TRANSPORT, DISTRIBUTION, AND THE FATE OF EMERGING CONTAMINANTS IN WASTEWATER-RECEIVING RIVERS UNDER MULTIPLE STRESS CONDITIONS

Ladislav Mandarić

Doctoral Thesis

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LADISLAV MANDARIĆ

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The doctoral program in Water Science and Technology

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Thesis submitted in fulfillment of the requirements for the degree of Doctor from the University of Girona

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Declare:

That the doctoral thesis entitled "**Transport, distribution, and the fate of emerging contaminants in wastewater-receiving rivers under multiple stress conditions**" presented by **Ladislav Mandarić** to obtain a doctoral degree from the University of Girona have been completed under my supervision.

For all intents and purposes, I hereby sign this document.

Signature

Prof. Sergi Sabater Cortés

Prof. Mira Petrović

Girona, April 2018

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This thesis is only a beginning of my journey.

LIST OF PUBLICATIONS

The results of this Ph.D. Thesis have been published or submitted in scientific journals included in the Journal Citation Report of the Institute of Scientific Information.

Chapter 1.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
EINECS	European Inventory of Existing Commercial Chemical Substances
EPA	Environmental Protection Agency
EQS	Environmental Quality Standards
D.F.	Average detection frequency
D.O.	Dissolved oxygen
Dow	Octanol/water distribution factor
ESI	Electrospray Ionisation
GC	Gas chromatography
H	Henry's law constant
HR-MS	High-resolution mass spectrometry
K_{biol}	Biodegradation rate constant
*K*d	Partition coefficient
*K*oc	Organic carbon/water partition coefficient
*K*ow	Octanol/water partition coefficient
LC	Liquid chromatography
LOD	Limit of detection
LOQ	Limit of quantification
NI	Negative electrospray ionization
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PCA	Principal Component Analysis
PCPs	Personal care product
PhACs	Pharmaceutically active compounds
PI	Positive electrospray ionization
p*K*a	Acidity
POPs	Persistent organic pollutants
PPCPs	Pharmaceuticals and personal care products
QqLIT-MS/MS	Triple quadrupole linear ion trap tandem mass spectrometry
QqTOF	Quadrupole time of flight
r	Pearson's moment correlation factor

SM	Supplementary material
SPE	Solid phase extraction
SRM	Selected reaction monitoring
TOF	Time of flight
UHPLC	Ultra-high-performance liquid chromatography
WFD	Water Framework Directive
WWTP	Wastewater treatment plant

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SUMMARY

The pharmaceutically active compounds (PhACs) are amongst the emerging contaminants of anthropogenic origin with the most continuous input into the aquatic environment.Their continuous arrival makes them pseudo-persistent contaminants, that is, being transformation and removal rates compensated by their continuous discharge into the environment. Once released to the aquatic environment, a number of processes govern their fate and transport. Biodegradation, abiotic oxidation, and hydrolysis, photolysis, adsorption/desorption, dissolution, volatilization, and dispersion are the most important in-stream attenuation processes involved. However, the relative importance of these processes depends on the rates at which they occur under natural environmental conditions. These rates are, in turn, dependent on the chemical structure and properties of the substance and its distribution in the various compartments of the environment. Therefore, understanding the transport, distribution, and fate of PhACs is a prerequisite for a thorough assessment of the risk they represent in wastewater-receiving rivers under multiple stress. Among multiple stressors in the Mediterranean aquatic environment, water scarcity has direct and indirect effects, on distribution and fate of the PhACs.

The main aim of this thesis was to establish a link between the urban origin of chemical contamination (e.g. PhACs) and other stressors, particularly associated to water scarcity (Chapter 1, 2 and 3). Research has been performed in one Alpine (Chapter 1) and two Mediterranean river basins (Chapter 2 and 3). Effects of the river flow variability on the recovery potential of the rivers (natural in-stream attenuation) have been studied in the tributary streams of the lower Ebro River (Chapter 2) and the Evrotas River (Chapter 3). Results have shown that occurrence and spatiotemporal distribution of PhACs in the fragile Alpine and Mediterranean aquatic environments is subjected to a strong intra-annual variability of the stream flow, while effects of multiple stress conditions may be amplified under water scarcity conditions (e.g. drought), thus resulting in the increased concentrations levels of PhACs in river water and sediments. Increased water travel time and simultaneously longer residence time of PhACs within the river stretch or waterbody during low flow conditions in the intermittent Mediterranean rivers and streams contributed considerably to the generally higher in-stream attenuation of PhACs.

RESUM (català)

Els compostos farmacèutics actius (PhACs) es troben entre els contaminants emergents d'origen antropogènic amb entrada contínuada en el medi aquàtic. La seva contínua arribada els fa contaminants pseudo-persistents, és a dir, en que la transformació i les taxes de remoció són compensades per la seva descàrrega contínua a la medi ambient. Un cop alliberats al medi aquàtic, diversos processos governen la seva destinació i el seu transport. La biodegradació, l'oxidació abiótica i la hidròlisi, la fotòlisi, l'adsorció / desorció, la dissolució, la volatilització i la dispersió són els processos d'atenuació més importants que esdevenen a la xarxa de drenatge. Tanmateix, la importància relativa d'aquests processos depèn de les taxes associades a les condicions ambientals naturals. Aquestes taxes, al seu torn, depenen de l'estructura química i de les propietats de la substància i de la seva distribució en els diferents compartiments de l'entorn. Per tant, comprendre el transport, la distribució i el destí dels PhACs és un requisit previ per a una avaluació exhaustiva del risc que representen en rius que són receptors d'aigües residuals i están sota múltiples estrès. Entre els estressors múltiples en el medi aquàtic mediterrani, l'escassetat d'aigua té efectes directes i indirectes sobre la distribució i el destí dels PhACs.

L'objectiu principal d'aquesta tesi ha estat establir un vincle entre l'origen urbà de la contaminació química (per exemple, els PhACs) i altres estressors, particularment associats a l'escassetat d'aigua (capítols 1, 2 i 3). Les investigacions s'han realitzat en un riu Alpi (Capítol 1) i dues conques del Mediterrani (Capítol 2 i 3). Els efectes de la variabilitat del flux fluvial sobre el potencial de recuperació dels rius (atenuació natural) han estat estudiats en rius del baix riu Ebre (capítol 2) i del riu Evrotas (capítol 3). Els resultats mostren l'aparició i la distribució espaciotemporal dels PhACs en els fràgils entorns aquàtics alpins i mediterranis, sotmesos a una forta variabilitat intra-anual del flux, mentre que els efectes de múltiples condicions d'estrès poden ser amplificades sota condicions d'escassetat d'aigua, que afavoreixen concentracions més elevades de PhACs en aigües i sediments. L'augment del temps del temps de residència dels PhACs durant les condicions de baix cabal als rius i rierols intermitents de la regió mediterrània contribueix a una més alta atenuació de les PhACs.

RESUMEN (castellano)

Los compuestos farmacéuticos activos (PhACs) se encuentran entre los contaminantes emergentes de origen antropogénico con entrada contínua en el medio acuático. Su continua llegada los hace contaminantes pseudo-persistentes, es decir, en que la transformación y las tasas de remoción son compensadas por su descarga continua al medio. Una vez liberados al medio acuático, varios procesos gobiernan su destino y su transporte. La biodegradación, la oxidación abiótica y la hidrólisis, la fotólisis, la adsorción / desorción, la disolución, la volatilización y la dispersión son los procesos de atenuación más importantes que se convierten en la red de drenaje. Sin embargo, la importancia relativa de estos procesos depende de las tasas asociadas a las condiciones ambientales naturales. Estas tasas, a su vez, dependen de la estructura química y de las propiedades de las sustancias y de su distribución en los diferentes compartimentos. Por tanto, comprender los mecanismos de transporte, distribución y destino de los PhACs es un requisito previo para una evaluación exhaustiva del riesgo que representan en ríos receptores de aguas residuales sometidos a múltiple estrés. Entre los estresores múltiples en el medio acuático mediterráneo, la escasez de agua tiene efectos directos e indirectos sobre la distribución y el destino de los PhACs.

El objetivo principal de esta tesis ha sido determinar el vínculo entre el origen urbano de la contaminación química (por ejemplo, los PhACs) y otros estresores, particularmente asociados a la escasez de agua (capítulos 1, 2 y 3). Las investigaciones se han realizado en un río Alpino (Capítulo 1) y dos cuencas Mediterráneas (Capítulo 2 y 3). Los efectos de la variabilidad del flujo fluvial sobre el potencial de recuperación de los ríos (atenuación natural) han sido estudiados en ríos del bajo río Ebro (capítulo 2) y del río Evrotas (capítulo 3). Los resultados muestran la aparición y la distribución espacio-temporal de los PhACs en los frágiles entornos acuáticos alpinos y mediterráneos, sometidos a una fuerte variabilidad intra-anual de flujo, mientras que los efectos de múltiple estrés pueden ser amplificadas bajo condiciones de escasez de agua, que favorecen concentraciones más elevadas de PhACs en aguas y sedimentos. El aumento del tiempo del tiempo de residencia de los PhACs durante las condiciones de bajo caudal en ríos y arroyos intermitentes de la región mediterránea contribuye a una más alta atenuación de las PhACs.

1. GENERAL INTRODUCTION

“When the well is dry, we know the worth of water.”

(Benjamin Franklin, 1706-1790)

1.1. Rivers, as the source of life

Water represents fundamental element responsible for life on the planet Earth which covers more than two-thirds of the Earth's surface. Within the water masses on the planet Earth, only 2.5% is fresh water, and surface waters represent only 1.2% of the fresh water. Most of the fresh surface water is present in the form of ice and permafrost (69%), while only 0.49% accounts to the rivers. Rivers are complex and dynamic ecosystems that transport water with sediments and dissolved materials and carry an important role in the water cycle, primary as drainage channels for surface water. However, in contrast to their areal extent, rivers represent a large fraction of Earth's biodiversity (30% of global vertebrate diversity and more than 40% of the total fish diversity), which in turn provides life-supporting system for humans (Dudgeon et al., 2006; Sabater et al., 2013). Therefore, rivers are a major source of life. The rivers biodiversity mainly reflects the diversity of environments they flow through and their heterogeneity and dynamism. Further, rivers provide different ecosystem services (i.e. water purification, flood control, nutrient transport etc.), which in turn depend on river structure and functioning (Hassan et al., 2005). However, the use of the river ecosystem services is only possible if rivers are in good health, which is challenged by decades of human exploitation. Freshwater biodiversity is declining faster than terrestrial or marine ecosystem, which can be attributed to the loss in the combined high species richness located in a small area (Sabater et al., 2013), and effects of different stressors such as water pollution, overexploitation, flow modifications, habitat degradation and invasion by exotic species (Allan and Flecker, 1993; Revenga et al., 2005). However, successful conservation of river ecosystems requires of an adequate consideration of additional drivers of aquatic stress such as the global climate change and multiple stress conditions, which can override or magnify the impacts of other stressors on the river structure and functioning.

1.2. The aquatic environment under multiple stress

Water represents one of the most important natural resources on Earth. Clean, accessible and safe water is the single, most important prerequisite for life, the

environment, healthy living and socio-economic development (UNEP, 2007). Throughout human history, the quality and quantity of water have represented a crucial factor for human health and the health of the Earth's environment. However, the dramatic continuous industrial and agricultural development of the past century has significantly deteriorated the environment and particularly the soil, lakes, rivers and other aquatic environments (Vörösmarty et al., 2010), and river ecosystems have deteriorated more than other aquatic ecosystems (Arthington and Welcomme, 1995). This fact can be attributed to the combined effects of multiple stressors such as the changes in the land uses, organic and chemical pollution (chemicals used in agriculture, solid and liquid urban and industrial wastewaters), overfishing, water abstraction, gravel and sand extraction, deforestation, reduction of riparian vegetation and proliferation of exotic and alien species (Vörösmarty et al., 2010).

The impact and relevance of multiple stressors differ regionally in Europe (EEA, 2012a). In the Alpine and continental Northern regions of Europe, hydropower production have dramatically changed aquatic hydrology, morphology, sediment transport and biodiversity, while river abstraction due to a rapid and intensive development of agriculture and flood protection systems represents the most important drivers of an aquatic degradation in the lowland areas of Northern and Central Europe (Hering et al., 2015). In the Mediterranean aquatic ecosystems have predominantly been affected by vegetation degradation, water scarcity, eutrophication, chemical and organic pollution, morphological changes and resource exploitation. Amongst them, all water scarcity seems to be the most important driver of change in the freshwater ecosystems since has the capability to aggravate the effects of multiple stressors by increasing the environmental concentration of different pollutants and their ecological effects (Petrovic et al., 2011). Though, it is expected that by 2050, more than 40% of the total global population in more than 54 countries will face problems of water stress or water scarcity (Fig.1.1.). Moreover, climate change may additionally increase the risk of foods and erosion in wet regions and of droughts in water-scarce regions (EEA, 2012b). Increased water temperatures and reduced river flow may exacerbate impacts of pollution and produce unexpected outcomes on the aquatic organisms and environment. Though, in the near future, an increase of diversion, regulation, and abstraction of river flow can as well be expected due to a combined effect of climate change and rapid growth of population (Poff et al., 2003; Palmer et al., 2008). Even though mutual interactions between different stressors may result in complex effects on both organisms and the environment (Coors and Meester,

2008; Ormerod et al., 2010), the knowledge regarding single stressor effects on the water bodies and their ecosystem functionality is notoriously limited and scarce, limiting our capacity to understand ecosystem responses to multiple stressors (Friberg, 2010).

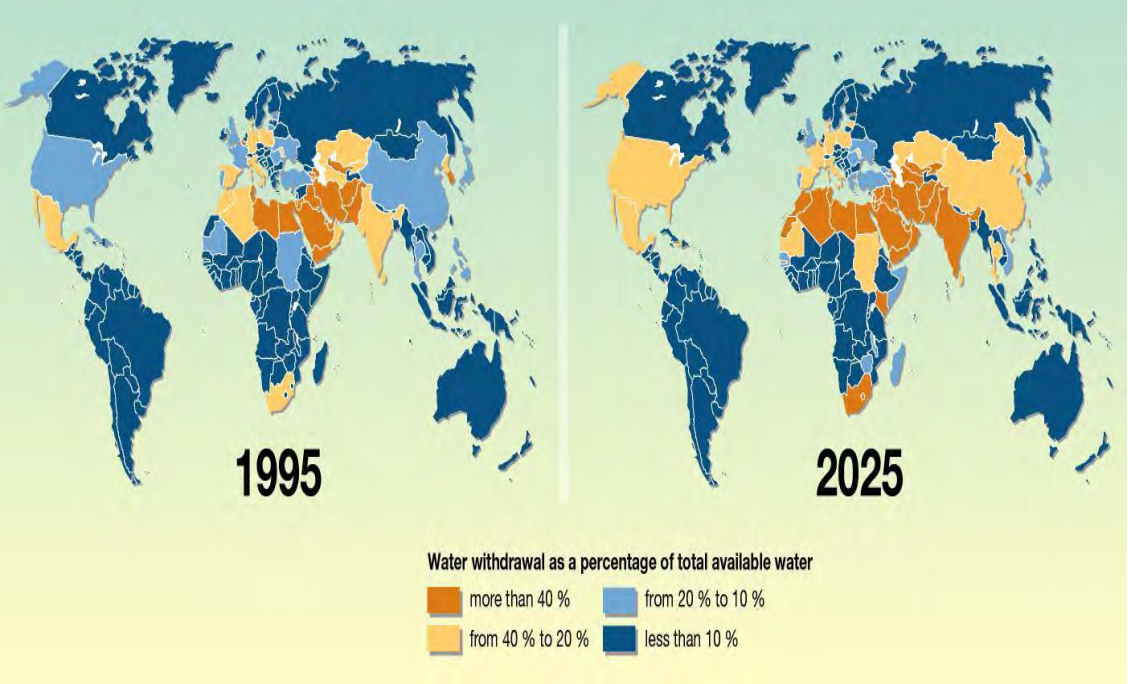

Figure 1.1. Water scarcity in the world. It was estimated that more than 2.8 billion people in 48 countries will face water stress or scarcity by 2025 (Gardner-Outlaw and Engelman 1997, UNEP 2008).

1.3. Rivers and chemical pollution

Almost one-third of all available freshwater is used for anthropogenic purposes (i.e. industry, agriculture and domestic use), which simultaneously results in their contamination by numerous different organic and inorganic contaminants. Amongst them, nutrient pollution of rivers represents one of the most widespread human impacts on the aquatic environment. Once discharged by urban and agricultural wastewaters, nutrients enter river ecosystems and stimulate excessive growths of primary producers (eutrophication), which in turn can physically and chemically alter the habitat structure by decreasing oxygen concentration, increasing the productivity of food web and increasing the pH of waters (Schindler 2006). Also, a wide array of heavy metals and other inorganic materials act as toxic pollutants in the aquatic environment. Industrial wastewaters and atmospheric decomposition are the most common source of heavy metal contamination in the aquatic environment, while the greatest concern regarding heavy metals is related to

their capability to bioaccumulate and bioconcentrate (the ability of a compound to enter organism from the water) in many aquatic organisms. However, biomagnification (increase in the concentration of a substance as you move up in the food chain) has led to increasing problems such as an excessive lead contamination of fish. Beyond nutrients and heavy metals, aquatic pollution due to acid precipitation, increased levels of suspended solids and thermal pollution may as well cause harm to aquatic organisms. Even though problems related to macropollutants (i.e. organic matter, nutrients) are very important, the occurrence of microcontaminants creates growing concern.The production of chemical products is expected continue increasing, while the European Inventory of Existing Commercial Chemical Substances (EINECS) estimates that there are currently more than 100 000 different commercially registered compounds in Europe. Eventually, the large number of these compounds will enter natural freshwater systems and pose a risk to the environment (Schwarzenbach et al., 2006).

1.4. Main sources and pathways of contaminants to the aquatic environment

Indirect or direct water pollution affects the entire biosphere of an aquatic environment. It normally occurs when pollutants are discharged into the aquatic environment without the previous removal treatment. The most common pathway for microcontaminants to reach water bodies is through point and non-point sources (Wu et al., 2013).

1.4.1. Point-source of pollution

Point source of pollution according to the U.S. Environmental Protection Agency (EPA) represents: “any single identifiable source of pollution from which pollutants are discharged, such as a pipe, ditch, ship or factory smokestack” (Hill, 1997). Different types of point-source pollutants determined in aquatic environment waters are as numerous as their sources (agriculture, industry and urban settlements) (Fig. 1.2.), while the highest concentrations of the pollutants are generally found in the proximity of the source (pipe end or an underground injection system) and decreasing concentrations farther away from the source. Examples of point-source pollution are industrial, agricultural and wastewater treatment plant (WWTP) effluents which are commonly being discharged to the rivers and streams. Even though WWTPs are basically designed to remove pathogens and suspended or flocculated matter, they are unable to remove other microcontaminants such as the

pharmaceutically active compounds (PhACs) and personal care products (PCPs) (Suárez et al., 2008; Gros et al., 2010; Ratola et al., 2012). Since 1980, health concerns related to microcontaminants have driven the development of new treatment technology (biotic and abiotic membranes, advanced oxidation and reduction, electrochemical treatments, combined processes, etc.). However, despite the range of advanced treatment options available, urban WWTPs typically use a secondary biological treatment such as conventional activated sludge, which removes only a fraction of the emerging contaminants. The contaminants most worrying are the persisting polar compounds of high solubility in water, which thus are able to penetrate through natural filtration and man-made treatments and present a potential risk in drinking water supply (Loos et al., 2009). However, commercial and industrial businesses use hazardous materials in manufacturing or maintenance, and then discharge various wastes from their operations. The raw materials and wastes may include pollutants such as solvents, petroleum products (such as oil and gasoline), or heavy metals.

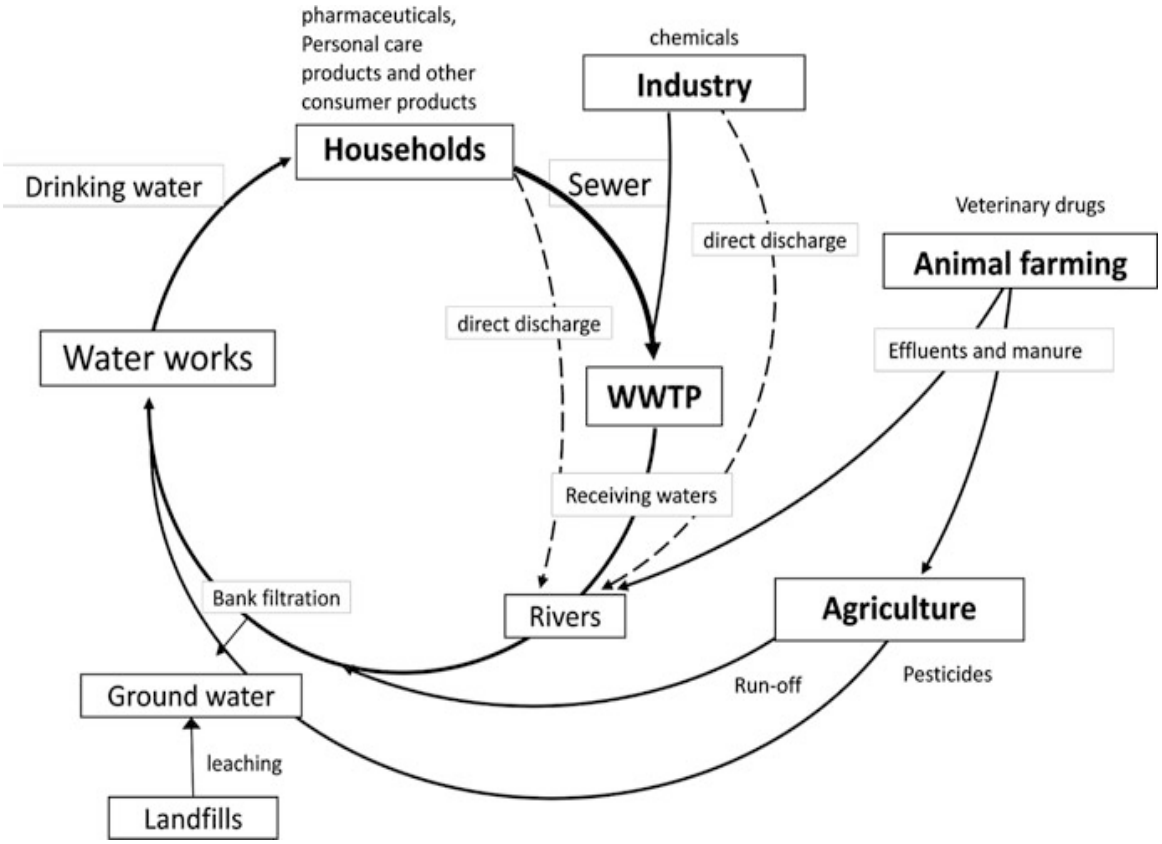

Figure 1.2. Microcontaminants within the water cycle.

1.4.2. Non-point source of pollution

Non-point pollution sources include a 'diffuse' pollution and refer to those inputs and impacts which occur over a wide area and are not easily attributed to a single source. In comparison with the point sources, non-point sources are usually associated with specific land uses. The non-point sources of pollution accounts for more than a half of all surface pollution and, therefore, represents the major threat to the aquatic ecosystems (Ongley et al., 2010; Darradi et al., 2012). Through the non-point source via different organic and inorganic pollutants are introduced which in turn can affect oxygen concentration, bury streambeds and have negative direct or indirect effects on the aquatic organisms and the environment (Norse, 2005). The most common non-point sources of pollution may include agrochemicals from agricultural areas, chemicals from urban runoff, sediment from improperly managed construction sites and eroding river banks, forestry, and mining, livestock bacteria and nutrients, wastewaters from septic systems, atmospheric deposition and hydromodifications. Also, microcontaminants may cause diffuse pollution as a result of activities such as farming and forestry. For instance, the leaching from manures applied as fertilizers, the runoff of pesticides used in agriculture and forestry, or the atmospheric deposition of industrial contaminants can all adversely affect the quality of surface and groundwater (Novotny, 1999). Other potential point sources of pollution by emerging contaminants include landfill sites, fish farms, power stations, and oil spillage from pipelines.

1.5. Fate and behavior of contaminants in the WWTPs and the aquatic environment

1.5.1. Elimination in the WWTPs

The physicochemical removal in WWTPs is of minor importance for polar microcontaminants like PhACs, whose elimination is largely dependent on microbial degradation in activated sludge tanks (Reemtsma and Jekel, 2006). In there, the removal of microcontaminants is related to two main processes: biodegradation and sorption to sludge, with a minor contribution of photolysis and volatilization to air (Robles-Molina et al., 2014).

1.5.1.1. Biodegradation

Biodegradation is perhaps the most complex process occurring in biological treatments. It is a catabolic process, but the pathways leading to the partial or total breakdown of contaminant molecules are not well known. Biodegradation can be achieved at stages of:

1. *Primary degradation*. Alteration of the chemical structure of a substance resulting in loss of a specific property of that substance.
2. *Environmentally acceptable*. Biodegradation to such an extent as to remove undesirable properties of the compound. This often corresponds to primary biodegradation, but it depends on the circumstances under which the products are discharged into the environment.
3. *Ultimate degradation*. Complete breakdown of a compound to either fully oxidized or reduced simple molecules (such as carbon dioxide/methane, nitrate/ammonium, and water).

