atorvastatine	83.1	2.65	134	157	27.2	59.7	148	278	166	231	63.0	274	61.0
Bezafibrate	5.22	0.91	52.3	1.62	1.21	3.02	29.5	35.0	26.3	21.0	0.32	31.0	3.12
BPA	562	37.1	4.27×10^3	147	66.2	87.9	166	238	400	387	110	1.01×10^3	92.0
Butylparaben	5.43	n.d.	18.4	19.2	1.82	n.d.	13.6	33.0	1.92	10.8	9.14	4.62	6.73
Caffeine	8.70×10^3	9.78×10^3	9.36×10^3	6.08×10^3	2.46×10^3	5.24×10^3	9.99×10^3	1.32×10^3	6.95×10^3	8.36×10^3	4.34×10^3	18.07×10^3	4.3×10^3
Chloramphenicol	2.01	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.41
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	68.4	1.12	52.2	7.01	10.0	50.2	52.1	133	80.9	93.8	47.5	71.8	72.0
Diclofenac	324	n.d.	290	303	68.0	123	324	380	386	320	327	348	275
Enelapril	379	n.d.	283	63.8	n.d.	n.d.	288	281	243	141	119	510	127
Ethylparaben	25.0	4.34	174	87.2	5.32	3.03	87.2	43.0	0.52	1.71	5.21	43.0	73.0
Etoricoxib	9.31	1.32	17.4	14.8	6.03	6.94	14.9	15.0	18.5	22.0	12.0	36.1	7.42
Flufenamic acid	126	0.84	78.0	75.2	26.4	86.7	136	175	178	205	48.9	415	95.3
Furosemide	411	n.d.	354	198	n.d.	268	444	700	557	598	266	927	310
Ibuprofen	11.0×10^3	2.32×10^3	12.60×10^3	6.51×10^3	2.57×10^3	6.99×10^3	7.97×10^3	1.42×10^3	7.79×10^3	10.3×10^3	5.58×10^3	11.5×10^3	57.6×10^3
Indomethacin	6.03	n.d.	0.62	n.d.	1.03	n.d.	4.52	7.32	n.d.	3.82	n.d.	n.d.	0.72
Lorazepam	30.6	33.0	26.0	18.1	17.0	29.4	30.2	51.0	43.1	35.3	13.7	92.0	30.0
Metformin	190	3.62	338	323	47.9	286	256	410	260	321	206	319	135
Methylparaben	354	24.2	388	625	59.0	132	286	1.28×10^3	36.5	24.8	164	115	610
Naproxen	2.56×10^3	50.4	3.58×10^3	632	570	1.84×10^3	2.85×10^3	3.38×10^3	2.55×10^3	2.85×10^3	2.10×10^3	3.02×10^3	2.00×10^3
Omeprazole	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	270	n.d.	n.d.	n.d.	n.d.	158
Paracetamol	2.83×10^3	4.94×10^3	5.92×10^3	6.08×10^3	3.15×10^3	4.52×10^3	4.34×10^3	6.78×10^3	1.86×10^3	3.81×10^3	5.50×10^3	4.50×10^3	5.35×10^3
Propylparaben	188	11.7	395	288	39.9	319	373	627	111	224	290	134	275
Salicylic acid	779	167	2.01×10^3	1.61×10^3	250	394	1.41×10^3	2.58×10^3	237	187	730	1.49×10^3	1.76×10^3
Simvastatin	2.06×10^3	n.d.	1.67×10^3	1.30×10^3	186	606	1.28×10^3	2.02×10^3	1.31×10^3	2.03×10^3	1.60×10^3	2.05×10^3	1.75×10^3
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	569	153	551	297	138	419	587	859	681	750	220	1.05×10^3	416
Triclocarban	0.74	0.42	n.d.	0.41	n.d.	0.53	1.72	1.51	1.12	0.63	0.91	0.82	0.71
Triclosan	102	40.4	99.5	77.0	50.0	n.d.	308	410	56.2	133	156	153	104
Warfarin	n.d.	n.d.	0.33	0.54	n.d.	0.45	n.d.	n.d.	1.15	n.d.	n.d.	0.21	n.d.

* WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
** n.d. = not detected

Table 2
Concentration of PPCPs (ng L^{-1}) in the effluents (e) of the WWTPs*.

Compound	eAS 25/11/2016	eCAT 22/11/2016	eCAT 13/01/2017	ePAL 14/12/2016	eSAL 13/01/2017	ePE 13/01/2017	ePI 22/11/2016	ePI 13/01/2017	ePII 22/11/2016	ePII 13/01/2017	ePS 25/11/2016	eQB 14/12/2016	eSU 25/11/2016
Alprazolam	3.20	n.d.**	n.d.	5.90	1.60	2.30	7.50	5.10	9.00	7.00	2.90	7.70	4.60
Atenolol	14.0	8.40	140	26.0	19.0	4.00	148	190	125	137	11.7	104	24.4
Atorvastatine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	152	143	52.9	146	n.d.	19.0	15.7
Bezafibrate	1.80	0.50	0.30	0.40	2.00	1.00	29.6	35.1	6.90	20.4	0.50	20.4	12.3
BPA	93.0	19.0	n.d.	35.8	11.0	41.0	181	165	65.3	240	71.0	221	83.0
Butylparaben	0.40	n.d.	n.d.	n.d.	n.d.	n.d.	0.20	0.20	n.d.	1.50	n.d.	n.d.	n.d.
Caffeine	8.80	5.50	43.0	149	28.9	36.0	15.3	72.0	40.4	151	26.8	455	40.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	14.1	1.40	0.20	7.10	3.50	7.30	50.1	76.1	53.6	96.7	24.5	32.8	31.0
Diclofenac	164	n.d.	n.d.	164	29.0	57.0	711	433	525	490	114	259	199
Enelapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	83.0	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	0.20	0.30	0.50	0.40	n.d.	0.50	n.d.	1.00	0.60	4.00	0.30
Etoricoxib	8.00	2.60	1.40	19.5	3.70	4.70	25.7	24.7	30.2	22.5	13.4	22.1	27.7
Flufenamic acid	137	0.40	n.d.	95.8	22.0	65.0	350	200	277	200	45.0	328	187
Furosemide	134	n.d.	n.d.	n.d.	2.00	30.0	904	550	552	630	66.1	427	313
Ibuprofen	n.d.	499	231	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.80	n.d.	7.90	n.d.	n.d.	n.d.
Lorazepam	18.1	n.d.	n.d.	42.9	8.60	17.0	61.3	54.4	63.1	57.1	28.0	46.6	36.5
Metformin	6.50	2.00	4.40	9.90	1.10	8.00	66.3	34.9	18.9	24.0	15.6	23.4	26.5
Methylparaben	20.6	n.d.	n.d.	13.6	5.60	4.60	29.1	40.0	20.2	35.0	16.9	30.1	28.7
Naproxen	23.0	n.d.	n.d.	26.3	n.d.	n.d.	75.4	n.d.	90.7	146	26.1	318	205
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	30.0	14.0	25.6	23.0	4.00	16.0	n.d.
Paracetamol	11.3	2.00	19.0	34.8	49.0	39.0	18.1	37.0	16.6	15.4	24.1	37.0	70.0
Propylparaben	1.30	n.d.	1.70	5.30	4.10	5.00	5.80	10.0	3.70	8.70	3.00	6.20	2.30
Salicylic acid	1.40	58.4	108	380	310	248	207	345	205	325	124	580	212
Simvastatin	n.d.	245	80.0	n.d.	n.d.	n.d.	n.d.	35.0	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	9.00	n.d.	14.8	n.d.	n.d.	n.d.
Tramadol	470	n.d.	3.50	576	120	467	1.10×10^3	994	1.28×10^3	1.30×10^3	273	11.6×10^3	666
Triclocarban	n.d.	0.40	n.d.	0.30	0.10	0.10	0.60	0.50	n.d.	0.4	1.20	0.40	0.50
Triclosan	24.0	n.d.	n.d.	22.6	4.30	n.d.	29.2	20.3	10.4	7.4	n.d.	14.0	26.3
Warfarin	0.50	n.d.	n.d.	0.30	n.d.	n.d.	n.d.	n.d.	0.80	0.7	n.d.	0.10	0.40

** WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
** n.d. = not detected

Table 3
Removal efficiency (%) for each PPCPs in each WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS).

Compound	AS 25/11/2016	CAT 22/11/2016	CAT 13/01/2017	PAL 14/12/2016	EPE 13/01/2017	PI 22/11/2016	PI 13/01/2017	PII 22/11/2016	PII 13/01/2017	PS 25/11/2016	EQB 14/12/2016	SAL 13/01/2017	SU 25/11/2016
Alprazolam	−37	/*	100	−47	22	−99	−18	−115	−75	−26	−9	−12	−146
Atenolol	89	−51	−120	77	98	37	43	19	44	86	60	17	86
Atorvastatine	100	100	100	100	100	−3	49	68	37	100	93	100	74
Bezafibrate	66	51	99	72	66	/	/	74	3	−67	34	−57	−291
BPA	83	49	100	76	53	−9	31	84	38	35	78	83	10
Butylparaben	93	/	100	100	/	98	99	100	86	100	100	100	100
Caffeine	100	100	100	98	99	100	99	99	98	99	97	99	99
Chloramphenicol	100	/	/	/	/	/	/	/	/	/	/	/	100
Clofibric acid	/	/	/	/	/	/	/	/	/	/	/	/	/
Codeine	79	−26	100	−1	85	4	43	34	−3	48	54	65	57
Diclofenac	49	/	100	46	54	−119	−14	−36	−53	65	26	57	28
Enelapril	100	/	100	100	/	100	70	100	100	100	100	/	100
Ethylparaben	100	100	100	100	87	100	99	100	42	89	91	90	100
Etoricoxib	14	−108	92	−31	32	−72	−65	−63	−2	−12	39	39	−275
Flufenamic acid	−8	48	100	−27	25	−158	−14	−56	2	8	21	17	−96
Furosemide	67	/	100	100	89	−103	21	1	−5	75	54	!	−1
Ibuprofen	100	79	98	100	100	100	100	100	100	100	100	100	100
Indomethacin	100	/	100	/	/	100	76	/	−108	/	/	100	100
Lorazepam	41	100	100	−137	42	−103	−7	−46	−62	−104	49	49	−22
Metformin	97	44	99	97	97	74	91	93	93	92	93	98	80
Methylparaben	94	100	100	98	96	90	97	45	−41	90	74	90	95
Naproxen	99	100	100	96	100	97	100	96	95	99	89	100	90
Omeprazole	/	/	100	/	/	!**	95	!	!	!	!	/	100
Paracetamol	100	100	100	99	99	100	99	99	100	100	99	98	99
Propylparaben	99	100	100	98	98	98	98	97	96	99	95	90	99
Salicylic acid	82	65	95	76	37	85	87	14	−74	83	61	−24	88
Simvastatin	100	!	95	100	100	100	98	100	100	100	100	100	100
Thiamphenicol	/	/	/	/	/	/	!	/	!	/	/	/	/
Tramadol	17	100	99	−94	−11	−89	−16	−88	−74	−24	−10	13	−60
Triclocarban	100	13	/	29	85	68	67	100	38	−31	49	!	26
Triclosan	76	100	100	71	/	91	95	82	94	100	91	91	75
Warfarin	!	/	100	39	100	/	/	26	!	/	71	/	!

* "/" means that compound was not detected in influent and effluent wastewater samples **"!" means that compound was detected only in effluent wastewater sample.

Table 4
Concentration of PPCPs (ng L^{-1}) in water samples (W.n°) of the Albufera Natural Park, Valencia, Spain.

Compound	W.1	W.4	W.5	W.6	W.7	W.10	W.11	W.12	W.14	W.15	W.16	W.17	W.18	W.19	W.20	W.21	W.22	W.23	W.26	W.27	W.29	W.30	W.31	W.32	W.33	W.34	W.36	W.37	W.38	W.39	W.40	W.41	W.42
Alprazolam	10.0	4.00	n.d.*	6.00	n.d.	n.d.	n.d.	1.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.00	n.d.	8.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	320	114	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	78	n.d.	n.d.	n.d.	92.0	52.0	221	72.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	1.00	n.d.	n.d.	1.00	n.d.	n.d.	n.d.	n.d.	21.0	n.d.	n.d.	n.d.	n.d.	1.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.00	1.00	n.d.	21.0	1.00	21.0	1.00	21.0	n.d.	1.00	21.0	1.00	n.d.
Bezafibrate	79.0	63.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.00	n.d.	2.00	n.d.	n.d.	n.d.	9.00	n.d.	75.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	185	145	150	120	48.0	65.0	75.0	56.0	70.0	25.0	51.0	48.0	72.0	45.0	140	57.0	31.0	12.0	19.0	115	140	190	115	158	60.0	205	197	54.0	150	158	130	81.0	150
Butylparaben	n.d.	n.d.	70.0	70.0	45.0	n.d.	n.d.	n.d.	n.d.	40.0	n.d.	n.d.	40.0	45.0	n.d.	40.0	n.d.	n.d.	n.d.	70.0	n.d.	n.d.	70.0	n.d.	40.0	n.d.	71.0	n.d.	70.0	70.0	42.0	42.0	n.d.
Caffeine	152	28.0	62.0	22.0	137	56.0	11.0	14.0	291	76.0	152	21.0	134	101	121	219	40.0	668	20.0	43.0	138	541	103	272	157	66.0	173	93.0	141	127	120	16.0	18.0
Chloramphenicol	n.d.	n.d.	n.d.	50.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	39.0	40.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	40.0	n.d.	50.0	n.d.	n.d.	50.0	n.d.	n.d.	n.d.
Clofibric acid	76.0	77.0	76.0	76.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	77.0	n.d.	n.d.	n.d.	n.d.	77.0	76.0	75.0	76.0	76.0	n.d.	75.0	76.0	n.d.	76.0	76.0	75.0	n.d.	80.0
Codeine	154	27.0	n.d.	26.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8.00	n.d.	n.d.	n.d.	7.00	16.0	n.d.	21.0	n.d.	n.d.	n.d.	36.0	30.0	84.0	12.0	n.d.	39.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	169	70.0	50.0	115	60.0	52.0	75.0	55.0	n.d.	75.0	90.0	67.0	72.0	63.0	n.d.	75.0	65.0	103	75.0	n.d.	45.0	95.0	65.0	82.0	78.0	66.0	n.d.	104	45.0	35.0	72.0	35.0	30.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	72.0	73.0	78.0	72.0	n.d.	82.0	n.d.	70.0	n.d.	70.0	70.0	70.0	n.d.	n.d.	n.d.	77.0	73.0	67.0	n.d.	75.0	66.0	67.0	80.0	79.0	70.0	76.0	65.0	n.d.	75.0	70.0	n.d.
Etoricoxib	18.0	4.00	3.00	8.00	1.00	n.d.	1.00	1.00	n.d.	n.d.	2.00	n.d.	n.d.	1.00	2.00	2.00	n.d.	2.00	n.d.	2.00	2.00	5.00	5.00	13.0	n.d.	n.d.	6.00	7.00	25.0	20.0	3.00	3.00	5.00
Flufenamic Acid	195	85.0	60.0	150	n.d.	1.00	n.d.	n.d.	1.00	2.00	4.00	2.00	n.d.	n.d.	61.0	7.00	1.00	15.0	n.d.	n.d.	n.d.	80.0	80.0	140	10.0	n.d.	n.d.	1.00	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	115	n.d.	74.0	48.0	n.d.	n.d.	n.d.	n.d.	70.0	90.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	65.0	n.d.	n.d.	n.d.	95.0	85.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	90.0	85.0	20.0	35.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	144	60.0	217	n.d.	n.d.	n.d.	90.0	n.d.	n.d.	43.0	n.d.	n.d.	n.d.
Indomethacin	56.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	25.0	n.d.	n.d.	n.d.	24.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	50.0	n.d.	25.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	88.0	15.0	n.d.	15.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	18.0	n.d.	n.d.	n.d.	n.d.	6.00	n.d.	31.0	n.d.	n.d.	n.d.	23.0	12.0	70.0	1.00	n.d.	n.d.	2.00	n.d.	n.d.	n.d.	5.00	n.d.
Metformin	251	66.0	n.d.	19.0	20.0	4.00	3.00	5.00	23.0	15.0	114	26.0	171	3.00	14.0	55.0	2.00	131	375	24.0	25.0	186	70.0	93.0	57.0	18.0	22.0	33.0	94.0	40.0	40.0	6.00	19.0
Methylparaben	75.0	75.0	107	73.0	82.0	74.0	75.0	80.0	77.0	75.0	79.0	72.0	75.0	74.0	n.d.	75.0	n.d.	82.0	75.0	n.d.	70.0	84.0	75.0	78.0	75.0	73.0	78.0	76.0	73.0	n.d.	75.0	82.0	74.0
Naproxen	195	145	n.d.	105	n.d.	n.d.	n.d.	n.d.	115	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	117	114	208	111	n.d.	n.d.	209	225	178	160	n.d.	86.0	n.d.	n.d.	n.d.	113	115	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	26.0	n.d.	5.00	n.d.	32.0	14.0	11.0	17.0	82.0	28.0	18.0	n.d.	32.0	31.0	11.0	40.0	n.d.	168	n.d.	25.0	33.0	75.0	17.0	37.0	49.0	43.0	47.0	23.0	23.0	25.0	15.0	23.0	26.0
Propylparaben	n.d.	88.0	75.0	n.d.	38.0	33.0	32.0	35.0	33.0	32.0	30.0	30.0	30.0	30.0	75.0	35.0	30.0	33.0	30.0	90.0	75.0	75.0	75.0	135	31.0	n.d.	75.0	31.0	75.0	70.0	32.0	n.d.	90.0
Salicylic Acid	99.0	88.0	75.0	113	690	602	n.d.	n.d.	840	282	249	n.d.	298	391	294	239	208	751	340	106	521	713	75.0	161	230	686	166	592	240	858	386	301	204
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	35.0	n.d.	n.d.	n.d.	n.d.	5.00	n.d.	1.00	n.d.	n.d.	5.00	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.00	35.0
Tramadol	12.6×10^2	197	1.00	523	n.d.	11.0	13.0	12.0	3.00	5.00	18.0	9.00	33.0	7.00	7.0	84.0	n.d.	106	n.d.	22.0	27.0	333	171	695	89.0	3.00	50.0	24.0	56.0	42.0	18.0	n.d.	5.00
Triclocarban	n.d.	15.0	13.0	n.d.	n.d.	2.00	n.d.	1.00	1.00	1.00	1.00	1.00	1.00	n.d.	n.d.	5.00	n.d.	1.00	n.d.	14.0	n.d.	1.00	13.0	n.d.	n.d.	n.d.	n.d.	1.00	13.0	13.0	15.0	1.00	15.0
Triclosan	65.0	28.0	n.d.	n.d.	n.d.	n.d.	44.0	50.0	60.0	65.0	n.d.	51.0	55.0	48.0	15.0	72.0	n.d.	52.0	44.0	n.d.	25.0	n.d.	52.0	56.0	50.0	48.0	50.0	n.d.	45.0	31.0	35.0	65.0	20.0
Warfarin	65.0	65.0	65.0	64.0	n.d.	45.0	n.d.	n.d.	n.d.	n.d.	45.0	n.d.	48.0	n.d.	65.0	45.0	n.d.	n.d.	45.0	n.d.	n.d.	65.0	70.0	70.0	45.0	65.0	n.d.	46.0	65.0	65.0	n.d.	46.0	n.d.

Table 5
Concentration of PPCPs (ng g^{-1}) in sediment samples (S.n°) of the Albufera Natural Park, Valencia, Spain.

Compound	S.5	S.9	S.10	S.15	S.16	S.17	S.18	S.23	S.26	S.30	S.33	S.34	S.35	S.36	S.37	S.38	S.39	S.40	S.41
Alprazolam	n.d.*	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	3.0	n.d.	n.d.	2.0	5.0	4.0	4.0	3.0	5.0	5.0	3.0	1.0	n.d.	1.0	4.0	n.d.	n.d.	16
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	1.0	n.d.	21	1.0	21	n.d.	1.0	21	n.d.	1.0	21
Bezafibrate	n.d.	n.d.	n.d.	3.0	n.d.	n.d.	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.0	3.0	n.d.
Bisphenol A	n.d.	15	20	5.0	14	7.0	10	21	7.0	20	18	20	2.0	n.d.	9.0	14	19	19	n.d.
Butylparaben	6.0	6.0	n.d.	6.0	7.0	n.d.	6.0	n.d.	n.d.	6.0	6.0	n.d.	6.0	n.d.	6.0	6.0	6.0	6.0	n.d.
Caffeine	6.0	9.0	8.0	10	7.0	5.0	8.0	8.0	6.0	7.0	6.0	9.0	6.0	4.0	5.0	4.0	6.0	10	7.0
Chloramphenicol	n.d.	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	5.0	n.d.	n.d.	n.d.	n.d.	5.0	5.0	5.0	n.d.	4.0	5.0	4.0	4.0	5.0	4.0	5.0	5.0	5.0
Codeine	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	3.0	3.0	8.0	8.0	10	6.0	7.0	5.0	n.d.	3.0	6.0	6.0	6.0	n.d.	5.0	3.0	8.0	4.0	4.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	17	15	n.d.	16	n.d.	n.d.	15	15	18	15	17	18	15	n.d.	15	17	15	18
Etoricoxib	1.0	n.d.	1.0	n.d.	n.d.	6.0	n.d.	1.0	1.0	1.0	1.0	1.0	n.d.	2.0	1.0	1.0	1.0	1.0	1.0
Flufenamic Acid	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Furosemide	10	9.0	9.0	12	14	22	12	22	9.0	13	15	48	10	9.0	9.0	9.0	9.0	9.0	10.0
Ibuprofen	47	13	10 x 10^1	24	22	30	35	70	22	7.0	23	29	63	n.d.	38	8.0	n.d.	28	4.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	4.0	2.0	1.0	1.0	5.0	3.0	1.0	4.0	1.0	2.0	2.0	1.0	2.0	1.0	1.0	1.0	2.0	1.0	1.0
Methylparaben	n.d.	13	13	n.d.	14	n.d.	13	n.d.	17	18	18	18	19	n.d.	13	n.d.	14	14	n.d.
Naproxen	n.d.	n.d.	n.d.	2.0	n.d.	n.d.	n.d.	31	5.0	n.d.	8.0	n.d.	n.d.	2.0	4.0	7.0	7.0	10.0	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	6.0	n.d.	2.0	2.0	1.0	n.d.	n.d.	33	n.d.	1.0	n.d.	n.d.	2.0	n.d.	6.0	6.0	3.0	n.d.
Propylparaben	4.0	2.0	n.d.	2.0	n.d.	n.d.	2.0	4.0	n.d.	2.0	9.0	9.0	9.0	9.0	12	9.0	9.0	9.0	9.0
Salicylic Acid	21	18	25	32	28	24	23	23	19	23	18	23	19	19	16	15	18	21	27
Simvastatin	8.0	21	21	13	n.d.	29	12	n.d.	n.d.	17	n.d.	12	n.d.	n.d.	n.d.	18	n.d.	n.d.	4.0
Thiamphenicol	12	n.d.	11	9.0	10	9.0	11	11	12	14	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.
Tramadol	n.d.	n.d.	1.0	n.d.	1.0	2.0	2.0	2.0	n.d.	13	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.0
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7	9	15	n.d.	8.0	10	5.0	5.0	12
Triclosan	10	14	8.0	7.0	8.0	8.0	13	18	9.0	17	8.0	9.0	8.0	8.0	8.0	8.0	9.0	8.0	8.0
Warfarin	8.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	8.0	8.0	8.0	8.0	9.0	8.0	8.0

* n.d. = not detected

Table 6
Concentration of PPCPs (ng g^{-1}) in soil samples (So.n°) of the Albufera Natural Park, Valencia, Spain.

Compound	So.1	So.2	So.3	So.4	So.5	So.6	So.7	So.8	So.9	So.10	So.11	So.12	So.13	So.14	So.15	So.16	So.17	So.20	So.23	So.24	So.25	So.26	So.29	So.30	So.31	So.32	So.33	So.34	So.35	So.41	So.42	So.43	So.44
Alprazolam	n.d.*	67	n.d.	67	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	1.0	n.d.	21	1.0	21	n.d.	1.0	21	n.d.	1.0	21	1.0	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	21	n.d.	n.d.	n.d.	n.d.	1.0
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	9.0	6.0	3.0	9.0	10	4.0	8.0	4.0	7.0	6.0	10	4.0	3.0	4.0	2.0	3.0	2.0	3.0	1.0	2.0	2.0	7.0	2.0	9.0	4.0	n.d.	3.0	15	8.0	9.0	11	7.0	9.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	n.d.	22	24	4.0	1.0	24	n.d.	3.0	24	n.d.	22	3.0	2.0	23	1.0	22	1.0	22	3.0	1.0	26	23	23	n.d.	23	1.0	23	3.0	22	16	13	n.d.	2.0
Chloramphenicol	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.0	n.d.	n.d.	n.d.	n.d.	n.d.	7.0
Diclofenac	2.0	3.0	1.0	1.0	n.d.	1.0	1.0	2.0	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	n.d.	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.0	n.d.	2.0	2.0	n.d.	n.d.	2.0	1.0	n.d.
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	3.0	n.d.	n.d.	n.d.	2.0	n.d.	n.d.	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.0	n.d.	n.d.	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	3.0	n.d.
Etoricoxib	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	51	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	2.0	4.0	10	n.d.	7.0	4.0	3.0	n.d.	3.0	n.d.	n.d.	n.d.	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.0	n.d.	n.d.	n.d.	n.d.	8.0	n.d.	4.0	n.d.	76	3.0	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	62	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62	n.d.	n.d.	62	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	n.d.	n.d.	n.d.	47	47	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	47	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	48	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	47	n.d.
Methylparaben	n.d.	3.0	2.0	2.0	2.0	3.0	3.0	2.0	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.0	n.d.	n.d.	2.0	n.d.	n.d.	2.0	2.0	2.0	n.d.	n.d.
Naproxen	1.0	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	1.0	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.0	n.d.	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	30	n.d.	n.d.	1.0	n.d.	n.d.	30	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	30	30	31	n.d.	n.d.	30	n.d.	n.d.	n.d.	n.d.	n.d.	30	n.d.	n.d.	31	n.d.	n.d.	n.d.	n.d.
Propylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	n.d.	2.0	n.d.	n.d.	1.0	n.d.	n.d.	1.0	1.0	n.d.	n.d.	n.d.	3.0	n.d.	21	22	n.d.	3.0	n.d.	n.d.	3.0	2.0	2.0	11	4.0	n.d.
Salicylic Acid	9.0	n.d.	n.d.	n.d.	2.0	n.d.	n.d.	n.d.	3.0	n.d.	2.0	2.0	20	2.0	6.0	n.d.	5.0	n.d.	2.0	1.0	n.d.	n.d.	n.d.	3.0	n.d.	n.d.	n.d.	6.0	18	n.d.	n.d.	n.d.	5.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.0
Tramadol	n.d.	n.d.	n.d.	2.0	n.d.	1.0	60	n.d.	60	n.d.	n.d.	n.d.	n.d.	n.d.	60	n.d.	60	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	60	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	60	n.d.	60
Triclocarban	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	4.0	3.0	n.d.	n.d.	n.d.	1.0	n.d.	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.0	n.d.	n.d.	1.0	n.d.	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	5.0	n.d.	n.d.	n.d.
Warfarin	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

* n.d. = not detected

Table 7
Statistical correlations between the studied pharmaceuticals in **soils** (** Significant correlation at level of P= 0.01. * Significant correlation at level of P= 0.05).

	Aten	Atorv	BZF	BisA	BPN	Caf	CPL	Cod	DFC	Etor	EPB	FlufA	Ibup	IMTN	LZM	Met	MPN	Nap	OPZ	Pmol	PPN	SalA	SVTN	TPL	Tram	TCBN	TCSN
Aten																											
Atorv	.592**																										
BZF																											
BisA																											
BPN	.417*	.448**																									
Caf																											
CPL			.726**																								
Cod																											
DFC																											
Etor																											
EPB							.391*																				
FlufA			.641**				.915**																				
Ibup																											
IMTN																											
LZM						.352*																					
Met						−.395*																					
MPN																											
Nap					.437*									.506**													
OPZ																											
Pmol				−.352*		.349*																					
PPN																											
SalA																			.375*								
SVTN																						.382*					
TPL								.697**																			
Tram																											
TCBN							.382*		.420*																		
TCSN					.419*		.436*					.482**															
War			.646**				.940**				.446**	.878**														.429*	.369*

Aten: Atenolol. **Atorv**: Atorvastatin. **BZF**: Bezafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffeine. **CPL**: Chloramphenicol. **ClorA**: Clofibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Eto**r: Etoricoxib. **EPB**: Ethylparaben. **FlufA**: Flufenamic Acid. **Ibup**: Ibuprofen. **IMTN**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: Naproxen. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic acid. **SVTN**: Simvastatin. **TPL**: Thiamphenicol**. Tram**: Tramadol. **TCB**N: Triclocarban. **TCSN**: Triclosan. **War**: Warfarin.

Table 8
Statistical correlations between pharmaceuticals in **sediments** (** Significant correlation at level of P= 0.01, * Significant correlation at level of P= 0.05).

	Alpraz	Aten	Atorv	BZF	BisA	BPN	Caf	CPL	ClorA	Cod	DFC	Etor	EPB	FlufA	Furo	Ibup	Met	MPN	OPZ	Pmol	PPN	SalA	SVTN	TPL	Tram	TCBN	TCSN	War
Alpraz																												−.377*
Aten																												
Atorv	.454**																											
BZF																												
BisA	−.363*	.363*																										
BPN				.371*																								
Caf				.522**	.375*																							
CPL																												
ClorA																												
Cod							.459**	.750**																				
DFC				.365*			.385*		−.337*																			
Etor		.349*				−.516**	−.366*																					
EPB			.347*		.402*				.329*																			
FlufA		.453**																										
Furo		.334*			.334*	−.401*				.408*																		
Ibup																												
Met									−.416**		.363*																	
MPN					.465**							−.332*	.370*	.330*														
OPZ					.375*											.376*												
Pmol											−.458**																	
PPN			.469**						.638**								−.329*											
SalA	.325*						.572**		−.561**		.515**										−.497**							
SVTN		.373*						.341*	−.456**			.393*									−.504**							
TPL			−.497**						−.652**	−.354*			−.330*			.362*	.454**				−.821**	.468**						
Tram		.461**							−.357*					.830**										.428**				
TCSN		.482**			.374*			.327*						.644**			.350*							.453**	.614**	−.409*		
War	−.377*	.395*	−.425**		.427**		.452**				.339*						.545**				−.581**			.492**		−.581**	.497**	

Alpraz: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Bezafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffeine. **CPL**: Chloramphenicol. **Clor A**: Clofibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **EPB**: Ethylparaben. **Fluf A**: Flufenamic Acid. **Furo**: Furosemide. **Ibup**: Ibuprofen. Met: Metformin. **MPN**: Methylparaben. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic acid. **SVTN**: Simvastatin. **TPL**: Thiamphenicol. **Tram:** Tramadol. **TCBN**: Triclocarban. **TCSN**: Triclosan. **War**: Warfarin.

Table 9
Statistical correlations between the studied pharmaceuticals in **waters** (** Significant correlation at level of P= 0.01, * Significant correlation at level of P= 0.05).

	Alpraz	Aten	Atorv	BZF	BisA	BPN	Caf	CPL	ClorA	Cod	DFC	Etor	EPB	FlufA	Furo	Ibup	IMTN	LZM	Met	MPN	Nap	Pmol	PPN	TPL	Tram
Aten	.830**																								
Atorv																									
BZF	.858**	.899**																							
BisA	.383*			.374*																					
BPN																									
CPL						.526**																			
ClorA					.906**																				
Cod	.871**	.929**		.830**	.423*				.358*																
DFC	.584**	.598**		.442**						.550**															
Etor	.469**	.410*		.410*	.532**				.538**	.472**															
FlufA	.908**	.773**		.745**	.454**				.503**	.828**	.530**	.416*													
Ibup					.422*				.498**	.372*				.393*	.368*										
IMTN	.356*	.521**								.589**	.421*			.450**		.510**									
LZM	.870**	.956**		.848**			.380*			.935**	.624**	.445**		.803**			.456**								
Met		.477**								.439*	.476**							.461**							
MPN											.376*		.377*												
Nap	.462**	.609**		.463**			.528**			.593**	.401*			.550**	.370*	.395*	.466**	.586**	.435*						
Pmol							.874**														.345*				
PPN					.427*				.554**		−.418*														
SalA			.354*				.513**															.572**			
TPL	.406*	.475**		.372*						.510**							.377*	.475**							
Tram	.951**	.890**		.808**	.401*				.371*	.953**	.641**	.514**		.899**			.534**	.924**	.423*		.546**			.494**	
TCBN						.435*			.535**														.480**		
TCSN																	.387*								
War	.412*	.386*		.374*	.448**				.401*	.362*		.473**		.570**				.364*							.419*

Aten: Atenolol. **Alpraz**: Alprazolam. **Atorv**: Atorvastatin. **BZF**: Bezafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **CPL**: Chloramphenicol. **ClorA**: Clofibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **FlufA**: Flufenamic Acid. **Ibup**: Ibuprofen. **IMTN**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **MPN**: Methylparaben. **Nap**: Naproxen. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic acid. **TPL**: Thiamphenicol. **Tram**: Tramadol. **TCBN**: Triclocarban. **TCSN**: Triclosan. **War**: Warfarin.

Table 10
Statistical correlations between pharmaceuticals and intrinsic **soil** characteristics (** Significant correlation at level of P = 0.01. * Significant correlation at level of P = 0.05).

	pH	EC	CO_3	OM	Na	K	Mg	Ca	CEC
Alpraz	−.380*	.410*			.451**				
BisA		.358*	.421*	.372*					
Ibup							.353*		
MPN	−.376*			.444**					
Nap						−.364*			
PPN			−.352*						
TPL		.354*			.446**				
TCSN									.359*
War		.396*		.414*					

EC: Electric conductivity. **$CO_3^=$**: Carbonates. **OM**: Organic Matter. **Na:** Sodium. **K:** Potasium. **Mg:** Magnesium. **Ca:** Calcium. **CEC**: Cation Exchange Capacity.
Alpraz: Alprazolam. **BisA**: Bisphenol A. **Ibup**: Ibuprofen. **MPN**: Methylparaben. **Nap**: Naproxen. **PPN**: Propylparaben. **TPL**: Thiamphenicol. **TCSN**: Triclosan. **War**: Warfarin.

Table 11
Statistical correlations between pharmaceuticals and intrinsic **sediment** characteristics (** Significant correlation at level of P = 0.01, * Significant correlation at level of P = 0.05).

	OM	$CO_3^=$	Sac	SandT	pH	EC	CEC
Alpraz					−.459**		
Aten							
Atorv							
BZF							
BisA	.408*						
BPN					.355*		
Caf			−.484**	.555**		−.325*	
CPL							
ClorA	.348*	.379*					
Cod							
DFC							
Etor						.384*	
EPB							
FlufA					.378*	−.398*	
Furo		−.382*					
Ibup	−.334*		−.366*	.345*			−.335*
Met							
MPN					.426**	−.579**	−.399*
OPZ						−.344*	
Pmol					.348*		
PPN	.512**	.477**	.565**	−.490**		.510**	.368*
SalA	−.501**	−.614**	−.612**	.582**			
SVTN					−.345*		−.328*
TPL		−.586**	−.470**	.406*		−.401*	
Tram							
TCSN							
War		−.402*				−.407*	

OM: Organic Matter. **$CO_3^=$**: Carbonates. **Sac**: Lime + clay fractions. **SandT**: Total sand fraction. **EC**: Electric conductivity. **CEC**: Cation Exchange Capacity.
Alpraz: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **BZF**: Bezafibrate. **BisA**: Bisphenol A. **BPN**: Butylparaben. **Caf**: Caffeine. **CPL**: Chloramphenicol. **Clor A**: Clofibric Acid. **Cod**: Codeine. **DFC**: Diclofenac. **Etor**: Etoricoxib. **EPB**: Ethylparaben. **Fluf A**: Flufenamic Acid. **Furo**: Furosemide. **Ibup**: Ibuprofen. **Met**: Metformin. **MPN**: Methylparaben. **OPZ**: Omeprazole. **Pmol**: Paracetamol. **PPN**: Propylparaben. **SalA**: Salicylic acid. **SVTN**: Simvastatin. **TPL**: Thiamphenicol. **Tram**: Tramadol. **TCSN**: Triclosan. **War**: Warfarin.

Table 12
Statistical correlations between the studied pharmaceuticals and intrinsic characteristics of **waters** (** Significant correlation at level of P = 0.01, * Significant correlation at level of P = 0.05).

	pH	T	EC	TDS	Rest	NaCl	DO%	Cl^-	NO_2^-	$NO3^=$	$SO4^=$	Na	K	Mg	Ca
Alpraz	−.446**														
Aten	−.414*														
Atorv							.354*								
BisA															
Caf			−.410*			−.365*						−.388*		−.385*	
ClorA				−.355*		−.345*					−.393*				−.361*
Cod	−.458**														
Enal									.721**						
EPB							.371*								
FlufA	−.398*														
Furo			−.361*		.381*							−.377*			
IMTN									.473**						
LZM	−.477**														
Met										.694**					
Nap							.359*		.387*					−.480**	
Pmol		−.354*	−.356*												
SalA		−.402*	−.387*									−.373*			
TPL	−.420*											.364*	.736**		
Tram	−.491**														
TCBN					.440*										−.355*

T: temperature (°C). **EC**: Electric Conductivity (dS/m). **TDS**: Total Dissolved Solids (mg/L). **Rest**: Resistivity (Ω). **DO%**: Dissolved Oxygen (%). **Cl^-**: Chlorides (mg/L). **NO_2^-**: Nitrites. **$NO_3^=$**: Nitrates (mg/L). **$SO_4^=$**: Sulfates (mg/L). **Alpraz**: Alprazolam. **Aten**: Atenolol. **Atorv**: Atorvastatin. **Caf**: Caffeine. **ClorA**: Clofibric Acid. **Cod**: Codeine. **EPB**: Ethylparaben. **FlufA**: Flufenamic Acid. **Furo**: Furosemide. **IMTN**: Indomethacin. **LZM**: Lorazepam. **Met**: Metformin. **Nap**: Naproxen. **Pmol**: Paracetamol. **SalA**: Salicylic Acid. **TPL**: Thiamphenicol. **Tram**: Tramadol. **TCBN**: Triclocarban.

environmental compartments. A previous solid-liquid extraction was performed for solid samples (1g), with the use of 15 mL of a mix containing Milli-Q water, McIlvaine–EDTA buffer and methanol (MeOH) in equal parts. The mixture was homogenized for 5 min by vortex agitation, sonicated for 10 min, and centrifuged for 6 min at 3000 rpm and 10°C. The supernatant was separated and diluted with Milli-Q water to 200 mL. Then, the dilution was treated such as water extraction procedure.

The clean-up that involves PPCPs isolation and concentration were performed by Solid Phase Extraction (SPE). Two methods employing different cartridges Strata-X and Strata-X-CW (Phenomenex, 33 µm, 200 mg/6 mL) characterized by a *polymeric reversed* and *polymeric weak cation-exchange* stationary phase, respectively, were used. Strata-X was activated with 6 mL MeOH, 6 mL Milli-Q water and with 6 mL 2mM *Sodium Dodecyl Sulphate* (SDS) *solution* (**SDS method**). While, Strata-X-CW was activated without SDS solution (**WC method**). The analytes were eluted with 6mL of MeOH and 3 mL of MeOH–DCM (50:50 v/v) for reversed phase and with 6 mL of MeOH–NH_4OH (95:5 v/v) for weak cation-exchange phase by gravity. The eluates were evaporated at 40°C and redissolved to 1 mL with mobile phase before injection.

Alprazolam, atorvastatin, caffeine, chloramphenicol, diclofenac, flufenamic acid, furosemide, ibuprofen, omeprazole, paracetamol and thiamphenicol were detected by *WC method* in water, sediment and soil matrix. While, atenolol, bezafibrate, butylparaben, clorfibric acid, enalapril, ethylparaben, etoricoxib, indomethacin, lorazepam, metformin, methylparaben, naproxen, propylparaben, salicylic acid, simvastatin tramadol, triclocarban, triclosan, warfarin by *SDS method*. Only bisphenol A and codeine were determined by both methods, *SDS* in water matrix and *WC* in sediment and soil.

Instrumental analysis was performed by 1260 Infinity UHPLC (ultra-high-performance liquid chromatography) system coupled to mass spectrometry with a triple quadrupole mass detector (6410 QqQ-MS) from Agilent Technologies (Santa Clara, CA, USA). The electrospray ionization (ESI) was applied in negative and positive mode. The mobile phase consisted of MeOH (solvent A) and water (solvent B) both with NH_4F at 2.5 mmol L^{-1} for negative mode and MeOH (sol-

vent A) and water (solvent B) with 0.1% formic acid in both solutions for positive mode. The calibration curves used to quantify the environmental contaminants were prepared in H_2O-MeOH (70-30) and in solvent with SDS to obtain correct quantification of those compounds.

The qualitative and quantitative analysis of each chromatogram were performed by MassHunter Workstation (version 10.0 Software) supplied by Agilent Technologies. The statistical relationship of the different contaminants between them and with the environmental parameters in the three matrices selected (water, soil and sediment) was carried out by Statistical package IBM SPSS (version 26.0).

The limits of detection (LODs) and limits of quantification (LOQs) were estimated experimentally, spiking blank samples, at the lowest concentration (10 ng g^{-1} and 50 μgL^{-1}), with the PPCPs pre-extraction and estimating the analyte concentration able to provide a signal-to-noise ratio of 3 and 10 respectively. The LODs ranged from 1.65 and 16.65 ngL^{-1} in waste and surface water, and from 0.33 and 6.67 ng g^{-1} dry weight (d.w.) in sediment and soil. Particularly, to established the matrix effects (ME) two eight point calibration curves (10, 25, 50, 75, 100, 250, 500, 1000 ng/mL) were compared: (i) one prepared in solvent (that is H_2O-MeOH (70-30) or this mixture with SDS depending on the method) and (ii) the other prepared in blank matrix extract, also redissolving the extract in H_2O-MeOH (70-30) or this mixture with SDS. Then, the ME was calculated according to the formula:

$$ME\ (\%) = \left(\frac{Slope\ of\ calibration\ curve\ in\ matrix}{Slope\ of\ calibration\ curve\ in\ solution} - 1 \right) \times 100 \quad (1)$$

This information together with other experimental information were described in the Sadutto [2] work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships, which have, or could be perceived to have, influenced the work reported in this article.

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ANNEX

Supplementary material

Dataset of pharmaceuticals and personal care products in a Mediterranean coastal wetland

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Table S1 - Individual PPCPs concentration (ng L^{-1}) obtained in each method replicates in the influents (i) of the WWTPs (*n=3*)

	iAS	iAS	iAS		iCAT	iCAT	iCAT		iCAT	iCAT	iCAT		iPAL	iPAL	iPAL		iSAL	iSAL	iSAL	
	25/11/2016	*25/11/2016*	*25/11/2016*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*		*14/12/2016*	*14/12/2016*	*14/12/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	2.6	1.7	2.6	2.3	n.d.	n.d.	n.d.	n.d.	2.9	2.0	2.3	2.4	4.5	3.4	4.1	4.0	1.7	1.0	1.5	1.4
Atenolol	133.1	132.6	132.4	132.7	5.7	5.3	5.8	5.6	63.7	63.0	63.8	63.5	113.4	112.8	113.7	113.3	23.4	22.8	22.5	22.9
Atorvastatin	83.4	82.6	83.3	83.1	2.7	2.0	3.1	2.6	134.4	133.6	134.3	134.1	157.3	156.5	157.5	157.1	27.6	27.1	26.9	27.2
Bezafibrate	5.5	4.9	5.2	5.2	1.1	0.5	1.1	0.9	52.8	52.2	51.9	52.3	1.8	1.0	2.0	1.6	1.8	1.0	0.8	1.2
Bisphenol A	562.1	561.5	561.8	561.8	37.2	36.5	37.6	37.1	4272.8	4272.2	4272.2	4272.4	147.4	146.5	147.1	147.0	66.3	65.8	66.5	66.2
Butylparaben	6.0	5.3	4.9	5.4	n.d.	n.d.	n.d.	n.d.	18.6	18.3	18.3	18.4	19.7	19.1	18.8	19.2	1.9	1.2	2.3	1.8
Caffeine	8705.4	8704.7	8704.3	8704.8	9777.7	9777.3	9777.8	9777.6	9360.2	9359.4	9359.5	9359.7	6084.8	6084.4	6084.3	6084.5	2462.2	2461.4	2461.2	2461.6
Chloramphenicol	2.6	1.9	1.5	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	68.7	68.2	68.3	68.4	1.5	0.5	1.3	1.1	52.8	51.9	51.9	52.2	7.5	6.7	6.8	7.0	10.5	9.5	10.0	10.0
Diclofenac	323.9	323.1	323.8	323.6	n.d.	n.d.	n.d.	n.d.	289.9	289.2	289.7	289.6	303.0	302.3	303.4	302.9	68.4	67.4	68.2	68.0
Enalapril	379.6	378.8	378.6	379.0	n.d.	n.d.	n.d.	n.d.	283.0	282.0	282.5	282.5	64.3	63.2	63.9	63.8	n.d.	n.d.	n.d.	n.d.
Ethylparaben	25.6	24.5	24.9	25.0	4.4	4.1	4.4	4.3	174.4	173.6	174.3	174.1	87.6	86.9	87.1	87.2	5.4	5.1	5.4	5.3
Etoricoxib	9.8	8.7	9.4	9.3	1.5	0.8	1.6	1.3	18.0	17.2	17.0	17.4	15.2	14.4	14.8	14.8	6.5	5.5	6.0	6.0
Flufenamic Acid	125.7	125.2	125.9	125.6	1.0	0.3	1.1	0.8	78.2	77.5	78.3	78.0	75.5	75.1	75.0	75.2	26.6	26.3	26.3	26.4
Furosemide	411.5	411.0	411.4	411.3	n.d.	n.d.	n.d.	n.d.	354.3	353.2	353.6	353.7	197.6	197.4	197.5	197.5	n.d.	n.d.	n.d.	n.d.
Ibuprofen	10987.4	10986.7	10986.9	10987.0	2326.2	2325.6	2325.9	2325.9	12598.0	12597.0	12597.2	12597.4	6505.4	6504.9	6505.6	6505.3	2565.4	2564.6	2565.0	2565.0
Indomethacin	6.4	5.8	5.8	6.0	n.d.	n.d.	n.d.	n.d.	1.1	0.5	0.2	0.6	n.d.	n.d.	n.d.	n.d.	1.4	0.7	0.9	1.0
Lorazepam	30.8	30.1	30.9	30.6	33.2	32.6	33.2	33.0	26.1	25.9	26.0	26.0	18.6	17.7	18.0	18.1	17.3	16.5	17.2	17.0
Metformin	190.1	189.6	190.3	190.0	3.7	3.2	3.9	3.6	338.2	337.6	338.5	338.1	323.5	322.8	322.7	323.0	48.4	47.8	47.5	47.9
Methylparaben	354.2	353.2	353.4	353.6	24.7	23.9	24.0	24.2	388.1	387.5	387.2	387.6	625.1	624.5	625.4	625.0	59.4	58.6	59.0	59.0
Naproxen	2558.1	2557.1	2557.3	2557.5	51.0	50.0	50.2	50.4	3584.4	3583.5	3584.1	3584.0	632.6	631.4	632.0	632.0	570.4	569.6	570.0	570.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.5	0.9	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	2833.7	2832.8	2833.4	2833.3	4939.3	4939.0	4939.3	4939.2	5921.9	5921.7	5921.8	5921.8	6084.6	6083.7	6084.6	6084.3	3150.2	3149.6	3150.2	3150.0
Propylparaben	188.6	187.7	188.6	188.3	12.0	11.4	11.7	11.7	395.3	394.8	395.5	395.2	288.5	287.8	287.4	287.9	40.5	39.7	39.5	39.9
Salicylic Acid	779.4	779.2	779.3	779.3	166.9	166.2	166.7	166.6	2013.6	2012.7	2012.7	2013.0	1613.2	1612.4	1613.4	1613.0	250.4	249.4	250.2	250.0
Simvastatin	2061.7	2061.2	2061.3	2061.4	n.d.	n.d.	n.d.	n.d.	1675.6	1674.8	1674.9	1675.1	1304.3	1303.8	1304.2	1304.1	186.3	185.4	185.7	185.8
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	568.9	568.7	568.8	568.8	153.0	152.6	152.8	152.8	550.8	550.3	550.7	550.6	297.7	296.6	297.0	297.1	138.7	137.8	138.7	138.4
Triclocarban	1.2	0.6	0.3	0.7	0.9	0.2	0.1	0.4	n.d.	n.d.	n.d.	n.d.	0.8	0.2	0.2	0.4	n.d.	n.d.	n.d.	n.d.
Triclosan	101.9	101.6	101.9	101.8	40.5	39.9	40.8	40.4	100.1	99.0	99.4	99.5	77.5	76.4	77.1	77.0	50.4	49.9	49.7	50.0
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.4	0.2	0.3	0.3	0.6	0.4	0.4	0.5	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