Two main mechanisms have been suggested: direct metabolization (i.e., the use of the microcontaminant as a source of carbon and/or energy by the biological community) and co-metabolism. Co-metabolism refers to the fortuitous degradation of a non growth substrate (i.e., the PhAC) in the obligate presence of a growth substrate or another transformable compound (e.g., dissolved or particulate organic carbon). Since the amounts of microcontaminant are usually too low to be used as a growth substrate, co-metabolism is supposed to be the main biodegradation pathway in activated sludge. However, given the complexity of the matrix and of the biological communities present, most likely direct metabolism and co-metabolism coexist in biological treatments, at different rates depending on the operational parameters of the facility and the overall quality of the raw water arriving into the WWTP. So far, the biodegradability of a compound has mostly been evaluated based on its biodegradation rate constant (K_{biol} ; L/gMLSSd) or k'_{bioS} (h^{-1}) from pseudo first order kinetic models. Though, in the Fig.1.3., can be seen proposed rules in order to evaluate the biodegradability of organic microcontaminants based on k_{bioS} (Joss et al., 2006). Therefore, compounds with k_{bioS} < 0.01 L/gMLSS d (e.g. carbamazepine) with removal efficiency of less than 20% primarily tend to persist during the biological treatment in WWTPs, while compounds (e.g. gemfibrozil) with k_{bioS} between 0.1 and 10 L/gMLSS are only moderately removed by biodegradation processes (removal efficiency

from 20%-90%). Thus, microcontaminants (e.g. acetaminophen) with k_{bioS}> 10 L/gMLSS d have shown removal efficiency greater than 90%in the wastewater treatment processes.

1.5.1.2. Sorption

Sorption to sludge is another relevant process contributing to the removal of organic contaminants from the liquid phase. Sorption between the aqueous compartment and the solid phase of the sludge or mixed liquor in a biological reactor continuously exchange pollutants in both directions (sorption and desorption). The mechanisms that sustain the process of sorption are complex and still not fully understood, and recently the colloidal fraction has been suggested to also play a significant role (Delgadillo-Mirquez et al., 2011). Sorption appears to be influenced by the characteristics of both the matrix and the pollutant. This complexity is frequently lumped in a linear formulation that uses a single sorption coefficient (Limousin et al., 2007), also referred as partition coefficient (Kd). Substantial effort has been devoted to the empirical quantification of Kd values for different compounds in particular WWTPs (see Pomiés et al., (2013) for a good compilation of Kd values in activated sludge, including PhACs), although the generation of Kd values from octanol-water partition coefficient (Kow) values is common practice as well (Jones et al., 2002).

However, because the Kd of PhACs depends on sludge characteristics (including pH), using Kow to derive Kd can lead to severe bias. In fact, sorption is known to depend on several mechanisms beyond the hydrophobic interactions summarized by Kow: electrostatic interactions, cationic exchanges, cationic bridges, surface complexation, and hydrogen bridges (Tolls, 2001). However, because sorption depends also on sludge characteristics, Kd values can vary widely among WWTPs, in a way that is nowadays difficult to predict. So far, it has been accepted that microcontaminants (e.g. ciprofloxacin, ofloxacin) with log Kow > 4.0 or log Dow (octanol/water distribution factor) > 3.0 have predominantly high sorption potential (i.e. Kd > 1000 L/kgMLSS) on the particulate phase, while compounds such as the clorfibric acid with log K_{ow} < 2.5 or log D_{ow} < 1.0 often experience low sorption (K_d < 300 L/kgMLSS) (Fig.1.3.). Though, in the case of log K_{ow} between 2.5 and 4 or 1<log D_{ow}< 3.0 microcontaminants show a medium tendency to sorb on the particulate phase (Luo et al., 2014).

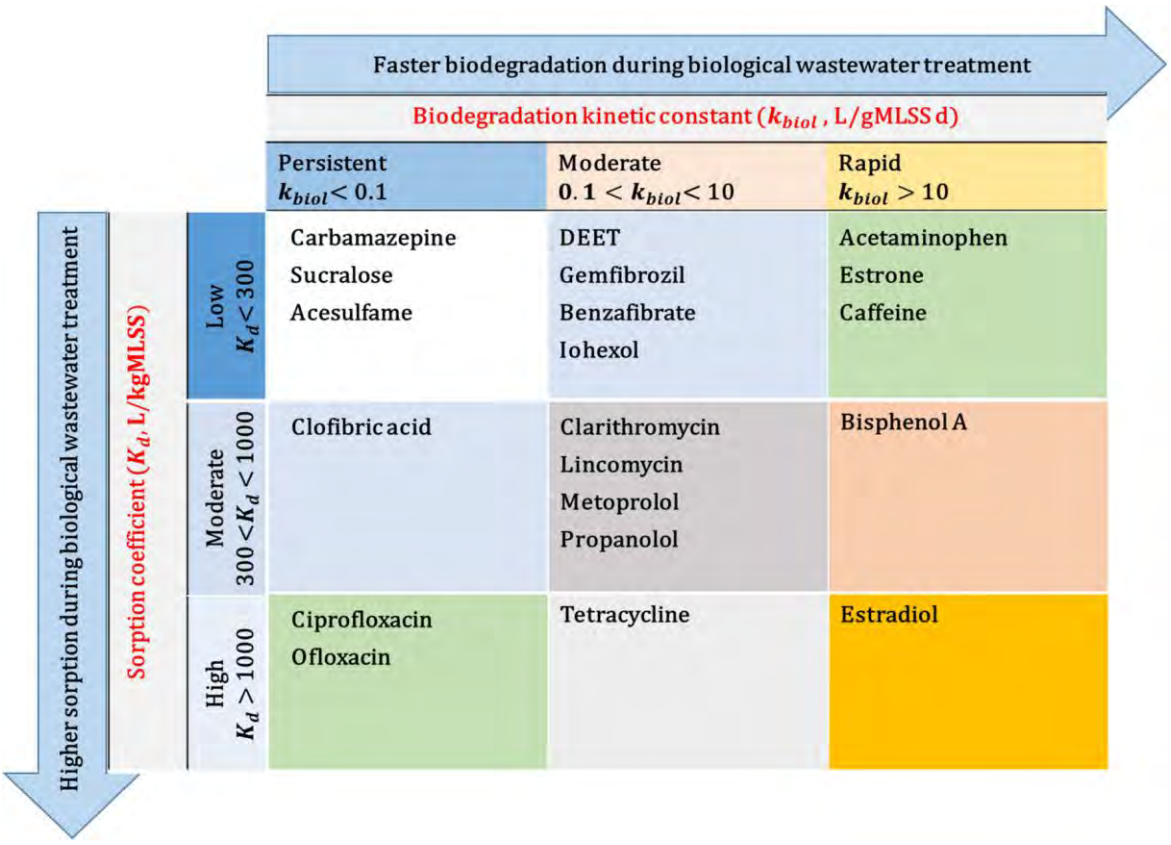

Figure 1.3. Rules proposed to evaluate the micropollutants tendency to sorption or biodegradation during biological wastewater treatment. Compounds with higher k_{bioS}> 10 L/gMLSS d will a have higher tendency to biodegradation, while compounds with high K_d > 1000 L/kgMLSS will sorb more onto particulate phase during biological wastewater treatment (From Tran et al., 2017).

1.5.2. In-stream attenuation: biotic and abiotic transformations in rivers

Once released to the environment, a number of processes govern the fate and transport of contaminants and control their concentrations. Most important are the physical processes of dispersion and dilution and chemical and biological processes such as biodegradation, abiotic oxidation and hydrolysis, photolysis, adsorption/ desorption, and volatilization (Fig. 1.4.). Since the basic concepts of these processes are already defined and discussed in Sect. 1.5.1., here we mention only some specificity when occurring in natural aquatic environment.

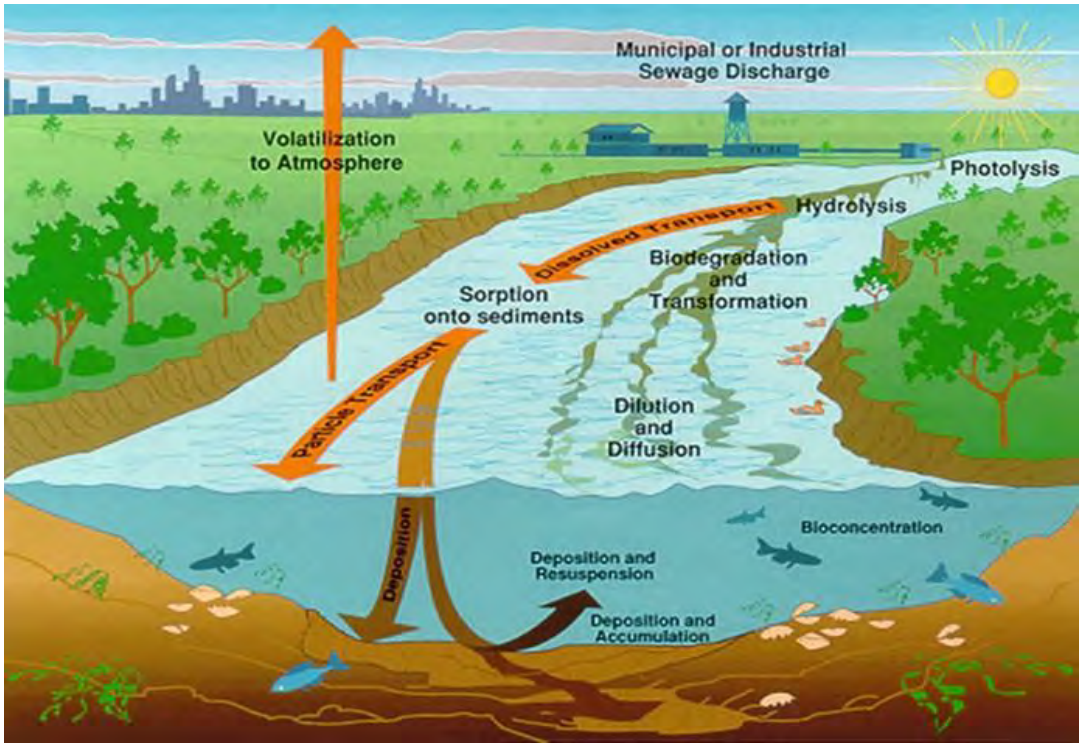

Figure 1.4. Fate of contaminants in the aquatic environment. In-stream physical processes that affect the concentration levels of PhACs, PCPs and other wastewater-derived chemicals (From Barber et al., 1995).

1.5.2.1. Biodegradation

Biodegradation can be defined as the biologically catalyzed reduction in complexity of chemical compounds. It is a catabolic process in which organic substances are broken down into smaller compounds by living microorganisms (Marinescu et al.., 2009).Generally, biodegradation is based on two processes: co-metabolism and growth.

Co-metabolism represents the metabolism of an organic compound in the presence of a growth substrate which is used as the primary energy and carbon source (Fritsche and Hofrichter, 2008). Different microorganisms are involved in the process of biodegradation including bacteria, fungi, and yeast. Biodegradation processes differ greatly, but usually, the final product of the degradation is carbon dioxide (Pramila et al., 2012). Though, organic material can be degraded aerobically (with oxygen), or anaerobically (without oxygen) (Fritsche and Hofrichter, 2008; Mrozik, 2003). Biodegradability is generally regarded as the most important property for environmental hazard assessment of organic microcontaminants. It is strongly dependent on environmental conditions, such as temperature, redox potential, and the microbial communities present. Also, the degree of bioavailability of a microcontaminant is important, i.e., accessibility of the compound to microorganisms and its uptake by microbial cells. Dissolved compounds generally are more bioavailable. Other important factors influencing the biodegradation are exposure time to biomass, availability of co-substrates (for compounds degraded co-metabolically), and the fraction of inert matter.

1.5.2.2. Photolysis

Direct photolysis in natural water involves the transformation of contaminants resulting from the direct absorption of a photon and should be distinguished from indirect photolysis, a second important abiotic degradation pathway in the environment. Indirect photolysis in natural water involves the transformation of contaminants due to energy transfer from naturally occurring photosensitizers or the transformation of a chemical due to reactions with transient oxidants such as hydroxyl radicals, singlet oxygen, and peroxy radicals.

1.5.2.3. Sorption

The interface between water and natural solids (e.g., suspended particulate matter and sediments in rivers) plays an important role in the transport of microcontaminants in river systems. Adsorption depends on both the surface characteristics and the properties of the contaminant. Neutral compounds tend to sorb onto solid organic matter, and cations and anions tend to sorb onto negatively (e.g., clay) and positively (e.g., iron oxide) charged surfaces, respectively. A number of other reactions like complex formations with metal ions, ion exchange, and hydrogen bindings also affect the partition of the organic

compound between the solid and the liquid phase. Once the contaminants are sorbed, they can be deposited and eventually become buried in the sediments. However, the buried contaminants can be remobilized, by resuspension of the sediments during flood events.

1.5.2.4. In-stream attenuation and physicochemical properties of the contaminants

The relative importance of the previously mentioned processes depends on the rates at which they occur under environmental conditions. These rates are, in turn, dependent on the chemical structure and properties of the substance and its distribution in the various compartments of the environment. The most important physical properties of contaminants are water solubility, acidity (pK_a), vapor pressure, Henry's law constant (H), hydrophobicity expressed as the K_{ow}, and the organic carbon/water partition coefficient (K_{oc}). The degree of ionization of ionizable and polar contaminants (many PhACs and pesticides), which depends on pH, affects their solubility, transport, sorption, and bioavailability. For an ionizable compound, acidic or basic, which can exist as neutral or dissociated form, the partitioning depends on pH and pK_a of the compound. In addition, the charged groups within the molecules can lead to ionic ion paring and complexation reactions with the particulate matter and microorganisms, thus contributing to partitioning the contaminants to the solids. For example, microcontaminants having carboxylic acid functionalities with pK_a values much less than 7 (such as some nonsteroidal anti-inflammatory drugs or polar pesticides) are likely to remain in the solution phase and removal by sorption to settling particles may be limited. For contaminants having functional groups that are prone to photolysis (e.g., conjugated aromatics, nitro-compounds, furans, phenols), a diverse set of photochemical processes are expected, and oxidative losses via reaction with mineral and humic substances also occur in sediments or soils. Photolytic reactions are often complex, involving various competing or parallel pathways and leading to multiple reaction products that may either be more toxic than the parent compound, retain the properties of the parent compound, or lose toxicity (Petrovic and Barcelo, 2007). Some of the above physical properties are strongly dependent on environmental conditions. For example, temperature strongly affects vapor pressure, water solubility, and, therefore, H. Temperature may also affect deposition. For example, the distribution of persistent organic pollutants (POPs) is inversely related to vapor pressure and thus to temperature. Lower temperatures favor greater partitioning from the vapor

phase to particles suspended in the atmosphere. The pH is also important in evaluating environmental processing of the compounds, even though they are not subject to hydrolytic reactions. The speciation of the compound will influence its partitioning behavior, as well as its light-absorbing properties. Some compounds have multiple pH-sensitive functional groups (e.g., tetracycline antibiotics have three or four pK_a values), which results in the possibility of protonated/positive, neutral (or zwitterionic), and deprotonated/negative forms of a drug being present depending on the pH of the specific water body. However, for the majority of emerging contaminants covered by this thesis (polar compounds such as PhACs, polar pesticides, personal care products, etc.), the attenuation in the aquatic environment is governed by three main processes: biodegradation, sunlight photolysis, and sorption to bed sediment. Table 1.1. gives an overview of the relative contribution of biodegradation, photolysis, and sorption to the attenuation of selected emerging contaminants with high potential to enter the aquatic environment.

Table 1.1. Environmental persistence and partitioning of selected emerging contaminants with relatively high potential ecological risk and high consumption. Note: +++ rapid, ++ medium, + slow, — very poor or nonexisting.

Compounds	Photolysis	Biodegradation	Sorption
Ciprofloxacin	++	–	+++
Sulfamethoxazole	++	+++	–
Naproxen	+++	+	++
Ibuprofen	+	+++	–
Diclofenac	+++	++	–
Mefenamic acid	+	+	–
Acetaminophen	+	+++	–
Carbamazepine	–	–	–
Propranolol	+++	+	+++
Gemfibrozil	–	–	–
Triclosan	++	++	+++
Methylparaben	–	+++	+

1.6. Chemical contaminants of emerging concern

The issue of environmental microcontaminants emerged in 1962 when Rachel Carson's "Silent Spring" described the detrimental effects of pesticides on the environment and on human health, making a call to consider unintended or unanticipated consequences of man-made chemicals released into the environment. The amount of nonpolar hazardous

compounds, i.e., POPs and heavy metals, released by the industry started to decrease in the 1970s when the legislation forced reduction at source and implementation of efficient WWTPs. The main concerns were related with the persistence of POPs in the environment, their bioaccumulation in human and animal tissues, and their biomagnification in food chains, which lead to significant impacts on both human health and the environment. Selected POPs were defined as priority pollutants, and intensive monitoring and control programs were implemented. To address the global concern, the United Nations signed a treaty in Stockholm, Sweden, in May 2001. Under the treaty, known as the Stockholm Convention, countries agreed to reduce or eliminate the production, use, and/or release of an initial twelve chemical groups, the so-called dirty dozen. Today, the emission of POPs has been reduced drastically by adopting appropriate measures and eliminating the dominant pollution sources.

In the European Union, water pollution is regulated under the Water Framework Directive (WFD) (Directive 2000/60/EC), which established a framework for community action in the field of water policy. The most recent European regulation set Environmental Quality Standards (EQS) for 45 priority substances (Directive 2013/39/EU) and established a watch list with 10 additional groups of substances (17 individual compounds) of possible concern that require targeted EU-wide monitoring in order to support the prioritization process in future reviews of the priority substance list. However, our technological society is using a continuously growing number of chemicals, which currently can be estimated in some hundreds of thousands of compounds (most of them organics) in daily use. Consequently, a wide range of man-made chemicals, designed for use in industry, in agriculture, or as consumer goods, are emitted, as well as many other chemicals unintentionally formed as by-products of industrial processes or of combustion. There is a widespread consensus that this kind of contamination requires legislative intervention. There are varying definitions for emerging contaminants, as well as discussion on the types of substances that should be included under this category. Norman network (http://www.norman-network.net/) defines “emerging substances” as substances that have been detected in the environment, which are not included in routine monitoring programs at the EU level, and whose fate, behavior, and (eco) toxicological effects are not well understood. On the other hand, “emerging pollutants” are defined as those pollutants not included in routine monitoring programs in the EU, but which may be candidates for future regulation, depending on research on their (eco) toxicity, on their potential health effects and public perception, or on their occurrence in the environment.

Although most people make no differentiation between emerging contaminants and emerging pollutants, contamination and pollution should not be seen as the same, since all pollutants are contaminants, but only those contaminants that can result in adverse biological effects are pollutants. Therefore, to differentiate emerging pollutants from emerging contaminants, the chemical analyses and information on their presence in the environment must be complemented with information on their bioavailability and toxicity. In this thesis, we deal with the emerging organic contaminants, defined as chemicals that occur in water resources and pose a potential environmental risk, although currently it cannot be clearly defined given the paucity of existing data. However, the primary focus of this thesis is on the PhACs, as emerging contaminants with one of the highest inputs into the aquatic environment. Currently, the most frequently discussed emerging substances are:

- Global organic contaminants (flame retardants, perfluorinated compounds, siloxanes etc.)
- Pharmaceuticals and sintetic hormones
- Personal care products (preservatives, UV filters, biocides, insect repellents, fragrances, etc.)
- Pesticides
- Nanoparticles
- Microplastics
- Industrial chemicals
- Biological metabolites and toxins
- Transformation products

1.7. Pharmaceutically active compounds

PhACs are a group of chemical substances that have medicinal properties and encompass all prescription, nonprescription, and over-the-counter (OTC) therapeutic drugs, in addition to veterinary drugs. They are produced worldwide on a 100,000 t scale, and in a vast array of contaminants of anthropogenic origin reaching our water supplies, PhACs are among the ones with the most continuous input into the environment. Most modern drugs are small organic compounds with a molecular weight below 500 Da, which are moderately water soluble as well as lipophilic, in order to be bioavailable and

biologically active. They are designed to have specific pharmacologic and physiologic effects at low doses, and thus, are inherently potent, and can produce unintended outcomes in wildlife (Halling-Sørensen et al., 1998).Their consumption will continue to increase due to the expanding population, inverting age structure, increase of per capita consumption, expanding potential markets, patent expirations, new target age-groups, etc. After the oral, parenteral, or topical administration, PhACs are excreted via the liver and kidneys as a mixture of parent compounds and metabolites that are usually more polar and hydrophilic than the original drug. After their usage for the intended purpose, a large fraction of these substances is discharged into the wastewater unchanged or in the form of degradation products that are often hardly eliminable in conventional WWTPs. Depending on the efficiency of the treatment and chemical nature of a compound, PhACs can reach surface and groundwaters. PhACs have been found in treated sewage effluents, surface waters, soil, and tap water. Although the levels are generally low, there is rising concern about potential long-term impacts to both humans and aquatic organisms as a result of the continuous environmental exposure to these compounds.

1.7.1. The occurrence of PhACs in the aquatic environment

The occurrence of the PhACs has been investigated in surface waters, groundwaters, and, occasionally, drinking water, in several countries around the world (Canada, Austria, Germany, England, Greece, Spain, USA, Switzerland, etc) (Heberer, 2002) (Table 1.2.). Recently, many studies have published on the source and occurrence as well as the fate of PhACs (Acuña et al., 2015; Lopez-Serna et al., 2012; Gros et al., 2012; Jelic et al.,2009). PhACs have shown to be ubiquitous contaminants in surface waters all around the world. A study performed by Ternes et al. (2001) detected PhACs in 31 out of 40 sampled streams and rivers. However, in drinking and ground water PhACs occurred less frequently. The same study performed by Ternes et al. (2001) has found 15% of all groundwater samples to be contaminated with PhACs with concentration levels higher than 0.1. μg/L. A majority of these analyzed samples, however, were from groundwater wells previously influenced by surface water (Ternes, 2001). However, most of the PhACs are present at low concentrations but many of them still raise health and environmental concerns (Schwarzenbach et al., 2006). There are more than 10,000 prescription and OTC PhACs which are registered and approved for usage today (Orange book, FDA). Hughes et al. (2013) estimated that fewer than 4% of PhACs have been analyzed for and detected in

freshwaters. Their analysis of all published studies (until March 2011) on PhACs in the environment showed that more than 50% of entries in the database correspond to just 14 compounds belonging to the groups of antibiotics, antiepileptics, cardiovascular drugs, and painkillers, being the most frequently monitored ibuprofen, acetaminophen, diclofenac, sulfamethoxazole, erythromycin, carbamazepine and fluoxetine. On the other hand, the analysis of published data reveals that some potentially very relevant drugs have not been studied at all. Therefore, the discharge of the PhACs and other emerging contaminants into the wastewater is not yet covered by the currently existing regulation. Since the compounds are not regulated there is no legal requirement to monitor them by the river basin authorities, so for many rivers and PhACs, there is no available data including data for European rivers such as the Ebro, Evrotas, and Adige. Around 4000 different PhACs are used as human and veterinary drugs (Howard and Muir, 2011; Mompelat et al., 2009) in Europe and USA. However, a small amount of them are monitored in the environment and less than 300 PhACs have been detected so far (Howard and Muir, 2001)

Table 1.2. Concentration ranges of 42 commonly detected PhACs, PCPs and other emerging contaminants in surface water (Adapted from Wilkinson et al., 2016).