Table S1 *(Continued)*

	iPE	iPE	iPE		iPI	iPI	iPI		iPI	iPI	iPI		iPII	iPII	iPII		iPII	iPII	iPII	
	13/01/2017	*13/01/2017*	*13/01/2017*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	3.5	2.9	2.6	3.0	4.0	3.3	4.1	3.8	4.4	3.7	4.8	4.3	4.4	4.0	4.2	4.2	4.1	3.8	4.1	4.0
Atenolol	162.3	161.6	161.5	161.8	236.7	235.9	235.7	236.1	335.1	334.5	335.4	335.0	154.4	153.8	153.5	153.9	244.1	243.8	244.1	244.0
Atorvastatin	59.8	59.5	59.8	59.7	148.7	147.8	148.1	148.2	278.1	277.6	278.3	278.0	166.8	165.8	166.6	166.4	231.4	230.5	231.1	231.0
Bezafibrate	3.6	2.6	2.8	3.0	30.0	29.3	29.2	29.5	35.6	34.6	34.8	35.0	26.7	26.2	26.0	26.3	21.6	20.7	20.7	21.0
Bisphenol A	88.3	87.8	87.6	87.9	166.6	165.9	166.7	166.4	238.6	237.7	237.7	238.0	400.1	399.4	399.6	399.7	387.2	386.6	387.2	387.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	14.2	13.5	13.1	13.6	33.5	32.6	32.9	33.0	2.5	1.8	1.4	1.9	11.0	10.5	10.9	10.8
Caffeine	5244.7	5244.0	5243.9	5244.2	9993.4	9992.8	9993.7	9993.3	13227.6	13226.6	13226.8	13227.0	6954.5	6953.4	6953.8	6953.9	8357.3	8356.6	8357.1	8357.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	50.5	49.7	50.4	50.2	52.5	51.5	52.3	52.1	133.4	132.4	133.2	133.0	81.4	80.6	80.7	80.9	93.9	93.6	93.9	93.8
Diclofenac	123.8	123.0	122.8	123.2	324.6	323.4	324.0	324.0	380.2	379.5	380.3	380.0	386.1	385.4	385.0	385.5	320.6	319.6	319.8	320.0
Enalapril	n.d.	n.d.	n.d.	n.d.	288.0	287.7	288.0	287.9	281.1	280.4	281.5	281.0	242.8	242.2	242.5	242.5	141.6	140.9	140.5	141.0
Ethylparaben	3.3	2.7	3.0	3.0	87.6	87.0	87.0	87.2	43.1	42.7	43.2	43.0	0.8	0.2	0.5	0.5	2.1	1.5	1.5	1.7
Etoricoxib	7.0	6.3	7.4	6.9	15.0	14.7	15.0	14.9	15.4	14.8	14.8	15.0	18.8	17.9	18.8	18.5	22.3	21.5	22.2	22.0
Flufenamic Acid	87.0	86.5	86.6	86.7	136.0	135.2	135.9	135.7	175.5	174.7	174.8	175.0	178.3	177.8	177.6	177.9	205.5	204.4	205.1	205.0
Furosemide	268.1	267.5	267.2	267.6	444.8	444.1	443.7	444.2	700.4	699.4	700.2	700.0	557.4	556.3	556.7	556.8	598.6	597.4	598.0	598.0
Ibuprofen	6992.5	6992.2	6992.5	6992.4	7968.7	7968.1	7967.8	7968.2	14190.5	14189.4	14190.1	14190.0	7699.9	7699.4	7700.1	7699.8	10340.3	10339.4	10340.3	10340.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	4.7	4.3	4.5	4.5	7.8	7.1	7.0	7.3	n.d.	n.d.	n.d.	n.d.	4.4	3.4	3.6	3.8
Lorazepam	29.7	29.2	29.3	29.4	30.5	29.9	30.2	30.2	51.4	50.9	50.7	51.0	43.5	42.7	43.1	43.1	35.5	35.2	35.2	35.3
Metformin	286.6	285.8	285.9	286.1	256.0	255.2	255.9	255.7	410.4	409.4	410.2	410.0	259.8	259.5	259.5	259.6	321.6	320.5	320.9	321.0
Methylparaben	132.2	131.9	132.2	132.1	287.0	286.0	286.2	286.4	1280.2	1279.4	1280.4	1280.0	37.0	36.0	36.5	36.5	25.0	24.2	25.2	24.8
Naproxen	1841.3	1840.6	1841.1	1841.0	2855.1	2854.3	2854.7	2854.7	3376.1	3375.5	3376.4	3376.0	2554.2	2553.6	2553.6	2553.8	2852.3	2851.6	2852.1	2852.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	270.2	269.8	270.0	270.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	4521.1	4520.2	4520.2	4520.5	4336.4	4335.9	4336.0	4336.1	6780.2	6779.7	6779.5	6779.8	1865.0	1864.1	1864.7	1864.6	3809.2	3808.5	3809.6	3809.1
Propylparaben	318.8	318.2	319.1	318.7	372.9	372.6	372.6	372.7	627.3	626.5	627.2	627.0	111.3	110.9	111.1	111.1	224.6	223.8	223.6	224.0
Salicylic Acid	393.7	393.0	394.1	393.6	1406.1	1405.1	1405.3	1405.5	2580.5	2579.4	2580.1	2580.0	237.6	236.8	237.5	237.3	187.1	186.7	187.2	187.0
Simvastatin	606.2	605.6	605.3	605.7	1279.3	1278.6	1279.1	1279.0	2023.1	2022.8	2023.1	2023.0	1314.7	1313.6	1314.3	1314.2	2025.5	2024.8	2024.7	2025.0
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	419.7	418.7	419.2	419.2	587.7	586.7	587.2	587.2	859.5	858.5	859.0	859.0	681.4	680.9	681.6	681.3	750.6	749.7	749.7	750.0
Triclocarban	0.6	0.4	0.6	0.5	2.3	1.6	1.2	1.7	1.9	1.1	1.5	1.5	1.3	0.6	1.4	1.1	0.9	0.2	0.7	0.6
Triclosan	n.d.	n.d.	n.d.	n.d.	308.1	307.4	307.3	307.6	410.1	409.8	410.1	410.0	56.4	55.6	56.6	56.2	132.7	132.0	132.8	132.5
Warfarin	0.6	0.3	0.4	0.4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.3	0.9	1.1	1.1	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* Cmean = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

Table S1. *(Continued)*

	iPS	iPS	iPS		iQB	iQB	iQB		iSU	iSU	iSU	
	25/11/2016	*25/11/2016*	*25/11/2016*		*14/12/2016*	*14/12/2016*	*14/12/2016*		*25/11/2016*	*25/11/2016*	*25/11/2016*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	2.8	1.7	2.4	2.3	7.7	6.7	6.9	7.1	2.3	1.3	2.1	1.9
Atenolol	82.4	81.6	82.0	82.0	257.4	256.8	256.8	257.0	174.5	174.0	174.7	174.4
Atorvastatin	63.5	62.5	63.0	63.0	274.1	273.8	274.1	274.0	61.4	60.7	60.9	61.0
Bezafibrate	0.4	0.3	0.3	0.3	31.4	30.6	31.0	31.0	3.2	2.9	3.2	3.1
Bisphenol A	110.4	109.5	110.1	110.0	1013.7	1012.9	1013.3	1013.3	92.3	91.5	92.2	92.0
Butylparaben	9.6	8.6	9.1	9.1	4.7	4.2	4.9	4.6	6.9	6.4	6.8	6.7
Caffeine	4335.3	4334.9	4334.8	4335.0	18066.0	18065.5	18066.2	18065.9	4320.1	4319.5	4320.4	4320.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.6	1.0	1.6	1.4
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	47.6	47.1	47.8	47.5	71.9	71.5	72.0	71.8	72.4	71.9	71.7	72.0
Diclofenac	327.0	326.7	326.7	326.8	348.4	347.7	347.9	348.0	275.5	274.9	274.6	275.0
Enalapril	119.1	118.6	119.3	119.0	510.3	509.8	509.9	510.0	127.4	126.8	126.5	126.9
Ethylparaben	5.6	4.6	5.4	5.2	43.6	42.8	42.6	43.0	73.4	72.4	73.2	73.0
Etoricoxib	12.2	11.8	12.0	12.0	36.4	35.5	36.4	36.1	7.5	7.1	7.6	7.4
Flufenamic Acid	49.0	48.7	49.0	48.9	415.1	414.5	415.4	415.0	95.8	94.7	95.4	95.3
Furosemide	266.2	265.6	266.2	266.0	927.4	926.9	926.7	927.0	310.2	309.5	310.3	310.0
Ibuprofen	5578.4	5577.9	5577.7	5578.0	11507.2	11507.0	11507.1	11507.1	57600.1	57599.5	57600.4	57600.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.8	0.5	0.7	0.7
Lorazepam	14.0	13.2	13.9	13.7	92.4	91.4	92.2	92.0	30.5	29.6	29.9	30.0
Metformin	206.4	205.9	205.7	206.0	319.3	318.8	318.6	318.9	135.1	134.3	134.4	134.6
Methylparaben	164.8	163.8	164.6	164.4	115.6	114.7	114.7	115.0	610.4	609.5	610.1	610.0
Naproxen	2101.3	2100.6	2101.1	2101.0	3015.1	3014.8	3015.1	3015.0	1999.3	1998.4	1999.3	1999.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	158.1	157.5	158.4	158.0
Paracetamol	5497.9	5497.5	5498.0	5497.8	4500.7	4500.1	4500.7	4500.5	5353.5	5352.7	5353.1	5353.1
Propylparaben	290.4	289.5	290.1	290.0	133.7	133.0	134.1	133.6	274.8	274.2	274.5	274.5
Salicylic Acid	730.4	729.6	730.0	730.0	1485.5	1484.6	1484.9	1485.0	1756.2	1755.5	1755.4	1755.7
Simvastatin	1600.5	1599.9	1599.6	1600.0	2049.8	2049.0	2048.8	2049.2	1747.0	1746.1	1747.0	1746.7
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	219.9	219.3	219.9	219.7	1050.5	1049.4	1050.1	1050.0	415.8	415.2	416.1	415.7
Triclocarban	1.5	0.5	0.7	0.9	1.1	0.7	0.6	0.8	0.8	0.7	0.7	0.7
Triclosan	155.6	155.4	155.5	155.5	153.3	152.5	153.2	153.0	104.5	104.0	104.4	104.3
Warfarin	n.d.	n.d.	n.d.	n.d.	0.2	0.2	0.2	0.2	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* Cmean = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

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Table S2 Individual PPCPs concentration (ng L^{-1}) obtained in each method replicates in the effluents (e) of the WWTPs (n=3)

	eAS	eAS	eAS		eCAT	eCAT	eCAT		eCAT	eCAT	eCAT		ePAL	ePAL	ePAL		eSAL	eSAL	eSAL	
	25/11/2016	*25/11/2016*	*25/11/2016*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*		*14/12/2016*	*14/12/2016*	*14/12/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	3.7	2.6	3.3	3.2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.0	5.6	6.1	5.9	1.3	2.1	1.4	1,6
Atenolol	14.4	13.5	14.1	14.0	8.7	8.1	8.4	8.4	140.2	139.7	140.1	140.0	26.6	25.6	25.8	26.0	19.0	19.3	18.7	19,0
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	2.1	1.6	1.7	1.8	0.8	n.d.	0.7	0.5	0.3	0.3	0.4	0.3	0.8	0.1	0.3	0.4	2.0	2.5	1.5	2,0
Bisphenol A	93.5	92.8	92.7	93.0	19.2	18.6	19.2	19.0	n.d.	n.d.	n.d.	n.d.	36.2	35.5	35.7	35.8	11.3	11.2	10.5	11,0
Butylparaben	0.6	0.2	0.4	0.4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	9.1	8.7	8.6	8.8	5.7	5.0	5.8	5.5	43.4	42.5	43.1	43.0	149.3	148.8	148.6	148.9	29.1	29.3	28.3	28,9
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	14.5	13.8	14.0	14.1	1.5	1.2	1.5	1.4	0.2	0.2	0.2	0.2	7.3	6.9	7.1	7.1	3.4	3.9	3.2	3,5
Diclofenac	164.0	163.6	164.1	163.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	164.2	163.5	163.1	163.6	28.7	29.6	28.7	29,0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.3	0.1	0.2	0.2	0.3	0.4	0.3	0.3	0.7	0.9	-0.1	0,5
Etoricoxib	8.1	7.4	8.5	8.0	2.7	2.4	2.7	2.6	2.0	0.8	1.4	1.4	20.0	18.9	19.6	19.5	3.7	4.3	3.1	3,7
Flufenamic Acid	136.5	136.0	136.1	136.2	0.4	0.3	0.5	0.4	n.d.	n.d.	n.d.	n.d.	96.0	95.3	96.1	95.8	22.0	22.6	21.4	22,0
Furosemide	135.0	134.0	134.2	134.4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.2	2.4	1.4	2,0
Ibuprofen	n.d.	n.d.	n.d.	n.d.	499.6	498.6	499.4	499.2	231.3	230.5	231.5	231.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	18.4	17.7	18.2	18.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	43.5	42.5	42.7	42.9	8.7	8.8	8.3	8,6
Metformin	7.1	6.4	6.0	6.5	2.3	1.5	2.2	2.0	4.5	4.3	4.4	4.4	10.4	9.7	9.6	9.9	1.4	1.2	0.7	1,1
Methylparaben	20.7	20.4	20.7	20.6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	13.8	13.5	13.5	13.6	5.3	6.1	5.4	5,6
Naproxen	23.1	22.9	23.0	23.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	26.6	25.7	26.6	26.3	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	11.9	11.0	11.0	11.3	2.5	1.6	1.9	2.0	19.3	18.8	18.9	19.0	35.2	34.7	34.5	34.8	49.4	49.2	48.4	49,0
Propylparaben	1.7	1.2	1.0	1.3	n.d.	n.d.	n.d.	n.d.	2.2	1.1	1.8	1.7	5.6	5.0	5.3	5.3	4.2	4.6	3.5	4,1
Salicylic Acid	142.5	141.7	141.8	142.0	58.8	58.3	58.1	58.4	108.3	107.5	108.2	108.0	380.2	379.7	379.5	379.8	310.2	310.4	309.4	310,0
Simvastatin	n.d.	n.d.	n.d.	n.d.	245.5	244.7	245.4	245.2	80.4	79.9	79.7	80.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	470.6	469.5	469.9	470.0	n.d.	n.d.	n.d.	n.d.	3.8	3.2	3.5	3.5	576.6	575.5	575.9	576.0	120.4	120.1	119.5	120,0
Triclocarban	n.d.	n.d.	n.d.	n.d.	0.7	0.3	0.3	0.4	n.d.	n.d.	n.d.	n.d.	0.5	0.2	0.2	0.3	0.1	0.3	n.d.	0,1
Triclosan	24.5	23.8	23.7	24.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	23.1	22.1	22.6	22.6	4.1	4.8	4.0	4,3
Warfarin	0.6	0.5	0.5	0.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.3	0.2	0.3	0.3	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* Cmean = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

Table S2 *(Continued)*

	ePE	ePE	ePE		ePI	ePI	ePI		ePI	ePI	ePI		ePII	ePII	ePII		ePII	ePII	ePII	
	13/01/2017	*13/01/2017*	*13/01/2017*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*		*22/11/2016*	*22/11/2016*	*22/11/2016*		*13/01/2017*	*13/01/2017*	*13/01/2017*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	2.7	1.8	2.4	2.3	7.9	6.9	7.7	7.5	5.2	4.6	5.5	5.1	9.3	8.4	9.3	9.0	7.5	6.5	7.0	7.0
Atenolol	4.5	3.4	4.1	4.0	148.5	147.4	147.8	147.9	190.9	190.1	190.2	190.4	124.8	124.1	125.2	124.7	136.9	136.4	136.8	136.7
Atorvastatin	n.d.	n.d.	n.d.	n.d.	152.4	151.8	152.7	152.3	142.6	142.0	142.9	142.5	53.4	52.7	52.6	52.9	146.4	145.7	145.9	146.0
Bezafibrate	1.2	0.9	0.8	1.0	29.9	29.2	29.7	29.6	35.6	34.9	34.8	35.1	7.2	6.4	7.1	6.9	20.5	19.8	20.9	20.4
Bisphenol A	41.1	40.7	41.2	41.0	180.9	180.7	180.8	180.8	165.3	164.7	165.0	165.0	65.8	64.7	65.4	65.3	240.6	239.5	239.9	240.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	0.5	0.1	n.d.	0.2	0.3	0.2	0.2	0.2	n.d.	n.d.	n.d.	n.d.	2.1	1.3	1.1	1.5
Caffeine	36.5	35.7	35.8	36.0	15.4	14.9	15.6	15.3	72.1	71.9	72.0	72.0	40.6	40.2	40.4	40.4	151.1	150.1	150.9	150.7
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	7.5	7.2	7.2	7.3	50.2	49.6	50.5	50.1	76.7	75.7	75.9	76.1	53.9	53.1	53.8	53.6	97.0	96.6	96.5	96.7
Diclofenac	57.3	56.4	57.3	57.0	711.2	711.0	711.1	711.1	433.4	432.5	433.1	433.0	525.7	524.9	525.0	525.2	490.3	489.6	490.1	490.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	83.3	82.7	83.0	83.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	0.4	0.4	0.4	0.4	n.d.	n.d.	n.d.	n.d.	1.0	0.1	0.4	0.5	n.d.	n.d.	n.d.	n.d.	1.6	0.7	0.7	1.0
Etoricoxib	4.9	4.1	5.1	4.7	26.2	25.2	25.7	25.7	25.2	24.1	24.8	24.7	30.4	29.8	30.4	30.2	22.8	21.9	22.8	22.5
Flufenamic Acid	65.2	64.5	65.3	65.0	350.2	349.2	349.4	349.6	200.6	199.8	199.6	200.0	277.8	276.8	277.3	277.3	200.1	199.8	200.1	200.0
Furosemide	30.3	29.8	29.9	30.0	903.8	903.4	903.3	903.5	550.3	549.9	549.8	550.0	552.2	551.9	552.2	552.1	630.2	629.5	630.0	629.9
Ibuprofen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.6	1.4	1.8	n.d.	n.d.	n.d.	n.d.	8.5	7.3	7.9	7.9
Lorazepam	17.6	16.6	16.8	17.0	61.4	61.0	61.5	61.3	54.6	54.0	54.6	54.4	63.7	62.7	62.9	63.1	57.5	56.7	57.1	57.1
Metformin	8.2	7.7	8.1	8.0	66.5	66.0	66.4	66.3	35.0	34.6	35.1	34.9	19.0	18.5	19.2	18.9	24.6	23.4	24.0	24.0
Methylparaben	4.7	4.0	5.1	4.6	29.7	28.8	28.8	29.1	40.6	39.6	39.8	40.0	20.8	20.0	19.8	20.2	35.6	34.5	34.9	35.0
Naproxen	n.d.	n.d.	n.d.	n.d.	76.0	75.0	75.2	75.4	n.d.	n.d.	n.d.	n.d.	90.9	90.5	90.7	90.7	146.6	145.8	145.6	146.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	30.1	29.9	30.0	30.0	14.4	13.5	14.1	14.0	26.0	25.1	25.7	25.6	23.5	22.5	23.0	23.0
Paracetamol	39.2	38.9	38.9	39.0	18.7	17.5	18.1	18.1	37.1	36.9	37.0	37.0	16.7	16.4	16.7	16.6	15.9	15.1	15.2	15.4
Propylparaben	5.1	4.6	5.3	5.0	5.9	5.4	6.1	5.8	10.4	9.9	9.7	10.0	3.9	3.1	4.1	3.7	8.8	8.1	9.2	8.7
Salicylic Acid	248.3	247.5	248.2	248.0	207.2	206.6	207.5	207.1	345.6	344.4	345.0	345.0	205.2	204.6	205.2	205.0	325.2	324.9	324.9	325.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	35.1	34.7	35.2	35.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	9.3	8.8	8.9	9.0	n.d.	n.d.	n.d.	n.d.	15.0	14.7	14.7	14.8
Tramadol	467.1	466.8	467.1	467.0	1110.6	1110.0	1110.9	1110.5	994.1	993.6	994.3	994.0	1280.5	1279.3	1279.9	1279.9	1302.6	1301.4	1302.0	1302.0
Triclocarban	0.2	0.1	0.1	0.1	0.6	0.6	0.7	0.6	0.5	0.5	0.6	0.5	n.d.	n.d.	n.d.	n.d.	0.5	0.4	0.4	0.4
Triclosan	n.d.	n.d.	n.d.	n.d.	29.7	28.7	29.2	29.2	20.7	20.1	20.1	20.3	10.7	10.0	10.5	10.4	7.6	7.3	7.3	7.4
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.8	0.7	0.8	0.8	0.7	0.7	0.8	0.7

a, b, c represent each replicate
* Cmean = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

Table S2 *(Continued)*

	ePS	ePS	ePS		eQB	eQB	eQB		eSU	eSU	eSU	
	25/11/2016	*25/11/2016*	*25/11/2016*		*14/12/2016*	*14/12/2016*	*14/12/2016*		*25/11/2016*	*25/11/2016*	*25/11/2016*	
Compound	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**	*a*	*b*	*c*	**Cmean**
Alprazolam	3.2	2.3	3.2	2.9	8.2	7.1	7.8	7.7	4.6	5.0	4.2	4.6
Atenolol	12.3	11.2	11.6	11.7	104.2	103.2	104.0	103.8	24.4	24.5	24.3	24.4
Atorvastatin	n.d.	n.d.	n.d.	n.d.	19.3	18.9	18.8	19.0	15.8	16.0	15.3	15.7
Bezafibrate	0.7	-0.1	0.9	0.5	21.0	20.0	20.2	20.4	12.2	12.9	11.8	12.3
Bisphenol A	71.3	70.9	70.8	71.0	221.5	220.9	220.6	221.0	82.9	83.2	82.9	83.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	27.0	26.6	26.8	26.8	455.1	454.3	455.3	454.9	39.9	40.2	39.9	40.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	24.9	24.2	24.4	24.5	33.1	32.7	32.6	32.8	31.5	31.1	30.4	31.0
Diclofenac	114.5	113.5	114.0	114.0	258.9	258.5	259.0	258.8	198.9	199.4	199.0	199.1
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	0.7	0.3	0.8	0.6	4.3	3.7	4.0	4.0	0.3	0.4	0.3	0.3
Etoricoxib	13.7	13.2	13.3	13.4	22.5	21.8	22.0	22.1	27.9	28.0	27.2	27.7
Flufenamic Acid	45.3	44.5	45.2	45.0	328.2	327.1	327.8	327.7	186.6	186.9	186.6	186.7
Furosemide	66.3	66.0	66.0	66.1	427.1	426.9	427.0	427.0	313.2	313.5	312.9	313.2
Ibuprofen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	28.5	27.4	28.1	28.0	47.0	46.5	46.3	46.6	36.4	37.0	36.1	36.5
Metformin	15.8	15.3	15.7	15.6	23.5	22.8	23.9	23.4	26.6	26.7	26.2	26.5
Methylparaben	17.4	16.7	16.6	16.9	30.3	29.5	30.5	30.1	28.6	29.3	28.2	28.7
Naproxen	26.4	26.0	25.9	26.1	318.3	317.9	317.8	318.0	205.3	205.3	204.7	205.1
Omeprazole	4.3	3.5	4.2	4.0	16.4	15.5	16.1	16.0	n.d.	n.d.	n.d.	n.d.
Paracetamol	24.4	23.7	24.2	24.1	37.6	36.9	36.5	37.0	70.3	70.3	69.4	70.0
Propylparaben	3.1	2.9	3.0	3.0	6.8	5.6	6.2	6.2	2.4	2.6	1.9	2.3
Salicylic Acid	124.4	123.7	124.8	124.3	580.2	579.9	579.9	580.0	212.0	212.3	211.7	212.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	273.6	272.6	272.8	273.0	1158.9	1157.8	1158.2	1158.3	665.9	666.3	665.5	665.9
Triclocarban	1.3	1.2	1.2	1.2	0.5	0.4	0.4	0.4	0.5	0.5	0.6	0.5
Triclosan	n.d.	n.d.	n.d.	n.d.	14.2	13.6	14.2	14.0	25.9	26.9	26.1	26.3
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.7	0.4	0.3	0.5

a, b, c represent each replicate
* Cmean = mean concentration
**WWTPs: Pinedo 1 (PI), Pinedo 2 (PII), Port de Catarroja (CAT), Quart - Benàger (QB), Sueca (SU), Perelló-Sueca (PS), Perellonet (PE), Palmar (PAL), Saler (SAL) and Albufera Sud (AS)
*** n.d.= not detected

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Table S3. Individual PPCPs concentration (ng L^{-1}) obtained in each method replicates) in water samples (W.n°) of the Albufera Natural Park, Valencia, Spain (n=3)

	W.1	W.1	W.1		W.4	W.4	W.4		W.5	W.5	W.5		W.6	W.6	W.6		W.7	W.7	W.7		W.10	W.10	W.10		W.11	W.11	W.11	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	9.6	9.7	10.3	10.0	4.0	4.0	4.0	4.0	n.d.	n.d.	n.d.	n.d.	5.8	6.1	5.9	6.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	320.0	320.1	320.0	320.0	114.0	114.0	114.1	114.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	0.8	0.9	0.9	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.0	1.0	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	79.5	78.8	78.7	79.0	63.4	63.1	62.7	63.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	185.1	184.4	185.5	185.0	144.8	145.3	144.6	145.0	149.7	150.0	150.3	150.0	120.4	119.6	120.0	120.0	48.0	47.6	47.8	48.0	64.6	65.5	65.2	65.0	74.7	74.9	75.4	75.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	69.5	70.4	70.1	70.0	70.2	69.8	70.0	70.0	45.6	44.6	44.8	45.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	152.5	151.7	151.8	152.0	28.1	28.6	27.5	28.0	61.8	62.0	62.2	62.0	22.1	21.7	22.2	22.0	131.0	130.6	131.1	131.0	55.6	55.9	56.5	56.0	11.0	11.0	11.3	11.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	50.2	49.5	50.3	50.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	76.4	75.7	75.9	76.0	77.0	77.3	76.6	77.0	75.4	76.2	76.4	76.0	76.4	75.7	75.9	76.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	154.5	153.5	154.0	154.0	26.6	27.5	26.8	27.0	n.d.	n.d.	n.d.	n.d.	26.6	25.7	25.7	26.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	169.4	168.7	168.9	169.0	69.8	70.4	69.7	70.0	49.6	50.3	50.1	50.0	115.5	114.4	115.1	115.0	60.6	59.7	60.3	60.0	51.8	51.6	52.3	52.0	74.9	74.9	75.5	75.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	71.4	72.3	72.3	72.0	73.1	72.7	73.2	73.0	78.3	77.8	77.9	78.0	71.4	72.3	72.3	72.0	n.d.	n.d.	n.d.	n.d.
Etoricoxib	18.6	17.5	17.9	18.0	4.4	4.6	3.9	4.0	2.5	3.4	3.1	3.0	8.6	7.9	7.5	8.0	1.5	0.7	0.8	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	195.2	194.4	195.4	195.0	85.0	85.4	84.9	85.0	59.7	59.8	60.5	60.0	150.1	149.6	150.3	150.0	n.d.	n.d.	n.d.	n.d.	0.7	0.9	1.4	1.0	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	115.0	115.6	114.8	115.0	n.d.	n.d.	n.d.	n.d.	74.3	73.4	74.3	74.0	48.6	47.7	47.7	48.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	90.1	89.9	90.0	90.0	84.8	85.3	84.6	85.0	19.4	20.5	20.1	20.0	35.3	34.7	35.0	35.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	56.3	55.8	55.9	56.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	88.1	87.7	88.2	88.0	15.5	15.2	14.7	15.0	n.d.	n.d.	n.d.	n.d.	15.5	14.9	14.8	15.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	251.4	250.8	250.8	251.0	65.7	66.1	65.7	66.0	n.d.	n.d.	n.d.	n.d.	19.4	18.7	18.9	19.0	20.3	19.9	20.1	20.0	3.6	3.9	4.5	4.0	2.8	2.9	3.3	3.0
Methylparaben	75.2	74.9	74.9	75.0	75.1	75.6	74.5	75.0	106.7	107.2	107.1	107.0	73.2	72.7	73.1	73.0	82.5	81.7	81.8	82.0	73.8	73.6	74.6	74.0	74.7	75.0	75.3	75.0
Naproxen	195.5	194.9	194.6	195.0	144.9	145.3	144.8	145.0	n.d.	n.d.	n.d.	n.d.	105.3	104.5	105.5	105.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	26.1	25.7	26.2	26.0	n.d.	0.5	-0.2	n.d.	4.9	4.8	5.3	5.0	n.d.	n.d.	n.d.	n.d.	32.5	31.9	32.5	32.0	13.9	13.7	14.4	14.0	10.2	11.1	11.1	11.0
Propylparaben	n.d.	n.d.	n.d.	n.d.	87.6	88.5	87.8	88.0	74.5	75.4	75.1	75.0	n.d.	n.d.	n.d.	n.d.	38.1	37.8	38.1	38.0	32.6	32.9	33.5	33.0	31.5	32.1	32.4	32.0
Salicylic Acid	99.5	98.7	98.8	99.0	87.9	88.1	87.5	88.0	74.6	75.0	75.4	75.0	113.4	112.5	113.1	113.0	690.3	689.5	689.9	690.0	601.6	601.6	602.2	602.0	n.d.	n.d.	n.d.	n.d.
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	35.4	34.8	34.8	35.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.6	5.2	5.2	5.0	n.d.	n.d.	n.d.	n.d.
Tramadol	1264.5	1263.6	1263.9	1264.0	197.1	197.5	196.8	197.0	0.4	1.1	1.5	1.0	522.3	522.6	523.2	523.0	n.d.	n.d.	n.d.	n.d.	10.7	11.1	11.2	11.0	12.4	13.4	13.2	13.0
Triclocarban	n.d.	n.d.	n.d.	n.d.	15.0	15.6	14.6	15.0	12.4	13.5	13.1	13.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.6	1.4	2.4	2.0	n.d.	n.d.	n.d.	n.d.
Triclosan	65.2	64.7	65.1	65.0	28.3	28.1	27.5	28.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	43.7	44.1	44.5	44.0
Warfarin	n.d.	n.d.	n.d.	n.d.	65.2	65.5	64.5	65.0	64.5	65.1	65.4	65.0	64.1	63.4	64.5	64.0	n.d.	n.d.	n.d.	n.d.	44.6	45.1	45.3	45.0	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S3 *(Continued)*

	W.12	W.12	W.12		W.14	W.14	W.14		W.15	W.15	W.15		W.16	W.16	W.16		W.17	W.17	W.17		W.18	W.18	W.18		W.19	W.19	W.19	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	1.3	0.6	1.1	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62.2	61.6	62.4	62.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	21.2	20.8	21.0	21.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.4	1.4	1.2	1.0
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-0.4	0.5	-0.1	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	56.7	55.6	56.0	56.0	70.1	69.9	70.0	70.0	24.9	24.7	25.4	25.0	51.4	50.5	51.1	51.0	47.7	48.6	47.7	48.0	71.8	72.3	71.9	72.0	44.5	45.1	45.4	45.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	39.6	40.2	40.2	40.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	40.0	40.4	39.6	40.0	44.9	45.3	44.8	45.0
Caffeine	14.0	13.8	14.0	14.0	291.2	290.9	291.2	291.0	75.4	76.2	76.4	76.0	152.4	151.8	151.8	152.0	20.7	21.2	21.1	21.0	134.2	134.9	133.8	134.0	100.4	101.1	101.5	101.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	39.1	39.3	38.6	39.0	39.8	40.7	40.4	40.0
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8.5	7.4	8.1	8.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	55.4	54.8	54.8	55.0	n.d.	n.d.	n.d.	n.d.	74.8	74.6	75.6	75.0	90.1	89.6	90.3	90.0	66.9	67.7	67.3	67.0	72.2	72.6	71.5	72.0	62.7	63.2	62.5	63.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.5	3.8	4.0	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	82.2	81.1	81.8	82.0	n.d.	n.d.	n.d.	n.d.	69.7	70.0	70.3	70.0	n.d.	n.d.	n.d.	n.d.	69.6	70.2	70.2	70.0	69.5	70.6	69.9	70.0	69.6	70.5	70.2	70.0
Etoricoxib	1.4	0.6	1.0	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.5	1.7	1.8	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.8	1.5	0.7	1.0
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	1.5	0.9	0.6	1.0	1.8	1.8	2.4	2.0	4.4	3.4	4.0	4.0	1.2	2.4	1.8	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	69.7	70.2	70.1	70.0	90.4	89.4	90.2	90.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	24.7	25.5	24.8	25.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	18.5	18.2	18.1	18.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	5.3	4.9	4.8	5.0	23.2	22.3	22.3	23.0	14.7	15.2	15.1	15.0	114.6	113.7	113.7	114.0	25.9	26.6	25.5	26.0	171.2	171.6	171.1	171.0	2.5	3.6	2.9	3.0
Methylparaben	79.8	79.5	79.5	80.0	77.4	76.5	77.4	77.0	75.0	74.9	75.4	75.0	79.3	78.5	79.2	79.0	70.7	71.5	70.5	71.0	74.8	75.1	74.2	75.0	73.9	74.1	74.0	74.0
Naproxen	n.d.	n.d.	n.d.	n.d.	115.7	114.8	115.4	115.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	17.6	16.7	17.3	17.0	82.5	81.7	81.8	82.0	27.7	28.2	28.1	28.0	18.1	17.9	18.0	18.0	n.d.	n.d.	n.d.	n.d.	32.2	32.4	31.4	32.0	30.7	31.3	31.0	31.0
Propylparaben	35.0	35.0	35.1	35.0	33.2	32.4	33.4	33.0	31.4	32.3	32.3	32.0	30.1	29.6	30.3	30.0	29.4	30.2	30.4	30.0	29.6	30.6	29.8	30.0	29.4	30.4	30.2	30.0
Salicylic Acid	n.d.	n.d.	n.d.	n.d.	840.1	839.6	840.3	840.0	281.5	281.8	282.4	282.0	249.6	248.5	248.9	249.0	n.d.	n.d.	n.d.	n.d.	297.8	298.6	297.6	298.0	390.9	391.5	390.6	391.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	1.1	0.5	1.4	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.2	4.5	5.1	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	12.2	11.7	12.1	12.0	3.2	2.5	3.3	3.0	4.6	5.2	5.2	5.0	18.5	17.6	17.9	18.0	8.5	9.6	9.2	9.0	32.7	33.6	33.0	33.0	n.d.	n.d.	n.d.	n.d.
Triclocarban	1.6	0.8	0.6	1.0	1.4	0.4	1.2	1.0	0.6	1.2	1.2	1.0	1.3	0.7	1.0	1.0	0.4	1.1	1.5	1.0	0.6	1.4	0.7	1.0	n.d.	n.d.	n.d.	n.d.
Triclosan	50.1	49.4	50.5	50.0	60.6	59.4	60.0	60.0	64.7	65.2	65.1	65.0	n.d.	n.d.	n.d.	n.d.	50.9	51.6	50.5	51.0	55.2	55.2	54.6	55.0	47.5	48.5	48.0	48.0
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	45.5	44.4	45.1	45.0	n.d.	n.d.	n.d.	n.d.	48.0	48.6	47.4	48.0	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} mean concentration
** n.d.= not detected

Table 3 *(Continued)*

	W.20	W.20	W.20		W.21	W.21	W.21		W.22	W.22	W.22		W.23	W.23	W.23		W.26	W.26	W.26		W.27	W.27	W.27		W.29	W.29	W.29	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	78.1	77.8	78.1	78.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.9	1.7	2.0
Bezafibrate	n.d.	n.d.	n.d.	n.d.	1.2	0.6	1.2	1.0	n.d.	n.d.	n.d.	n.d.	2.2	1.5	2.6	2.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	139.4	140.4	140.2	140.0	57.4	56.6	57.0	57.0	30.9	30.6	30.6	30.7	11.8	11.6	12.6	12.0	18.9	19.5	18.6	19.0	115.5	114.3	114.9	114.9	140.6	139.9	139.5	140.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	40.5	39.5	40.0	40.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	70.6	69.6	69.8	70.0	n.d.	n.d.	n.d.	n.d.
Caffeine	120.5	120.9	121.6	121.0	219.1	218.9	219.0	219.0	40.1	39.9	40.0	40.0	668.3	667.5	668.2	668.0	20.1	20.3	19.6	20.0	43.3	42.4	43.3	43.0	138.2	137.7	138.1	138.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	76.6	76.8	77.6	77.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	77.4	76.9	76.7	77.0	76.2	75.7	76.1	76.0
Codeine	6.9	7.0	7.1	7.0	16.4	15.8	15.8	16.0	n.d.	n.d.	n.d.	n.d.	20.7	20.4	21.3	20.8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	n.d.	n.d.	n.d.	n.d.	75.1	74.8	75.1	75.0	65.5	64.7	65.4	65.2	102.6	102.8	103.6	103.0	74.8	75.4	74.8	75.0	n.d.	n.d.	n.d.	n.d.	45.2	44.7	45.4	45.1
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	77.3	76.4	77.3	77.0	72.8	73.5	72.7	73.0	67.4	66.8	66.8	67.0	n.d.	n.d.	n.d.	n.d.
Etoricoxib	1.7	2.1	2.2	2.0	2.3	1.5	2.2	2.0	n.d.	n.d.	n.d.	n.d.	2.4	1.5	2.1	2.0	n.d.	n.d.	n.d.	n.d.	2.4	1.4	2.2	2.0	2.5	1.9	1.6	2.0
Flufenamic Acid	60.6	60.9	61.2	60.9	7.2	6.9	6.9	7.0	1.1	0.5	1.4	1.0	15.0	14.8	15.2	15.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	64.6	64.8	65.6	65.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	144.4	143.5	144.1	144.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	24.2	23.7	24.1	24.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	6.5	5.8	5.7	6.0	n.d.	n.d.	n.d.	n.d.	30.9	30.6	31.5	31.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	13.8	13.9	14.3	14.0	55.6	54.8	54.9	55.1	2.3	1.5	2.2	2.0	130.5	130.3	131.3	130.7	374.8	375.4	374.8	375.0	24.3	23.8	24.2	24.1	25.5	24.6	24.9	25.0
Methylparaben	n.d.	n.d.	n.d.	n.d.	75.4	74.9	74.7	75.0	n.d.	n.d.	n.d.	n.d.	81.7	81.7	82.6	82.0	75.3	75.2	74.5	75.0	n.d.	n.d.	n.d.	n.d.	70.1	69.5	70.4	70.0
Naproxen	n.d.	n.d.	n.d.	n.d.	117.6	116.4	117.0	117.0	114.4	113.4	114.2	114.0	208.1	207.4	208.5	208.0	110.9	111.3	110.8	111.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	10.9	10.7	11.7	11.1	40.1	39.8	40.1	40.0	n.d.	n.d.	n.d.	n.d.	168.0	167.5	168.5	168.0	n.d.	n.d.	n.d.	n.d.	25.5	24.4	25.1	25.0	33.3	32.1	32.7	32.7
Propylparaben	74.4	75.1	75.5	75.0	35.3	34.6	35.7	35.2	30.4	29.8	29.8	30.0	32.8	32.8	33.4	33.0	29.7	30.6	29.7	30.0	90.4	89.8	89.8	90.0	75.5	74.8	74.7	75.0
Salicylic Acid	293.6	294.2	294.2	294.0	239.4	238.9	238.7	239.0	208.5	207.5	207.7	207.9	750.6	750.8	751.6	751.0	339.6	340.5	339.9	340.0	106.0	105.4	106.3	105.9	521.6	520.8	520.6	521.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.2	4.7	5.1	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	6.5	7.0	7.5	7.0	84.2	83.5	84.3	84.0	n.d.	n.d.	n.d.	n.d.	106.0	105.4	106.3	105.9	n.d.	n.d.	n.d.	n.d.	22.1	21.5	22.4	22.0	27.2	26.4	27.4	27.0
Triclocarban	n.d.	n.d.	n.d.	n.d.	5.4	4.4	4.9	4.9	n.d.	n.d.	n.d.	n.d.	1.5	0.4	1.1	1.0	n.d.	n.d.	n.d.	n.d.	14.1	13.4	14.5	14.0	n.d.	n.d.	n.d.	n.d.
Triclosan	14.8	15.0	15.2	15.0	72.2	71.5	72.3	72.0	n.d.	n.d.	n.d.	n.d.	51.9	51.8	52.3	52.0	44.1	44.3	43.6	44.0	n.d.	n.d.	n.d.	n.d.	25.3	24.9	25.4	25.2
Warfarin	64.6	64.6	65.5	64.9	45.5	44.6	44.9	45.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	44.9	45.2	44.9	45.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S3 *(Continued)*

	W.30	W.30	W.30		W.31	W.31	W.31		W.32	W.32	W.32		W.33	W.33	W.33		W.34	W.34	W.34		W.36	W.36	W.36		W.37	W.37	W.37	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	1.7	2.5	1.8	2.0	n.d.	n.d.	n.d.	n.d.	8.4	7.9	7.7	8.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	91.8	92.3	91.9	92.0	52.9	52.0	52.0	52.3	221.2	220.4	221.4	221.0	71.6	72.5	71.9	72.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	1.2	1.3	0.5	1.0	n.d.	n.d.	n.d.	n.d.	21.1	20.8	21.1	21.0	0.6	1.5	0.9	1.0	21.2	20.7	21.1	21.0	1.1	1.1	0.8	1.0	21.1	20.6	20.7	20.8
Bezafibrate	8.9	9.3	8.8	9.0	n.d.	n.d.	n.d.	n.d.	75.4	74.6	75.0	75.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	190.1	190.4	189.5	190.0	115.3	114.5	115.2	115.0	158.3	157.5	158.2	158.0	60.4	60.3	59.6	60.1	205.3	204.9	204.8	205.0	196.9	197.2	196.9	197.0	54.3	53.5	54.2	54.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	70.1	69.5	70.4	70.0	n.d.	n.d.	n.d.	n.d.	40.2	40.3	39.5	40.0	n.d.	n.d.	n.d.	n.d.	71.1	71.2	70.7	71.0	n.d.	n.d.	n.d.	n.d.
Caffeine	540.9	541.2	540.9	541.0	103.6	102.5	102.9	103.0	272.6	271.7	271.7	272.0	156.7	157.5	156.8	157.0	66.4	65.7	65.9	66.0	172.5	173.5	172.7	172.9	93.5	92.8	92.7	93.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	39.8	40.6	39.6	40.0	n.d.	n.d.	n.d.	n.d.	49.7	50.6	49.7	50.0	n.d.	n.d.	n.d.	n.d.
Clofibric acid	74.9	75.3	74.8	75.0	76.7	75.7	75.9	76.1	76.3	75.8	75.9	76.0	n.d.	n.d.	n.d.	n.d.	75.5	74.7	74.8	75.0	75.7	76.5	75.8	76.0	n.d.	n.d.	n.d.	n.d.
Codeine	35.7	36.5	35.8	36.0	30.4	29.7	29.9	30.0	84.2	83.8	84.0	84.0	11.7	12.6	11.7	12.0	n.d.	n.d.	n.d.	n.d.	39.0	39.5	38.5	39.0	n.d.	n.d.	n.d.	n.d.
Diclofenac	94.7	95.6	94.7	95.0	65.6	64.5	64.9	65.0	82.6	81.8	81.6	82.0	78.0	78.3	77.7	78.0	66.3	65.6	66.1	66.0	n.d.	n.d.	n.d.	n.d.	104.5	103.5	104.0	104.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.8	8.4	7.8	8.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	74.9	75.4	74.7	75.0	66.6	65.8	65.6	66.0	67.5	66.9	66.6	67.0	79.9	80.5	79.6	80.0	79.5	78.8	78.7	79.0	70.4	70.2	69.4	70.0	76.5	75.9	75.6	76.0
Etoricoxib	5.4	5.1	4.5	5.0	5.5	4.4	5.1	5.0	13.6	12.6	12.8	13.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.7	6.5	5.8	6.0	7.4	6.9	6.7	7.0
Flufenamic Acid	79.8	80.6	79.6	80.0	80.1	79.5	80.4	80.0	140.2	139.7	140.1	140.0	10.1	10.0	9.6	9.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.2	0.6	1.2	1.0
Furosemide	95.3	95.2	94.5	95.0	85.4	84.8	84.8	85.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	59.9	60.5	59.6	60.0	217.0	216.6	216.5	216.7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	89.7	90.5	89.8	90.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	50.6	49.8	49.6	50.0	n.d.	n.d.	n.d.	n.d.	25.0	25.3	24.7	25.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	23.1	23.4	22.5	23.0	12.5	11.9	11.6	12.0	70.2	69.4	70.4	70.0	1.0	1.4	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.4	2.2	2.0
Metformin	185.9	186.6	185.8	186.1	70.6	69.4	70.0	70.0	93.3	92.6	93.1	93.0	57.4	57.1	56.5	57.0	18.7	17.9	17.7	18.1	21.8	22.4	21.5	21.9	33.6	32.8	32.6	33.0
Methylparaben	84.0	84.6	83.4	84.0	75.5	74.6	74.9	75.0	78.5	77.4	78.1	78.0	74.8	75.5	74.7	75.0	73.6	72.9	72.5	73.0	78.2	78.2	77.6	78.0	76.4	75.4	76.2	76.0
Naproxen	209.0	209.4	208.6	209.0	225.6	224.8	224.6	225.0	178.6	177.6	177.8	178.0	159.8	160.7	160.1	160.2	n.d.	n.d.	n.d.	n.d.	86.1	86.2	85.7	86.0	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	74.9	75.5	74.6	75.0	17.3	16.6	17.1	17.0	37.3	36.7	37.0	37.0	49.0	49.2	48.8	49.0	43.3	42.8	42.9	43.0	47.2	47.4	46.4	47.0	23.2	22.4	23.4	23.0
Propylparaben	75.2	75.4	74.4	75.0	75.3	74.8	74.9	75.0	135.2	134.6	135.2	135.0	31.2	31.3	30.5	31.0	n.d.	n.d.	n.d.	n.d.	74.7	75.6	75.0	75.1	31.2	30.8	31.0	31.0
Salicylic Acid	713.0	713.4	712.6	713.0	75.1	74.7	75.2	75.0	161.6	160.6	160.8	161.0	230.1	230.5	229.4	230.0	686.2	685.6	686.2	686.0	166.0	166.3	165.7	166.0	592.9	592.0	592.3	592.4
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	332.9	333.4	332.7	333.0	171.4	170.4	171.2	171.0	696.0	695.2	695.0	695.4	88.6	89.6	88.8	89.0	n.d.	n.d.	n.d.	n.d.	49.9	49.9	49.6	49.8	24.5	23.6	23.9	24.0
Triclocarban	1.1	1.3	0.6	1.0	13.5	12.5	13.0	13.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.5	0.4	1.1	1.0
Triclosan	n.d.	n.d.	n.d.	n.d.	52.1	51.5	52.4	52.0	56.1	55.5	56.4	56.0	49.8	50.4	49.2	49.8	48.7	47.9	48.0	48.2	50.3	50.2	49.8	50.1	n.d.	n.d.	n.d.	n.d.
Warfarin	64.8	65.6	64.6	65.0	70.1	69.1	69.9	69.7	70.4	69.5	70.1	70.0	44.6	45.2	44.0	44.6	65.0	64.0	64.8	64.6	n.d.	n.d.	n.d.	n.d.	46.7	45.9	46.6	46.4

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S3 *(Continued)*

	W.38	W.38	W.38		W.39	W.39	W.39		W.40	W.40	W.40		W.41	W.41	W.41		W.42	W.42	W.42	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	1.1	0.5	1.1	0.9	21.5	20.6	20.9	21.0	0.5	1.6	0.9	1.0	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	149.6	150.0	150.4	150.0	158.5	157.8	157.7	158.0	130.4	129.7	129.9	130.0	80.7	81.6	80.7	81.0	149.6	150.6	149.8	150.0
Butylparaben	69.9	69.9	70.2	70.0	70.2	69.6	70.2	70.0	42.2	41.4	42.4	42.0	41.7	42.5	41.8	42.0	n.d.	n.d.	n.d.	n.d.
Caffeine	140.8	141.0	141.2	141.0	127.3	126.9	126.8	127.0	120.6	119.7	120.3	120.2	16.2	16.1	15.7	16.0	17.9	18.8	18.2	18.3
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	50.6	49.6	49.8	50.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	75.7	76.1	76.2	76.0	76.2	75.6	76.2	76.0	75.5	74.5	75.0	75.0	n.d.	n.d.	n.d.	n.d.	80.1	80.3	79.9	80.1
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	44.4	45.4	45.2	45.0	35.3	34.9	34.8	35.0	72.5	72.2	72.2	72.3	35.2	35.2	34.6	35.0	30.0	30.0	29.7	29.9
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	64.4	65.1	65.5	65.0	n.d.	n.d.	n.d.	n.d.	75.5	74.5	74.7	74.9	70.2	70.4	69.4	70.0	n.d.	n.d.	n.d.	n.d.
Etoricoxib	24.8	24.9	25.6	25.1	20.2	19.6	20.2	20.0	3.4	2.8	2.8	3.0	3.2	3.2	2.6	3.0	5.1	5.5	4.4	5.0
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	n.d.	n.d.	n.d.	n.d.	43.5	42.4	43.1	43.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.9	5.5	4.6	5.0	n.d.	n.d.	n.d.	n.d.
Metformin	93.9	93.5	94.6	94.0	40.5	39.9	39.6	40.0	40.2	39.9	39.9	40.0	5.7	6.6	5.7	6.0	19.1	19.2	18.7	19.0
Methylparaben	72.6	73.4	73.3	73.1	n.d.	n.d.	n.d.	n.d.	75.2	74.4	75.4	75.0	82.4	82.2	81.4	82.0	74.1	74.1	73.8	74.0
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	113.6	112.9	112.5	113.0	115.4	115.8	114.7	115.3	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	22.7	23.5	23.4	23.2	25.4	24.9	24.7	25.0	15.4	14.5	15.1	15.0	22.7	23.6	22.7	23.0	25.8	26.3	25.9	26.0
Propylparaben	74.7	75.2	75.1	75.0	70.1	69.7	70.2	70.0	32.4	31.8	31.8	32.0	n.d.	n.d.	n.d.	n.d.	90.4	90.1	89.5	90.0
Salicylic Acid	239.7	239.9	240.4	240.0	858.6	857.9	857.8	858.1	386.6	385.5	385.9	386.0	301.2	301.3	300.8	301.1	203.7	204.4	203.9	204.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.9	5.5	4.6	5.0	34.7	35.5	34.8	35.0
Tramadol	55.8	55.9	56.3	56.0	42.4	41.7	41.9	42.0	18.2	17.7	18.1	18.0	n.d.	n.d.	n.d.	n.d.	5.1	5.3	4.6	5.0
Triclocarban	12.8	12.6	13.6	13.0	13.8	12.6	13.2	13.2	15.3	14.9	14.8	15.0	1.3	1.1	0.6	1.0	15.1	15.1	14.8	15.0
Triclosan	44.8	44.8	45.4	45.0	31.3	30.9	30.8	31.0	35.4	34.6	35.0	35.0	64.6	65.5	64.9	65.0	19.7	20.1	19.6	19.8
Warfarin	64.7	65.1	65.2	65.0	65.5	64.9	64.9	65.1	n.d.	n.d.	n.d.	n.d.	46.0	46.2	45.2	45.8	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S4. Individual PPCPs concentration (ng g^{-1}) in sediment samples (S.n°) of the Albufera Natural Park, Valencia, Spain (n=3)