Contaminant Class	Contaminant	Surface water (ng/L)
Analgesic	Ibuprofen	1-2370[a]
	Diclofenac	<0.5-253[a,g]
	Paracetamol	110-10000[b,c,g]
	Codine	12-1000[b,c]
	Naproxen	<1-81[o]
Antibiotic	Amoxicillin	<2.5-245[a]
	Erythromycin	<05-159[a]
	Triclosan	140-2300[b,c]
	Trimethoprim	<1-2[p]
	Sulfamethoxazole	<1-46[p]
Antidepressant	Amitriptyline	66-207[a]
	Fluoxetine	5.8-120[a,b]
	Venlafaxine	1.1-35[a]
Antineoplastic	Ifosfamide	0.05-0.14[d]
	Cyclophosphamide	0.05-0.17[d]
	Tamoxifen	<0.05-25[n]
Alkylphenols	4-nonylphenol	165.8-1187.6[e]
	4-*t*-octylphenol	2.4-14.5[e]
Beta Blocker	Metoprolol	<0.5-10[a]
	Atenolol	<1-487[a]

Hormones/Steroids	17a-ethynylestradiol	<0.98-10.2[g]
	17b-estradiol	0.1-200[a,b]
	19-norethisterone	48-872[a,b]
	Coprostanol	<1-2717[h]
Lipid regulator	Bezafibrate	<10-60[a]
	Gemfibrozil	48-79[0]
Musk Compounds	Linalool	<0.5-0.6[q]
	Isobornyl acetate	<0.18-0.65[q]
	Aroflorone	<0.17-0.48[q]
Perfluoroalkyls	8:2 Fluorotelomer Alcohol	<0.9-1.97[m]
	Perfluorobutane sulfonic acid*	2.4-125[f,g]
	Perfluoro-2-propoxypropanoic acid*	<1-630[l]
	Perfluorononanoic acid	0.03-209[f,g]
	Perfluorooctanoic acid	0.16-189f[g]
	Perfluorooctane sulfonic acid	0.4-2709[f,g]
Plasticizer	Bisphenol-A	140-12000[a,b,c,g]
	Bisphenol-S**	<1.02-306[g]
	Bisphenol-AF**	<1-246[i]
	Bisphenol-F**	<1-1110[i]
	Diethyphthalate	200-420[b,c]
Ultraviolet Filters	Benzophenone-4	<1-600[k]
	2-Phenylbenzimidazole-5- sulfuric acid	<1-20[k]

Note: *Compound used or proposed as a replacement for long-chain (>C7) perfluorinated compounds; **Compound used or proposed as a replacement for bisphenol-A; [a]Petrie et al.(2015),[b]Kolpin et al. (2002); [c]Boyd et al. (2004); [d]Buerge et al. (2006a); [e]Wang and Xu, (2012); [f]Llorca et al. (2012); [g]Wilkinson et al. (2017); [h]Peng et al. (2008); [I]Yang et al. (2014); [j]Yamazaki et al. (2015); [k]Rodil et al. (2012); [l]Sun et al. (2016); [m]Mahmoud et al. (2009); [n]Coetsier et al. (2009); [o]Li. (2014); [p]Van Stempvoort et al. (2013); [q]Relić et al. (2017).

1.7.2. Environmental impacts of PhACs

So far, PhACs have been detected in drinking water of many countries at ng/L concentration levels or lower (Mittelstaedt, 2003), and currently there is no evidence that these concentration levels may have detrimental effects on human health. This is mostly due to that detected concentration levels of PhACs in drinking water are several orders of magnitude lower than doses prescribed for human use (Webb et al., 2003). Media reports of PhACs in surface water are raising concerns regarding effects of some endocrine disruption compounds and antibiotics (Brooymans, 2005; Mittelstaedt, 2003). However, the primary focus regarding the impact of PhACs in the environment is ecosystem rather than human health (Sanderson et al., 2003; Schulman et al., 2002). In surface water, certain PhACs have been found to have effects on aquatic organisms at µg/L and ng/L concentration levels. Many studies have reported feminization of fish in surface waters due

to exposure to active ingredients of oral contraceptives (EE2, Jobling et al., 1998; Larsson et al., 1999; Purdom et al., 1994), while environmental risk assessments results indicated that some PhACs such as ibuprofen, paracetamol, gemfibrozil, mefenamic acid, and oxytetracycline were present in the aquatic environment in levels sufficient to harm aquatic living organisms (Henschel et al., 1997; Jones et al.,2002; Sanderson et al., 2003; Halling-Sørensen, 2000; Tauxe-Wuersch et al., 2005). Previous studies have also shown that exposure to diclofenac (non-steroidal anti-inflammatory drug) reduced the feeding rate and/or activity in Japanese medaka fish (Nassef et al., 2010). Similar effects on fish were also reported for carbamazepine, while other studies have shown that it can as well negatively affect the reproduction of chironomid invertebrates (Oetken et al., 2005). Additionally, PhACs have also been found to affect algae (Halling-Sørensen, 2000), bacteria (Kümmerer & Henninger, 2003) and as well invertebrates in laboratory studies (Brooks et al., 2003). Even though it is believed that acute effects of PhACs are unlikely to happen, the knowledge regarding potential subtle, long-term and possibly multigenerational effects on the aquatic organism is notoriously limited and scarce. This might be particularly relevant since PhACs may act in a variety of unexpected ways on non-target aquatic organisms (Daughton & Ternes, 1999), with potential effects on the complex trophic webs of river ecocystems. However, in the environment, PhACs are normally present as mixtures and not as a single compound. Pomati et al. (2006) and Cleuvers (2003) have reported that PhACs mixtures may have even greater effects on the aquatic organisms than the single PhACs. Therefore, future toxicological studies must not only study the effects of single PhACs on organisms but must as well assess the effects of exposure to different mixtures of PhACs (Cleuvers, 2003).

1.7.3. Monitoring the PhACs in the aquatic environment

Numerous analytical methods have been developed in the last two decades for the determination of different classes of PhACs in environmental samples (water, sediment, soil, biota). Generally, the identification and quantification of PhACs at the low concentrations they occur in complex environmental matrices requires of analytical methods of high sensitivity and selectivity, which typically rely on liquid or gas chromatography (LC or GC) coupled to mass spectrometry (MS). The application of advanced low- or high-resolution MS instruments in the environmental analysis has allowed the determination of a broader range of compounds and, thus, a more

comprehensive assessment of environmental contaminants. The preferred analytical approach is based on target analysis of preselected compounds of interest, using tandem MS instruments. Over the years, a gradual shift from class-specific methods to multi-residue methods for simultaneous analysis of a large number of target compounds, belonging to different classes, has occurred. For example, Gros et al. (2012) developed a method to determine 81 PhAC residues, covering various therapeutic groups, and some of their main metabolites, in surface and treated waters (influent and effluent wastewaters, river, reservoirs, sea, and drinking water); Baker and Kasprzyk-Hordern, (2011) defined a multi-residue method for the environmental monitoring of 65 stimulants, opioid and morphine derivatives, benzodiazepines, antidepressants, dissociative anesthetics, drug precursors, human urine indicators, and their metabolites in wastewater and surface water. Jelić et al. (2009) developed a simple and sensitive method for simultaneous analysis of 43 pharmaceutical compounds in sewage sludge and sediment samples, while Vazquez-Roig et al. (2010) defined a multi-residue method for determination of PhACs in soils and sediments. Finally, Huerta et al. (2013) developed a multi-residue method for determination of PhACs in fish tissues by ultra-high-performance liquid chromatography tandem mass spectrometry. However, the advances in analytical instrumentation and analytical capabilities do not provide the answer to many important questions such as the following ones: Which compounds should be monitored? Is it worthy to monitor hundreds of PhACs that analytical chemists are capable of analyzing today? Is chemical analysis of specific compounds sufficient to assess contaminants present in the environment? The current analytical approach has another drawback. The majority of analytical methods only focus on parent target compounds and rarely include metabolites and transformation products, which sometimes can be more toxic and persistent than the original compounds. One reason for that trend is that the majority of transformation products are not known and many of those that are known are not commercially available or are too expensive. But the main reason is that all relevant contaminants, metabolites, and transformation products that may be encountered in the aquatic environment are impossible to be included in any targeted multi-residue method, making therefore a strong case for the application of nontarget screening protocols using high-resolution mass spectrometry (HR-MS) (Eichhorn et al., 2012; Chiaia-Hernandez et al., 2013). In comparison to triple quadrupole mass spectrometers, which operate at a unit resolution for specific target analytes, HR-MS instruments such as time of flight (TOF), quadrupole time of flight (QqTOF), and Orbitrap mass spectrometers are capable of acquiring full-scan mass spectra at high

resolution for all analytes having, therefore, the unique potential of retrospective data analysis for compounds not included in the first data processing. Accurate mass full-scan MS permits analysis of a large number of compounds and their degradation products that fall outside the scope of target methods. However, general screening for unknown substances is time-consuming and expensive and is often shattered by problems, such as lack of mass spectral libraries. Therefore, the main challenge is to prioritize contaminants and decide on the significance of the chemical data. Effect-related analysis focused on relevant compounds, nowadays seems to be the most appropriate way to assess and study environmental contamination.

1.8. Objectives, hypotheses, and outline of the thesis

1.8.1. Problem definition

Amongst the vast array of emerging contaminants of anthropogenic origin reaching river ecosystems, PhACs are among the ones with the most continuous input into the environment. Once released, a number of processes govern their fate and transport. Biodegradation, abiotic oxidation, and hydrolysis, photolysis, adsorption/desorption, dissolution, volatilization, and dispersion are the most important processes involved. The relative importance of these processes depends on the rates at which they occur under natural environmental conditions. These rates are, in turn, dependent on the chemical structure and properties of the substance and its distribution in the various compartments of the environment. Therefore, understanding the **transport, distribution**, and **fate of PhACs** is a prerequisite for a thorough assessment of the risk they represent in wastewater-receiving rivers under **multiple stress**. Amongst the co-occurring stressors with PhACs, water scarcity is key in the Mediterranean rivers, with direct and indirect effects. Water scarcity can drive the effects of other stressors acting upon river ecosystems and lead to intermittency in water flow, with implications for water quality and the fate of PhACs. Water scarcity can also amplify the effects of water pollution by reducing the natural dilution capacity of rivers, while extreme events such floods can change the pattern of PhACs transport and distribution between phases (solid-aqueous). Other common situations, also tackled in this thesis, are the pulse contribution of snowmelt and tourism which may complicate the prediction of the distribution and fate of the PhACs.

1.8.2. Thesis hypothesis

The thesis main aim is to relate chemical contamination with co-occurring stressors which might affect their distribution in the environment. Therefore, the following hypotheses are tested:

1. **H1.** An anomalous hydrological variability will affect the in-stream and sediment concentration levels of emerging contaminants.
2. **H2.** The occurrence of multiple stressors (human impacts in touristic areas, wastewater treatment type, the co-occurrence of urban and agricultural pollution) will affect the distribution patterns of emerging contaminants in water and sediments.
3. **H3.** The recovery potential of rivers to deplete pharmaceutical products (natural in-stream attenuation) will be largely determined by the river flow variation and interruption.

1.8.3. Research objectives

The thesis contributes to the knowledge on the transport, distribution, and fate of PhACs under multiple stress conditions. I will use three environmentally different case studies of wastewater-receiving rivers to show how the distribution patterns are affected in potentially contrasting situations. This general objective is differentiated as follows:

- **O1.** To evaluate the PhACs pollution in an Alpine river (Adige) and in two Mediterranean rivers (Evrotas and lower Ebro).
- **O2.** To evaluate the spatial variability of PhACs in the studied rivers.
- **O3.** To evaluate the temporal variability of PhACs related to river hydrology.
- **O4.** To determine the effects of different environmental variables on the in-stream attenuation of PhACs and their distribution between water and sediments.

1.8.4. Thesis outline

Figure 1.5., shows the organizational structure of the “Results and discussion” section of the thesis with the different chapters, associated hypothesis, and journals where papers have been published or submitted. The main hypothesis of the thesis forms the focal

chapters (Chapter 1 to Chapter 3), with each of these corresponding to a scientific paper. The present section represents a general introduction of the thesis, while the following section "Results and discussion" is a synthesis that integrates the results from each of the individual chapters/papers and presents a comprehensive discussion in relation to each of the objectives of the work. Finally, several annexes have been included with relevant complementary information.

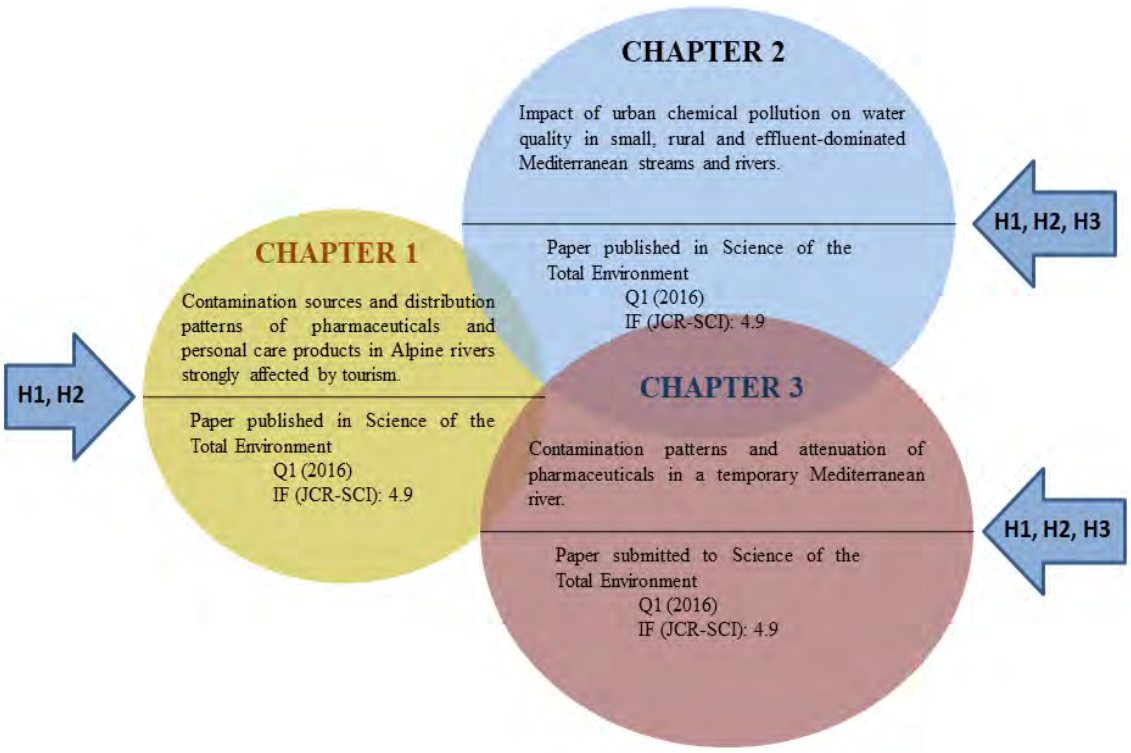

Figure 1.5. The organizational structure of "Results and discussion" thesis section with the different chapters, associated hypothesis, and journals where papers have been published or submitted.

2. RESULTS AND DISCUSSION

Chapter 1.

Contamination sources and distribution patterns of pharmaceuticals and personal care products in Alpine rivers strongly affected by tourism

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Contamination sources and distribution patterns of pharmaceuticals and personal care products in Alpine rivers strongly affected by tourism

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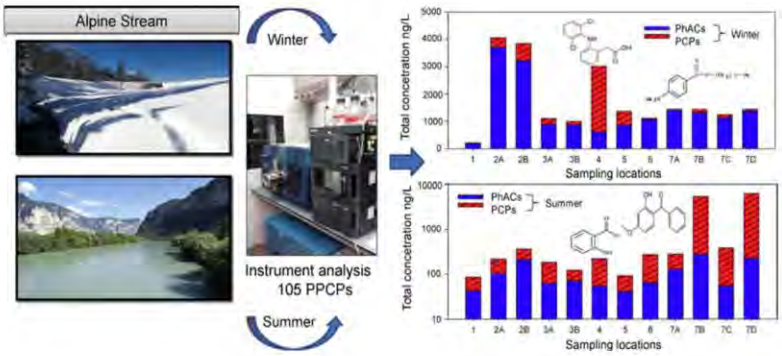
HIGHLIGHTS

- The occurrence patterns of pharmaceuticals and personal care products have been investigated in the Alpine river basin.
- Correlations between tourist arrivals and concentrations of pharmaceuticals and personal care products have been performed.
- High concentrations of pharmaceuticals and personal care products have been observed at sampling sites affected by tourism.

GRAPHICAL ABSTRACT



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ABSTRACT

Knowledge regarding the impact of tourism on the emergence of pharmaceuticals and personal care products (PPCPs) in Alpine river waters is limited and scarce. Therefore, a study on the occurrence patterns and spatiotemporal variability of 105 PPCPs in an Alpine river basin located in the Trentino-Alto Adige region (North-Eastern Italy) has been conducted. We observed that the total concentration of analyzed PPCPs was generally higher in all sampling sites during winter than in the summer. The analysis of tourist data revealed that during both

Abbreviations: ADAF, Anti-icer fluid; APPI, Atmospheric pressure photo-ionization; AVB, Avobenzone; BP1, Benzophenone 1; BP3, Benzophenone 3; BZT, 1-H-Benzotriazole; DHMB, 2,2′-Dihydroxy-4-methoxybenzophenone; DMeBZT, 5,6-Dimethyl-1-H-benzotriazole; EPB, Ethyl paraben; ESI, Electrospray ionization; Et-PABA, Ethyl-*p*-aminobenzoic acid; LOD, Limit of detection; LOQ, Limit of quantification; MeBZT, 4-Methyl-benzotriazole; NI, Negative electrospray ionization; NSAID, Non-steroidal anti-inflammatory drug; OC, Octocrylene; ODPABA, Octyl-dimethyl-*p*-aminobenzoic acid; p, Probability; PCPs, Personal care products; PhACs, Pharmaceutically active compounds; PI, Positive electrospray ionization; PLE, Pressurized liquid extraction; PPCPs, Pharmaceuticals and personal care products; r, Pearson moment correlation factor; ROS, Reactive oxygen species; SM, Supplementary material; SPE, Solid phase extraction; SPE-HPLC-MS^2, Solid phase extraction- high performance liquid chromatography–tandem mass spectrometry; SRM, Selected reaction monitoring; UHPLC-QqLIT-MS^2, Ultra-high-performance liquid chromatography coupled to triple quadrupole linear ion trap mass spectrometry; WWTPs, Wastewater treatment plants; 4HB, 4-Hydroxybenzophenone; 4MBC, 3-(4′-Methylbenzylidene) camphor.

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sampling campaigns the number of tourists was lower in the downstream sites in comparison with the upstream area of the basin (Val di Sole). Particularly, sampling sites located near important tourist resorts have shown the highest abundance of the PPCPs during winter, being analgesics/anti-inflammatories, antihypertensives and antibiotics the most abundant pharmaceutically active compounds (PhACs). Diclofenac showed the highest concentration amongst PhACs, reaching concentrations up to 675 ng L^{-1} in the sampling site situated downstream of the Tonale wastewater treatment plant (WWTP). Antihypertensives were found at concentrations >300 ng L^{-1}, while antibiotics were quantified up to 196 ng L^{-1}, respectively. Amongst personal care products (PCPs), the most abundant compound was octyl-dimethyl-*p*-aminobenzoic acid (ODPABA) with concentrations reaching up to 748 ng L^{-1} in the sampling site situated within the Rotaliana district. In general, concentrations and detection frequencies were higher in water than in the sediment samples. The most frequently detected PhACs in sediments from both sampling campaigns were antibiotics, while amongst PCPs in sediments, octocrylene (OC) showed the highest concentration in both sampling campaigns. As a result, this study highlights the potential impact of tourism on the water quality of the Alpine aquatic ecosystems.

1. Introduction

Pharmaceuticals and personal care products (PPCPs) include prescription drugs, non-prescription drugs, veterinary drugs and consumer chemicals typically found in fragrances, sun-screen agents, lipsticks, shampoos, hair colors and cosmetic products (Daughton and Ternes, 1999; Boxall et al., 2012). PPCPs are considered emerging contaminants and can enter the aquatic ecosystem via multiple pathways, including human excretion, unused drugs and products, agricultural and livestock practices (Jorgensen and Halling-Sorensen, 2000; Ort et al., 2010; Rosi-Marshall and Royer, 2012; Boxall et al., 2012; Tijani et al., 2016). However, the main pathway for PPCPs to freshwaters is through wastewater effluents as a result of incomplete removal in the wastewater treatment (Hirsch et al., 1999; Daughton and Ternes, 1999; Giger et al., 2003; Ternes et al., 2004). Because of their continuous release into the aquatic environment via waste water treatment plants (WWTP) effluents, PPCPs may act as pseudo-persistent contaminants (Ellis, 2006), and as such may cause unwanted and unexpected effects on the living organisms and environment (Daughton and Ternes, 1999; Ferrari et al., 2003; Stackelberg et al., 2004; Fent et al., 2006; Ortiz de García et al., 2014). PPCPs in the aquatic environment have been recognized as one of the most urgent environmental issues during the last decade (Jones et al., 2001; Richardson and Ternes, 2005). Concentrations of PPCPs range from ng L^{-1} to μg L^{-1}, while their occurrence in water varies across different regions and seasons (Moldovan, 2006; Kasprzyk-Hordern et al., 2008; Fernández et al., 2010; Yoon et al., 2010; Spongberg et al., 2011). It is therefore highly relevant to understand their temporal and spatial variability and distribution (Musolff, 2009).

The relevance of PPCPs associated with touristic activity in Alpine ecosystems is however largely unknown. So far, the impact of tourism on river water quality has mostly been approached through the monitoring of the physicochemical and microbiological parameters (White et al., 1978; Rodriguez, 1987; Almeida et al., 2007; Rashid and Romshoo, 2013; Bhadula et al., 2014). Even though several studies have reported concentrations of PPCPs in large rivers (Celano et al., 2014; Meffe and de Bustamante, 2014), studies regarding the occurrence of PPCPs in the Alpine streams remain limited (see e.g., Repice et al., 2013). Therefore, the potential environmental threats to the aquatic environment associated with touristic fluxes and PPCPs in the Alpine regions requires investigation. In this context the Adige river basin, which is located in the South-Eastern Italian Alps, may be considered representative of the situation characterizing Alpine regions with intense touristic activity; hundreds of kilometers of ski slopes and an extraordinary variety of landscapes make this region a cutting-edge tourist destination during summer and winter months. As a consequence, a strong seasonality on consumption and use of PPCPs and their arrival to the river system is likely to be expected. Waste water treated effluents have been identified as the main sources of contamination in the Adige catchment (Caserini et al., 2004; Repice et al., 2013), while extensive hydropower exploitation (Zolezzi et al., 2009, 2011), which has induced significant alterations of the streamflow regimes in both the main stem and tributaries (Majone et al., 2016), is likely to enhance the sensitivity of the river ecosystem to PPCP loads.

Therefore, the present study aims (1) to define the occurrence patterns of contaminants in relation to their sources (tourist arrivals, resident population), and (2) to relate the temporal variability (summer–winter) of PPCPs to the varying environmental variables (water flow, temperature), in water and sediments.

2. Materials and methods

2.1. Basin and sampling sites description

The Adige River has a total length of 410 km, being the second longest river in Italy after the Po. It rises from 1586 m a.s.l. (46.834444, 10.514722) in the proximity of Lake Resia, flows in the Southern-East Alps, and reaches the Adriatic Sea at Rosolina a Mare, south of Venice (45.149722, 12.320278) (Chiogna et al., 2016). The catchment includes 298 glaciers with a total surface of 128 km^2, which is reducing rapidly as a consequence of the observed rising trend of temperature (Lutz et al., 2016). Streamflow shows a typical Alpine character, with a principal maximum in summer, due to snow melting, and a secondary maximum in autumn, which may become dominant depending on the intensity of cyclonic storms. The minimum and maximum river flows of Adige and Noce rivers are shown in the Table 1S (SM) of the Supplementary material (SM). The mean streamflow at Trento gauging station is 203 $m^3 s^{-1}$ with a contributing area of 9763 km^2. This gauging station is the most representative of streamflow at the sampling location 6 and locations downstream city of Trento. Two sampling campaigns were conducted at 12 locations in the Adige main stem and the Noce tributary (See Fig. 1). The WWTPs located immediately upstream of the sampling locations are also shown in Fig. 1. Daily outflows from WWTPs were obtained from Agenzia per la Depurazione of the Province of Trento (https://adep.provincia.tn.it/Agenzia-per-la-Depurazione-ADEP). Finally, the main characteristics of the treatment process, population served and average daily WWTP outflows for sampling periods (Feb 15th–17th and Jul 3rd–5th, 2015) are provided in the Table 2S (SM). Tourist arrivals can be expected to be one of the most relevant driving factors influencing PPCPs concentrations. Tourist arrivals were retrieved from the dataset provided by ISPAT, http://www.statistica.provincia.tn, at a monthly resolution for the year 2015 (Fig. 2). Resident population in each municipality was downloaded from http://www.istat.it/it/ at the available time step of 1 year. The sub-catchment draining to each sampling point was identified (Table 1). Tourist arrivals were used as a proxy for tourism impact while the resident population was used as a proxy for urban centers.