	S.5	S.5	S.5		S.9	S.9	S.9		S.10	S.10	S.10		S.15	S.15	S.15		S.16	S.16	S.16		S.17	S.17	S.17		S.18	S.18	S.18	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	3.5	2.7	2.8	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.5	1.5	1.8	4.8	5.3	4.9	5.0	4.3	3.6	4.7	4.2
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.6	3.6	2.8	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.5	2.7	2.8	3.0
Bisphenol A	n.d.	n.d.	n.d.	n.d.	15.2	14.4	15.4	15.0	20.6	19.8	19.9	20.1	4.7	5.6	4.7	5.0	14.5	13.6	13.9	14.0	6.5	7.6	6.9	7.0	10.6	9.8	9.6	10.0
Butylparaben	6.4	5.7	5.9	6.0	6.1	5.6	6.3	6.0	n.d.	n.d.	n.d.	n.d.	5.7	6.4	5.9	6.0	7.4	6.5	7.1	7.0	n.d.	n.d.	n.d.	n.d.	6.6	5.4	6.0	6.0
Caffeine	6.1	5.8	6.1	6.0	9.5	8.5	9.0	9.0	8.5	7.5	8.0	8.0	10.2	10.3	9.8	10.1	7.2	6.5	7.0	6.9	4.9	5.6	4.5	5.0	8.1	7.9	8.0	8.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	4.4	3.7	3.9	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	5.1	4.6	5.3	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.1	4.7	5.2	5.0
Codeine	n.d.	n.d.	n.d.	n.d.	1.3	0.5	1.2	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	3.2	2.9	2.9	3.0	3.6	2.7	2.7	3.0	8.4	7.6	8.0	8.0	8.0	8.4	7.6	8.0	10.5	9.6	9.9	10.0	6.1	6.7	5.8	6.2	7.6	6.7	6.7	7.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	17.3	16.8	16.9	17.0	15.1	14.7	15.2	15.0	n.d.	n.d.	n.d.	n.d.	16.6	15.9	15.5	16.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Etoricoxib	1.2	0.4	1.4	1.0	n.d.	n.d.	n.d.	n.d.	1.5	0.7	0.8	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.3	6.3	5.4	6.0	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	2.5	1.7	1.8	2.0	2.3	1.6	2.1	2.0	2.2	1.6	2.2	2.0	1.8	2.4	1.8	2.0	2.1	1.9	2.0	2.0	2.3	2.3	1.4	2.0	2.5	1.9	1.6	2.0
Furosemide	10.1	9.5	10.4	10.0	9.2	8.5	9.3	9.0	9.4	8.9	8.7	9.0	12.2	12.4	11.4	12.0	14.1	13.7	14.2	14.0	22.0	22.5	21.5	22.0	12.6	12.0	11.7	12.1
Ibuprofen	47.2	46.8	47.0	47.0	13.4	12.7	12.9	13.0	100.4	99.6	100.0	100.0	23.8	24.3	23.9	24.0	22.2	21.7	22.1	22.0	29.8	30.3	29.9	30.0	35.5	34.8	34.7	35.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	4.3	3.8	3.9	4.0	2.3	1.8	1.9	2.0	1.5	0.4	1.1	1.0	1.2	1.0	0.5	0.9	5.2	4.4	5.4	5.0	3.3	3.3	2.4	3.0	1.4	0.7	0.9	1.0
Methylparaben	n.d.	n.d.	n.d.	n.d.	13.1	12.8	13.1	13.0	13.4	12.8	12.8	13.0	n.d.	n.d.	n.d.	n.d.	14.6	13.4	14.0	14.0	n.d.	n.d.	n.d.	n.d.	13.6	12.8	12.6	13.0
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.0	2.4	1.6	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	6.5	5.6	5.9	6.0	n.d.	n.d.	n.d.	n.d.	1.6	2.6	1.8	2.0	2.6	1.7	1.7	2.0	0.6	1.6	0.8	1.0	n.d.	n.d.	n.d.	n.d.
Propylparaben	4.2	3.4	4.4	4.0	2.2	1.4	2.4	2.0	n.d.	n.d.	n.d.	n.d.	2.1	2.4	1.5	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.6	1.4	2.0	2.0
Salicylic Acid	21.1	20.4	21.5	21.0	18.4	17.5	18.1	18.0	25.6	24.8	24.6	25.0	31.9	32.2	31.9	32.0	28.2	27.6	28.5	28.1	23.8	24.5	23.7	24.0	23.1	22.8	23.1	23.0
Simvastatin	8.1	7.4	8.5	8.0	21.2	20.9	20.9	21.0	21.5	20.5	20.7	20.9	13.0	13.6	12.4	13.0	n.d.	n.d.	n.d.	n.d.	29.0	29.3	28.7	29.0	12.3	11.5	12.2	12.0
Thiamphenicol	12.4	11.8	11.8	12.0	n.d.	n.d.	n.d.	n.d.	11.5	10.9	10.6	11.0	9.0	9.2	8.8	9.0	10.6	9.7	9.7	10.0	9.2	9.3	8.5	9.0	11.3	10.9	10.8	11.0
Tramadol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.4	0.6	1.0	1.0	n.d.	n.d.	n.d.	n.d.	1.4	0.8	0.8	1.0	2.0	2.4	1.6	2.0	2.2	1.9	1.9	2.0
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	10.5	9.5	10.0	10.0	14.6	13.5	13.9	14.0	8.6	7.5	7.9	8.0	7.2	7.5	6.6	7.1	8.3	7.9	7.8	8.0	7.4	8.3	7.7	7.8	13.0	12.5	12.9	12.8
Warfarin	8.6	7.7	7.7	8.0	9.1	8.9	9.0	9.0	9.2	8.5	9.3	9.0	9.0	9.2	8.8	9.0	9.3	8.4	9.3	9.0	9.3	9.2	8.5	9.0	9.2	8.9	8.9	9.0

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S4 *(Continued)*

	S.23	S.23	S.23		S.26	S.26	S.26		S.30	S.30	S.30		S.33	S.33	S.33		S.34	S.34	S.34		S.35	S.35	S.35		S.36	S.36	S.36	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	4.3	3.8	3.9	4.0	3.6	2.6	3.1	3.1	4.8	5.5	4.7	5.0	4.9	5.4	4.7	5.0	3.5	2.8	2.7	3.0	1.0	1.2	0.8	1.0	n.d.	n.d.	n.d.	n.d.
Atorvastatin	2.1	1.7	2.2	2.0	1.1	0.9	1.0	1.0	n.d.	n.d.	n.d.	n.d.	20.9	21.6	20.5	21.0	1.1	0.8	1.1	1.0	20.8	21.4	20.8	21.0	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	21.1	20.8	21.1	21.0	7.6	6.9	6.5	7.0	19.9	20.2	19.9	20.0	18.2	18.1	17.7	18.0	20.3	19.6	20.1	20.0	2.4	2.1	1.5	2.0	n.d.	n.d.	n.d.	n.d.
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.2	6.1	5.7	6.0	6.5	6.1	5.4	6.0	n.d.	n.d.	n.d.	n.d.	6.1	6.2	5.7	6.0	n.d.	n.d.	n.d.	n.d.
Caffeine	8.5	7.5	8.0	8.0	6.3	5.9	5.8	6.0	7.1	7.2	6.7	7.0	6.3	6.2	5.5	6.0	9.1	8.7	9.2	9.0	6.0	6.6	5.4	6.0	4.3	3.5	4.2	4.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	5.1	4.7	5.2	5.0	5.1	4.5	5.4	5.0	n.d.	n.d.	n.d.	n.d.	4.2	4.6	3.5	4.1	5.3	4.9	4.8	5.0	3.8	4.5	3.7	4.0	4.1	3.4	4.5	4.0
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.4	0.5	1.1	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	5.6	4.6	4.8	5.0	n.d.	n.d.	n.d.	n.d.	3.2	3.3	2.5	3.0	5.8	6.4	5.8	6.0	6.6	5.9	5.5	6.0	5.5	6.6	5.9	6.0	n.d.	n.d.	n.d.	n.d.
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	15.6	14.5	14.9	15.0	15.6	14.7	14.7	15.0	17.9	18.4	17.7	18.0	15.3	15.3	14.4	15.0	17.4	16.9	16.7	17.0	18.2	18.3	17.5	18.0	15.1	14.6	15.3	15.0
Etoricoxib	1.5	0.5	1.0	1.0	1.2	0.8	1.0	1.0	1.3	1.1	0.6	1.0	1.2	1.1	0.7	1.0	1.5	0.7	0.8	1.0	n.d.	n.d.	n.d.	n.d.	2.4	1.7	1.9	2.0
Flufenamic Acid	2.4	1.6	2.0	2.0	2.2	1.5	2.3	2.0	3.0	3.1	2.9	3.0	1.8	2.4	1.8	2.0	2.5	1.7	1.8	2.0	1.6	2.6	1.8	2.0	2.4	1.8	1.8	2.0
Furosemide	22.3	21.9	21.8	22.0	9.2	8.8	9.0	9.0	12.8	13.4	12.8	13.0	14.9	15.6	14.5	15.0	48.2	47.5	48.6	48.1	9.9	10.2	9.9	10.0	9.4	8.8	8.8	9.0
Ibuprofen	70.4	69.7	70.2	70.1	22.2	21.9	21.9	22.0	7.2	7.1	6.7	7.0	23.2	23.3	22.5	23.0	29.5	28.7	28.8	29.0	62.8	63.4	62.8	63.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	4.4	3.5	4.1	4.0	1.6	0.6	0.8	1.0	2.0	2.5	1.8	2.1	1.5	2.6	1.9	2.0	1.3	0.9	0.8	1.0	2.2	2.4	1.4	2.0	1.5	0.8	0.7	1.0
Methylparaben	n.d.	n.d.	n.d.	n.d.	17.5	16.6	16.9	17.0	17.9	18.4	17.7	18.0	17.8	18.3	17.9	18.0	18.4	17.8	17.8	18.0	18.6	19.5	18.9	19.0	n.d.	n.d.	n.d.	n.d.
Naproxen	31.4	30.5	31.1	31.0	5.4	4.9	4.7	5.0	n.d.	n.d.	n.d.	n.d.	8.0	8.6	7.4	8.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.2	1.9	1.9	2.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.1	0.9	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	32.9	32.2	33.3	32.8	n.d.	n.d.	n.d.	n.d.	1.2	1.2	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.3	1.5	2.2	2.0
Propylparaben	4.3	3.5	3.3	3.7	n.d.	n.d.	n.d.	n.d.	1.8	2.4	1.8	2.0	8.9	9.6	8.5	9.0	9.5	8.7	8.8	9.0	9.0	9.4	8.6	9.0	9.2	8.9	8.9	9.0
Salicylic Acid	23.4	22.5	23.1	23.0	19.2	18.5	19.3	19.0	23.4	23.1	22.5	23.0	18.5	18.1	17.4	18.0	23.6	22.9	22.5	23.0	19.0	19.4	18.6	19.0	19.3	18.6	19.1	19.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	16.9	17.2	16.9	17.0	n.d.	n.d.	n.d.	n.d.	12.6	11.8	12.2	12.2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	11.3	10.6	11.1	11.0	12.2	11.4	12.4	12.0	13.6	14.5	13.9	14.0	n.d.	n.d.	n.d.	n.d.	1.5	0.9	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	2.1	1.7	2.2	2.0	n.d.	n.d.	n.d.	n.d.	13.5	13.2	12.6	13.1	2.0	2.5	1.5	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.9	7.5	6.6	7.0	9.5	8.6	9.2	9.1	15.3	15.1	14.6	15.0	n.d.	n.d.	n.d.	n.d.
Triclosan	18.6	17.9	17.5	18.0	9.1	8.6	9.3	9.0	17.2	17.3	17.1	17.2	8.0	8.6	7.4	8.0	9.6	8.9	8.5	9.0	8.1	8.4	7.5	8.0	8.5	7.5	8.3	8.1
Warfarin	9.6	8.8	8.6	9.0	9.7	8.6	9.0	9.1	9.3	9.0	8.4	8.9	9.1	9.2	8.7	9.0	9.5	8.8	8.7	9.0	8.4	8.1	7.5	8.0	8.3	7.9	7.8	8.0

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S4 *(Continued)*

	S.37	S.37	S.37		S.38	S.38	S.38		S.39	S.39	S.39	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	1.3	1.0	1.3	1.2	4.0	4.2	3.8	4.0	n.d.	n.d.	n.d.	n.d.
Atorvastatin	1.6	1.0	0.7	1.1	21.2	21.2	20.6	21.0	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.8	3.3	2.9	3.0
Bisphenol A	9.3	8.8	9.2	9.1	13.7	14.6	13.7	14.0	18.9	19.3	18.8	19.0
Butylparaben	6.5	5.6	5.9	6.0	6.5	6.1	5.4	6.0	5.8	6.6	5.6	6.0
Caffeine	5.3	4.9	4.8	5.0	3.9	4.4	3.7	4.0	5.9	6.5	5.6	6.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	5.4	4.6	5.0	5.0	3.8	4.5	3.7	4.0	4.8	5.5	4.7	5.0
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	5.3	4.8	4.9	5.0	2.9	3.6	2.5	3.0	7.9	8.2	7.9	8.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	14.8	15.6	14.6	15.0	17.0	17.1	16.3	16.8
Etoricoxib	1.4	0.6	1.0	1.0	1.5	1.1	0.4	1.0	0.7	1.5	0.8	1.0
Flufenamic Acid	2.5	1.8	1.7	2.0	1.7	2.6	2.0	2.1	2.3	2.3	1.4	2.0
Furosemide	9.4	8.8	8.8	9.0	8.9	9.3	8.8	9.0	8.8	9.6	8.6	9.0
Ibuprofen	38.3	37.5	38.5	38.1	8.1	8.5	7.4	8.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	1.1	0.7	1.2	1.0	1.0	1.7	0.6	1.1	1.8	2.5	1.7	2.0
Methylparaben	13.4	12.8	12.8	13.0	n.d.	n.d.	n.d.	n.d.	13.8	14.3	13.9	14.0
Naproxen	4.2	3.4	4.4	4.0	7.0	7.5	6.5	7.0	7.1	7.5	6.4	7.0
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	6.0	6.5	5.5	6.0	5.7	6.5	5.8	6.0
Propylparaben	12.3	11.7	12.0	12.0	9.1	9.1	8.8	9.0	9.1	9.4	8.5	9.0
Salicylic Acid	16.3	15.8	15.9	16.0	14.8	15.5	14.7	15.0	17.9	18.6	17.5	18.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	17.9	18.6	17.5	18.0	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclocarban	8.2	7.7	8.1	8.0	10.1	10.3	9.6	10.0	5.1	5.3	4.6	5.0
Triclosan	8.2	7.9	7.9	8.0	7.7	8.4	7.9	8.0	9.0	9.5	8.5	9.0
Warfarin	8.1	7.5	7.8	7.8	7.7	8.7	7.9	8.1	9.3	9.5	8.5	9.1

a, b, c represent each replicate

* C_{mean} = mean concentration

** n.d.= not detected

Table S5. Individual PPCPs concentration (ng g^{-1}) in soil samples (So.n°) of the Albufera Natural Park, Valencia, Spain (n=3) .

	So.1	So.1	So.1		So.2	So.2	So.2		So.3	So.3	So.3		So.4	So.4	So.4		So.5	So.5	So.5		So.6	So.6	So.6		So.7	So.7	So.7	
Compound	*A*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	67.4	66.9	66.7	67.0	n.d.	n.d.	n.d.	n.d.	67.9	67.0	67.0	67.3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	8.9	8.7	9.0	8.9	6.2	5.6	6.2	6.0	3.3	2.5	3.2	3.0	9.6	8.8	8.6	9.0	10.3	9.4	10.0	9.9	4.2	4.3	3.8	4.1	8.1	7.5	8.4	8.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	n.d.	n.d.	n.d.	n.d.	22.4	21.5	22.1	22.0	24.4	23.5	24.1	24.0	4.4	3.8	4.1	4.1	1.1	0.4	1.5	1.0	24.1	24.7	23.5	24.1	n.d.	n.d.	n.d.	n.d.
Chloramphenicol	0.8	0.9	0.7	0.8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	2.1	1.7	2.1	2.0	3.1	2.4	3.5	3.0	1.3	0.7	1.0	1.0	1.5	0.8	0.7	1.0	n.d.	n.d.	n.d.	n.d.	1.4	1.5	0.7	1.2	1.2	0.7	1.1	1.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	3.0	3.1	3.1	3.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.2	1.9	1.9	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Etoricoxib	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	0.7	1.0	0.9	0.5	-0.2	-0.3	n.d.	n.d.	n.d.	n.d.	n.d.	51.3	50.6	51.1	51.0
Flufenamic Acid	1.1	1.1	1.0	1.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	1.8	1.9	2.3	2.0	4.4	3.5	4.1	4.0	10.7	9.8	9.8	10.1	n.d.	n.d.	n.d.	n.d.	7.3	6.6	7.1	7.0	4.0	4.5	3.5	4.0	3.6	2.7	2.7	3.0
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.4	0.6	1.0	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62.2	61.9	61.9	62.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	47.1	46.8	47.1	47.0	47.4	46.5	47.4	47.1	n.d.	n.d.	n.d.	n.d.	1.1	0.5	1.4	1.0
Methylparaben	n.d.	n.d.	n.d.	n.d.	3.1	2.6	3.3	3.0	2.2	1.5	2.3	2.0	2.6	1.7	1.7	2.0	2.5	1.4	2.1	2.0	2.7	3.6	2.7	3.0	3.2	2.6	3.5	3.1
Naproxen	0.8	1.1	1.1	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.9	1.5	0.6	1.0	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.2	1.6	2.2	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	30.3	29.3	30.1	29.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.3	0.7	1.0	n.d.	n.d.	n.d.	n.d.
Propylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.1	1.4	2.5	2.0
Salicylic Acid	8.8	8.7	8.7	8.7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.8	1.8	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.6	1.9	1.8	2.1	n.d.	n.d.	n.d.	n.d.	1.2	1.3	0.5	1.0	60.1	59.2	60.1	59.8
Triclocarban	0.9	0.9	0.9	0.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	3.9	4.0	4.0	4.0	3.3	2.7	3.0	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.2	1.1	0.7	1.0	n.d.	n.d.	n.d.	n.d.
Warfarin	0.9	1.0	1.1	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S5 *(Continued)*

	So.8	So.8	So.8		So.9	So.9	So.9		So.10	So.10	So.10		So.11	So.11	So.11		So.12	So.12	So.12		So.13	So.13	So.13		So.14	So.14	So.14	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	2.3	1.5	1.6	1.8	1.1	0.6	1.0	0.9	n.d.	n.d.	n.d.	n.d.	21.5	20.5	21.3	21.1	0.7	1.0	0.4	0.7	21.1	20.9	21.0	21.0	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	4.4	3.6	4.0	4.0	7.3	6.8	6.9	7.0	6.1	5.9	6.5	6.2	10.3	9.4	10.3	10.0	4.5	4.3	3.8	4.2	3.4	3.0	2.9	3.1	3.7	4.5	3.8	4.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	3.3	2.5	3.2	3.0	24.6	23.7	24.3	24.2	n.d.	n.d.	n.d.	n.d.	22.5	21.6	22.5	22.2	3.0	3.1	2.9	3.0	2.6	1.7	1.7	2.0	23.0	23.5	22.5	23.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.8	1.5	0.7	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	2.5	1.4	2.1	2.0	1.4	0.4	1.2	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	3.6	2.9	2.5	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Etoricoxib	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	n.d.	n.d.	n.d.	n.d.	3.4	2.6	3.0	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.4	2.4	3.2	3.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62.1	61.8	62.1	62.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	62.0	62.1	61.6	61.9
Metformin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	47.9	47.5	46.8	47.4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Methylparaben	n.d.	n.d.	n.d.	n.d.	2.6	1.7	1.7	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.2	0.5	0.9
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.3	3.7	4.0	4.0	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	30.5	29.9	29.6	30.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Propylparaben	n.d.	n.d.	n.d.	n.d.	2.6	1.9	1.5	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.0	1.1	0.9	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Salicylic Acid	n.d.	n.d.	n.d.	n.d.	3.6	2.7	2.7	3.0	n.d.	n.d.	n.d.	n.d.	2.4	1.6	2.0	2.0	1.9	2.5	1.9	2.1	20.8	19.6	20.2	20.2	1.7	2.4	1.9	2.0
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	n.d.	n.d.	n.d.	n.d.	60.2	59.4	60.4	60.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	n.d.	n.d.	n.d.	n.d.	1.3	0.6	1.4	1.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S5 *(Continued)*

	So.15	So.15	So.15		So.16	So.16	So.16		So.17	So.17	So.17		So.20	So.20	So.20		So.23	So.23	So.23		So.24	So.24	So.24		So.25	So.25	So.25	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	1.1	0.7	1.2	1.0	21.1	20.7	21.2	21.0	n.d.	n.d.	n.d.	n.d.	1.2	0.8	1.0	1.0	21.3	20.9	20.8	21.0	1.3	0.4	1.3	1.0	n.d.	n.d.	n.d.	n.d.
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	2.6	1.7	2.3	2.2	3.1	2.8	3.1	3.0	2.1	1.5	2.4	2.0	3.1	2.8	3.1	3.0	1.5	0.9	0.6	1.0	2.2	1.7	2.1	2.0	2.1	1.4	2.5	2.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	1.5	0.9	0.6	1.0	22.9	22.3	22.0	22.4	1.4	0.7	0.9	1.0	22.5	21.6	21.9	22.0	3.6	2.5	2.9	3.0	1.0	0.3	1.1	0.8	26.6	25.6	26.1	26.1
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Diclofenac	n.d.	n.d.	n.d.	n.d.	2.2	1.4	2.4	2.0	n.d.	n.d.	n.d.	n.d.	2.5	1.5	2.0	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Etoricoxib	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Methylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.5	0.8	0.7	1.0	1.6	0.8	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	4.3	3.2	3.9	3.8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	30.9	30.1	30.2	30.4	30.2	29.1	29.8	29.7	31.3	30.4	31.3	31.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	30.4	29.8	29.8	30.0
Propylparaben	1.6	0.8	0.6	1.0	1.6	0.8	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.3	3.0	3.0	3.1	n.d.	n.d.	n.d.	n.d.
Salicylic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	5.2	4.4	5.4	5.0	n.d.	n.d.	n.d.	n.d.	2.4	1.5	2.1	2.0	1.1	0.9	1.0	1.0	n.d.	n.d.	n.d.	n.d.
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	60.6	59.9	60.4	60.3	n.d.	n.d.	n.d.	n.d.	60.6	59.9	59.5	60.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.1	3.4	4.5	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S5 *(Continued)*

	So.26	So.26	So.26		So.29	So.29	So.29		So.30	So.30	So.30		So.31	So.31	So.31		So.32	So.32	So.32		So.33	So.33	So.33		So.34	So.34	So.34	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	1.4	0.5	1.1	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	21.1	21.4	21.1	21.2
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	7.1	7.5	7.0	7.2	2.5	2.1	2.0	2.2	9.0	8.6	9.1	8.9	4.6	3.9	3.5	4.0	n.d.	n.d.	n.d.	n.d.	3.6	2.9	2.5	3.0	15.0	15.1	14.9	15.0
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	22.9	23.5	22.6	23.0	23.5	22.9	22.9	23.1	n.d.	n.d.	n.d.	n.d.	23.3	22.5	23.2	23.0	1.2	0.7	0.8	0.9	23.4	22.5	23.1	23.0	3.4	3.2	2.4	3.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.3	6.8	6.9	7.0	n.d.	n.d.	n.d.	n.d.
Diclofenac	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.5	2.7	2.8	3.0	n.d.	n.d.	n.d.	n.d.	2.3	1.4	2.3	2.0	1.8	2.3	1.9	2.0
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	3.1	2.7	2.9	2.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.4	1.6	2.6	2.2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Etoricoxib	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	7.1	7.2	6.7	7.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8.2	7.9	7.9	8.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	0.9	1.5	0.6	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	48.2	47.4	48.4	48.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Methylparaben	n.d.	n.d.	n.d.	n.d.	4.1	3.4	4.5	4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.1	1.6	2.3	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.5	2.9	2.6	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	30.6	30.0	30.0	30.2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Propylparaben	21.0	21.2	20.8	21.0	22.5	21.4	22.1	22.0	n.d.	n.d.	n.d.	n.d.	3.3	2.4	3.3	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.7	2.7	2.8	2.7
Salicylic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.6	2.9	2.5	3.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.1	6.2	6.0	6.1
Simvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tramadol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	60.2	59.9	59.9	60.0	n.d.	n.d.	n.d.	n.d.	1.8	1.2	0.9	1.3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.6	1.6	1.8	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	0.8	1.7	1.1	1.2	n.d.	n.d.	n.d.	n.d.	1.3	0.5	1.2	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d.= not detected

Table S5. *(Continued)*

	So.35	So.35	So.35		So.41	So.41	So.41		So.42	So.42	So.42		So.43	So.43	So.43		So.44	So.44	So.44	
Compound	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}	*a*	*b*	*c*	C_{mean}
Alprazolam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Atenolol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.9	0.6	1.5	1.0
Atorvastatin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bezafibrate	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Bisphenol A	8.1	7.7	8.2	8.0	9.7	8.9	9.0	9.2	11.4	10.7	10.9	11.0	7.2	6.7	7.4	7.1	9.1	9.3	9.5	9.3
Butylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Caffeine	22.1	21.4	21.9	21.8	16.2	15.5	16.3	16.0	13.5	12.8	12.7	13.0	n.d.	n.d.	n.d.	n.d.	1.8	2.1	2.1	2.0
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Clofibric acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.2	7.2	7.5	7.3
Diclofenac	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.2	1.5	2.3	2.0	1.2	0.7	1.1	1.0	n.d.	n.d.	n.d.	n.d.
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ethylparaben	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.3	2.5	3.2	3.0	n.d.	n.d.	n.d.	n.d.
Etoricoxib	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Flufenamic Acid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Furosemide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ibuprofen	4.2	3.5	4.6	4.1	n.d.	n.d.	n.d.	n.d.	76.2	75.5	76.6	76.1	3.1	2.5	3.4	3.0	n.d.	n.d.	n.d.	n.d.
Indomethacin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Metformin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	47.1	46.8	47.1	47.0	n.d.	n.d.	n.d.	n.d.
Methylparaben	2.6	1.8	1.6	2.0	2.2	1.5	2.3	2.0	2.1	1.4	2.5	2.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.6	0.6	0.8	1.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Omeprazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Paracetamol	31.1	30.6	31.3	31.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Propylparaben	2.5	1.8	1.7	2.0	2.6	1.7	1.7	2.0	10.9	10.7	10.8	10.8	4.4	3.8	3.8	4.0	n.d.	n.d.	n.d.	n.d.
Salicylic Acid	18.2	17.9	18.2	18.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	4.6	5.0	5.4	5.0
Simvastatin	1.5	0.9	1.5	1.3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Thiamphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.5	3.1	3.1	2.9
Tramadol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	60.6	59.5	59.9	60.0	n.d.	n.d.	n.d.	n.d.	59.9	60.3	60.4	60.2
Triclocarban	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Triclosan	n.d.	n.d.	n.d.	n.d.	5.4	4.4	5.2	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Warfarin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

a, b, c represent each replicate
* C_{mean} = mean concentration
** n.d. = not detected

Table S6 - SDS and WC method in water matrix. Linearity (R^2), limit of detection (LOD), limit of quantification (LOQ) and matrix effect (ME).

PPCPs	R^2	LODs (ngL^{-1})	LOQs (ngL^{-1})	% ME
	SDS method			
Atenolol	0.99	15.00	45.00	-54
Bezafibrate	0.99	1.65	5.00	-6
Bisphenol A	0.99	6.65	20.00	-4
Butylparaben	0.99	1.65	5.00	49
Clofibric Acid	0.99	11.65	35.00	-56
Codeine	0.98	5.00	15.00	-46
Enalapril	0.99	1.65	5.00	55
Ethylparaben	0.99	1.65	5.00	-53
Etoricoxib	0.99	8.35	25.00	-98
Indomethacin	0.98	6.65	20.00	-86
Lorazepam	0.99	1.65	5.00	-94
Metformin	0.99	1.65	5.00	-69
Methylparaben	0.99	5.00	15.00	-49
Naproxen	0.98	3.35	10.00	-25
Propylparaben	0.99	1.65	5.00	50
Salicylic Acid	0.99	6.65	20.00	-52
Simvastatin	0.99	16.65	50.00	-95
Tramadol	0.99	1.65	5.00	-97
Triclocarban	0.99	1.65	5.00	-31
Triclosan	0.99	5.00	15.00	9
Warfarin	0.99	1.65	5.00	61
	WC method			
Alprazolam	0.99	1.65	5.00	-8
Atorvastatin	0.99	1.65	5.00	20
Caffeine	0.99	1.65	5.00	-76
Chloramphenicol	0.99	5.00	15.00	-28
Diclofenac	0.99	8.35	25.00	28
Flufenamic Acid	0.99	1.65	5.00	0
Furosemide	0.99	21.65	65.00	-56
Ibuprofen	0.99	3.30	10.00	3
Omeprazole	0.99	3.35	10.00	-40
Paracetamol	0.99	6.65	20.00	-90
Thiamphenicol	0.99	13.35	40.00	-49

Table S7- SDS and WC method in sediment and soil matrix. Linearity (R^2), limit of detection (LOD), limit of quantification (LOQ) and matrix effect (ME).

PPCPs	R^2	LODs (ng g^{-1} d.w.)	LOQs (ng g^{-1} d.w.)	% ME
	SDS method			
Atenolol	0.99	6.33	19.00	-15
Bezafibrate	0.99	0.33	1.00	-86
Butylparaben	0.99	0.33	1.00	-15
Clofibric Acid	0.99	2.33	7.00	24
Enalapril	0.99	0.33	1.00	8
Ethylparaben	0.99	0.33	1.00	-69
Etoricoxib	0.99	2.00	6.00	16
Indomethacin	0.98	1.33	4.00	-86
Lorazepam	0.99	0.33	1.00	2
Metformin	0.99	6.67	20.00	-6
Methylparaben	0.99	1.33	4.00	-63
Naproxen	0.98	1.33	4.00	-60
Propylparaben	0.99	0.33	1.00	-8
Salicylic Acid	0.99	0.33	1.00	-52
Simvastatin	0.99	4.00	12.00	70
Tramadol	0.99	0.67	2.00	-2
Triclocarban	0.99	1.67	5.00	-74
Triclosan	0.99	1.33	4.00	-81
Warfarin	0.99	0.33	1.00	-60
	WC method			
Alprazolam	0.99	0.33	1.00	2
Atorvastatin	0.99	0.33	1.00	7
Bisphenol A	0.99	0.67	2.00	-6
Caffeine	0.99	0.33	1.00	-6
Chloramphenicol	0.99	0.67	2.00	-9
Codeine	0.99	1.67	5.00	-27
Diclofenac	0.99	2.33	7.00	-1
Flufenamic Acid	0.99	1.33	4.00	8
Furosemide	0.99	5.00	15.00	-4
Ibuprofen	0.99	0.66	2.00	24
Omeprazole	0.99	6.67	20.00	70
Paracetamol	0.99	1.67	5.00	-20
Thiamphenicol	0.99	2.67	8.00	-15

SECCIÓN 4.
RESUMEN

01.

CONTAMINANTES EMERGENTES: FÁRMACOS Y PRODUCTOS PARA EL CUIDADO PERSONAL

La contaminación medio ambiental, debida a la actividad antrópica, ha crecido de forma exponencial en el último siglo. De hecho, muchos trabajos publicados hablan sobre la determinación de compuestos orgánicos en distintas matrices medioambientales. Algunos de estos principios activos son definidos como ***contaminantes emergentes*** (EC), porque tan sólo se han podido detectar durante estos últimos años gracias a la implantación de nuevas técnicas analíticas más sensibles. Recientemente, parte de ellos fueron añadidos en la "watch list" ("lista de observación"), debido a sus efectos adversos en el medio acuático, que establece la Directiva marco del agua de la EU [1, 2]. Por estas razones, esta tesis se ha centrado en una clase de contaminantes, fiel reflejo de la presión antrópica, los fármacos y productos del cuidado personal (PPCPs), incluyendo 32 compuestos seleccionados, con características físico-químicas específicas que se determinaron en varias matrices: aguas superficiales y residuales, sedimentos y suelos.

01.1 Una visión global sobre la preparación de muestras acuosas para determinar los PPCPs

La revisión realizada, que constituye la primera sección de esta tesis, presenta los principales procedimientos empleados, hasta hoy, para la preparación de muestras de agua, con el fin de extraer fármacos y producto para el cuidado personal, antes de ser analizados y detectados por técnicas cromatográficas (como, por ejemplo, la cromatografía liquida (LC) o de gases (GC) acopladas a espectrómetros de masas). Los PPCPs se aíslan, generalmente, a través de la Extracción en Fase Solida (SPE), una técnica que permite limpiar la muestra de los numerosos interferentes presentes en la matriz. Los sorbentes más usados, que constituyen las fases estacionarias de los cartuchos, trabajan en fase inversa, son de natura polimérica y presentan, en las terminaciones de las cadenas, sustituyentes específicos, como vinil-pirrolidona (ej. Oasis® HLB, Strata®X and Cleanert® PEP) y poliestireno-divinil-benceno (ej. Isolute® ENV+, Chromabond® HR-X and Bond ElutTM ENV). Estos permiten trabajar con un importante abanico de PPCPs, incluyendo compuestos de natura acida, básica y neutra. Otro tipo de cartuchos de extracción en fase solida son los denominados de "modo mixto" porque combinan el sorbente polimérico, con un intercambiador iónico que puede ser catiónico y aniónico, así como débil o fuerte, y se usa para garantizar la extracción optima de un rango de compuestos con características similares de acidez (intercambio aniónico) o basicidad (intercambio catiónico). Los resultados de la revisión destacan también la importancia de evaluar los distintos parámetros del método como peso sorbente (mg), capacidad (mL) y tamaño de poro (µm) de cada cartucho. Estos parámetros son importantes porque pueden influir sobre la eficiencia de las columnas, considerando las posibles interactuaciones entre los analitos y las superficies de los sorbentes. Generalmente, la cantidad de sorbente oscila entre 60 y 600 mg, y la más utilizada es de 200 mg. Respecto a las capacidades las más utilizadas son de 3 y 6 mL.

El volumen de muestra usado juega un papel clave, ya que este, casi siempre, es directamente proporcionado al efecto matriz, que puede interferir con los análisis, alterando la señal de los analitos. Se suele extraer volúmenes de muestras iguales o superiores a los 200 mL, en los 74% de los casos. Esta técnica consta de 4 pasos. El primer paso es el *acondicionamiento* de la fase estacionaria para favorecer la interacción del sorbente con los analitos, mediante un mecanismo llamado "solvatación". Los solventes que se utilizan con más frecuencia para este acondicionamiento son el metanol, seguido de una solución acuosa. El segundo, es el *paso de la muestra* a velocidad constante. Sucesivamente, para eliminar las impurezas retenidas en el empaque SPE, se aplica una *solución de lavado*, que suele ser agua destilada con eventuales ajustes de pH, y se aplica el vacío para secar los cartuchos. El último paso, la *elución,* favorece la recuperación de todos los analitos objecto de estudio, que interactúan con el sorbente formando enlaces de distinta natura química-física. En el caso de los fármacos extraídos con fases inversas clásicas, el eluyente más común es el metanol, con o sin ajuste de pH y solo o mezclado con otros solventes (ej. diclorometano). Finalmente, el extracto se evapora bajo una corriente de nitrógeno y se reconstituye para obtener la solución con los PPCPs concentrados. Esta solución, a veces viene filtrada con filtros de jeringa (compuestos de: nylon, PVDF, PTFE, RC, GHP, PP, etc.) y luego inyectada en el equipo analítico de referencia.

Otro aspecto que reseñar es la importancia de la preservación y conservación de las muestras, que generalmente se suelen enriquecer, antes de conservarlas y extraerlas, con compuestos o soluciones conservantes. Los compuestos más usados son agentes de carga, quelantes, antioxidantes, antimicrobianos, tensioactivos, etc. [3, 4]. Seguramente el más utilizado es el EDTA (ácido etilendiaminotetraacético), un agente quelante que puede mejorar la eficiencia de extracción de ciertos fármacos que también forman complejos con metales, como los antibióticos, liberando así los PPCPs [5]. Otros conservantes usados son antimicrobianos, como formaldehído, cloruro sódico, azida sódico y ácido cítrico, o antioxidantes, como ácido ascórbico y tiosulfato sódico. En la gran mayoría de los trabajos estudiados para realizar la revisión, se vio también cómo muchos se centran en el ajuste del pH de las muestras (pH=2-3), para evitar fenómenos de degradación y ionización, o para alcanzar el valor óptimo para la extracción. Otro pretratamiento aplicado en la preparación de muestras de aguas es la filtración, cuya función consiste en eliminar sustancias en suspensión, como partículas, coloides y microorganismos para evitar la obstrucción de los cartuchos SPE o interferencias importantes durante los otros procedimientos. Los filtros más usados son de microfibra de vidrio, con mallas que varían dentro del rango 0.20 – 1.60 µm.

Finalmente, se describen también técnicas emergentes como alternativas ventajosas a la clásica SPE, algunas de ellas definidas "Green-Chemistry" ("Química Verde") porque se centran en procedimientos más respetuosos con el medio ambiente, intentando reducir el uso de materiales como disolventes orgánicos y reactivos, como por ejemplo las microextracciones: Microextracción Líquido-Líquido Dispersiva (DLLME) o la

microextracción en fase sólida (SPME), caracterizadas por un procedimiento de limpieza muy rápido y volúmenes muy pequeños tanto de muestra como de disolvente extraente/eluyente, que reducen los residuos generados. Otras proponen dispositivos alternativos que mejoran la eficacia de la extracción, como el descrito por Tomai and et.[6], quienes proponen una extracción en fase solida con el uso de un dispositivo (oxidized buckypaper (BP) para Stir-Disc) que combinaba las propiedades de los nanotubos de carbono y la agitación magnética, mejorando de forma importante la eficacia y sensibilidad del proceso.

01.2 Perspectivas futuras para el desarrollo de nuevos métodos de residuos múltiples

Sin duda, el principal desafío en este campo es el desarrollo de nuevos métodos que puedan reducir el tiempo y los costos de los análisis, adoptando un enfoque respetuoso con el medioambiente que al mismo tiempo pueda permitir aislar una gama cada vez más amplia de PPCPs, incluyendo compuestos con propriedades (ej. la polaridad) completamente diferentes. El uso de métodos que combinan sorbentes con diferentes características químico-físicas, ya sea en el mismo cartucho, en paralelo, o incluso en serie para poder ampliar esta ventana de búsqueda es la tendencia más extendida [7, 8]. Sin embargo, para lograr este objetivo, es interesante ampliar el conocimiento sobre los mecanismos de interacción que ocurren entre los analitos y las fases estacionarias, y así identificar los mejores sorbentes, y proponer nuevas combinaciones. Definitivamente, otra perspectiva en la que se trabaja es mejorar e implementar el desarrollo de nuevas técnicas automatizadas, que permitan una preconcentración de los analitos en línea (On-line) y una limpieza de la matriz (clean-up) eficaz y rápida.

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02.

EL DESARROLLO DE LA METODOLOGÍA ANALÍTICA

Teniendo en cuenta todas las consideraciones resumidas en el apartado anterior (**01**) sobre la importancia científica de una correcta preparación de la muestra antes de ser analizada, en esta tesis, en primer lugar, se optimizó de forma sistemática las variables involucradas en la extracción en fase sólida de fármacos, para averiguar las mejores condiciones para aislar los PPCPs. El método desarrollado se basa en la utilización de "fases mixtas", sobre cuya eficacia, especialmente cuando se aplican a un rango de compuestos que carece de similitudes en cuanto a su carácter ácido, básico o neutro , existe todavía un importante desconocimiento.

A continuación, se describen las condiciones cromatográficas adoptadas, los diferentes estudios realizados para optimizar las recuperaciones tanto en agua como en sedimento y finalmente las dos nuevas metódicas prepuestas.

02.1 Método de determinación: Cromatografía líquida acoplada a un espectrómetro de masas en tándem con analizador de triple cuadrupolo

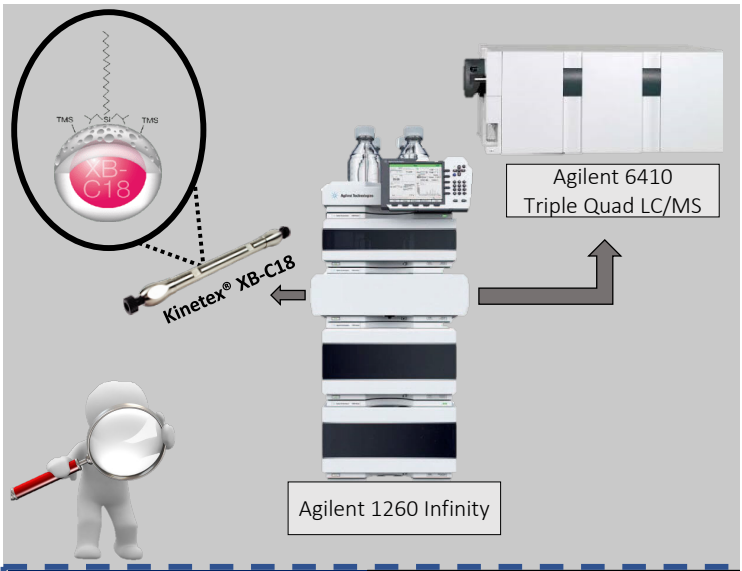
Los PPCPs seleccionados se separaron mediante cromatografía liquida de alta resolución (Agilent 1260 Infinity HPLC), y se identificaron gracias al acoplamiento con un espectrómetro de masas diferenciado por un triple cuadrupolo (Agilent 6410 triple-quadrupole mass spectromer). La cromatografía liquida es ideal para trabajar con estructuras orgánicas polares y moderadamente polares, y por esto es la técnica más utilizada en la determinación de fármacos que suelen tener polaridades medias altas.

La columna empleada para realizar las separaciones cromatográficas es una Kinetex® XB-C18 (Phenomenex), 50 x 2.10 mm (longitud x diámetro interno), 1.7 µm (tamaño de partícula) y 100 Å (tamaño de poro). El mecanismo de separación de esta columna es por fase inversa, gracias a la fase estacionaria constituida por un núcleo sólido de suporte de silicio, donde hay presentes cadenas de alquilo (octadecilo [C18]) con dos cadenas laterales de isobutilo y terminaciones TMS (tetrametilsilano) (**Figura R1**). Estas cadenas permiten una importante formación de enlaces de hidrógeno con los analitos y por tanto una mayor retención en la columna.

El espectrómetro en uso disponía como fuente de ionización la electrospray (ESI), que permitió trabajar en modalidad negativa (ESI-), más específica por compuestos ácidos, y en modalidad positiva (ESI+), por la determinación de PPCP con carácter básico o neutro. Las fases móviles utilizadas en la ESI- fueron: (A) 2.5 mM de fluoruro amónico en agua y (B) 2.5 mM de fluoruro amónico en metanol (MeOH). En la ESI+: (A) 0.1% de ácido fórmico en agua y (B) 0.1% de ácido fórmico en metanol. Se trabajó en gradiente, empezando la cursa cromatográfica con el 30% de la fase A, para después aumentar progresivamente hasta el 95%

(en el min 12) y manteniéndolo 8 min más hasta finalizar la inyección. El flujo constante fue de 0.2 mL/min, y cada muestra ha sido inyectada con un volumen de 5 µL. Los parámetros de espectrometría de masas fueron optimizados para los compuestos estudiados, a través el uso del software "*Agilent MassHunter Optimizer*", determinando los iones productos, la energía de colisión y el fragmentador. La modalidad de los análisis fue la *Monitorización de Reacciones Múltiples* (MRM). Todas las transiciones y los parámetros de cada compuesto han sido reportados en la *Tabla S2* (ANEXO de la *Publicación 2*). Finalmente, en la **Figura R1** se observa la esquematización de la fase estacionaria de la columna, el sistema HPLC/MS-MS, los PPCP buscados, diferenciándolos según el modo de ionización, las fases móviles utilizadas y las categorías terapéuticas de cada principio activo.

Figura R1- Esquema de la instrumentación utilizada para detectar los fármacos y los productos para el cuidado personal.



ESI (-): (A) = 2,5mM de NH_4F en H_2O (B) = 2,5mM de NH_4F en MeOH		ESI (+): (A) = 0,1% de ácido fórmico en H_2O (B) = 0,1% de ácido fórmico en MeOH	
Compuesto	**Categoría terapéutica**	**Compuesto**	**Categoría terapéutica**
Ácido clofíbrico	Regulador de lípidos	**Alprazolam**	Ansiolítico
Ácido flufenámico	Analgésico	**Atenolol**	Antihipertensivo
Ácido salicílico	Analgésico/Anticoagulante	**Atorvastatina**	Regulador de lípidos
Bezafibrato	Regulador de lípidos	**Cafeína**	Estimulante SNC
Bisfenol A	Aditivo plástico	**Codeína**	Analgésico
Butilparabeno	Preservativo	**Enalapril**	Antihipertensivo
Cloranfenicol	Antibiótico	**Etoricoxib**	Analgésico
Diclofenaco	Analgésico	**Lorazepam**	Ansiolítico
Etilparabeno	Preservativo	**Metformina**	Antidiabético
Furosemida	Antihipertensivo	**Omeprazol**	Gastrointestinal
Ibuprofeno	Analgésico	**Paracetamol**	Analgésico
Indometacina	Antibiótico	**Simvastatina**	Regulador de lípidos
Metilparabeno	Preservativo	**Tramadol**	Analgésico
Naproxeno	Analgésico		
Propiliparabeno	Preservativo		
Tiamfenicol	Antibiótico		
Triclocarbán	Antibacteriano		
Triclosán	Antibacteriano		
Warfarina	Anticoagulante		

02.2 Procedimiento de extracción solido-liquido (SLE)

El procedimiento para la extracción solido-liquido (SLE) de los PPCPs en sedimentos y suelos se basó en el método propuesto por Carmona et al. [1]. La mezcla de los disolventes de extracción estaba constituida por 5 mL de cada: MeOH, agua Milli-Q y el buffer McIlvaine-EDTA (pH=4,5), añadidos por separado a 1 g de muestra liofilizada (sedimentos) o secada al aire (suelos). El conjunto se homogeneiza agitando 5 min (Vortex) y sonicando 10 min. Finalmente, se centrifuga por 6 min a 3000 rpm y el sobrenadante se diluye a 200 mL con agua Milli-Q, antes de ser extraído por Extracción en Fase Solida (SPE).