2.2. Sampling campaign

Extensive sampling campaigns were conducted on February 15th–17th (winter season with the large touristic presence in the upstream sites, and low streamflow) and July 3rd–5th, 2015 (summer season with an appreciable touristic presence in the downstream sites, and high streamflow due to snow melting). Sediment and composite water samples were taken in two different periods (February 2015, and July 2015) in 12 sampling points (See Fig. 1). Sediment samples were collected with a small inox spade from the uppermost 10 cm sediment layer of both left and right banks and then mixed. They were then sieved on site with a 2 mm mesh sieve. Samples were subsequently stored in high-density polyethylene (HDPE) Ø 88 1 L bottles. Liquid samples, taken on the top of the water level, were collected on the left, center and right river side and then mixed. Water samples for the analysis of pharmaceutically active compounds (PhACs) were stored in 1 L gray PE bottles, while water samples for the personal care products (PCPs) analysis were stored in 500 mL amber glass bottles. Later on, samples were transported to the laboratory in a refrigerated isothermal container (dry ice) and stored at −20 °C until extraction. Characterization of the water bodies was completed by measuring additional parameters at all sampling sites (See Table 3S, SM). Water temperature and specific electrical conductivity at the standard temperature of 25 °C were measured with an Aquatroll 200 multi-parameter probe, while turbidity was measured by a Ponsel IR optical turbidimeter. River velocity was measured by a Decatur Electronics Europe Inc. radar gun

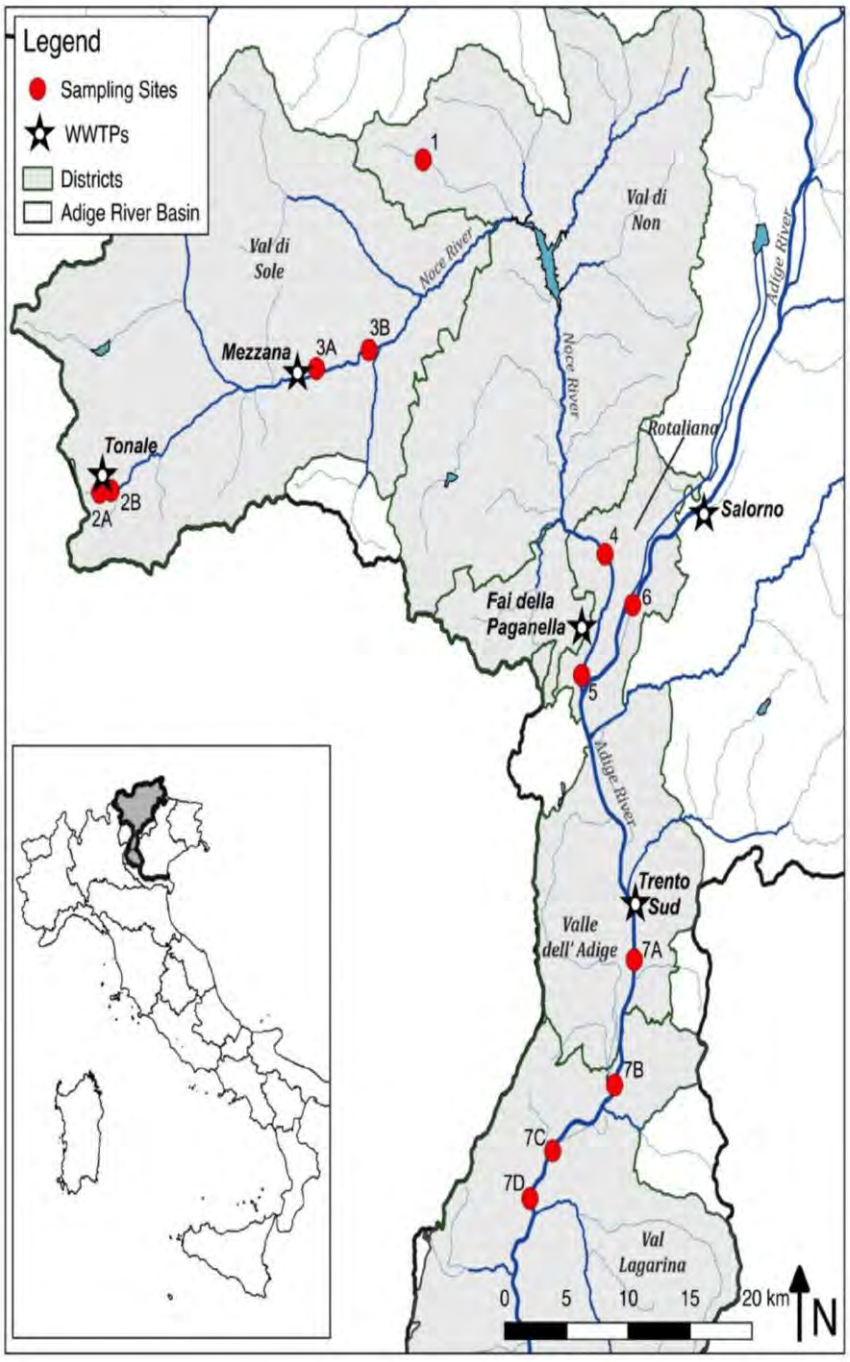

Fig. 1. Sampling sites (red dots) in Adige river basin and the associated WWTPs (black stars). Boundaries of districts including the sampling sites are also presented (green lines). The bottom left inset shows the location of the Adige basin within the Italian territory.

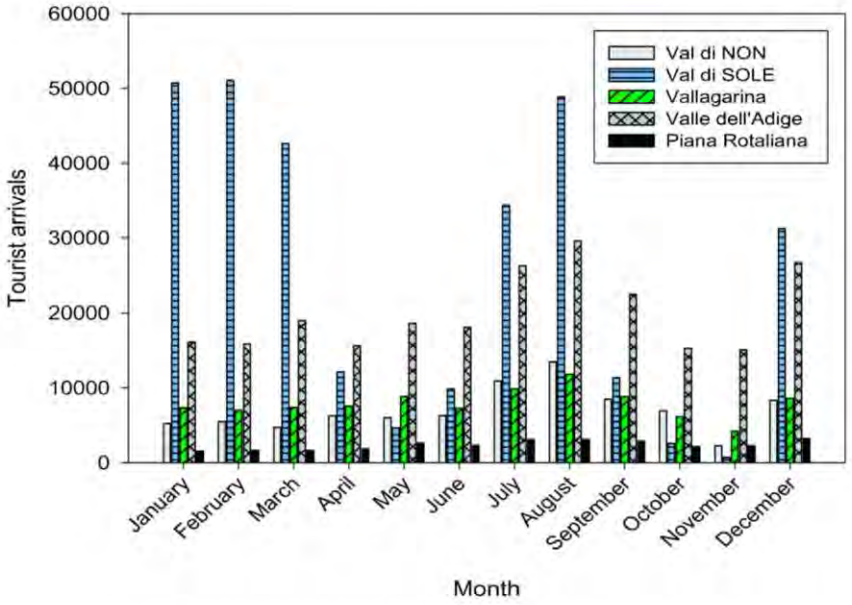

Fig. 2. Tourist arrivals at the district level in the Adige river basin for the year 2015.

(Welber et al., 2016), except at sites 2A–2B and 3B where tracers test with bromine (in winter campaign) and NaCl (in summer) was conducted. Records of daily streamflow at the sampling sites were obtained from the Ufficio Dighe of the Province of Trento (http://www.floods.it). The closest hydrometer with available time series was assigned to each sampling site. Since site 1 is located in an area without hydrometers, streamflow was obtained from hydrological simulations performed with the hydrological model GEOTRANSF (Bellin et al., 2016). Daily average river flow during the sampling days for each location was calculated on the basis of the sub-daily values (recorded every hour) and the resulting values are shown in Fig. 3 (notice the use of the logarithmic scale for the water discharge, which attenuates the seasonal differences for values larger than 1 $m^3 s^{-1}$).

2.3. Statistical methods

In order to explore the relationship between PPCP levels and their drivers (tourist arrivals, resident population), we calculated Pearson moment correlation factor (r) (Puth et al., 2014). We used the sum of compounds in each family for each sampling location to perform pairwise correlation with the tourist arrivals (February and July 2015), and the resident population in each municipality. Pairwise correlations were performed for water and sediment samples and the results of the analysis are shown in the Table 4S (SM). For each calculated probability (p), the significance threshold was set at 0.05. Statistical analysis was performed using SigmaPlot version 11 software (Richmond, CA).

2.4. Sample preparation and analysis

All chemical standards used in this research were of high purity grade (>90%) and they are listed in Table 5S in the SM. Following the preparation, standards were stored on −20 °C. Fresh stock antibiotic solutions were prepared every month due to their limited stability while the stock solutions for the rest of substances were renewed every three months.

2.4.1. Pharmaceutically active compounds

The PhACs analysis in water samples was conducted following the method developed by Gros et al. (2012). The analyses were carried out with an off-line solid phase extraction (SPE) followed by ultra-high-performance liquid chromatography coupled to triple quadrupole linear ion trap tandem mass spectrometry (UHPLC-QqLIT-MS^2). Chromatographic separations were carried out with a Waters Acquity Ultra-Performance™ liquid chromatography system, coupled to a

Table 1
Overview of the sampling sites along the Adige (main stem) and Noce rivers (tributary).

Sampling site	Catchment	Coordinates (X_UTM/ Y_UTM)	Districts	Resident population	Comment
1	Noce	648,165/5,143,139	Val di Non	255	Reference site in almost pristine conditions, at Bresimo
2A and 2B	Noce	623,630/5,124,045; 623,931/5,124,161	Val di Sole	282	Example of headwater with low water discharge at the Tonale pass impacted by the release of a WWTP
3A and 3B	Noce	639,983/5,131,178; 644,011/5132242	Val di Sole	2186	Headwater at Mezzana, downstream WB2 impacted by both WWTP release and hydropeaking (Majone et al., 2016)
4	Noce	662,113/5,120,547	Rotaliana	12,508	Lower course of the Noce at Mezzocorona, downstream of two reservoirs in series, one with large capacity (160 10^6 m^3)
5	Noce	660,322/5,113,612	Rotaliana	1732	Lower course of the Noce at Zambana, downstream WB4 and the restitution of a large hydropower plant
6	Adige	664,228/5,117,638	Rotaliana	3699	Located in the main stem of the Adige at Faedo upstream the city of Trento and the main tributaries in the Trentino region (Noce, Avisio and Fersina)
7A, 7B, 7C, 7D	Adige	664,351/5,097,306; 662,850/5,090,139; 658,085/5,086,360; 656,357/5,083,642	Valle dell'Adige, Vallagarina	126,423	Four (4) sites between Mattarello and Rovereto, downstream the city of Trento

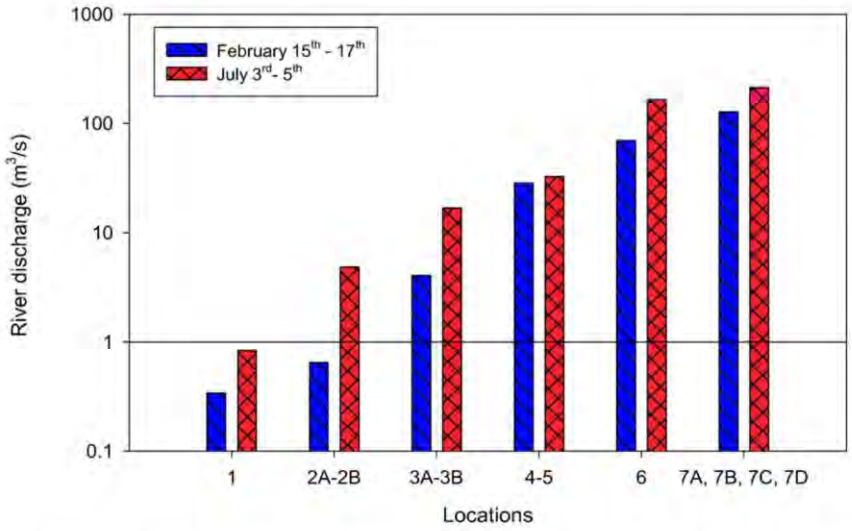

Fig. 3. Daily average river flow ($m^3\ s^{-1}$) during the sampling day at the different sampling locations (campaigns February and July 2015); measured by hydrometric stations or simulated with the GEOTRANSF model (Bellin et al., 2016). Notice the logarithmic scale of the ordinate.

5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer (Applied Biosystems, Foster City, CA, USA) with a turbo Ion Spray source. Furthermore, the target analytes were eluted from the column into the chromatograph with the LC-mobile phase, and the separation was achieved with two binary pump systems (Milford, MA, USA), using an Acquity HSS T_3 column (50 mm × 2.1 mm i.d., 1.8 μm particle size) for the compounds analyzed under positive electrospray ionization (PI) and an Acquity BEH C_{18} column (50 mm × 2.1 mm i.d., 1.7 μm particle size) for the ones analyzed under negative electrospray ionization (NI), both purchased from Waters Corporation. Electrospray Ionization (ESI) and selected reaction monitoring (SRM) modes were selected for the MS^2 detection. Prior to the instrument analysis, standard mixture containing all isotopically labeled standards was added in the extracts as an internal standard. Quantification was carried out by isotope dilution.

The analysis of PhACs in sediment samples was carried out according to the method developed by Jelić et al. (2009). Previously freeze-dried and homogenized sediment samples were extracted by pressurized liquid extraction (PLE) using an ASE 300 Accelerated Solvent Extractor (Dionex, Sunnyvale, CA, USA) equipped with 11 mL stainless extraction cells. The extracts of sediment obtained by PLE (~22 mL) were diluted in 500 mL of HPLC water (methanol ˜ 5%) and processed by SPE using the Oasis HLB cartridges (200 mg, 6 mL). The resulting extracts were evaporated under a gentle stream of nitrogen and reconstituted with the internal standard solution to a final volume of 1 mL. The analyses of the samples were carried out by UHPLC-MS^2 in the same analytical platform as for the water samples.

2.4.2. Personal care products

The analysis of PCPs in water samples was conducted following the method developed by Gago-Ferrero et al. (2013). The analyses were carried out by on-line solid phase extraction-high performance liquid chromatography–tandem mass spectrometry (SPE-HPLC-MS^2). The analyses were carried out on a Transcend LX System chromatograph with Equan™ Technology coupled to a TSQ Vantage, both from Thermo Scientific (Sunnyvale, CA, USA). For the on-line SPE extraction on the Equan™, a column HyperSep PEP from Thermo Scientific was used. Five ml of the water samples were infused through the column. Further, the target analytes were eluted from the column into the chromatograph with the LC-mobile phase, where the separation was achieved using a LiChroCART® Purospher® STAR® RP-18 ec (125 mm × 2.0 mm i.d., 5 μm particle size) analytical column from Merck preceded by a guard column LiChroCART® 4-4 Purospher® STAR® RP-18 ec (5 μm particle size). Atmospheric Pressure Photoionization (APPI) and SRM modes were selected for the MS^2 detection. Before the instrument analysis, a standard mixture containing all isotopically labeled standards was added in the extracts as an internal standard. Quantification was carried out by isotope dilution.

PCPs in sediment samples were determined according to the method by Gago-Ferrero et al. (2011a), using frozen-dried and homogenized samples. After the addition of the surrogate standards to the samples, the target analytes were extracted by PLE in an ASE-350 Accelerated Solvent Extractor (Thermo Fisher Scientifics). The resulting extracts were brought to 25 mL with MeOH and aliquots of 2 mL were then filtered using a 0.45 μm nylon syringe filter into LC-vials. These solutions were allowed to evaporate under a gentle stream of nitrogen and reconstituted with the internal standard solution to a final volume of 1 mL. The analyses of the samples were carried out by HPLC-MS^2 in the same analytical platform as for the water samples, disabling the on-line configuration. Other experimental conditions were the same as those for water analysis. Method performance parameters of PPCPs including the limits of detections (LODs), limits of quantifications (LOQ) and recovery rates are summarized in Tables 6S and 7S (SM).

3. Results

3.1. Occurrence and spatial distribution of selected PPCPs in winter

Overall, 36 out of the 80 PhACs investigated were detected in the winter water samples with the concentrations above LOQ (Table 8S, SM). The predominant pharmaceutical class detected was the analgesics/anti-inflammatory class (Fig. 4). Others, in order of contribution, were antihypertensives, antibiotics, diuretics and the psychiatric drugs. The analgesics/anti-inflammatories ibuprofen, diclofenac and salicylic acid were ubiquitous, with diclofenac, furosemide and valsartan being the PhACs presenting the highest concentrations (>300 ng L^{-1}). The samples with the highest total concentration in winter were sites 2A and 2B, located downstream of the Tonale WWTP (See Fig. 1), which collects wastewater from a large ski resort. Also, in winter waters the total concentration of analgesics/anti-inflammatories was positively correlated with the tourist arrivals ($r = 0.897$; $p < 0.05$) (Table 4S, SM). Regarding analgesics/anti-inflammatories, acetaminophen and naproxen were also often detected (92% of the samples), followed by codeine and ketoprofen with 75% positive detections. The highest total concentrations of analgesics/anti-inflammatory drugs were at sites 2A and 2B (See Fig. 4 and Table 8S in SM), with a concentration of diclofenac of 675 ng L^{-1} at site 2B and 569 ng L^{-1} at site 2A, respectively. Differences in concentrations between the individual

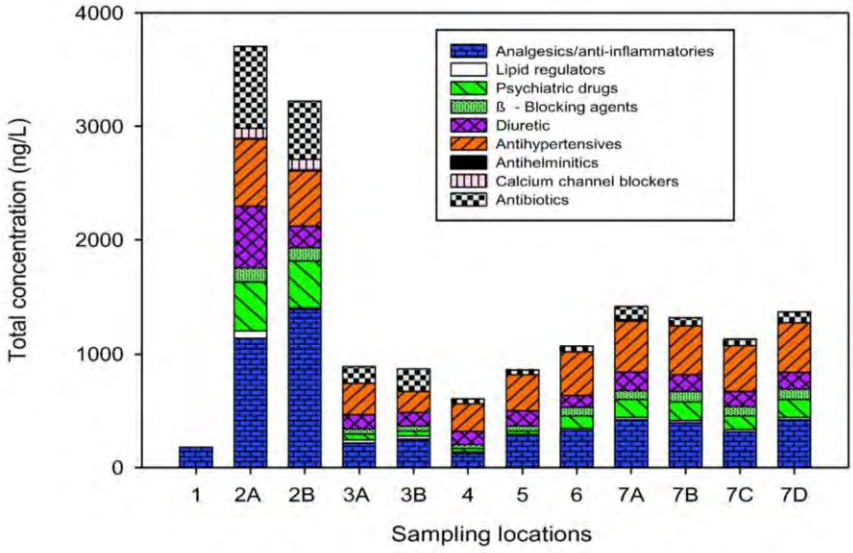

Fig. 4. Total concentrations of PhACs in water samples by categories in all sampling locations: winter period.

sampling points were a result of increased river flow and the consequent dilution effect. Acetaminophen, ketoprofen and ibuprofen had also increased concentrations at sites 2A and 2B (>100 ng L^{-1}). In comparison with analgesics/anti-inflammatories, the total concentration of antihypertensive drugs in winter waters was positively and significantly correlated with the resident population ($r = 0.815$; $p < 0.05$). Amongst antihypertensive drugs, valsartan was the most abundant PhAC with detection frequency of 92%. The highest concentrations of valsartan occurred downstream the municipality of Trento (sites 7A to 7D) associated to WWTP Trento Sud (See Fig. 1 and Table 1), with concentrations exceeding 300 ng L^{-1}, respectively (Table 8S, SM). Increased concentrations of valsartan and other antihypertensive drugs were also detected at sites 2A and 2B (>100 ng L^{-1}). Amongst antibacterial drugs, trimethoprim and sulfamethoxazole were the most frequently detected PhACs (detection frequency of 92%). The highest concentrations of trimethoprim, sulfamethoxazole, clarithromycin and metronidazole were also detected at sampling sites 2A and 2B (>100 ng L^{-1}), while total concentration of antibiotics was positively and significantly correlated with the tourist arrivals ($r = 0.960$; $p < 0.05$). Finally, β-blocking agents were detected in concentrations <70 ng L^{-1} and their total concentration was marginally correlated with the resident population ($r = 0.774$; $p < 0.1$). The high abundance of PhACs in sites 2A and 2B during winter may be explained by increased number of tourist arrivals (Fig. 2) coupled with low flow conditions (Fig. 3).

All analyzed samples contained between 1 and 10 different substances of PCPs residues. Overall, 13 out of the 25 investigated PCPs were detected with the concentrations above LOQ (See Table 8S in the SM). Amongst them, the UV filter octyl-dimethyl-*p*-aminobenzoic acid (ODPABA) was ubiquitous (Fig. 5). 4-Methyl-benzotriazole (MeBZT) was also very frequently detected, in 92% of the samples, followed by the UV stabilizer 5, 6-dimethyl-1-H-benzotriazole (DMeBZT) and the paraben preservative ethyl paraben (EPB), both with 67% positive detections. Within the PCPs, the product with the maximum concentration was ODPABA (748 ng L^{-1} at site 4; see Fig. 5). Other two benzotriazole UV stabilizers (UV328 and UV329) showed concentrations of 669 and 553 ng L^{-1}, respectively, and were also frequently

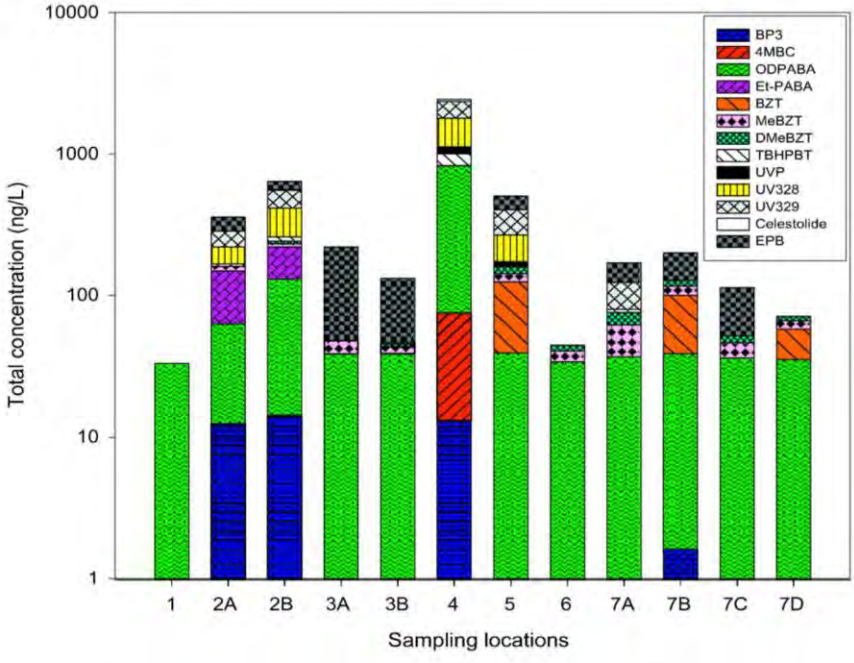

Fig. 5. Total concentrations of PCPs in water samples at all sampling locations: winter period. Notice the logarithmic scale of the ordinate.

detected. Fragrances were seldom found (17% frequency) and occurred at concentrations below 75 ng L^{-1} in the sites 4 and 2B. Another source of PCPs to sampling site 4 is the nearby city of Trento.

Concentrations and detection frequencies of PPCPs in winter were lower in sediments than in water samples (See Table 9S, SM). Only 7 pharmaceutical compounds were detected in the sediments with the concentrations above LOQ. Amongst them, clarithromycin was detected in 83% of the samples, and trimethoprim in 58% of the samples. Clarithromycin was most common in sites 2A and 2B, (58.1 ng g^{-1} and 44.1 ng g^{-1}, respectively). Other PhACs were quantified with concentrations <20 ng g^{-1}, respectively.

Regarding PCPs, only three UV filters were detected in the winter samples of sediments with the concentrations above LOQ (Table 9S, SM). Ethyl-*p*-aminobenzoic acid (Et-PABA, 67%), octocrylene (OC, 58%) and 3-(4′-methylbenzylidene) camphor (4MBC, 50%) showed concentrations below 8 ng g^{-1}/dw. The total concentrations of camphors and PABA derivatives which are typically used in sunscreen lotions and other skincare products were significantly and positively correlated with the resident population ($r = 0.959$, $p < 0.05$; $r = 0.973$, $p < 0.05$). All sediments contained at least one UV filter, but OC was the compound measured at the highest concentration. In particular, the sediment sample collected at site 7B showed the highest load of total PCPs, with a value of 8.30 ng g^{-1}/dw, being OCs more than half of these. This UV filter is also a sunscreen agent that protects against UV-B and some UV-A rays.

3.2. Occurrence and spatial distribution of selected PPCPs in summer

In summer only 15 out of the 80 PhACs were detected with concentrations above LOQ, and usually in lower concentrations than in winter. Most of the PhAC families were positively correlated during this period with the resident population ($p < 0.1$, Table 4S, SM). The analgesics/anti-inflammatory salicylic acid was ubiquitous, while diuretic hydrochlorothiazide and the antihypertensive irbesartan were detected in the 92% of the samples (Table 8S, SM). The predominant PhACs were analgesics/anti-inflammatories (Fig. 6), strongly and positively correlated with the resident population ($r = 0.887$; $p < 0.01$). Salicylic acid reached concentrations of 244 ng L^{-1} at site 7B, and ketoprofen reached 67.1 ng L^{-1} at sampling site 2B. Other analgesics/anti-inflammatory drugs were sporadically detected. Diuretics and antihypertensives were significantly correlated with the resident population ($p < 0.05$). Amongst diuretics, hydrochlorothiazide was the most abundant compound with concentrations up to 14.7 ng L^{-1} at the site 7B. Irbesartan and valsartan were the most abundant antihypertensive drugs, though concentrations were below 8 ng L^{-1}. Additionally, antibiotics were marginally correlated with the resident population ($r = 0.872$; $p < 0.1$); with tetracycline being quantified up to 73.8 ng L^{-1} at sampling site 7A. Other antibiotics were quantified at levels below 18 ng L^{-1}, respectively. Finally, psychiatric drugs were marginally correlated with the resident population and predominantly detected at sampling sites downstream of the city of Trento.

Regarding PCPs, only 7 compounds were detected with the concentrations above LOQ and between 3 and 5 were simultaneously observed in the same sample (Table 8S, SM). In summer water, the total concentrations of benzophenones and benzotriazoles were significantly and positively correlated ($p < 0.01$) with the resident population (Table 4S, SM). The most polluted site was 7D located downstream Trento (Fig. 7). Benzophenone BP3 was ubiquitous, whereas the two benzotriazoles 1-H-benzotriazole (BZT) and MeBZT were present in 92% of the waters, mainly in the lower part of the basin. In particular, BZT experienced a significant frequency and concentration increase. Similarly, BP3 was detected more often in summer than in winter and at higher concentrations (5720 ng L^{-1} at site 7D), mostly in the lower part of the catchment (Fig. 7). Besides, two of its metabolites benzophenone 1 (BP1) and 2, 2′-dihydroxy-4-methoxybenzophenone (DHMB) could be observed in 25% and 17% of the samples.

Very few PhACs were detected in the summer samples of sediments, usually at very low concentrations. Clarithromycin, acetaminophen and metoprolol were detected (Table 9S, SM). In this period, the samples with the highest concentrations were collected at sites 2A and 2B, where clarithromycin was measured at 1.56 ng g^{-1} and 1.71 ng g^{-1}, respectively. Regarding PCPs in sediments, 4-hydroxybenzophenone (4HB) and OC were the most observed PCPs, which were found in 17% of the samples. The maximum load of UV filters, 644 ng g^{-1}/dw was observed in 2B sampling site and corresponded almost entirely to OC (Table 9S, SM). This value is far above the maximum measured load in winter, 8.30 ng g^{-1}/dw.

4. Discussion

Overall, detected PPCPs concentrations during winter in the Adige were higher than in the summer period. One of the most significant factors for the PPCPs concentrations differences between the two periods was larger dilution by snow melting occurring in summer, while in

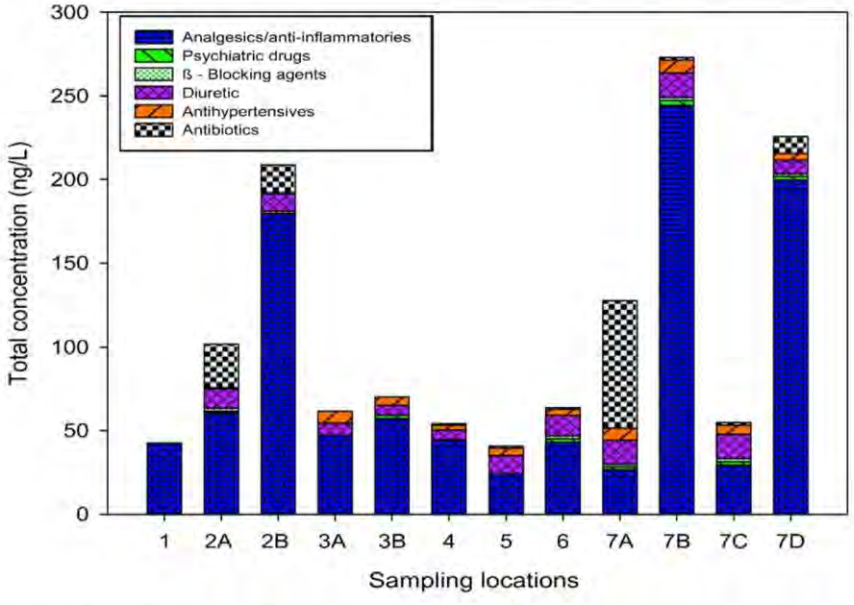

Fig. 6. Total concentrations of PhACs in water samples by categories in all sampling locations: summer period.

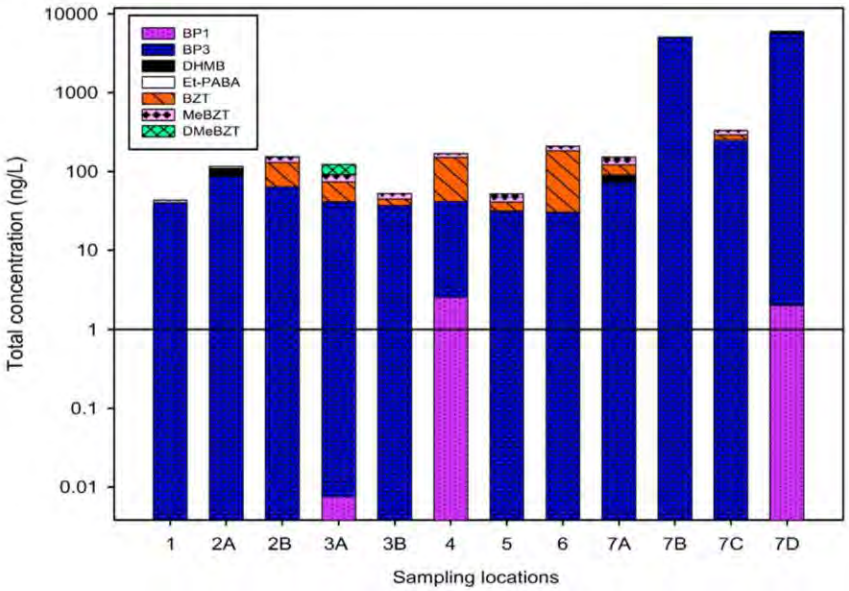

Fig. 7. Total concentrations of PCPs in water samples at all sampling locations: summer period. Notice the logarithmic scale of the ordinate.

winter the predominance of solid precipitations resulted in low streamflow and thereby reduced dilution (Fig. 3). The second important factor affecting PPCPs concentrations was tourism. Val di Sole, located upstream on the Noce River, is a district characterized by intense winter tourism arrivals (Fig. 2). During February, tourist arrivals in Val di Sole accounted for 76.4% of the total population residing in the area, while this percentage was 9.7% in Valle dell'Adige and Vallagarina and 5.2% in Rotaliana (See Fig. 2). Therefore, the joint effect of low streamflow and a high number of tourists during winter resulted in the overall higher concentrations of PPCPs, especially in the sites located within Val di Sole (2A/2B and 3A/3B) (See Fig. 1). On the contrary, PPCPs concentrations which were detected in the downstream area of the basin during winter were overall lower in comparison with the uppermost part, due to a higher river flow in the lower part of the basin and lower number of tourist arrivals (See Fig. 2). Even though the PhACs consumption during winter is overall higher than in the summer (Osorio et al., 2012), high abundance of detected PhACs in Val di Sole could be additionally explained by the increased number of tourist arrivals (76.4% of the total population) during the winter period. In winter water, analgesics/anti-inflammatories concentrations were associated to tourist arrivals (Table 4S, SM). Ski resorts surrounding the Val di Sole produce wastewater treated at the WWTPs of Tonale and Mezzana (See Fig. 1 and Table 2S in SM), and this could explain that the most abundant compound was an analgesic/anti-inflammatory (diclofenac). The non-steroidal anti-inflammatory (NSAID) diclofenac is a compound typically used in the treatment of the sports injuries such as joint pain and inflammation (Galer et al., 2000). This medicine works by reducing substances in the body that cause pain and inflammation and is mostly used in an oral form or as a topical cream. Amongst analgesics/anti-inflammatories, ketoprofen was another NSAID predominantly detected in the sampling sites 2A and 2B. Same as diclofenac, ketoprofen is also available as a gel, which can be applied directly to the skin to help relieve muscle and joint pain in the sports injuries (Derry et al., 2015). Analgesics/anti-inflammatories acetaminophen and naproxen were also detected with the highest concentrations in sampling sites 2A and 2B. Acetaminophen and naproxen are pain relievers and fever reducers (Hanks and McKenzie, 2016). In the sampling sites 2A and 2B, the highest concentrations of the antibiotics trimethoprim, metronidazole, clarithromycin and sulfamethoxazole were detected. These antibiotics are usually used in order to treat certain bacterial infections, such as pneumonia, bronchitis, urinary tract infections and infections of the ears, sinuses, skin, and throat (Liou et al., 2016; Tsaganos et al., 2016; Vahlensieck et al., 2016). It is common to observe the drugs during winter in order to treat cold-related illnesses (Liu et al., 2014). Antihypertensive drugs were significantly correlated with the resident population, therefore pointing out urban centers as the main source. The most abundant antihypertensive drug was valsartan and it was detected with the highest concentrations in the sites along the main stem of the Adige River, downstream the highly urbanized areas of the city of Trento. Valsartan is mainly used in the treatment of high blood pressure, heart failure, and in order to enhance the living chances after the heart attack (Kaplinsky, 2016). Even though touristic seasonal variations and streamflow are affecting PhACs occurrence, increased concentrations in the winter water can be also attributed to decreased operational conditions, configuration and performance of WWTPs during cold weather (Hua et al., 2006; Gros et al., 2009; Osorio et al., 2012; Azzouz and Ballesteros, 2013; Sari et al., 2014). Higher concentrations and detection frequencies during low-flow conditions have also been reported elsewhere (Kolpin et al., 2004; Tewari et al., 2013; Dai et al., 2015).

Contrastingly, PCPs were not positively correlated with the tourist arrivals during winter. PCPs are not only incorporated in cosmetics but also occur in a wide range of products (plastics, adhesives, rubber, paint) (Gackowska et al., 2014; Ramos et al., 2015). The most abundant PCP compound was ODPABA, particularly in the downstream sites (4, see Fig. 1). Usually, ODPABA is added in conjunction with UV-A filters, being the most popular BP3. This compound is a powerful UV-B absorber, widely used in cosmetics as sunscreen (Molins-Delgado et al., 2015a). Also EPB, a paraben occurred in winter. The parabens are a family of compounds extensively used as preservatives in the food, pharmaceutical, and personal care product industries, though its use is controversial for its potential carcinogenic and endocrine disruption properties (Molins-Delgado et al., 2016b). The frequent detection of MeBZT and DMeBZT in winter water may be associated with their wide use as UV absorbers in a variety of plastic products as well as anticorrosive agents, e.g., in aircraft deicer and anti-icer fluid (ADAF), and for so-called silver protection in dishwasher detergents. Due to their high water solubility, low biodegradability and limited sorption tendency, they are only partly removed in wastewater treatment (Molins-Delgado et al., 2015b). Therefore, as a result of their extensive and varied use, benzotriazoles are often detected in river waters (Kiss and Fries, 2009; Herrero et al., 2014; Alotaibi et al., 2015). Amongst detected benzotriazoles, UV 328 and UV 329 were the most abundant compounds and both are efficient light stabilizers added to polyestyrene, poly (methyl methacrylate), polyester and ABS resins.

Overall concentrations of detected PPCPs were lower in the summer period. One of the most important factors influencing PPCPs concentrations during summer was higher dilution due to snow melting (See Fig. 3). Also, overall decrease in the consumption of PhACs in comparison with the winter period could account for these differences (Osorio et al., 2012). Daily WWTPs outflows were lower during summer (Table 2S, SM). Even though the number of tourists increased in the lower area of the basin during this period, the percentage of tourists only increased the resident population by 4.8% in Valle dell'Adige and Vallagarina and 4.2% in Rotaliana (See Fig. 2). Also, detected PPCPs concentrations during summer in the upstream sites were lower than in the downstream sites. This fact could be attributed to the combined effect of an increased stream flow and a significant decrease in the number of tourist arrivals in Val di Sole during summer months. The PhACs occurrence was associated with the population density in the area, while the profile of detected PhACs was also characteristic. Analgesics/anti-inflammatories, diuretics and antihypertensives were positively and significantly correlated with the resident population (Table 4S, SM). In this period salicylic acid and the hydrochlorothiazide (used for hypertension, congestive heart failure, symptomatic edema, diabetes insipidus and renal tubular acidosis) (Sohn et al., 2016) were the most frequent. Also, benzophenones and benzotriazoles were significantly and positively correlated with the resident population (Table 4S, SM). The highest PCP load in summer was 6000 ng L^{-1}, 2.5-folds higher than in winter (2417 ng L^{-1}). Therefore, taking into account the positive and significant correlation of PCPs with the resident population, the increase of PCPs during summer especially occurs at the sampling sites downstream the municipality of Trento. Additionally, high summer temperatures could also account for the overall decreased PPCPs concentrations during summer, both because of the better elimination of PPCPs in WWTPs (Vieno et al., 2005; Onesios et al., 2009; Dai et al., 2015), as well as by the decrease of human consumption and increased natural degradation (photodegradation and biodegradation) (Osorio et al., 2012). The increased concentrations of PPCPs during winter and their decreased concentrations during summer were in accordance with the previous research in this field (Vieno et al., 2005; Wu et al., 2009; Martín et al., 2011; Veach and Bernot, 2011; Osorio et al., 2012) and different performance studies of WWTPs during different seasons (Sui et al., 2011; Lacey et al., 2012).

Our measurements indicated that the accumulation of PPCPs in sediments was moderate in comparison to water samples. Miao et al. (2002) reported that only the less polar pharmaceuticals may sorb to the deposit in sediments and suspended particles. Generally, compounds with basic characteristics (pKa > 7) showed higher tendency to bind to sediments such as clarithromycin (pKa 8.9), hydrochlorothiazide (pKa 7.9), metroprolol (pKa 14.1) and acetaminophen (pKa 9.38); which is expected having in mind the rather polar characteristics of studied compounds and their low tendency to sorb to sediment (Silva et al., 2011). The overall concentrations of PhACs in the winter samples of sediments were higher than those detected in the summer samples, possibly as a result of higher biodegradation during summer as a consequence of higher temperatures. The lower part of the catchment had the most contaminated sediments with PCPs, likely because of the accumulation of the transported materials along the basin. Also, the most abundant compound in sediments from both sampling campaigns was OC. Within organic UV filters, OC is of particular concern due to its high lipophilicity (log Kow 6.88), stability, and resistance to photo-degradation. However, it can trigger the formation of potentially harmful ROS (reactive oxygen species) free radicals when it releases the absorbed energy. The widespread distribution of this sunscreen, along with the high concentrations determined in sewage sludge and sediments (Gago-Ferrero et al., 2011a; Gago-Ferrero et al., 2011b), appears to be correlated with its extensive use of beauty and hygiene products, especially, because both protects in UVA and UVB regions, and improves the absorbing potential of other organic UV filters, such as BP3, EHMC, and avobenzone (AVB) (Gaspar and Maia Campos, 2006). Higher concentrations of OC occurred downstream the city of Trento.

Our observed concentrations of PPCPs fell within the ranges reported in the literature (Heberer, 2002; Pal et al., 2010; Ramos et al., 2015), while detected concentrations were typically in ng L^{-1}–μg L^{-1} level. Even though studies regarding spatiotemporal distribution of PPCPs are not frequent in the Alpine environments, our detected concentrations were comparable with studies performed by other authors elsewhere (Ashton et al., 2004; Kasprzyk-Hordern et al., 2008; Fernández et al., 2010; Liu et al., 2010; López-Serna et al., 2012; Gago-Ferrero et al., 2013; Wu et al., 2013; Acuña et al., 2014). The occurrence of PPCPs in fragile environments, like the Alpine aquatic ecosystems, represents an important threat due to their pseudo-persistency which can result in the acute effects on the environment and human health (Halling-Sorensen et al., 1998; Brausch and Rand, 2011). Even though acute toxicity of PPCPs in the Adige River is unlikely to occur due to their usually very low environmental concentrations and lack of chronic toxicity data regarding the effects of long-term and low-level exposures (Ávila and García, 2015), seasonal touristic fluxes have shown to be a very important factor accounting for the overall PPCPs pollution of this Alpine ecosystem.

Finally, Alpine aquatic environments are extremely fragile systems to multiple stressors (Buckley, 2000; Brown et al., 2007; Hauer et al., 2007; Woodward, 2009). Combined and interacting influences of overexploitation, water pollution, flow modification, degradation of habitat and invasion by exotic species represent main threats for global freshwater biodiversity and particularly for Alpine aquatic environments (Dudgeon et al., 2006). In the case of the Adige River, additional threats to the aquatic ecosystem include hydropeaking and thermopeaking due to hydropower production, climate change impacts, and emerging and regulated pollutants released by WWTPs (Kračun-Kolarević et al., 2016). In this work, we have shown that seasonal touristic fluxes can represent one of the most important drivers for the PPCPs pollution of this Alpine aquatic ecosystem.

5. Concluding remarks

Results of this research highlight tourism as a significant contributor to the overall PPCPs pollution of the Alpine aquatic environment. The occurrence of PPCPs in Alpine rivers is associated with seasonal variation of river streamflow (low flow in winter and high flow in summer) as well as the fluctuation of tourist arrivals during the year. In the case of the Adige River, results show evidence of the strong tourism impact on the Alpine river quality. The concentrations of quantifiable PPCPs were typically in the ng L^{-1}–μg L^{-1} range, with detected values being in general higher during winter than during summer. This variation could be jointly attributed to low flow conditions, cold-water temperatures and increased number of tourist arrivals, especially in Val di Sole. Concentrations of selected PPCPs during winter in the downstream sites were significantly lower than in the upstream sites due to the higher streamflow (dilution effect) and lower number of tourist arrivals. During summer the pattern was reversed, and higher concentrations of PPCPs occurred in the downstream, a highly urbanized area of the basin. Nevertheless, despite the amount of the PPCPs data collected, the analysis of the available information would benefit from a complementary exploration of the ecotoxicological relevance of the PPCPs and their metabolites in the Alpine aquatic environment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2017.02.185.

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Chapter 2.

Impact of urban chemical pollution on water quality in small, rural and effluent-dominated Mediterranean streams and rivers

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Impact of urban chemical pollution on water quality in small, rural and effluent-dominated Mediterranean streams and rivers

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HIGHLIGHTS

- Effluent-dominated streams showed higher concentration levels of pharmaceuticals.
- Non-steroidal anti-inflammatory drugs were the most ubiquitous compounds detected.
- Travel time is an important factor affecting the in-stream attenuation of pharmaceuticals.
- After 100 min of travel time concentrations equalized with the background concentrations.

GRAPHICAL ABSTRACT

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ABSTRACT

The impact and occurrence of wastewater (treated and untreated) derived pharmaceutically active compounds (PhACs) have been investigated in small, rural and effluent-dominated tributaries of the lower Ebro River located in the North-Eastern Spain (Catalonia). We have observed the predominant effect of stream flow and consequently dilution factor on the concentration levels of detected PhACs that combined with the absence of wastewater treatment plants (WWTP) resulted in 12 times higher concentrations in streams with direct discharge of untreated wastewater. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most ubiquitous compounds, in terms of both individual concentration and frequency of detection. In the sites impacted by raw wastewater, acetaminophen and ibuprofen showed the highest concentrations among all analyzed PhACs, reaching concentrations up to 7.78 μg L^{-1} and 2.66 μg L^{-1}, respectively. However, PhACs detected in the sites impacted by treated wastewater showed generally lower concentration levels and frequencies of detection. Also, effluent-dominated streams showed higher concentration levels of PhACs due to a generally lower stream flows and small dilution factors. However, concentration levels of detected PhACs were dependent on the hydraulic travel time and distance from the discharge point and related with the in-stream attenuation. As a result, this study highlights the combined impact of hydrological and chemical stressors on the water quality of the rural Mediterranean aquatic ecosystems.

Abbreviations: D.F., detection frequency; ESI, electrospray ionization; HRT, hydraulic retention time; LOD, limit of detection; LOQ, limit of quantification; MANOVA, multivariate analysis of variance; Ni, negative electrospray ionization; NSAIDs, non-steroidal anti-inflammatory drugs; OTC, over-the-counter; PhACs, pharmaceutically active compounds; PI, positive electrospray ionization; QqLIT-MS/MS, quadrupole linear ion trap tandem mass spectrometry; r, Pearson moment correlation factor; SM, supplementary material; SPE, solid phase extraction; SRM, selected reaction monitoring; UHPLC, ultra-high-performance liquid chromatography; WWTP, wastewater treatment plant.

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1. Introduction

Pharmaceutically active compounds (PhACs) include all prescription and non-prescription over-the-counter (OTC) drugs and represent an important group of emerging environmental contaminants (Richardson and Ternes, 2005). Even though PhACs can enter aquatic ecosystem through many pathways such as human excretion, disposal of unused and expired drugs, agricultural and livestock practices (Jorgensen and Halling-Sorensen, 2000; Vera-Candioti et al., 2008; Boxall et al., 2012; Tijani et al., 2016), treated and untreated (raw) wastewater discharges represent the main route of entrance (Heberer, 2002; Vieno et al., 2005). As a result of their continuous release into the aquatic environment, PhACs are considered as pseudo-persistent compounds and as such may cause unwanted and unexpected effects on the living organisms and environment (Daughton and Ternes, 1999; Hirsch et al., 1999; Dietrich et al., 2002; Ellis, 2006). Many PhACs in surface waters do not exhibit acute toxicity due to their usually very low environmental concentrations but instead have a rather significant cumulative effect on the metabolism of aquatic organisms and on the ecosystem as a whole (Halling-Sorensen et al., 1998; Daughton and Ternes, 1999). However, due to lack of chronic toxicity data regarding the effects of long-term and low-level PhACs exposures (Ávila and García, 2015), further investigation of PhACs toxicity in the aquatic environment is required.

The capacity of rivers to naturally attenuate PhACs relates to water turbidity, temperature, water flow, biofilm biomass, pH, dissolved oxygen and even mixing between surface and subsurface compartments (Lin et al., 2006; Acuña et al., 2014). However, impact of contaminants downstream from wastewater discharge is mostly determined by distance and in-stream attenuation processes such as biotransformation, photolysis, sorption and volatilization (Vieno et al., 2005; Brooks et al., 2006; Gurr and Reinhard, 2006; Barber et al., 2013; Chiffre et al., 2016), while dilution, together with the hydraulic travel time (time it takes for a body of water to travel between wastewater discharge point and downstream sampling site) represents the critical components in estimating concentration levels of PhACs in rivers (Rueda et al., 2006; Keller et al., 2014).

So far, the presence of PhACs in treated effluents from wastewater treatment plants (WWTPs) and their receiving waters has been ranged in ng L^{-1} up to μg L^{-1} (Da Silva et al., 2012; Verlicchi et al., 2012; Luo et al., 2014). However, the research literature on the impact of PhACs from untreated wastewaters remains notoriously limited. Further, most research regarding the occurrence of PhACs in waste and surface waters has been limited to larger river systems supporting high population densities (Fernández et al., 2010; Jelic et al., 2011; Fernández-López et al., 2016; Osorio et al., 2016), while knowledge regarding the impact of PhACs occurrence in surface waters of small perennial and non-perennial Mediterranean rural streams remains limited and scarce (Skoulikidis et al., 2017).

In this work, the main objective is to study combined effect of hydrological (flow, hydraulic travel time) and chemical stressors (urban pollution, wastewater treatment) in small, Mediterranean streams and rivers of the lower Ebro River, spanning in their dilution capacity. These systems experience strong seasonal river flow variability, and are prone to eutrophication, hypoxia and increased levels of agricultural and industrial pollutants due to the intense human pressure they receive (Cooper et al., 2013; López-Doval et al., 2013; Acuña et al., 2014; Petrovic et al., 2011). In some cases, these systems receive municipal and industrial wastewaters that dominate the stream flow (Hassan and Egozi, 2001; Poff and Zimmerman, 2010). Consequently, effluent-dominated streams represent the worst-case scenarios for PhACs exposure to aquatic ecosystem and human population (Brooks et al., 2006), since they have higher PhACs concentrations than those having dilution, being irrespective of the type of received wastewater (treated or untreated).

2. Materials and methods

2.1. Basin and sampling sites description

This study was performed in a series of small to medium-sized tributaries of the lower Ebro River basin (Sabater et al., 2009) (See Fig. 1). These systems show typical Mediterranean interannual hydrological variations and seasonal flow reductions in summer and floods in spring and autumn (Gasith and Resh, 1999). All are characterized by a small resident population (Table 1.), with forest and non-irrigational agriculture as the main land uses upstream of the studied sites. Three sampling campaigns were performed at eleven different sites (See Table 1 and Fig. 1), all previously defined with a control (upstream) and impact (downstream) reaches of the wastewater discharge. Three sites received treated wastewaters (effluents from nearby WWTPs), while eight others were impacted by a discharge of raw (untreated) wastewater (Fig. 1). Five sites presented effluent-dominated stream flows (See Fig. 1S in Supplementary material, SM), particularly during October 2015 that was the driest period studied. Effluents were in all cases of urban origin. The daily outflows from WWTPs were obtained from the Agència Catalana de l'Aigua (http://aca-web.gencat.cat/aca/appmanager/aca), and the main characteristics of the treatment process, population served and average monthly WWTP outflows are provided in Table **1**S (SM). The resident population in each municipality concerning the effluents was obtained from the IDESCAT (Catalan Government, 2017) and INE (Spanish Government, 2017).