Se realizó un estudio de recuperación para evaluar cómo los tres disolventes pudiesen mejorar o afectar la extracción de los sedimentos. Con este fin, se examinó el comportamiento utilizando: (i) exclusivamente agua Milli-Q; (ii) agua Milli-Q y el buffer McIlvaine-EDTA (*mezcla 1*); (iii) MeOH, agua MilliQ y el buffer McIlvaine-EDTA (*mezcla 2*). La elección de estos disolventes se hizo porque la polaridad de los analitos es de alta a moderada (como ya comentado previamente) por lo que serán solubles en solventes polares. Además, algunos fármacos, como los antibióticos, tienden a formar complejos con los cationes inorgánicos presentes en las arcillas y por lo tanto se recomienda el uso de un agente complejante como el EDTA. Este primer estudio fue realizado en ausencia y presencia de una muestra de sedimento, para evaluar la eficiencia de las mezclas de extracción en el momento de interactuar con la SPE y también para ver como la matriz influye sobre la recuperación. Posteriormente, la SPE se realizó a través del cartucho con sorbente clásico HLB (Strata-X), activado con 6 mL de MeOH y 6 mL de agua Milli-Q. Una vez pasada la muestra, lo cartuchos se dejaron secar con vacío para 15 min y los analitos se eluyeron con 6 ml MeOH y 3 ml de MeOH/DCM (diclorometano) (v/v, 1:1). En los resultados obtenidos exclusivamente con los disolventes se observa que, para la mayoría de los PPCP, las recuperaciones obtenidas con cualquiera de ellos fueron similares, registrando diferencias de ± 10 puntos porcentuales. En algunos casos el uso exclusivo de agua Milli-Q favoreció la extracción (como por el bisfenol A, diclofenaco y la furosemida), indicando un efecto negativo del MeOH, debido a su mayor poder eluyente que puede reducir la retención en la SPE. Al contrario, la *mezcla 2* tuvo los mejores resultados para la simvastatina, tramadol, cafeína y etoricoxib, muy probablemente gracias a la actividad complejante del EDTA. Además, se comprobó cómo la evaporación del extracto, obtenido por SPE, pueda afectar a la recuperación. En cuanto este procedimiento incluye diferentes parámetros, como la temperatura del plato, el flujo de nitrógeno y el tiempo de evaporación, que pueden degradar las estructuras de los compuestos más volátiles y termolábiles. La prueba fue realizada con la *mezcla 2*, fortificándola con concentraciones más altas (200 µg/L), y diluyendo el extracto final (6 mL MeOH) con agua para obtener una proporción 70-30 (H_2O-MeOH), de tal manera que se elimine el paso de evaporación. Resultados interesantes se observaron para algunos de los compuestos estudiados (por ej. alprazolam, codeína, enalapril, lorazepam, etc.) pero se decidió no eliminar este paso porque las recuperaciones si bien fueron algo mejores, no sufrieron una reducción significativa (las máximas perdidas debidas a este proceso fueron

de un 20%), y la eliminación de la evaporación reduce del factor de concentración y como consecuencia la sensibilidad del método. A continuación, se comprobó que también en presencia del sedimento, las recuperaciones mejores eran con los disolventes de la *mezcla 2*. Pero se observó que algunos analitos básicos, caracterizados por sus altas polaridades y tendencia a ionizarse a pH ambiental (ej. metformina, etoricoxib, simvastatina), no proporcionaron recuperaciones apropiadas. Y teniendo en cuenta la importancia de estos compuestos desde un punto de vista medioambiental, ya que sus presencias en el medio ambiente han sido ampliamente constatadas, a pesar de las bajas recuperaciones, se intentó estudiar y optimizar las condiciones de otro paso en la preparación de la muestra: la *Extracción En Fase Solida* (SPE).

02.3 Optimización de la Extracción en Fase Solida (SPE)

En esta tesis doctoral, los cartuchos testados para la SPE fueron dos, comprados en Phenomenex (Torrance, CA, USA). El primero, *Strata®-X (33µm, 200 mg/6mL)* caracterizado por un sorbente de natura polimérica que trabaja en fase inversa. El segundo, *Strata®-X-CW (33µm, 200 mg/6mL),* un sorbente polimérico con un intercambiador catiónico débil, generalmente usado para aislar compuestos básicos.

La optimización de la SPE se hizo a través distintos ensayos. Los protocolos aplicados fueron los siguientes:

· La activación de los cartuchos fue realizada mediante el uso de 6 mL de MeOH y 6 mL de H_2O, y en algunos casos también se utilizaron 6 mL de una *solución acuosa 2 mM de SDS* (*dodecil sulfato de sodio*).

· A continuación, 200 o 250 mL de muestra pasaron por los mismos a velocidad constante, gracias al uso del vacío. Los cartuchos se limpiaron con 6 mL de H_2O y se dejaron secar 15 min y los analitos se eluyeron mediante fuerza de gravedad.

· En el caso del *Strata®-X* con 6 mL de MeOH y 3 mL MeOH/DCM (1:1). Mientras, en el cartucho a intercambio iónico con 6 mL MeOH/NH_4OH (33%) (amoniaco) (95:5).

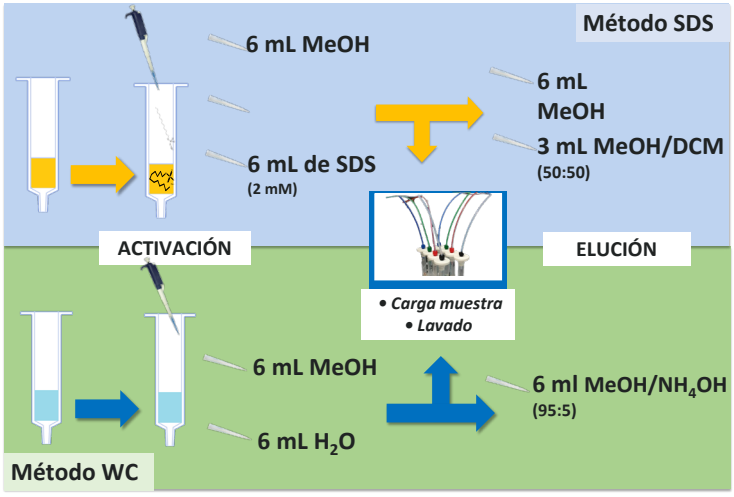
· Posteriormente, los extractos se evaporan mediante el evaporador de nitrógeno Stuart® (T = 40 °C) y se reconstituyen con 1 mL H_2O-MeOH (70:30).

Se evaluó si el uso de la *solución SDS,* durante la activación, contribuye a mejorar la retención de algunos compuestos que registraban recuperaciones muy bajas. A tal fin, se hicieron estudios de recuperaciones, usando la *mezcla 2*, y condicionando los dos sorbentes con y sin SDS. El SDS, queda adsorbido en la fase estacionaria HLB y forma un par iónico

con los analitos catiónicos favoreciendo su retención. Como, por ejemplo, en el caso de la metformina, extraída con los cartuchos Strata-X, que pasó de una recuperación irrisoria (2%) al 109%, o como por la simvastatina de un 30% a 130%. En la *Tabla S5* (ANEXO de la *Publicación 2*) se puede observar que los mejores resultados con SDS se obtuvieron con Strata-X, aunque los resultados también fueron buenos para Strata-X-CW (más de la mitad de los PPCPs con recuperaciones > del 70%), con la excepción de algunos compuestos difíciles de recuperar como la indometacina, la metformina y el omeprazol. La reducción de la recuperación con el intercambio catiónico, activado por SDS, probablemente fue debida al fenómeno de competencia entre las moléculas de SDS y los PPCPs para ocupar el sitio activo de la fase estacionaria, reduciendo la formación del par iónico y entonces la retención de los analitos. Además, se evaluó por este sorbente, si el ajuste ácido del pH de la muestra (pH=2,5), en ausencia de SDS, podía mejorar la extracción. Los resultados mostraron cómo en la mayoría de los casos los porcentajes de recuperación eran parecidos, aunque el tramadol presentaba un incremento alrededor del 30%, y algunos PPCPs presentaron una disminución de la recuperación debida, muy probablemente, a una degradación estructural de la molécula a pH acido (ej. omeprazol).

Finalmente, comparando los resultados obtenidos con los distintos cartuchos en presencia o menos del SDS, se propusieron dos métodos de extracción representados gráficamente en la **Figura R2**. El ***método SDS***, caracterizado por el cartucho Strata-X, que viene activado con metanol, agua, y la solución de SDS (6 mL de cada disolvente). El ***método WC***, en el cual se usa el cartucho a intercambio catiónico (Strata-X-CW), que viene condicionado sin la solución de SDS. Este sorbente generalmente se usa para extraer compuestos básicos, y aquí se propuso para recuperar también compuestos ácidos por la buena ventana de recuperación obtenida (48-101%), con excepción de la indometacina y del triclocarban.

Figura R2 – Grafica del protocolo de Extracción en Fase Solida (SPE) de los dos métodos propuestos. En naranja está representado el cartucho Strata®-X (método SDS) con la presencia del SDS (sodio dodecil sulfato) y en azul clarito el cartucho Strata®-X-CW (método CW).



02.4 Validación del método

Los métodos fueron validados para aguas superficiales (ríos, lagos, etc.) y sedimento, determinando los límites de detección y cuantificación (LODs y LOQs), la desviación standard relativa (%RSD) y el efecto matriz (ME) por cada principio activo. En los estudios de recuperación, se eligieron blancos, realizando un análisis previo para evaluar la presencia o no de los contaminantes. Donde esto no fue posible, el área del pico del analito presente en el blanco se restó del área del pico de las muestras enriquecidas.

La cuantificación se realizó por patrón interno o externo, dependiendo del compuesto, tal y como se describe en la *Tabla S2* (ANEXO de la *Publicación 2*). Se utilizaron tres rectas de calibrado distintas: una para el modo de ionización negativo (ESI-) solubilizando los patrones en H_2O-MeOH (70:30, v/v) y dos por la modalidad positiva (ESI+). Una idéntica a la anterior y otra disolviendo los PPCPs en una solución SDS(2mM)-MeOH (70:30, v/v), ya que se observó que algunos compuestos, como el tramadol, en presencia del SDS modificaban el tiempo de retención. Los R^2 de las rectas fueron siempre mayor de 0,998 mostrando un comportamiento adecuado en cualquier de los disolventes usados, y también en los extractos de matriz. Además, se realizaron test de recuperaciones con los dos métodos y en cuatro distintos niveles, tanto en agua (50, 125, 250 y 500 ngL^{-1}) como en sedimentos (10, 25, 50 y 100 ng g^{-1}). Las deviaciones estándar, índices de reproducibilidad del método, fueron buenas con valores inferiores al 23% para los dos métodos y para todos los PPCPs.

Los límites de cuantificación (LOQs) en agua oscilaron entre 5 y 75 ngL^{-1} con el *método SDS*. El valor registrado más común y el más bajo fue 5 ngL^{-1}, y los compuestos menos sensibles fueron la furosemida (75 ngL^{-1}) y el omeprazol (no recuperado). Mientras, con el *método WC* el rango de los LOQs estaba entre 5 y 65 ngL^{-1}, con la única excepción de la simvastatina (115 ngL^{-1}). Casi la mitad de las substancias analizadas presentaban el valor más bajo (5 ngL^{-1}).

En cambio, en los sedimentos, con el *método SDS se obtuvieron* LOQs entre 1 y 20 ng g^{-1}, para la metformina (identificada como la menos sensible). Con el uso de los cartuchos mixtos de intercambio catiónico, la sensibilidad oscilo de 1 a 30 ng g^{-1} y la simvastatina se destacó por su menor sensibilidad.

Las recuperaciones fueron mayores del 80% para más de la mitad de los compuestos seleccionados. Comparando las recuperaciones del nivel más alto (500 ngL^{-1} y 100 ng g^{-1}) se observa cómo el *método WC* tiene mejores recuperaciones para la atorvastatina, cafeína y omeprazol en las dos matrices, y esto es más apreciable en los sedimentos. Mientras, en agua, las cuantificaciones con el *método SDS* de indometacina, triclosán, bisfenol A y triclocarban enseñaban un aumento de la recuperación entre 26 y 54 puntos porcentuales, con la diferencia más alta para el triclocarban.

Los efectos de matriz (% ME) fueron calculados con la siguiente ecuación:

$$ME\ (\%) = \left(\frac{p_{extr.}}{p_{se}} - 1\right) x\ 100$$

Donde el $p_{extr.}$ es la pendiente de la ecuación linear del extracto fortificado y p_{se} es la pendiente de la ecuación de la recta del calibrado obtenida con los patrones preparados en disolvente. Los resultados han sido compilados en las *Tablas 1-4* (Publicación 2). El *método SDS* presenta recuperaciones mejores para muchos compuestos, pero también efectos de matriz más elevados. La *Figura 4* (Publicación 2) representa los porcentajes de PPCPs distribuidos según los ME absolutos y las recuperaciones y muestra la tendencia general de los dos métodos.

Finalmente, los resultados nos muestran que ambos métodos tienen ventajas y desventajas, dependiendo de la matriz y del compuesto buscado. En la *Tabla S6* (ANEXO Publicación 2), se analiza gráficamente el mejor método para cada PPCP y matriz. Por ejemplo, el *m. WC* es el mejor para determinar atorvastatina y omeprazol. Además, es la condición ideal en agua para buscar furosemida, tiamfenicol y alprazolam, y en sedimento, para recuperar diclofenaco, ibuprofeno y cafeína. En cambio, el *m. SDS* en muestras de agua resulta más eficaz por el bisfenol A, indometacina, tramadol, triclocarban y triclosán, y en muestras de sedimentos para el bezafibrato, enalapril, metformina, simvastatina y triclosán.

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03.

APLICACIÓN DE LOS MÉTODOS A MUESTRAS DEL PARQUE NATURAL DE L'ALBUFERA

Los métodos propuestos en el anterior apartado (**02**) se aplicaron a muestras (agua, sedimento y suelo) del Parque Natural de L'Albufera tomadas de diciembre (2016) a febrero (2017). Este parque, con un área de 21120 hectáreas, se encuentra a unos 10 km de la ciudad de Valencia (España) y se caracteriza por la presencia de cultivos de arroz, cítricos y huertas. La hidromorfología de la zona se diferencia por la presencia del río Turia al norte, del río Júcar y su afluente (río Magro) al suroeste, y una red de sesenta y tres canales y acequias que llevan el agua al lago de L'Albufera, situado en el centro del parque. Por obtener una visión global del estado de contaminación del área, se eligieron 43 puntos de muestreo ubicados en toda la zona, incluyendo 84 muestras totales de sedimentos, suelos y aguas superficiales. Todas las muestras recogidas, que se diferenciaban por los puntos, las coordenadas y por la tipología de suelo y agua, han sido reportadas en la *Tabla S2* (ANEXO Publicación 3). Además, se realizó un seguimiento de las aguas residuales en entrada y salida de diez estaciones depuradoras de aguas residuales (EDAR), situadas en el parque o alrededor del mismo, para averiguar si estas aguas pudrieran ser una fuente antropogénica de contaminación, ya que muchas de ellas se utilizan para el riego.

03.1. Aguas residuales

Las diez depuradoras, situadas alrededor del humedal, elegidas para detectar la presencia de los PPCPs en los influentes y efluentes, fueron: *Pinedo 1* (PI), *Pinedo 2* (PII), *Port de Catarroja* (CAT), *Quart Benager* (QB), *Sueca* (SU), *Perelló-Sueca* (PS), *Perelló* (PE), *Palmar* (PAL), *Saler* (SAL) y *Albufera Sud* (AS). Sus principales características, relativas a los tratamientos aplicados han sido reportadas en la *Tabla S3* del ANEXO Publicación 3.

En los influentes, de los 32 PPCP analizados, no se detectaron ni el tiamfenicol y ni el ácido clofíbrico. Este resultado es comparable con los obtenidos para la mayoría de las aguas residuales de España y de otras partes del mundo, donde, estos compuestos raramente han sido detectado, o donde presentaban concentraciones bajas (<107 ng L^{-1}) [1-4]. El número de compuestos detectados en cada influente osciló entre 24 y 29, y veintiuno de ellos se encontraron en todas las depuradoras (alprazolam, bezafibrato, BPA, cafeína, diclofenaco, etilparabeno, etoricoxib, ácido flufenámico, ibuprofeno, lorazepam, metformina, metilparabeno, naproxeno, paracetamol, propilparabeno, ácido salicílico, simvastatina y tramadol). De estos, cafeína, ibuprofeno, naproxeno, paracetamol y simvastatina fueron los que presentaban las concentraciones más altas (valores medianos > 1000 ngL^{-1}), esta tendencia también fue de acuerdo a las reportadas en Europa, América y Asia [4, 5]. Las concentraciones altas pueden ser justificadas por el uso intensivo de estos compuestos. Analgésicos y antiinflamatorios (paracetamol, ibuprofeno y naproxeno) se dispensan frecuentemente sin prescripción médica. La simvastatina es una de las estatinas más usada para reducir los niveles de colesterol. La cafeína es también ampliamente usada en bebidas energéticas y cómo componente farmacéutico. La concentración más alta detectada en todos los influentes se encontró en la depuradora de *Sueca*, donde se registró la presencia de 57600 ngL^{-1} de ibuprofeno. Finalmente, triclosán, enalapril y furosemida presentaban una alta fre-

cuencia (>80%) y concentraciones importantes (entre 102 y 310 ngL^{-1}).

Se analizaron también las muestras de salida (efluentes), para evaluar la posible contaminación del agua reutilizada para regar los campos, y para poder determinar la eficiencia de cada depuradora en la remoción de estos contaminantes orgánicos. En este caso, el número de principios activos detectado en cada depuradora oscilaba de 19 a 24. Los fármacos encontrados con alta frecuencia (≥ 80%) y una elevada concentración media (> 100 ngL^{-1}) fueron diclofenaco, ácido flufenámico, furosemida, ácido salicílico y tramadol. Muchos efluentes presentaron concentraciones altas de tramadol, con el pico mayor de 1291 ng L^{-1} en la depuradora de *Pinedo 2*. Este resultado se puede atribuir a una baja eficiencia de las EDARs en la remoción de este principio activo, como ya ocurrió en otros estudios [6-8]. Solamente tres de las diez EDAR monitoreadas mostraban una eficiencia positiva en la eliminación de tramadol, y en dos de ellas se aplicó un tratamiento de cloración. Esto está de acuerdo con la solución propuesta en el trabajo de Antonopoulou [9] que proponía tratamientos oxidativos avanzados para favorecer la eliminación del tramadol.

Por último, se calculó la eficiencia media y no media en la eliminación de cada compuesto como reportado en la *Figura 2* (ANEXO Publicación 3) y en la *Tabla 3* (ANEXO Publicación 4). La figura describe gráficamente la eficiencia de eliminación de los PPCP incluyendo tres tendencias: alta, media y baja. Los compuestos con peor remoción han sido alprazolam, atenolol, bezafibrato, diclofenaco, etoricoxib, ácido flufenámico, lorazepam y tramadol. En algunos casos se registraron también valores de remoción negativos, esto podría explicarse por las reacciones químicas que son capaces de formar el producto dentro de las EDAR, o por la liberación del compuesto a partir de la desorción de material particulado (lodo) durante los tratamientos de las aguas residuales o por pequeñas diferencias entre el muestreo del afluente y efluente. Mientras, las mejores eliminaciones se registraron para 13 contaminantes, dentro de los cuales, cafeína, ibuprofeno, paracetamol y metformina.

03.2. Aguas superficiales

Treinta y dos aguas superficiales, que incluían ríos, canales, acequias y muestras del lago, fueron tomadas y analizadas. En ninguna muestra se encontró omeprazol o atorvastatina. Por el contrario, cafeína y bisfenol A (BPA) se detectaron en todas, con un rango de concentraciones que iba respetivamente de 12 a 205 ng L^{-1}, y de 11 a 668 ng L^{-1}. Importante es subrayar que el bisfenol es un componente ubicuo presente en numerosos envases para alimentos, bebidas y productos para el cuidado personal. Además, la concentración de este compuesto es regulada por diferentes instituciones, como la FDA (Food and Drug Administration) y EFSA (European Food Safety Authority) debido a sus efectos adversos para la salud [10].

Los PPCPs que se diferenciaron por presentar una elevada concentración media (≥ 50 ngL^{-1}) e incidencia (≥ 50%) eran diclofenaco, metilparabeno, metformina, tramadol y ácido

salicílico. Otros, cómo, atorvastatina, etilparabeno, etoricoxib, ácido flufenámico, paracetamol, propilparabeno, triclocarban, triclosán y warfarina registraban frecuencias altas, pero concentraciones medias más bajas (< 50 ngL^{-1}). Se observó también que algunos contaminantes (ej. atorvastatina, naproxeno, furosemida, ibuprofeno, etc.) se detectaban esporádicamente, pero a concentraciones elevadas, esto muy probablemente es un indicador de la liberación periódica de agua no tratada en algunos puntos, lo que podría explicar porque estos compuestos, que deberían haber sido eliminados en las EDAR, aparecieran en altas concentraciones.
Finalmente, los picos más altos fueron registrados para metformina (375 ngL^{-1}), cafeína (668 ngL^{-1}) y ácido salicílico (858 ngL^{-1}).

03.3. Sedimentos

El número de muestras de sedimentos analizados (19) era inferior al de las otras matrices medioambientales. Esto fue porque recientemente muchos canales habían sido recubiertos con hormigón, y otros, recubiertos desde más antiguo, se limpian periódicamente, y aún no habían acumulado una cantidad suficiente de sedimento.

Veintidós contaminantes se detectaron con frecuencia (en casi la mitad de las muestras). Cinco de estos (BPA, etilparabeno, furosemida, ibuprofeno y acido salicílico) registraron una concentración media superior a 10 ng g^{-1}. Otro comportamiento interesante se observó para 15 compuestos, con una presencia frecuente (> 42% de las muestras), pero con bajas concentraciones (< 10ng g^{-1}), cómo, por ejemplo, atenolol, cafeína y diclofenaco. Los picos más altos se cuantificaron en el caso de furosemida (48 ng g^{-1}) e ibuprofeno (100 ng g^{-1}).

Una consideración importante es que algunos compuestos a pesar de que presentar una buena solubilidad en agua (ej. atenolol, cafeína, metilparabeno y tiamfenicol) se detectaron en esta matriz con una elevada frecuencia. La misma tendencia se observa en otros estudios publicados en el pasado. Lo que sugiere que otros mecanismos distintos a la interacción hidrofóbica, contribuyen también a la retención y acumulación de estas substancias, cómo, por ejemplo, la retención iónica que puede ocurrir en arcilla presente en los sedimentos. En el caso de los parabenos, existe la posibilidad de que se formen in situ a partir de la degradación de otros parabenos (con cadenas de alquilo más grandes) presentes en el agua.

03.4. Suelos

Se analizaron treinta y tres muestras de suelos. Los compuestos detectados con mayor frecuencia (casi en el 40% de los análisis) fueron 7 (con el pico máximo de 26 ng g^{-1}): BPA, cafeína, diclofenaco, ácido salicílico, propilparabeno, atenolol y metilparabeno. De estos,

el BPA se encontró casi siempre (31 muestras) con una concentración media de 6 ng g^{-1}. Mientras, las concentraciones más altas se registraron por tramadol (60 ng g^{-1}), lorazepam (62ng g^{-1}), alprazolam (67 ng g^{-1}) e ibuprofeno (76 ng g^{-1}).

La mayoría de los PPCPs se detectaron solo en una muestra. Se consideró como no relevantes aquellos compuestos encontrados en pocas muestras (entre una y seis muestras) y a concentraciones bajas (<7 ng g^{-1}). Esta tendencia podría explicarse por el hecho de que la contaminación del suelo no es tan directa, cómo en el caso del agua y los sedimentos. Los PPCPs llegan al suelo a través del agua de riego o del uso de enmiendas orgánicas y por esto no siempre tienen la capacidad de acumularse en esta matriz.

03.5. Estado de contaminación del Parque Natural de L'Albufera: evolución temporal (2008-2017)

Se decidió comparar los resultados obtenidos en este estudio, con otro trabajo publicado por nuestro grupo de investigación en el 2011 [11]. Donde se analizaron las mismas matrices (aguas, sedimentos y suelos) recogidas en 20 puntos de muestreo en el mismo Parque, objeto de estudio de la presente tesis. Los PPCPs comparables (porque formaban parte de los analitos seleccionados también en el estudio anterior) fueron cinco: codeína, ácido clofíbrico, diclofenaco, ibuprofeno y paracetamol.

En las muestras de agua todos los compuestos (con excepción del ibuprofeno) se han detectado en el presente estudio con mayor abundancia con un incremento, para casi todo los PPCPs (excepto codeína) incluido en el rango entre 23 y 48%. Respecto a los valores de las concentraciones, también fueron más altos en los resultados de esta tesis (con excepción del ácido clofíbrico).

Los sedimentos del 2008 mostraron una mayor incidencia de codeína y paracetamol (> de 56 y 16 puntos porcentuales), pero sin embargo la concentración media de paracetamol fue mayor en el 2017 (3.00 vs 0.66 ng g^{-1}). Y los restante PPCPs fueron más abundantes en el estudio más reciente, por ejemplo, el diclofenaco registró una frecuencia del 89%, mientras en el pasado no fue detectado.

Por último, en los suelos, casi todos los contaminantes (a excepción del paracetamol) buscados en el 2008 no se detectaron. Mientras, en el 2017, codeína, ibuprofeno y diclofenaco se encontraron entre el 9 y el 45 % de las muestras. Finalmente, el ácido clofíbrico no estaba presente en ninguna muestra de los dos estudios.