2.2. Sampling campaign

Extensive sampling campaigns were conducted on April 2015 (wet period), on October 2015 (dry period) and April 2016 (relatively wet

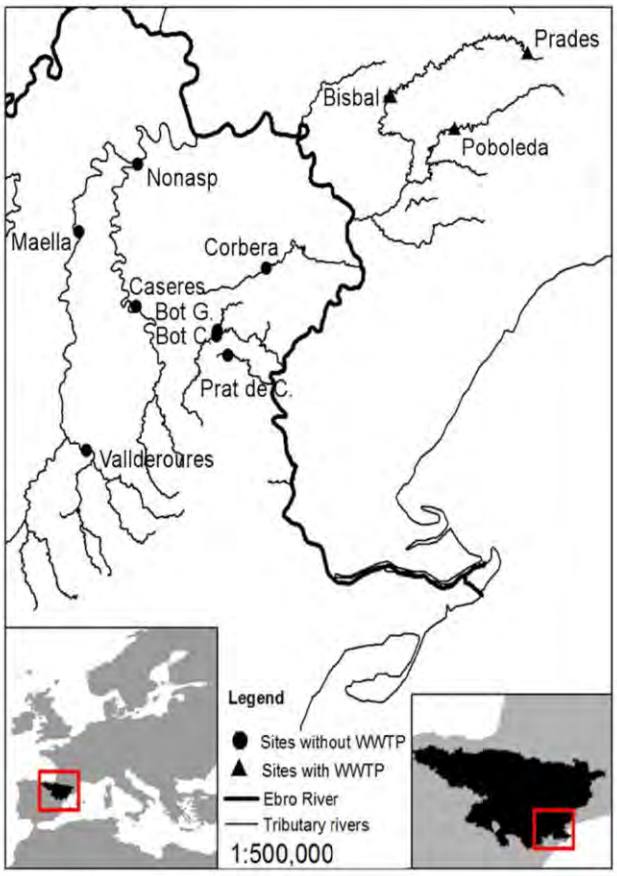

Fig. 1. Sampling sites (black dots and triangles) in the lower Ebro River basin. The bottom left inset shows the location of the Ebro River basin within the Europe and the Iberian Peninsula, while the bottom right inset shows the location of the lower Ebro River basin.

Table 1
Overview of the sampling sites along the studied river and stream tributaries of the lower Ebro River.

Site	River	Effluent	Population (2012)	Distance to site (m)[a]	Comments (discharge point)
Prades	Prades Stream	WWTP	651	95	Direct pipe
Bisbal de Falset	Montsant	WWTP	227	190	Direct pipe
Poboleda	Siurana	WWTP	1025	100	Direct pipe
Nonasp	Algars	Untreated	1064	440	First sampling campaign 240 m of open channel
Caseres	Algars	Untreated	284	480	Direct pipe
Maella	Matarranya	Untreated	1986	1230	Direct pipe
Vallderoures	Matarranya	Untreated	2335	530	Direct pipe
Bot - Canaleta	Canaleta	Untreated	678	885	Direct pipe
Bot - Gandesa	Gandesa Stream	Untreated	678	65	Open channel of 245 m before the river
Prat de Comte	Xalamera Stream	Untreated	183	40	Direct pipe
Corbera d'Ebre	Sec	Untreated	1204	50	Open channel of 40 m before the river

[a] Distance between wastewater discharge points and downstream sampling sites.

period). A total of 24 untreated wastewater samples, 9 treated WWTP effluent samples and 66 river water samples were collected (See Fig. 1 and Table 1). Single grab water samples for the PhACs analysis were collected and stored in 1 L gray PE bottles. Later on, samples were transported in a refrigerated isothermal container (dry ice), and stored at −20 °C until extraction. At impact sites, water was sampled after the complete mixing of wastewater and river water. In all sites, hourly measurements of water level were performed with level loggers (Solinst Levelogger, Canada) (Table 2S, SM). Water depth, water velocity, and discharge were measured during each sampling campaign with an acoustic Doppler velocity meter (ADV; Flow Tracker, SonTek Handheld-AD®, P-4077) (Fig. 2S and Table 2S, SM). Water temperature, pH, and electrical conductivity were measured in situ using hand-held probes (WTW, Weilheim, Germany).

2.3. Sample preparation and analysis

2.3.1. Chemicals and reagents

All chemical standards used in this research were of high purity grade (>90%). Following the preparation, standards were stored on −20 °C. Fresh stock antibiotic solutions were prepared every month due to their limited stability while the stock solutions for the rest of substances were renewed every three months. For more detailed information regarding chemicals and reagents used, see Table 3S (SM).

2.3.2. Analytical method

The PhACs analysis in water samples was conducted following the method developed by Gros et al. (2012). The analyses were carried out with an off-line solid phase extraction (SPE) followed by ultra-high-performance liquid chromatography coupled to triple quadrupole linear ion trap tandem mass spectrometry (UHPLC-QqLIT-MS/MS). Prior to the SPE, water samples were filtered through 1 μm glass fiber filters and by 0.45 μm nylon membrane filters (Whatman, U.K.). Filtered and previously spiked water samples were extracted by SPE using Oasis HLB (60 mg, 3 mL) cartridges. These extracts were evaporated under a gentle stream of nitrogen and reconstituted to a final volume of 1 mL. Before the instrument analysis, water samples were fortified with 10 μL of a 1 ng/μL standard mixture containing all isotopically labeled standards. Chromatographic separations were carried out with a Waters Acquity Ultra-Performance™ liquid chromatography system, coupled to a 5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer (Applied Biosystems, Foster City, CA, USA) with a turbo Ion Spray source. The target analytes were eluted from the column into the chromatograph with the LC-mobile phase, and the separation was achieved with two binary pump systems (Milford, MA, USA), using an Acquity HSS T_3 column (50 mm × 2.1 mm i.d., 1.8 μm particle size) for the compounds analyzed under positive electrospray ionization (PI) and an Acquity BEH C_{18} column (50 mm × 2.1 mm i.d., 1.7 μm particle size) for the ones analyzed under negative electrospray ionization (NI), both purchased from Waters Corporation. For the analysis in the (PI) mode, methanol and 10 mM formic acid/ammonium formate (pH 3.2) were used as a mobile phase at the flow rate of 0.5 mL/min. However, for the analysis in the (NI) mode, acetonitrile and 5 mM ammonium acetate/ammonia (pH = 8) were used as a mobile phase at the flow rate of 0.6 mL/min. The sample volume injected was 5 μL for both modes, while information regarding the gradient elution is provided in the SM. Electrospray Ionization (ESI) and selected reaction monitoring (SRM) modes were selected for the MS^2 detection. A summary of the optimum values and SRM transitions is available in the Table 4S (SM). Finally, all data were acquired and processed using Analyst 1.5.1 software, while quantification was carried out by isotope dilution. Method performance parameters of target compounds including limits of detections (LODs), limits of quantifications (LOQs) and recovery rates are summarized in Table 5S (SM).

2.4. Statistical analysis

The normal distribution of all variables was checked with the Shapiro-Wilk test and log-transformed when necessary. In all statistical analysis, undetected compounds and compounds below LOQ were given the corresponding LOD/2 and LOQ/2 value. Mann-Whitney *U* tests were performed to assess for the statistical differences in the total PhACs concentrations (sum of all compounds) between the upstream and downstream sampling sites. This test was also used to determine the statistical differences in the individual concentrations of PhACs. However, the Kruskal-Wallis test by ranks was used to test the statistical significance in the total PhACs concentrations in control sites and in wastewater discharge points between each sampling campaign. The relevance of factors (period, effluent-dominance, and wastewater treatment) on the total concentrations of PhACs (sum of compounds in each family of compounds) in the impact sites was evaluated by means of Multivariate Analysis of Variance (MANOVA). Given the significance of the overall test, the univariate main effects were examined, while Bonferroni correction was applied to *p*-values in order to control family-wise error rate (Dunn, 1961). Results of the statistical analysis performed are shown in Table 6S (SM). The relationship between the total PhACs concentrations and the resident population was explored by Pearson moment correlation factor (r). All analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, U.S.A.).

3. Results

3.1. Occurrence of PhACs in wastewaters

Detection frequencies (D.F.), minimum, maximum and individual concentrations of PhACs detected (>LOQ) in wastewaters are listed in Table 7S (SM). The occurrence and spatiotemporal distribution of PhACs in untreated and treated wastewater are shown in Fig. 2. The resident population was correlated to the total PhACs concentrations (sum of all compounds) in untreated and treated wastewater ($r = 0.64$, April 2015; $r = 0.68$, October 2015; $r = 0.71$, April 2016; $p < 0.05$). In all

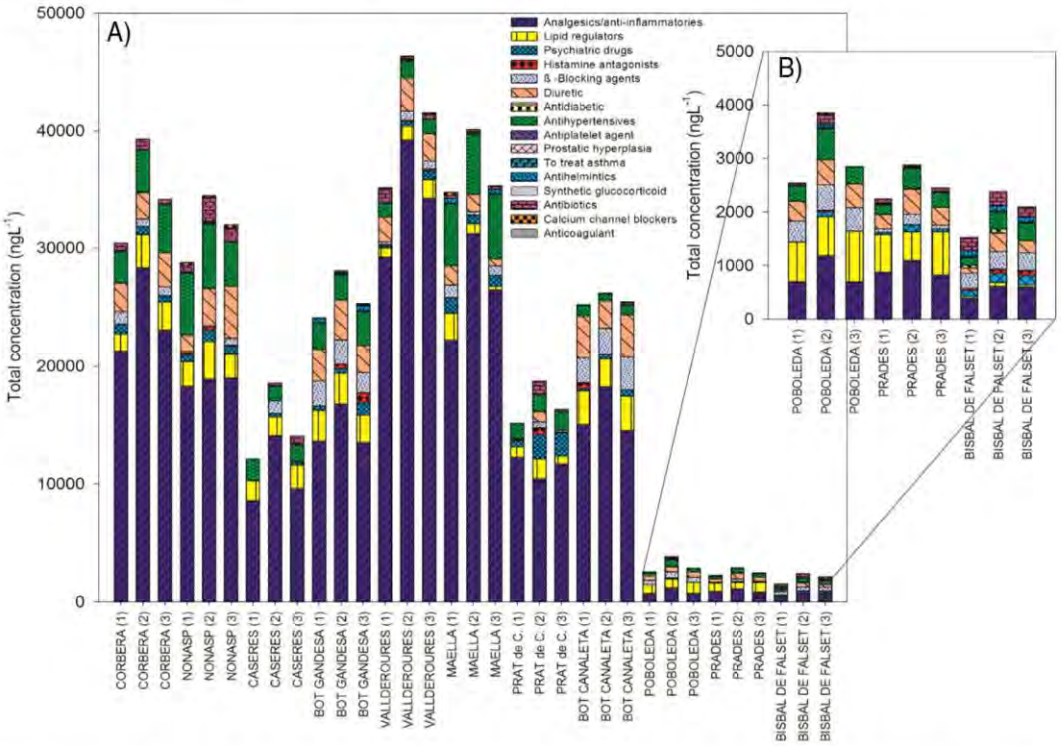

Fig. 2. Spatiotemporal distribution of PhACs by their therapeutic groups in the wastewater: A) Untreated and treated wastewater presented together B) Detailed view of treated wastewater (WWTP effluent). Note in parentheses: (1) wet period (April 2015), (2) dry period (October 2015), (3) relatively wet period (April 2016).

sampling campaigns, 60 different PhACs out of the 68 monitored were detected, and 3 of them were detected in at least two of the three sampling campaigns, and 3 in only one campaign (Table 7S, SM). There were no statistically significant seasonal differences in the total PhACs concentrations in treated and untreated wastewaters (Kruskal-Wallis test by ranks; $p > 0.05$). Maximum concentration levels of detected PhACs in raw wastewater ranged from 2.87 ng L^{-1} to 17.5 μg L^{-1}. The non-steroidal anti-inflammatory drugs (NSAIDs) were the most ubiquitous compounds (See Fig. 2 and Table 7S, SM), together with antihypertensives, diuretics, lipid regulators, β-blocking agents, psychiatric drugs, and antibiotics. The analgesics/anti-inflammatories acetaminophen, ibuprofen and salicylic acid, the lipid regulator gemfibrozil, the psychiatric drug venlafaxine, the β-blocking agent atenolol and the antihypertensive valsartan were ubiquitous in untreated wastewaters. The highest concentrations detected were for acetaminophen (maximum concentrations up to 18 μg L^{-1}), ibuprofen (13.5 μg L^{-1}) and naproxen (6.43 μg L^{-1}) (Table 7S, SM).

Regarding treated wastewater, the highest total concentration of PhACs was 12 times lower (Fig. 2) than in untreated raw wastewater. However, in all sampling campaigns, 56 different PhACs out of the 68 monitored were detected, and 11 of them were detected in at least two of the three sampling campaigns, and 9 in only one campaign (Table 7S, SM). Concentration levels of detected PhACs were in the low to the medium ng L^{-1} range. In treated wastewaters, 30.6% of the total PhACs concentrations corresponded to the analgesics/anti-inflammatories, while other therapeutic groups in order of contribution were lipid regulators, diuretics, antihypertensives, β-blocking agents, antibiotics, psychiatric drugs and antihelmintics. The analgesics/anti-inflammatories were generally the most ubiquitous compounds, and salicylic acid was the PhAC with the highest concentration detected (622 ng L^{-1}) (Table 7S, SM).

3.2. Occurrence of PhACs in the upstream (control) sites

Overall, 46 different PhACs out of the 68 monitored were detected in all sampling campaigns, 14 of them were detected in at least two of the three sampling campaigns, and 13 in only one campaign (Figs. 3 and 4, Table 8S, SM). There were no statistically significant seasonal differences in total PhACs concentrations (Kruskal-Wallis test by ranks; $p > 0.05$). The upstream site with the highest total PhACs concentrations detected was Corbera d'Ebre (435 ng L^{-1}–1079 ng L^{-1}), while in the remaining control sites total concentrations were lower (in the <LOQ up to 103 ng L^{-1} range) (Figs. 3 and 4).The most ubiquitous therapeutic groups of PhACs were analgesics/anti-inflammatories, followed by antihypertensives. Overall, the analgesics/anti-inflammatories (maximum concentration detected and average detection frequency in parenthesis) salicylic acid (88.1 ng L^{-1}, 85%) and acetaminophen (25.5 ng L^{-1}, 73%) were the most frequently detected, while the β-blocking agent atenolol (4.14 ng L^{-1}, 64%), was also frequently detected (Table 8S, SM).

3.3. Occurrence of PhACs in the downstream (impact) sites

The occurrence and spatiotemporal distribution of detected PhACs (>LOQ) in the impact sites are shown in Fig. 3, Fig. 4 and Table 9S (SM). Mann-Whitney *U* test confirmed the significant and positive differences in the total PhACs concentrations (sum of all compounds) between the upstream and downstream sampling sites ($p < 0.001$). In the sites impacted by untreated (raw) wastewater, only 56 different PhACs out of the 68 monitored were detected, and 9 of them were detected in at least two of the three sampling campaigns, and 3 in only one campaign. All detected PhACs in the upstream sites were also present in the downstream sites, while in comparison with the discharged raw wastewater the overall PhACs concentration levels were lower at the downstream sites. The total concentrations of detected PhACs were generally higher in the dry than in the wet and relatively wet season (Fig. 3). The analgesics/anti-inflammatories were generally the most ubiquitous PhACs, followed by antihypertensives, diuretics, lipid regulators, psychiatric drugs, β-blocking agents, and antibiotics. The most abundant PhACs (maximum concentrations and average detection frequencies in parenthesis) were acetaminophen (7.78 μg L^{-1}, 100%), ibuprofen (2.66 μg L^{-1}, 75%), salicylic acid (1.72 μg L^{-1}, 96%) and naproxen (1.47 μg L^{-1}, 92%) (Table 9S, SM).

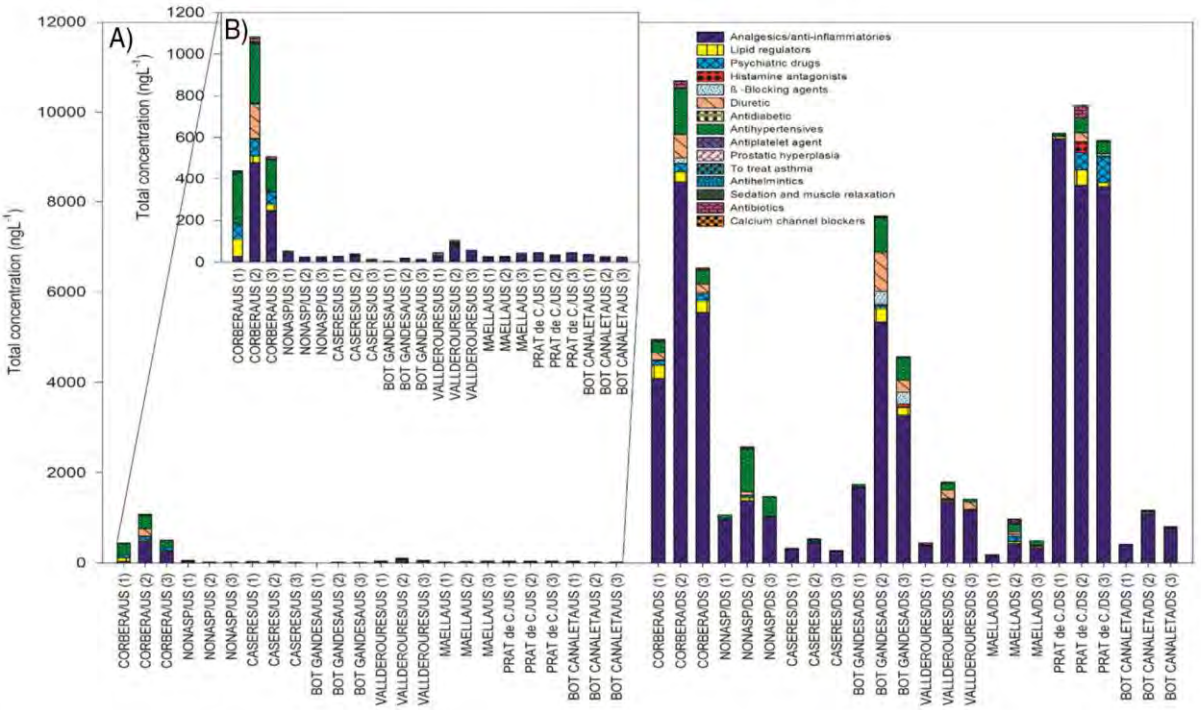

Fig. 3. Spatiotemporal distribution of PhACs by their therapeutic groups in control and impact sites, respectively upstream (US) and downstream (DS) from the untreated wastewater discharge point: A) Control and impact sites presented together B) Detailed view of control sites. Note in parentheses: (1) wet period (April 2015), (2) dry period (October 2015), (3) relatively wet period (April 2016).

In the sites impacted by treated wastewater, only 49 different PhACs were detected, and 12 of them were detected in at least two of the three sampling campaigns, and 13 in only one campaign. The total concentrations of detected PhACs were generally higher in dry than in the wet and relatively wet season (Fig. 4). The analgesics/anti-inflammatories, antihypertensives, diuretics, lipid regulators and cholesterol lowering statin drugs, β-blocking agents, psychiatric drugs and antibiotics were the most widely detected therapeutic groups. The analgesics/anti-inflammatories (maximum concentration in parenthesis) salicylic acid (99.3 ng L^{-1}) and acetaminophen (45.9 ng L^{-1}) and the antihypertensive valsartan (179 ng L^{-1}) were present in all analyzed samples.

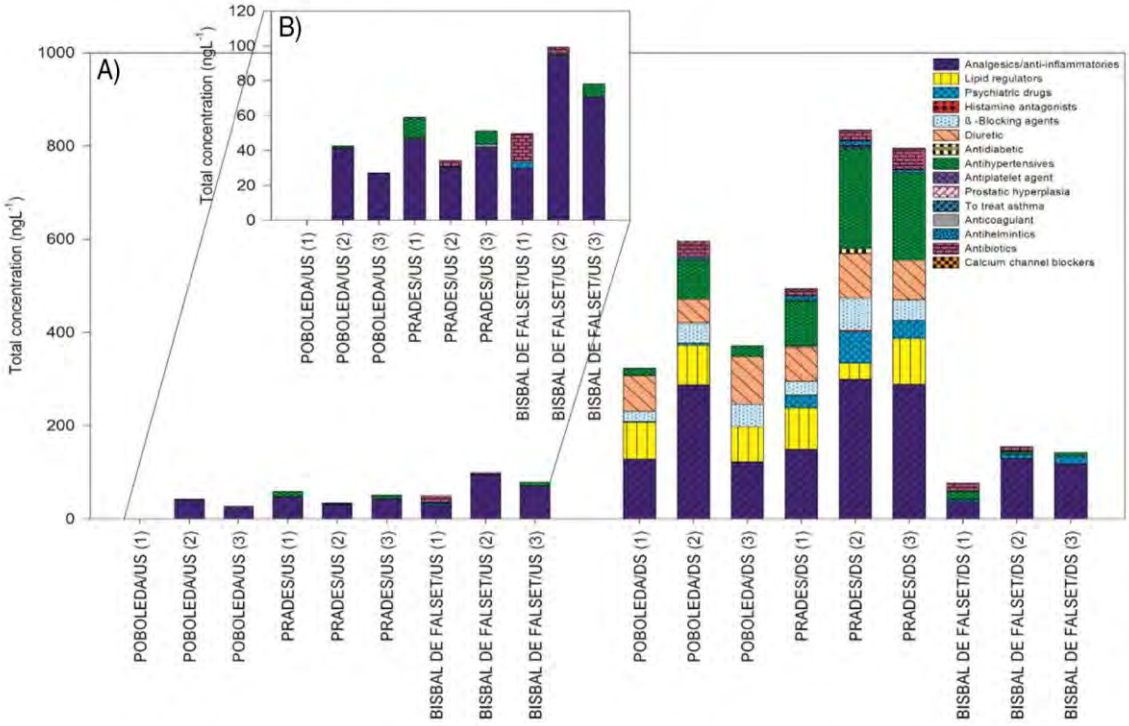

Fig. 4. Spatiotemporal distribution of PhACs by their therapeutic groups in control and impact sites, respectively upstream (US) and downstream (DS) from the treated wastewater discharge point: A) Control and impact sites presented together B) Detailed view of control sites. Note in parentheses: (1) wet period (April 2015), (2) dry period (October 2015), (3) relatively wet period (April 2016).

The MANOVA revealed significant multivariate main effects of treatment, ($p < 0.001$), effluent dominance ($p < 0.001$) and season ($p = 0.032$) on the total concentrations of PhACs (sum of compounds in each family of compounds) in the impact sites (See Table 6S, SM). The most significant univariate main effects of treatment were for analgesics/anti-inflammatories ($p < 0.00555$), while the most significant univariate main effects of effluent-dominance were for analgesics/anti-inflammatories ($p < 0.00555$), lipid regulators and cholesterol lowering statin drugs ($p < 0.00555$), β-blocking agents ($p < 0.00555$), antihypertensives ($p < 0.00555$) and antihelminthics ($p < 0.00555$) (Table 6S, SM). Even though significant univariate effects of seasons were revealed for analgesics/anti-inflammatories, β-blocking agents, histamine H1 and H2 receptor antagonists and antibiotics with applied $p < 0.05$, non-significant univariate effects of the season were revealed when Bonferroni correction was applied ($p > 0.00555$) (Table 6S, SM).

4. Discussion

4.1. PhACs in raw and treated wastewater

The detected concentrations of PhACs in wastewater were within the reported ranges (Verlicchi et al., 2012), while NSAIDs were the most ubiquitous compounds in both treated and untreated wastewater (Fig. 2). This fact could be explained by their availability as non-prescription OTC drugs (Reemtsma et al., 2006), and the widespread practice of self-medication (Hours Pérez et al., 2007; Ortiz de García et al., 2013). However, lower concentrations of NSAIDs (ibuprofen, acetaminophen, salicylic acid, naproxen and indomethacine) were detected in treated effluents due to their generally high elimination efficiencies (60–100%) in the WWTPs (Gros et al., 2010; Verlicchi et al., 2012; Kosma et al., 2014; Richardson and Ternes, 2014; Papageorgiou et al., 2016). Moreover, high concentration of the β-blocking agent atenolol, the lipid regulators and cholesterol lowering statin drugs gemfibrozil and bezafibrate, the antihypertensive valsartan and the antidiabetic furosemide in WWTP effluents, can be attributed to their incomplete removal (Castiglioni et al., 2006; Behera et al., 2011; Jelic et al., 2011; Al Aukidy et al., 2014; Verlicchi et al., 2012). Even though the total concentrations of PhACs in raw and treated wastewater samples were unrelated to the period, lower concentration levels of PhACs (especially NSAIDs) were detected in the first and the third sampling campaign, probably due to the increased rainfall and subsequent dilution effect (Kasprzyk-Hordern et al., 2009; Lacey et al., 2012; Papageorgiou et al., 2016). The precipitation runoff from urban areas may increase the total wastewater flow in combined sewer systems and result in a dilution of PhACs concentrations and other wastewater contaminants (Faber and Bierl, 2012), though removal efficiency is decreased due to reduced hydraulic retention time (HRT) (Sui et al., 2011).

4.2. Treated and untreated wastewater impacts on river downstream

The concentration levels of detected PhACs were generally low in the control sites, except in the Sec River (Corbera d'Ebre), where relatively high concentrations could be related to the discharges from the town of Gandesa, located 2 km upstream (Fig. 3). However, in comparison with the upstream (control) sites generally higher concentration levels of PhACs have been detected in the downstream (impact) sites, therefore, confirming the urban wastewater discharges (treated and untreated) as the main source of contamination.

The analysis of PhACs concentrations in the impact sites revealed the main effects of treatment on the total concentration of PhACs. Therefore, generally lower concentrations of PhACs were detected in the sites impacted by treated wastewater, and particularly for the analgesics/anti-inflammatories. This fact could be attributed to their generally high removal rates in the WWTPs (especially acetaminophen and ibuprofen) (Verlicchi et al., 2012) (See Fig. 5). The concentration levels of detected PhACs in sites receiving raw wastewater were comparable to those occurring in small streams impacted by wastewater discharges from larger WWTPs (Comoretto and Chiron, 2005; Brun et al., 2006), where dilution was irrelevant. Another important factor affecting the total concentration levels of detected PhACs was the effluent dominance of the stream, and this was consistent for the majority of studied pharmaceutical families. In such a way, higher concentrations of PhACs were detected in the effluent-dominated streams (Corbera d'Ebre, Prat de Comte, Bot – Gandesa, Poboleda, and Prades) than otherwise (Figs. 3 and 4). The stream flows in effluent-dominated sites were significantly lower than the stream flows in the effluent non-dominated sites; this also applies to the upstream (control) sites (See Fig. 1S and 2S, SM). The combination of low stream flow together with little-to-no upstream dilution might account for the generally higher concentration levels of PhACs in the effluent-dominated streams (Brooks et al., 2006).

Moreover, sampling period was also revealed as another important factor affecting the total concentrations of PhACs. The higher river flows and associated higher dilution effects as a result of an increased rainfall during spring may, therefore, account for the overall lower total concentrations of PhACs during the 1st and the 3rd sampling campaign (Figs. 3 and 4). Similar low concentrations and detection frequencies of PhACs during high-flow conditions have been reported elsewhere (Gros et al., 2007; Fernández et al., 2010; Osorio et al., 2012; Osorio et al., 2016).

However, as it can be seen in Fig. 6, an impact of discharged treated and untreated wastewater in the studied impact sites was high, while the total concentrations of detected PhACs in the studied streams decreased with the increasing distance (discharge point-impact site) and finally after 400-600 m (depending on the river characteristics and river flow) equalized with the background concentrations in the upstream (control) sites. This decrease of the total PhACs concentrations with increasing distance may be attributed to the effect of different in-stream chemical-biological attenuation processes of the contaminants, related with their specific hydraulic travel time in each of the sites (Fig. 6). Consequently, at sites with shorter hydraulic travel time PhACs will generally show lower elimination rates due to a shorter residence time of substances within the river stretch and lower flow velocity of the surface water (Conley et al., 2008). Also, in streams that are not dominated with the wastewater (treated or untreated), PhACs with shorter half-life times such as acetaminophen (1.7 ± 1.0 h), diclofenac (1.6 ± 0.5 h), ibuprofen (2.0 ± 1.1 h) and atenolol (2.1 ± 1.4 h) will generally show higher in-stream elimination rates in comparison with the PhACs showing longer half-life times (Acuña et al., 2014; Aymerich et al., 2016). However, due to continuous inputs and little-to-no upstream dilution in the small effluent-dominated streams and rivers also PhACs with the short half-life times may reach high concentrations as for example measured for acetaminophen (max conc. 7.78 μg L^{-1}, Table 9S, SM). Increased concentration levels of detected PhACs in the small and effluent-dominated streams have been detected in other studies as well (Brun et al., 2006; Waiser et al., 2011; Marsik et al., 2017). Except for dilution and mixing, other factors affecting in-stream concentration levels of PhACs include landscape characteristics (e.g., drainage area, soil/sediment type and groundwater input) and chemical-biological degradation processes such as sorption, biodegradation, and photolysis (Vieno et al., 2005; Osorio et al., 2012; Osorio et al., 2016). In comparison with the untreated (raw) wastewaters, the main elimination pathway affecting concentration levels of PhACs in surface waters receiving treated WWTP effluents may be attributed to the photolysis (Brun et al., 2006; Fono et al., 2006; Petrovic and Barcelo, 2007; Aymerich et al., 2016). However, little is known about the pathways leading to a partial or total breakdown of PhACs molecules during photolysis which may lead to multiple reaction products that can be more or less toxic than the parent compounds (Petrovic and Barcelo, 2007). A significant decrease of PhACs concentrations downstream of the WWTP discharge points as a result of different in-stream natural attenuation processes have also been reported elsewhere (Vieno et al., 2005; Lindqvist et al., 2005). Even though, the in-

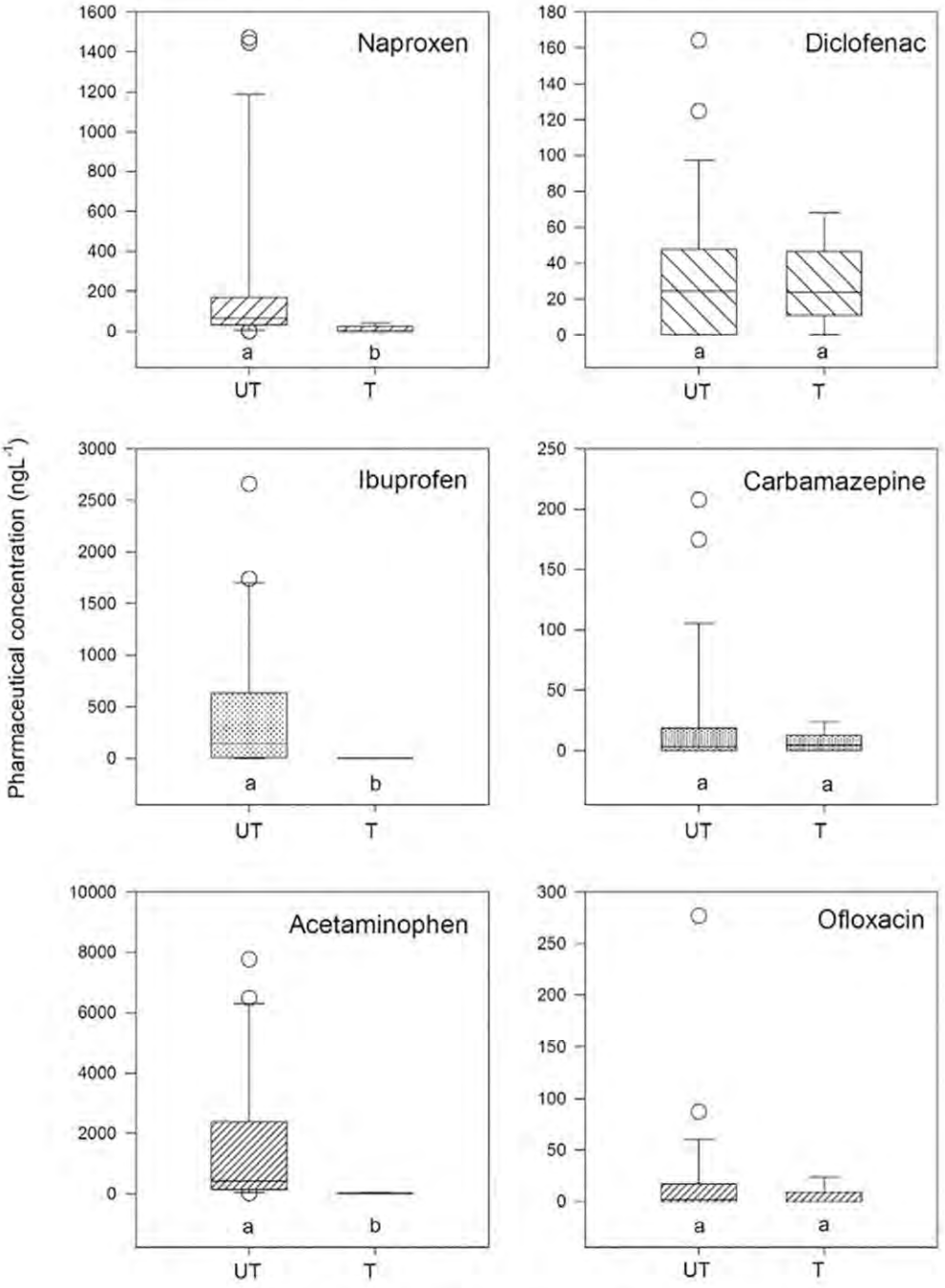

Fig. 5. Comparison of individual pharmaceutical concentrations (median, 25th, 75th quartiles, 5th and 95th centiles) in regards to downstream sampling sites impacted by untreated (UT) and treated (T) wastewater. The comparison performed using Mann-Whitney test. Within each figure, box plots with the same letter indicate no significant difference.

stream fate of pharmaceuticals in rivers is still only partly understood, Brun et al. (2006) have reported that PhACs with higher octanol/water partition coefficient (log Kow) (i.e., 3.0–3.5) will show higher tendency to absorb in sediments and suspended particles and settle on the bottom of the stream. However, for chemical compounds such as PhACs, the partitioning depends on pH and pKa of the compound (da Silva et al., 2011). Therefore, for example, PhACs with carboxylic acid functionalities with pKa values much less than 7 (such as NSAIDs) will be more likely to remain in the aqueous phase (Acuña et al., 2014). Finally, the studies regarding eco-toxicological effects of PhACs in aquatic environments (Halling-Sorensen et al., 1998; Fent et al., 2006; Brausch and Rand, 2011), have largely neglected effluent-dominated streams with variable hydrology such as the Mediterranean (Daughton and Ternes, 1999). Some of these combine low upstream dilution and low stream flow, requiring an understanding of the in-stream attenuation processes governing the fate of PhACs and their potential ecotoxicological effects.

5. Concluding remarks

The occurrence of PhACs in Mediterranean aquatic ecosystems is associated with the seasonal variation of the stream flow (flow reductions in summer and floods in spring and autumn), while in the case of the medium-sized tributaries of the lower Ebro River basin results showed evidence of the strong urban impact on the river quality. The total concentrations of detected PhACs in both raw and treated wastewater were positively and significantly correlated with the resident population,

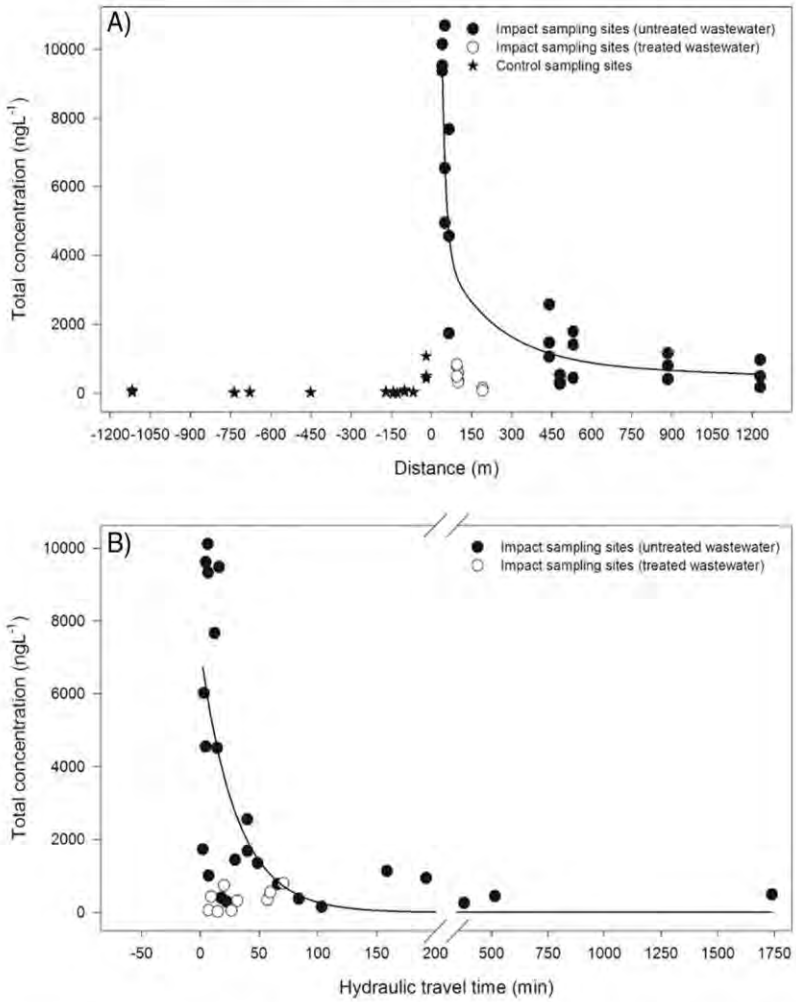

Fig. 6. Dynamics of treated and untreated wastewater in impact sites with respect to: A) Distance between the wastewater discharge points and downstream (impact) sampling sites (negative values on the x-axis depict distances between upstream control sites and wastewater discharge points) and B) Hydraulic travel time (the origin $t = 0$ indicates the location of emission). Notice that the total PhACs concentrations on the y-axis are presented without background concentrations.

confirming the urban origin of wastewaters. However, significant differences in the total PhACs concentrations between the upstream and downstream sampling sites confirmed the relevance of wastewater discharges (treated and untreated) as significant sources of contamination. Overall, due to a lower stream flow and small dilution factor, effluent-dominated streams showed generally higher concentration levels of PhACs. NSAIDs were the most ubiquitous compounds in both downstream sites impacted by treated and untreated wastewater, while due to an absence of the WWTPs the total concentration levels of PhACs were 12 times higher in the sites impacted by untreated wastewater than in the sites impacted by treated wastewater. Also, apart from dilution and chemical-biological degradation processes, different distances from the wastewater discharge point to the downstream (impact) sampling site and related with their specific hydraulic travel time showed to be an important factor affecting the in-stream attenuation of PhACs. However, further investigation is required in order to fully understand the in-stream attenuation processes governing the fate of PhACs and their potential ecotoxicological effects in the small and rural Mediterranean rivers affected by treated and untreated wastewaters.

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Appendix A. Supplemenatary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2017.09.128.

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Chapter 3.

Contamination patterns and attenuation of pharmaceuticals in a temporary Mediterranean river

Contamination patterns and attenuation of pharmaceuticals in a temporary Mediterranean river

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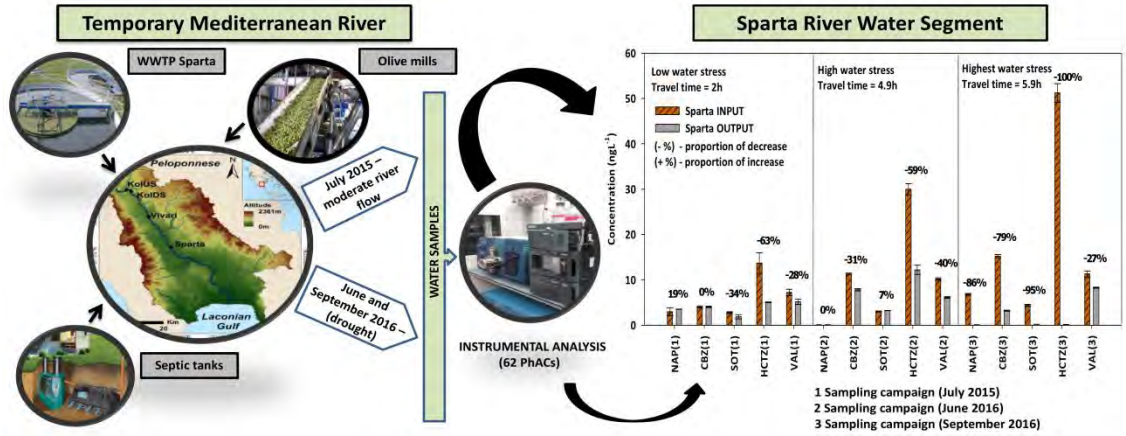
Graphical abstract:



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Abstract:

The contamination patterns and fate of pharmaceutically active compounds (PhACs) were investigated in the Evrotas River (Southern Greece). This is a temporary river with differing levels of water stress and water quality impairment in a number of its reaches. Three sampling campaigns were conducted in order to capture different levels of water stress and water quality. Four sampling sites located on the main channel of the Evrotas River were sampled in July 2015 (moderate stream flow), and June and September 2016 (low stream flow). Discharge of urban wastewater has been determined as the main source of pollution, with PhACs, nutrients and other physicochemical parameters considerably increasing downstream the wastewater treatment plant (WWTP) of Sparta city. Due to the pronounced hydrological variation of the Evrotas River, generally, the highest concentrations of PhACs have been detected during low flow conditions. Simultaneously, low flow resulted in an increased water travel time and consequently longer residence time that accounted for the higher attenuation of most PhACs. The average decrease in total concentration of PhACs within the studied waterbody segment (downstream of Sparta city) increased from 22% in July 2015 to 25% in June 2016 and 77% in September 2016. The PhACs with the highest average concentration decrease throughout the sampling campaigns were hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen.

Keywords: Pharmaceuticals; Temporary rivers; Mediterranean; Attenuation; Occurrence and distribution

1. Introduction

Mediterranean streams and rivers are characterized by inter-annual hydrological variations encompassing floods in spring and autumn and droughts in summer (Sabater et al., 2008), which in turn can cause headwater and middle-order streams to become intermittent, or even to dry out for an extended period (Lake, 2003). Consequently, temporary streams and rivers in the Mediterranean basin are amongst the most complex and dynamic freshwater ecosystems, and at the same time, highly fragile (Larned et al., 2010; Acuña et al., 2014a). These systems are affected by strong hydrological and anthropogenic pressures resulting from extensive water abstraction, river fragmentation and climate change (Larned et al., 2010; Acuña et al., 2014a; Skoulikidis et al., 2017).

Water quantity pressures are further accentuated by nutrient enrichment and microcontaminants pollution from urban and industrial wastewaters, and by organic pollution from municipal wastewaters and agricultural activities (Meybeck 2004; Vorosmarty et al., 2010). Amongst the microcontaminants, the use of pharmaceutically active compounds (PhACs) for both human and veterinary applications results in a vast array of products reaching aquatic environments. PhACs are a group of chemical substances with pharmacologic and physiologic properties and include all prescription, nonprescription, and over-the-counter (OTC) therapeutic drugs, in addition to veterinary drugs (Richardson and Ternes, 2005). Following their administration, PhACs are excreted as a mixture of parent compounds and metabolites that are usually more polar and hydrophilic than the original drug, while large fraction of these substances is discharged into the wastewater in the form of degradation products that are often poorly eliminated in conventional wastewater treatment plants (WWTPs, Gros et al., 2010; Ratola et al., 2012). PhACs are being discharged into the aquatic environment through different sources, i.e. human excretion, disposal of unused and expired drugs, agricultural and livestock practices (Halling-Sorensen et al., 1998; Boxall et al., 2012; Tijani et al., 2016), and reach the environment as treated or untreated wastewater discharges (Heberer, 2002; Vieno et al., 2005). Their continuous discharge into the aquatic environment makes the PhACs pseudo-persistent contaminants (transformation and removal rates are compensated by their continuous discharge into the environment), and as such may cause adverse effects on living organisms and the environment (Daughton and Ternes, 1999; Halling-Sorensen et al., 1998). For example, there is evidence that PhACs, such as antidepressants, psychiatric drugs, hormones, and antihistamines can induce behavioral changes in fish, affecting fish aggression, reproduction and feeding activity, thus, in turn, directly affecting individual fitness and indirectly affecting food webs and ecosystem processes (Schultz et al., 2011; Brodin et al., 2014; Sharifan and Ma, 2017).

Once released into the aquatic environment, PhACs undergo different in-stream attenuation processes (i.e. biotransformation, photolysis, sorption, volatilization). These processes are related to the specific characteristics of the PhACs, the physicochemical and biological parameters of the river (Gurr and Reinhard, 2006; Kunkel and Radke, 2008), and to the specific dilution capacity and water travel time within the study reach or waterbody (Rueda et al., 2006; Keller et al., 2014). There is, however, limited knowledge regarding the fate, behavior, and transport of PhACs in Mediterranean aquatic ecosystems,

compared to other pollutants (Halling-Sorensen et al., 1998; Kolpin et al 2002; Golet, 2002; Moldovan, 2006; Acuña et al., 2014b), while the functioning of in-stream attenuation mechanisms is not completely understood (Kunkel and Radke, 2011), particularly in the Mediterranean river systems (Al Aukidy et al., 2012; López-Serna et al., 2012; Stasinakis, 2012; Stamatis et al., 2013; Nannou et al., 2015). Also, few studies have detailed the fate and in-stream attenuation of PhACs during different seasons (Pal et al., 2010), especially together with the other organic micropollutants (Biales et al., 2015; Fairbaim et al., 2016; Garrido et al., 2016) and during heavy rainfall and floods (Pailler et al., 2009). However, concentration levels of PhACs in the Mediterranean streams and rivers depend as well on numerous factors such as the land uses and the hydrometeorological conditions. Therefore, reduced dilution capacity of Mediterranean streams and rivers during dry periods may result with the increased concentration levels of PhACs and other organic micropollutants (Almeida et al., 2014; Sabater et al., 2016), while due to an increased rainfall and subsequent dilution capacity during wet periods, generally lower concentration levels of PhACs may be expected (Kasprzyk-Hordern et al., 2009; Lacey et al., 2012; Papageorgiou et al., 2016). Though, during heavy rainfall events in the Mediterranean, flow augmentation, sediments resuspension, combined sewer overflows resuspension, and reduced hydraulic retention time in the WWTPs, leads to a particularly increased in-stream concentration levels of PhACs (Cowling et al., 2005; Sui et al., 2011; Osorio et al., 2012; Osorio et al., 2014; Corada-Fernández et al., 2017; Reoyo-Prats et al., 2018). Therefore, determining the PhACs concentrations and their fate mechanisms in the Mediterranean aquatic environment is important in order to assess their environmental risk (Boxall et al., 2012), particularly during drought and heavy rainfall events.

The main objectives of this study were to i) determine the concentration patterns of PhACs in a temporary Mediterranean river affected by agricultural and urban pollution; ii) estimate the recovery potential (natural in-stream attenuation of contaminants) in the water bodies studied, and iii) define the joint effects of hydrological (river flow) and chemical stressors (urban and agricultural pollution) on the occurrence and distribution of PhACs in this Mediterranean river.

2. Materials and methods

2.1. Study area

The study was conducted at the Evrotas River, a biogeographically isolated basin in the southernmost Balkan Peninsula, in Southern Peloponnese, Greece (Fig.1). The Evrotas River is a large (2418km^2), mid-altitude Mediterranean basin, with the river flowing unobstructed between the mountain ranges of Taygetos (2,407 m a.s.l.) and Parnon (1,904 m a.s.l.), and entering after 90 km into the Lakonian Gulf. Along the course of the Evrotas, numerous permanent and temporary karstic springs contribute to river runoff (Vardakas et al., 2015). The mountainous area of the basin is mostly formed by Mesozoic-Palaeogene limestone and impermeable rocks (schists and flysch), while the lower parts of the river basin are formed of extensive alluvial aquifers (Pliocene and Quaternary sediments, Skoulikidis et al., 2011). The Evrotas River Basin has an average annual temperature of 16°C and a mean annual precipitation of 803 mm (2000-2008), with wet and cool winters and warm and dry summers (Nikolaidis et al., 2009). The combined effects of water abstraction and natural drought result in the partial desiccation of the river in late summer-early autumn (Skoulikidis et al., 2011).

The main sources of municipal sewage in the study area is the city of Sparta (population of 16,239), which has a sewage collection system (with not all of the households, however, connected to it) and WWTP that discharges treated effluents into the Evrotas River. The smaller communities upstream are served by septic tanks and cesspools. The Evrotas River, therefore, receives the treated sewage of Sparta and untreated wastewaters from nearby communities. However, during the dry period, the WWTP may not operate sufficiently and/or cesspool waste dumping may occur, as evident by the zero dissolved oxygen (D.O.) values recorded repeatedly and for periods of several days downstream the WWTP effluent discharge point (Lampou et al., 2015). These add to the disposal of agro-industrial wastes and agrochemical pollution (oil mill wastes, wastes from orange juice production, Markantonatos et al., 1996; Skoulikidis et al., 2011).