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04.

INFLUENCIAS ANTROPOGÉNICAS: GEODISTRIBUCIÓN DE LOS PPCPs Y CONSIDERACIONES ESTADÍSTICAS

Los datos relacionados con la presencia de PPCPs en las distintas matrices, permitió observar la distribución geográfica en todo el territorio y evaluar la presión antrópica, dependiendo del área involucrada, calculando las diferencias estadísticamente significativas entre las concentraciones de los contaminantes en diferentes áreas. En este estudio también se correlaciona las concentraciones de PPCPs en cada punto con los parámetros medioambientales (tipos de agua, ubicación, usos del suelo, pH, etc.)

04.1. Distribución de los PPCP

Las concentraciones más altas se registraban en los puntos cercanos a las depuradoras en la parte norte del parque, cerca de la ciudad de Valencia, y especialmente cerca del Río Turia. Esto se justifica por la importante presión antropogénica derivada de esta ciudad, donde el consumo de estas sustancias es mucho mayor y donde hay una densidad de población catorce veces mayor que en la zona sur del Parque, con 1.280.000 habitantes solo en Valencia y su área metropolitana frente a los 91.000 de la zona sur. También se obtuvieron resultados parecidos en otros trabajos, donde la cercanía a una EDAR, que sirve a una población importante, contribuía para que se registrasen concentraciones altas. Cómo, por ejemplo, en el delta del Ebro (España) [1], en el estuario del Amazonas (Brasil) [2] o en las redes de riego de Al-Hassa (Arabia Saudita) [3].

El ANOVA realizado muestra diferencias significativas entre las zonas (norte o sur), para algunos compuestos: atenolol, BPA, cafeína, ácido clofíbrico y flufenámico, furosemida, tramadol e ibuprofeno. Todos estos PPCPs presentaban concentraciones más altas en el norte, excepto el ibuprofeno que muestra las concentraciones más elevadas en el sur, probablemente debido a la descarga de aguas residuales sin tratar de pequeños pueblos o distritos (ya que las EDAR tienen una alta eficiencia de eliminación por este compuesto).

Además, se evaluó la contaminación de las aguas diferenciándolas por tipología de fuente o uso: lago, ríos, canales que conectan el lago con el mar, o canales de arroz, cítricos y huertas. Por ejemplo, las aguas utilizadas para regar los arrozales registraron una concentración significativamente más elevada de ácido flufenámico, tramadol, atenolol y cafeína. Estos últimos tres presentaban también valores significativamente altos para el agua usada para regar las huertas. Por otra parte, en el lago, algunos PPCPs registraban concentraciones más bajas comparadas con las otras fuentes de agua (ej. atenolol, furosemida y naproxeno) muestra de la degradación de estos compuestos en el medioambiente debido a factores bióticos y abióticos.

Los ***sedimentos***, como se ha comentado anteriormente, tenían concentraciones más altas que los suelos. También para esta matriz se obtuvieron diferencias significativas para las distintas áreas estudiadas. En particular, en el sur se detectaron las concentraciones más altas para cafeína, ibuprofeno (cómo en el caso del agua), ácido salicílico y simvastatina,

mientras, en el norte, las concentraciones más elevadas fueron para triclocarban y los parabenos (etil- y metil-). Estos resultados podrían reflejar una depuración de las aguas residuales más deficiente para estos contaminantes en el sur, y en el norte un alto ato consumo de productos para el cuido personal asociable con el estilo de vida urbano de la ciudad de Valencia.

Por otro lado, los niveles de PPCPs en los sedimentos de los canales de riego de los cultivos de la huerta y los del lago mostraron diferencias estadísticamente significativas entre ellos y con otras fuentes de agua para trece compuestos (ej. atenolol, cafeína, ibuprofeno, warfarina, etc.). Finalmente, considerando el distinto uso del suelo, las mayores diferencias se presentaron entre los cultivos de cítricos y las huertas.

En cuanto a los ***suelos*** la zona norte registró los valores más importantes para los parabenos, alprazolam y metformina. Mientras, en la zona sur los PPCPs que presentaron mayores concentraciones fueron atenolol, etoricoxib y tramadol. Asimismo, dependiendo del tipo de agua utilizada para el riego del suelo se observaron diferencias significativas, principalmente entre las zonas regadas por el agua del lago y las de los cítricos. Por ejemplo, en el área de los cítricos, diclofenaco, metilparabeno, simvastatina, ibuprofeno, paracetamol y alprazolam registraban las concentraciones más elevadas. Con respecto a la diferenciación por usos del suelo, las zonas pantanosas cercanas al lago y los suelos de huerta mostraron las diferencias más marcadas, cómo en el caso de atenolol, BPA, etoricoxib y ácido salicílico.

04.2 Consideraciones estadísticas: correlaciones con los parámetros medioambientales

Las principales correlaciones entre las características físico-químicas de las muestras y la distribución de los fármacos se incluyen en esta tesis. Los resultados muestran cómo el *pH* es la característica del *agua* que tiene más conexión con la mayoría de los fármacos de este estudio presentando una relación inversa, lo que significa que cuanto mayor es el pH, menor es la concentración de fármacos. Esto se puede explicar porque muchas propiedades de los PPCPs, como la solubilidad, la polaridad, las constantes de disociación ácida (valores de pKa) y el coeficiente de distribución (KD), dependen del pH. Además, otro fenómeno que parece influir en la dinámica de los productos farmacéuticos es la *salinización,* qué se debe principalmente a la intrusión marina en las aguas subterráneas, promovida por la sobreexplotación de los acuíferos. Esto se traduce con repercusiones en las relaciones estadísticas observadas entre los PPCPs y los parámetros químicos de la muestra (conductividad eléctrica, resistividad, Mg y K). La salinidad disminuye (correlación negativa) o aumenta (correlación positiva) la solubilidad en el agua de los contaminantes, dependiendo de las propiedades fisicoquímicas de los mismos. Además, se observó también una relación positiva relevante entre la presencia de nitratos o nitritos y algunos compuestos

específicos (enalapril, metformina e indometacina). Esta correlación se podría justificar por la conexión que existe entre estos PPCPs, los NO_3^- y los NO_2^- en sus características farmacocinéticas en el metabolismo humano y de otros mamíferos [4], una actividad que también podría manifestarse en el medioambiente por la presencia de numerosas enzimas.

En la matriz de ***sedimento***, la movilidad de los PPCPs está influenciada firmemente por la conductividad eléctrica, la cantidad de carbonato de calcio y el pH. Además, juegan un papel clave las fracciones de partículas (limo, arcilla y arena total) con las que algunas substancias pueden interactuar y asociarse viéndose dañadas en la recuperación. Así es en los casos de cafeína, ibuprofeno, propilparabeno o ácido salicílico, cómo confirmado por los modelos de regresión lineal.

Finalmente, en el ***suelo***, como en el agua, la salinidad (con los parámetros que dependen de ella: conductividad eléctrica, Na^+, K^+, etc.) es el principal factor que influye en las relaciones estadísticas entre los fármacos y las características del suelo. Adicionalmente, la influencia de la materia orgánica y de los carbonatos fue más significativa que la que se encontró en el sedimento, lo cual fue confirmado por los modelos de regresión lineal y el PCA (40,91% de varianza explicada).

05.

EVALUACIÓN DEL RIESGO AMBIENTAL

El posible impacto sobre el ecosistema de estos compuestos fue evaluado considerando el índice de riesgo ecológico o cociente de riesgo (HQ) para tres niveles tróficos de los ecosistemas acuáticos (*algae, Daphnia Magna y pez*). Esté índice tiene en cuenta la relación entre exposición (marcada por las concentraciones medias y máximas encontradas en las muestras de agua) y toxicidad (a través de la concentración letal LC_{50} de los valores sin efecto observable). Estos últimos valores se obtuvieron mediante el software ECOSAR™, que los calcula a través de los modelos QSAR (relación cuantitativa estructura-actividad). Teniendo en cuenta que el nivel de riesgo ecológico puede encontrarse en tres rangos distintos, alto riesgo (HQ > 1), riesgo moderato (0.1 < HQ ≤ 1) o bajo (HQ < 0.1), los resultados evidenciaban que la mayoría de los PPCPs registraban un bajo riesgo ecológico. El mayor HQ (calculado con las concentraciones medias) fue el de la cafeína, la cual presentaba un riesgo moderado en algas, que es el organismo más sensible de los tres (de acuerdo con los descrito anteriormente en literatura). Mientras, el HQ, determinado con las concentraciones máximas, registró el riesgo de la cafeína como alto (HQ > 1), y el riesgo del tramadol como moderado para los tres niveles tróficos.

Además, se evaluó el HQ en cada punto como a la suma de todos los contaminantes presentes en cada muestra de agua analizada, sumando los índices de riesgo ecológico de cada compuesto (ΣHQ). Los resultados nos enseñaban como el sistema acuático fuese seguro para las *dafnias y los peces* (aunque dos puntos proporcionan valores mayores de 0.1 para peces) y menos para las *algas verdes*. Por este último organismo fue interesante observar que los dos puntos de muestreo más cercanos a la ciudad de Valencia registraban un alto índice de riesgo ecológico, debido a la sumatoria de los PPCPs.

Afortunadamente, esta evaluación sobre el impacto ecológico muestra que la calidad del agua del parque Natural de La Albufera, con respecto a la presencia de los PPCPs que se estudiaron, sigue siendo apropiada para asegurar el desarrollo de la biota. Pero, el estudio marca también la importancia de seguir monitoreando estos parámetros para asegurar la viabilidad futura del parque, ya que la calidad del agua se mostró en parte comprometida por la presencia de estos compuestos.

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CONCLUSIONES

ES

CONCLUSIONES

Según los objetivos establecidos en la presente tesis doctoral, la investigación llevada a cabo y los resultados obtenidos, se han alcanzado las siguientes conclusiones:

Primera. La revisión bibliográfica realizada muestra que actualmente, la extracción en fase sólida, off-line y en el formato de cartucho constituye el procedimiento más común para extraer PPCPs de las matrices acuosas. Muchos de los métodos más recientes e innovadores se basan en la combinación de sorbentes en el mismo cartucho (mixed mode) o de varios cartuchos con distintos sorbentes en paralelo o en tándem, para ampliar el número de substancias detectables, incluyendo aquellas con polaridades muy diferentes.

Segunda. La evaluación sistemática de dos procedimientos analíticos basados en la extracción en fase sólida, a través del *método SDS* (formación de par iónico) y del *método WC* (mixed mode), para detectar los PPCPs en agua y sedimentos, demostró que estos métodos son ventajosos para fármacos básicos y neutros que son de alta a moderadamente polares y están ionizados a pH medioambientales. Además, pueden proporcionar también parámetros de validación adecuados para los productos de carácter ácido.

Tercera. El *método WC*, en agua, proporcionó límites de cuantificación (LOQ) entre 5 y 65 ngL^{-1}, con la única excepción de la simvastatina (LOQ 115 ngL^{-1}). En sedimento, los LOQs alcanzados eran de 1 a 30 ng g^{-1}. Se describen por primera vez recuperaciones para los compuestos ácidos utilizando sorbentes mixtos que incluyen un intercambiador catiónico débil, recomendados generalmente para extraer compuestos básicos. Estas fueron adecuadas (para el 80 % de los compuestos ≥ 70%).

Cuarta. El *método SDS*, caracterizado por la activación de los cartuchos (de sorbente clásico tipo balance hidrófilo-lipófilo) con *Dodecil Sulfato* (contraión), permitió alcanzar mejores recuperaciones de algunos PPCPs problemáticos de carácter básico cómo metformina, simvastatina, naproxeno, tramadol y etoricoxib. Los LOQs, en agua, varían entre 5 y 75 ng L^{-1}. Mientras, en sedimento, entre 1 y 20 ng g^{-1}.

Quinta. El estudio y optimización de los métodos de extracción muestra que es posible perfeccionar los procedimientos analíticos para obtener las mejores recuperaciones para el creciente número de PPCPs detectados frecuentemente en las muestras ambientales.

Sexta. El seguimiento de los patrones de contaminación realizado en el Parque Natural de L'Albufera muestra la contribución de la presión antrópica a la alteración del ecosistema, ya que se encontró un gran porcentaje de los PPCPs estudiados, en las distintas matrices, a concentraciones de ng L^{-1} en aguas y ng g^{-1} en suelos y sedimentos.

Séptima. Varios fármacos se detectaron con altas frecuencias en las aguas superficiales. Cafeína y bisfenol A se detectaron en todas las muestras. Metformina (375 ngL^{-1}), cafeína (668 ngL^{-1}), ácido salicílico (858 ngL^{-1}) y tramadol (1264 ngL^{-1}) presentaron las mayores concentraciones. Suelos y sedimentos también mostraron la presencia de varios PPCPs. Las concentraciones más altas (>60 ng g^{-1}) fueron destacadas por ibuprofeno, alprazolam y lorazepam.

Octava. Los influentes de diez depuradoras, que rodean el Parque, muestran concentraciones altas (>1000 ngL^{-1}) de cafeína, ibuprofeno, naproxeno, paracetamol y simvastatina. Los compuestos que peor se eliminan han sido alprazolam, atenolol, bezafibrato, diclofenaco, etoricoxib, ácido flufenámico, lorazepam y tramadol. Las concentraciones detectadas en los efluentes de las depuradoras indican que estas pueden ser consideradas unas de las fuerzas antropogénicas en juego en la contaminación del parque.

Novena. El análisis estadístico realizado, así como la distribución espacial, indicaron que la presencia de algunos compuestos estaba relacionada con las características del lugar. Existen diferencias significativas entre las partes norte y sur del parque, según el tipo de agua y los usos del suelo, probablemente relacionadas con las prácticas agrícolas y los distintos origines de las aguas utilizadas.

Decima. La evaluación del riesgo ambiental para los contaminantes emergentes indica que la cafeína es el único PPCP que puede representar un riesgo significativo, y que, en concentraciones más altas, el tramadol también puede ser motivo de preocupación. Sin embargo, el agua, aunque todavía de calidad aceptable, presenta un riesgo importante hacia a los organismos más sensibles, si se consideran las sumas de los PPCPs presentes en cada muestra.

Definitivamente, la **conclusión general** es que los resultados de esta tesis han permitido, a través de una revisión bibliográfica, desarrollar dos métodos analíticos robustos para determinar numerosos *PPCPs* en distintitas matrices medioambientales. Los mismos métodos se han podido aplicar a muestras reales para evaluar el estado de contaminación de un parqué natural como lo de L'Albufera, evaluando algunas de las posibles fuerzas antropogénicas en juego. Los resultados señalaron la importancia de optimizar los tratamientos de remoción y el desarrollo de nuevas barreras para evitar los vertidos de *contaminantes emergentes* a estos entornos sensibles. Seguramente, un seguimiento crónico de este sitio podría ayudar a proporcionar datos a las autoridades competentes para poder intervenir en caso de alto riesgo para la salud humana y ambiental. Finalmente, es necesaria la realización de más estudios sobre el impacto ecotoxicológico a corto y largo plazo en especies animales y vegetales, teniendo también en cuenta el posible efecto sinérgico de los PPCPs.

EN

CONCLUSIONS

According to the objectives established in this PhD thesis, the research carried out and the results obtained the conclusions are:

First. The review carried out shows that *Solid Phase Extraction*, off-line mode and cartridge format is currently the most common procedure to extract PPCPs from aqueous matrices. Many of the newest and most innovative methods rely on combining sorbents in the same cartridge (mixed mode) or multiple cartridges with different sorbents in parallel or in tandem, to expand the number of detectable substances, including those characterized by very different polarities.

Second. The systematic evaluation of two analytical procedures based on solid phase extraction, through the *SDS method* (formation of ion pairs) and the *WC method* (mixed mode), to detect PPCPs in water and sediments, showed that these methods are advantageous for basic and neutral drugs, characterized by medium-high polarity and that ionize at ambient pH. Furthermore, they can provide adequate validation parameters even for acid products.

Third. The *WC method*, in water, provided limits of quantification (LOQs) between 5 and 65 ngL^{-1}, with only exception of simvastatin (LOQ 115 ngL^{-1}). In sediments, the LOQs

achieved ranged from 1 to 30 ng g^{-1}. For the first time, recoveries of acidic compounds are described with the use of mixed sorbents that include a weak cation exchanger, generally recommended to extract basic compounds. These recoveries were appropriate (for 80% of compounds ≥ 70%).

Fourth. The *SDS method*, characterized by the cartridge activation (characterized by the classic hydrophilic-lipophilic balance sorbent) with Sodium Dodecyl Sulphate (SDS), allowed to obtain better recoveries of some problematic PPCPs of a basic nature, such as metformin, simvastatin, naproxen, tramadol and etoricoxib. The LOQs, in water, were between 5 and 75 ng L^{-1}. While, in sediments, were between 1 and 20 ng g^{-1}.

Fifth. The study and optimization of extraction methods show that it is possible to improve the analytical procedures to obtain better recoveries for an increasing number of PPCPs, which are frequently detected in environmental samples.

Sixth. The pollution monitoring models carried out in the Albufera Natural Park shows the contribution of anthropogenic pressure to the ecosystem alteration, since a large percentage of the PPCPs studied, that were found in the different matrices, at ngL^{-1} concentrations in water and ng g^{-1} in soils and sediments.

Seventh. Several medicaments have been detected with high frequencies in surface waters. Caffeine and bisphenol A were determined in all samples. Metformin (375 ngL^{-1}), caffeine (668 ngL^{-1}), salicylic acid (858 ngL^{-1}) and tramadol (1264 ngL^{-1}) had the highest concentrations. Soils and sediments also showed contamination by various PPCPs. The highest concentrations (> 60 ng g^{-1}) have been identified for ibuprofen, alprazolam and lorazepam.

Eight. The influents of ten WWTPs, located at surrounding area of the Park, show high concentrations (> 1000 ngL^{-1}) for caffeine, ibuprofen, naproxen, paracetamol and simvastatin. The worst removed compounds were alprazolam, atenolol, bezafibrate, diclofenac, etoricoxib, flufenamic acid, lorazepam and tramadol. The concentrations detected in the effluent wastewater indicate that these can be considered one of the anthropic forces that play a role in the pollution of the Park.

Ninth. The statistical analysis carried out, as well as the spatial distribution, indicated that the presence of some compounds was related to the characteristics of the place. There are significant differences between the northern and southern areas of the park, depending on the type of water and land use, probably linked to agricultural practices and the different origin of the water used.

Tenth. The environmental risk assessment of emerging contaminants indicates that *caffeine* is the only PPCP that can pose a significant risk and that, at higher concentrations,

tramadol can also be a cause for concern. However, water, although still of acceptable quality, presents a significant risk to the most sensitive organisms, if we consider the sums of PPCPs present in each sample.

Surely, the **general conclusion** is that the results of this PhD thesis have enabled, through a bibliographic review, to develop two robust analytical methods to determine numerous *PPCPs* in different environmental matrices. The same methods were applied to real samples to evaluate the *contamination status* of a natural park such as the Albufera, evaluating some of the possible anthropogenic forces at play. Results indicated the importance to optimize removal treatments and to develop new barriers to prevent the emerging contaminants release into these sensitive environments.

IT

CONCLUSIONI

In base agli obiettivi stabiliti in questa tesi di dottorato, alla ricerca svolta e ai risultati ottenuti, sono state raggiunte le seguenti conclusioni:

Prima. La revisione bibliografica effettuata mostra che attualmente l'estrazione in fase solida, off-line e in formato cartucce è la procedura più comune per estrarre PPCPs in matrici acquose. Molti dei metodi più recenti e innovativi si basano sulla combinazione di sorbenti nella stessa cartuccia (mixed mode) o di più cartucce con diversi sorbenti in parallelo o in tandem, per espandere il ventaglio di sostanze rilevabili, includendo analiti con polarità molto diverse.

Seconda. La valutazione sistematica di due procedure analitiche basate sull'estrazione in fase solida, attraverso il *metodo SDS* (formazione di coppie ioniche) e il *metodo WC* (mixed mode), per determinare i PPCPs in acqua e sedimenti, ha mostrato che questi metodi sono vantaggiosi per farmaci basici e neutri, con polarità medio-alte e che si ionizzano a pH ambientali. Inoltre, possono fornire parametri di convalida adeguati anche per i prodotti acidi.

Terza. Il *metodo WC*, in acqua, ha fornito limiti di quantificazione (LOQs) compresi tra 5 e 65 ngL^{-1}, con la sola eccezione della simvastatina (LOQ 115 ngL^{-1}). Nei sedimenti, i

LOQs raggiunti erano compresi tra 1 e 30 ng g^{-1}. Importanti recuperi per composti acidi (per l'80% dei composti ≥ 70%) sono descritti per la prima volta con sorbenti misti che includono uno scambiatore cationico debole, generalmente consigliato per estrarre composti basici.

Quarta. Il *metodo SDS*, caratterizzato dall'attivazione delle cartucce (caraterrizzate dal classico sorbente idrofilo-lipofilo equilibrio, HLB) con *laurilsolfato di sodio (SDS)*, ha permesso di ottenere migliori recuperi di alcuni PPCPs problematici di natura basica, quali metformina, simvastatina, naprossene, tramadolo ed etoricoxib. I LOQs, in acqua, variano tra 5 e 75 ng L^{-1}. Mentre, nei sedimenti, tra 1 e 20 ng g^{-1}.

Quinta. Lo studio e l'ottimizzazione dei metodi di estrazione mostrano che è possibile potenziare le procedure analitiche per ottenere recuperi migliori per un numero crescente di PPCPs, i quali sono frequentemente rilevati nei campioni ambientali.

Sesta. Il monitoraggio dei modelli di inquinamento effettuato nel Parco Naturale dell'Albufera mostra il contributo della pressione antropica all'alterazione dell'ecosistema, poiché una grande percentuale dei PPCPs studiati è stata trovata nelle diverse matrici, a concentrazioni di ng L^{-1} in acqua e ng g^{-1} in terreni e sedimenti.

Settima. Diversi farmaci sono stati rilevati con alte frequenze nelle acque superficiali. La caffeina e il bisfenolo A sono stati determinati in tutti i campioni. La metformina (375 ngL^{-1}), la caffeina (668 ngL^{-1}), l'acido salicilico (858 ngL^{-1}) e il tramadolo (1264 ngL^{-1}) presentavano le concentrazioni più elevate. Anche suoli e sedimenti hanno mostrato una contaminazione da parte dei vari PPCPs. Le concentrazioni più elevate (> 60 ng g^{-1}) sono state identificate nell'ibuprofene, alprazolam e lorazepam.

Ottava. Gli influenti di dieci impianti di depurazione, che circondano il Parco, mostrano alte concentrazioni (>1000 ngL^{-1}) di caffeina, ibuprofene, naprossene, paracetamolo e simvastatina. I composti peggiormente rimossi sono stati alprazolam, atenololo, bezafibrato, diclofenac, etoricoxib, acido flufenamico, lorazepam e tramadolo. Le concentrazioni rilevate negli effluenti degli impianti di depurazione indicano che questi possono essere considerati una delle forze antropiche in gioco nell'inquinamento del parco.

Nona. L'analisi statistica effettuata, così come la distribuzione spaziale, ha indicato che la presenza di alcuni composti era correlata alle caratteristiche del luogo. Esistono differenze significative tra la parte settentrionale e quella meridionale del parco, a seconda del tipo di utilizzo dell'acqua e del suolo, probabilmente legate alle pratiche agricole e alla diversa provenienza delle acque utilizzate.

Decima. La valutazione del rischio ambientale dei contaminanti emergenti indica che la *caffeina* è l'unico PPCP che può rappresentare un rischio significativo e che, a concen-

trazioni più elevate, anche il *tramadolo* può essere motivo di preoccupazione. Tuttavia, l'acqua, sebbene ancora di qualità accettabile, presenta un rischio significativo nei confronti degli organismi più sensibili, se si considerano le somme dei PPCPs presenti in ogni campione.

In definitiva, la **conclusione principale** è che i risultati di questa tesi hanno permesso, attraverso una revisione bibliografica, di sviluppare due metodi analitici robusti per determinare numerosi *PPCPs* in diverse matrici ambientali. Gli stessi metodi sono stati applicati a campioni reali per valutare lo stato di contaminazione di un parco naturale come l'Albufera, valutando alcune delle possibili forze antropiche in gioco. I risultati hanno indicato l'importanza di ottimizzare i trattamenti di rimozione e di sviluppare nuove barriere per evitare lo scarico di *inquinanti emergenti* in questi ambienti sensibili. Certamente, un monitoraggio cronico di quest'area potrebbe aiutare a fornire dati alle autorità competenti per poter intervenire in caso di alto rischio per la salute umana e ambientale. Infine, sono sicuramente necessari ulteriori studi sull'impatto eco-tossicologico a breve e lungo termine nelle specie animali e vegetali, tenendo anche conto del possibile effetto sinergico dei PPCPs.

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Diseño editorial de Eva Martín Pérez.

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