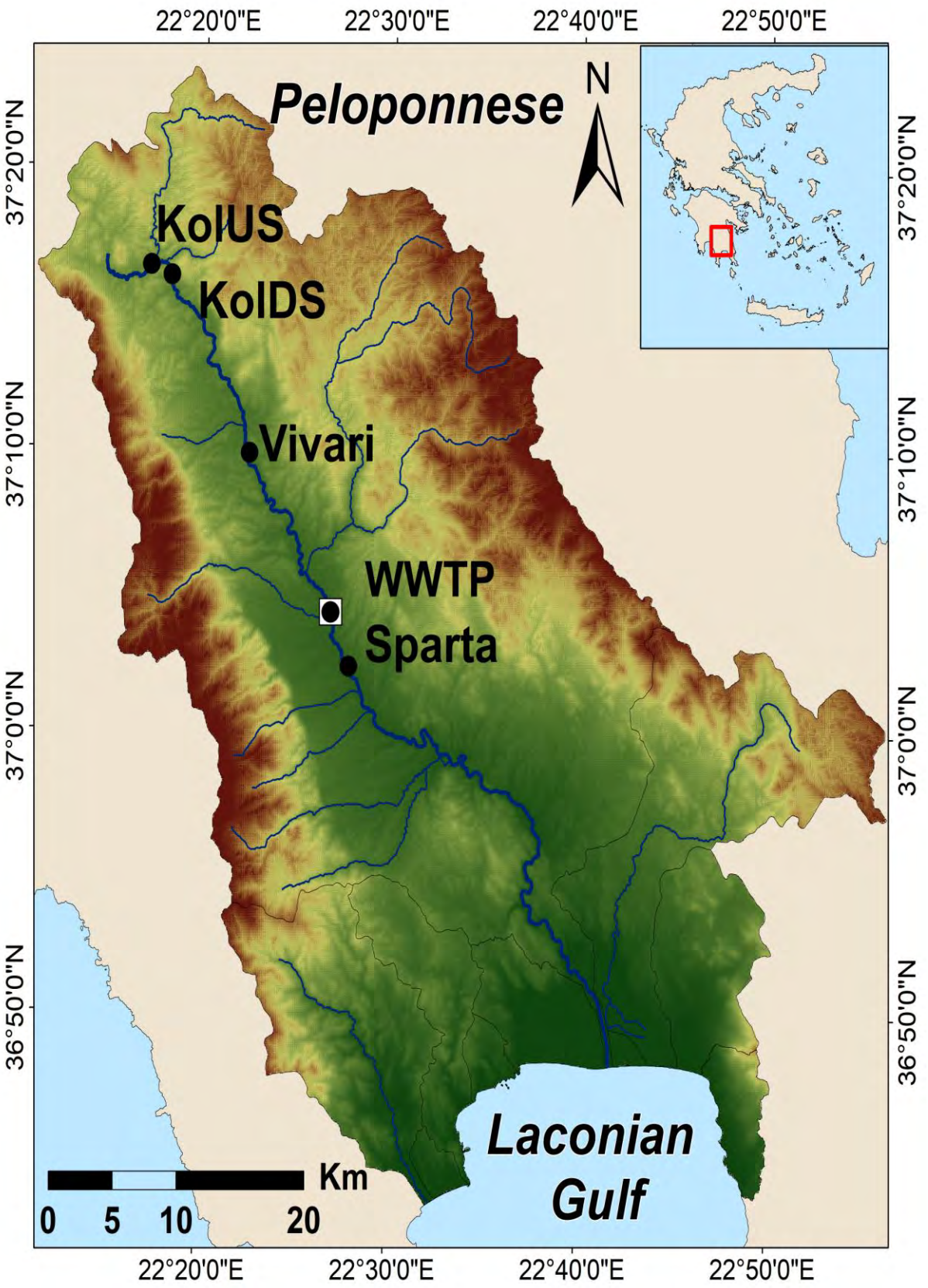

Figure 1. The Evrotas River catchment and the four sampling sites. The upper right inset shows the location of the Evrotas River Basin within Greece.

2.2. Sampling sites and collection

Three sampling campaigns were conducted by scientists of the Hellenic Centre for Marine Research in order to capture different levels of water stress and water quality. Four sampling sites located on the main channel of the Evrotas River were sampled in July 2015 (moderate stream flow), and June and September 2016 (low stream flow) (Fig.1). Composite water samples for the analysis of PhACs were collected from surface waters in the left, center and right river side of the stream channel (20-30 cm below the water surface), and then mixed and transferred to 1L polyethylene bottles. Samples were transported in refrigerated isothermal containers (dry ice), and stored at -20°C until extraction by scientists of the Catalan Institute for Water Research. The two upstream sampling sites (KolUS and KolDS) are respectively located in a perennial river section with relatively undisturbed characteristics (KolUS) and in an intermittent river section which dries up partially during late summer, due to natural and artificial desiccation (KolDS, Fig.1, Table 1). The Vivari and Sparta sampling sites are located in the middle section of the Evrotas River (Fig. 1). Both sites have overall higher river discharge and wider active channel than the upstream sampling sites. Vivari is a relatively undisturbed perrenial site with dense riparian woodlands, fed by several karstic springs. The Sparta sampling site is located 20 km further downstream and is a degraded intermittent reach with diffuse pollution from agriculture and point-source pollution from the nearby WWTP, together with pollution from cesspool waste dumping, and olive mill and orange juice processing wastewaters (Lampou et al., 2015; Kalogianni et al., 2017; Karaouzas et al., 2017). The main characteristics of the treatment process, population served and average monthly WWTP outflows of the Sparta WWTP for the sampling periods of July 2015, June and September 2016 were retrieved from the dataset provided by YPEKA (http://astikalimata.ypeka.gr). The measured average monthly outflows from the WWTP located 4603m upstream of the sampling site 'Sparta' ranged respectively between 3662 m^3d^{-1} and 4163 m^3d^{-1} (Table 1S of the Supplementary material, SM) during the sampling periods. The WWTP serves a population of approximately 20,000 inhabitants with sewage and sludge treatment lines. Resident population data were retrieved from the dataset provided by the Hellenic Statistical Authority (http://www.statistics.gr) (Table 1).

Table 1. Overview of the sampling sites along the Evrotas River Basin.

Sampling site	Catchment	Coordinates		Resident population	Distance from Skortinou springs (m)	Comment
		Latitude (φ)	Longitude (λ)			
KOL US	Evrotas	37°15'5.83"N	22°15'54.00"E	1203	3,165	Low agricultural activities, sparse human settlement, almost pristine riparian forest.
KOL DS	Evrotas	37°16'6.90"N	22°18'15.16"E	1540	8,555	In summer, reduced to scattered deep pools. Then dries up completely, due to natural and artificial desiccation.
VIVARI	Evrotas	37°9'51.85"N	22°22'30.00"E	3876	24,252	Active river channel with a discharge much higher compared to upstream reaches. Fed by several karstic springs. Dense riparian woodlands and aquatic macrophytes locally.
SPARTA	Evrotas	37°2'20.69"N	22°27'50.78"E	32404	45,194	Diffuse pollution from agriculture. Point source pollution (effluents of Sparta WWTP/olive oil mill wastes). Hydromorphological modification (water abstraction / river bank modifications).

2.3. Environmental data collection and nutrient analyses

Water flow data were obtained in the field using a Water Flow meter OTT C20. Several point measurements of water flow were taken at cross sections and then integrated in order to calculate average river flow. Daily average river flow (m^3s^{-1}) was calculated for the sampling periods and for periods of 14 and 28 days prior to each sampling date for each sampling site (Fig.2). Due to the lack of long-term daily measurements in the study area, calculations were estimates based on the SWAT model (Neitsch et al., 2011) developed by Gamvroudis (2016) for the Evrotas River Basin. In order to additionally explore the natural in-stream attenuation of PhACs, we have applied a Lagrangian sampling design to the sampling sites. This design follows the same parcel of water as it moves downstream (Zuellig et al., 2007). Preliminary dye tests (NaCl) were used to determine water travel time between the sample-collection sites (input and output of each waterbody segments) (Kilpatrick and Cobb, 1985). For this study, travel time was defined as ‘‘the amount of elapsed time for the dye peak to travel between two monitoring sites’’ (Zuellig et al., 2007). The distance between the input and output of each waterbody segment, together with the corresponding water travel time in each of the sampling campaigns, are presented in Table 2S, in SM. However, in this manuscript, we have decided to graphically show the in-stream attenuation only at the Sparta waterbody segment, due to a fact that in the other sampling sites a much lower number of PhACs has been detected, while site KolDS was dry in the second and third sampling campaign. The land uses classes distribution of the sites was based on CORINE 2012 database (European Environmental Agency, 2012) (Table 3S, SM). The type of agricultural land uses and livestock units per sampling site are shown in Table 4S, in SM.

Physicochemical variables such as D.O. concentration (mgL^{-1}), pH, water temperature ($^{\circ}C$) and conductivity ($\mu S\ cm^{-1}$) were measured in situ (Table 5S, SM) using a Portable multiparameter Aquaprobe AP-200 with a GPS Aquameter (Aquaread AP 2000). Water samples for nutrient analysis were transferred at laboratories of the Hellenic Centre for Marine Research and filtered through 0.45μm cellulose ester membrane filters (Whatman, U.K.). Nitrite (NO_2^-, mgL^{-1}), and orthophosphate (PO_4^{3-}, mgL^{-1}) concentrations were determined by a Skalar San++ Continuous Flow Analyzer (Boltz and Mellon, 1948; Navone, 1964). Nitrate (NO_3^-, mgL^{-1}) concentrations were determined using both Ion

Chromatography and a Skalar Automatic Analyzer, while the concentration of the ammonium (NH_4^+, mgL^{-1}) was determined using a Skalar Automatic Analyzer.

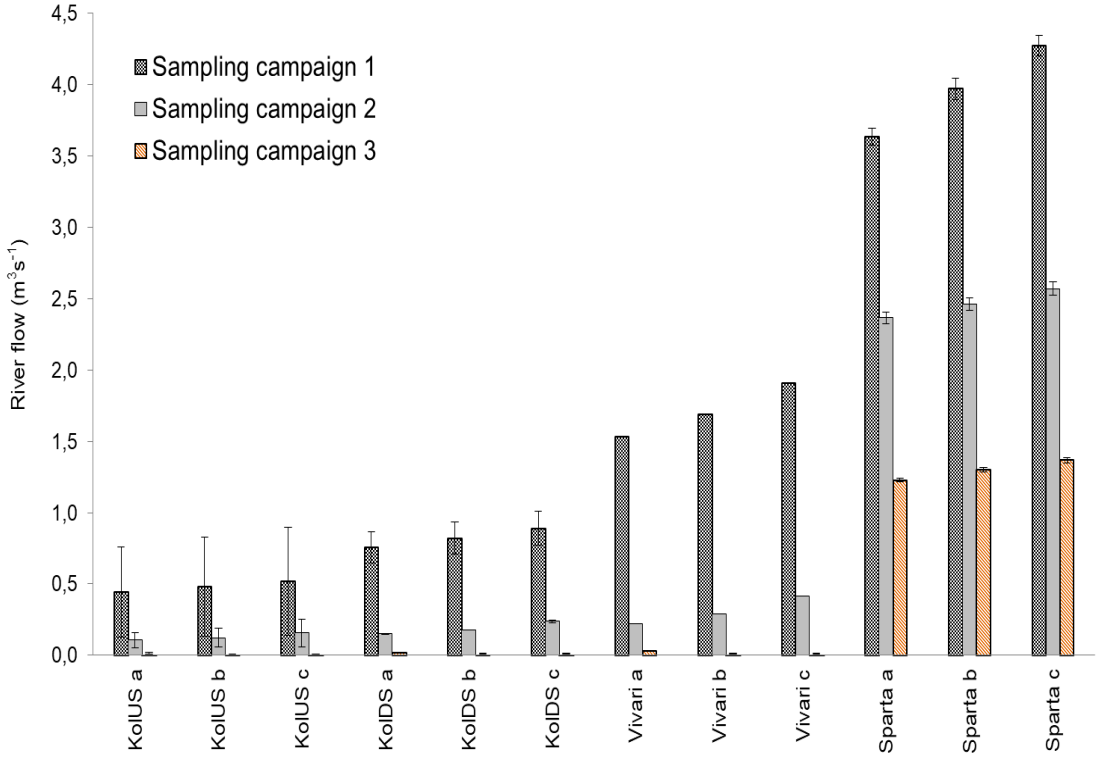

Figure 2. Daily average river flow (m^3s^{-1}) during the sampling days (a) and for periods of 14 (b) and 28 (c) days prior to each sampling date for each sampling site (simulated with the SWAT model, Neitsch et al., 2011). Numbers 1-3 in the legend indicate the three sampling periods: 1 (July 2015), 2 (June 2016), 3 (September 2016), while error bars show standard deviation.

2.4. Sample preparation and analysis

Chemical standards used in this research are listed in Table 6S in the SM. Following the preparation, standards were stored at -20°C. Fresh stock antibiotic solutions were prepared every month due to their limited stability, while the stock solutions for the rest of the substances were renewed every three months.

2.4.1. Analytical method

The PhACs analysis of water samples was conducted at laboratories of the Catalan Institute for Water Research following the method developed by Gros et al. (2012). The analyses were carried out with an off-line solid phase extraction (SPE), followed by ultra-

high-performance liquid chromatography coupled to triple quadrupole linear ion trap tandem mass spectrometry (UHPLC-QqLIT-MS/MS). Prior to the SPE, water samples were filtered through 1μm glass fiber filters and by 0.45 μm nylon membrane filters (Whatman, U.K.). Later on, filtered and previously spiked water samples were extracted by SPE using Oasis HLB (60mg, 3mL) cartridges, while extracts were evaporated under a gentle stream of nitrogen and reconstituted to a final volume of 1 ml. Reconstituted water samples were then fortified with 10μL of a 1ng/μL standard mixture containing all isotopically labeled standards. Chromatographic separations were carried out with a Waters Acquity Ultra-Performance™ liquid chromatography system, coupled to a 5500 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer (Applied Biosystems, Foster City, CA, USA) with a turbo Ion Spray source. The separation was achieved with two binary pump systems (Milford, MA, USA), using an Acquity HSS T_3 column (50 mm × 2.1 mm i.d., 1.8 μm particle size) for the compounds analyzed under positive electrospray ionization (PI) and an Acquity BEH C_{18} column (50 mm × 2.1 mm i.d., 1.7 μm particle size) for the ones analyzed under negative electrospray ionization (NI), both purchased from Waters Corporation. For the analysis in the (PI) mode, methanol and 10mM formic acid/ammonium formate (pH 3.2) were used as a mobile phase at the flow rate of 0.5mL/min. However, for the analysis in the (NI) mode, acetonitrile and 5mM ammonium acetate/ammonia (pH=8) were used as a mobile phase at the flow rate of 0.6mL/min. The sample volume injected was 5 μL for both modes. Electrospray Ionisation (ESI) and selected reaction monitoring (SRM) modes were selected for the MS^2 detection. Finally, all data were acquired and processed using Analyst 1.5.1 software, while quantification was carried out by isotope dilution. Method performance parameters of target compounds including limits of detections (LODs), limits of quantifications (LOQs) and recovery rates are summarized in Table 7S (SM).

2.5. Statistical analysis

The variables were checked for normal distribution using the Shapiro-Wilk test. Pearson's moment correlation factor (r) was performed between the candidate variables, and those strongly correlated (correlation coefficient was > 0.8) were unselected from further statistical analysis to avoid multicollinearity. PhACs with undetected values and values <LOQ were replaced by the corresponding values equal to one-half of LOD and one-half of LOQ (Farnham et al., 2002). Two separate Principal Component Analysis

(PCA) were performed in order to explore the variability of i) nutrients and physicochemical variables and ii) PhACs concentrations of each family of compounds. The relationships between the score values of the physicochemical PCA and of the PhACs PCA, as well as with land uses were explored with a Pearson correlation analysis. The score values were normalized by subtracting the mean and dividing it by the standard deviation before the analysis. Additionally, Pearson correlation was used to explore the relationship between the proportion of PhACs decrease within the Sparta waterbody segment and the corresponding water travel time and temperature throughout the sampling campaigns. All analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, U.S.A.).

3. Results

3.1. Hydrological characterization

Water flow in the Evrotas River ranged from 0.008 m^3s^{-1} to 4.28 m^3s^{-1} (Fig.2). In all sampling campaigns, water flow was generally higher downstream than in the upstream sampling sites due to vertical and lateral inputs. The hydrology of the river showed a large variability between sampling periods; water flow during July 2015 was 1.6 times higher than June 2016 and 3.13 times higher than September 2016. Consequently, water travel time between the input and output of the Sparta waterbody segment (3.7km) increased from 2h (July 2015) to 4.9h and 5.9h respectively in June and September 2016 (Table 2S, SM).

3.2. Chemical variables

Potassium and nitrite concentrations were not considered for further analysis, due to multicollinearity with other chemical variables. Throughout the sampling campaigns, the Sparta sampling site was the most polluted site as indicated by high concentrations (median, minimum-maximum) of NO_3^- (0.61 mgL^{-1}, 0.30 mgL^{-1} - 1.6 mgL^{-1}), NH_4^+ (0.01 mgL^{-1}, 0.01 mgL^{-1} - 0.25 mgL^{-1}), K^+ (0.76 mgL^{-1}, 0.62 mgL^{-1} -2.4 mgL^{-1}), Cl^-(11 mgL^{-1}, 7.1 mgL^{-1} - 18 mgL^{-1}), PO_4^{3-}(0.002 mgL^{-1}, 0.0004 mgL^{-1} - 0.052 mgL^{-1}) and of conductivity (492 $\mu ScmL^{-1}$, 139 $\mu ScmL^{-1}$ - 651 $\mu ScmL^{-1}$) (Table 5S, SM). Concentration levels of D.O. in this site were similar to the other sites in July 2015, but they were much lower in both June and September 2016. In all sampling sites, higher concentrations levels of studied variables were observed during periods with the lower stream flow (June and

September 2016), whereas NO_3^- and PO_4^{3-} levels were higher during higher flow conditions (July 2015). River water temperature ranged between 16.6°C and 25.5°C throughout the sampling campaigns, while generally higher temperatures in the Sparta sampling site were recorded during June and September 2016 reaching 25.5°C and 23.4°C, respectively (Table 5S, SM). The PCA using physicochemical variables (Fig.1S, SM) explained 48.8% variability in the first axis and 25.6% variability in the second axis. The scores of the first component were significantly correlated with urban land uses ($r = 0.89$, $p < 0.001$).

3.3. PhACs concentrations

Eleven (11) different PhACs out of the 62 monitored were detected (Table 8S, SM), nine of them in at least two of the three sampling campaigns, and two in only one campaign. Additionally, two PhACs were detected with concentration levels < LOQ. The total concentrations of detected PhACs (sum of all compounds per each sampling site) were generally higher during low stream flow (June and September 2016) than during high stream flow (July 2015, Fig. 2 and Fig.3). The diuretics and the analgesics/anti-inflammatory class were the most abundant, followed by antihypertensives, psychiatric drugs, β -blocking agents and antibiotics (Fig. 3). The concentration levels ranged from 0.31 ngL^{-1} up to 51 ngL^{-1}, while the highest number and individual concentration levels of PhACs were predominantly detected during low flow periods (June and September 2016). The diuretic hydrochlorothiazide (average detection frequency, D.F. 50%) and the analgesic/anti-inflammatory ketoprofen (D.F. 17%) were those with the highest concentrations detected in all sampling campaigns, reaching up to 51 ngL^{-1} and 45 ngL^{-1}, respectively. The antihypertensive valsartan was the most frequently detected PhAC (D.F. 67%) reaching concentrations up to 9.8 ngL^{-1} in the period with the lowest flow (Table 8S, SM).

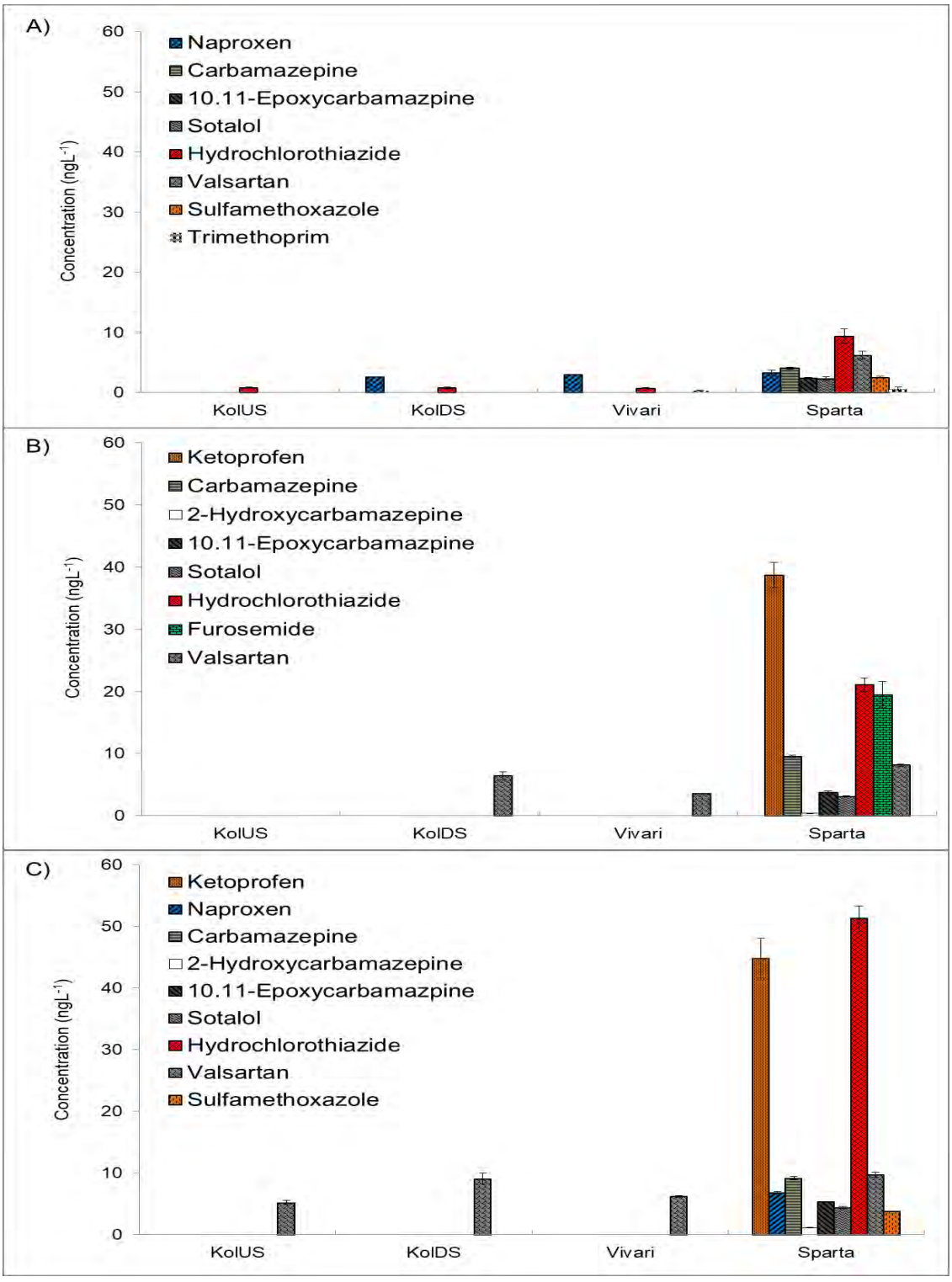

Figure 3. Spatio-temporal distribution of individual PhACs concentrations (input-output average concentration) in each waterbody segment: A) 1st sampling campaign (July 2015-high stream flow) B) 2nd sampling campaign (June 2016-low stream flow), C) 3rd sampling campaign (September 2016-lowest stream flow). The error bars show standard deviation.

The analgesics/anti-inflammatory naproxen, the psychiatric drugs carbamazepine and 10.11-epoxycarbamazpine and the β -blocking agent sotalol were detected in 25%-33% of all samples analyzed, with concentrations ranging between 2.3 ngL^{-1} and 9.5 ngL^{-1}. The total PhACs concentrations (sum of all compounds) in sampling sites situated upstream of Sparta ranged between 0.84 ngL^{-1} and 9.1 ngL^{-1}, respectively (Fig. 3). The highest total concentration of PhACs occurred in the Sparta sampling site, where total PhACs concentration (sum of all compounds in each family of compounds) in September 2016 was 1.3 times higher than the total concentration in June 2016 and 4.4 times higher than in July 2015 (Fig. 3). The first axis of the PCA performed with the PhACs (Fig. 2S, SM) accounted for 79.1% of the total variability, with psychiatric drugs, β-blocking agents, diuretics and the analgesics/anti-inflammatories being the variables that contributed most. The variability of the first component was significantly correlated with urban land uses ($r = 0.96$, $p < 0.001$).

3.4. Natural attenuation of PhACs (Sparta)

The in-stream attenuation at the Sparta river segment was highly variable among the PhACs detected and the different sampling periods (Fig. 4; the physicochemical properties of individual PhACs are shown in Table 2). Overall, the average proportion of decrease for PhACs increased from 22% in July 2015 up to 25% and 77% in June and September 2016 respectively. The PhACs with the highest average concentration decrease throughout the sampling campaigns was hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen. Additionally, the proportion of PhACs decrease within the Sparta waterbody segment was positively and significantly correlated with the water travel time in each of the sampling campaigns ($r = 0.50$, $p < 0.005$). Consequently, PhACs detected within the Sparta river segment in conditions of longer water travel time in June and September 2016 showed higher elimination rates. However, no significant correlation was detected between water temperature and the proportion of PhACs decrease ($p > 0.005$).

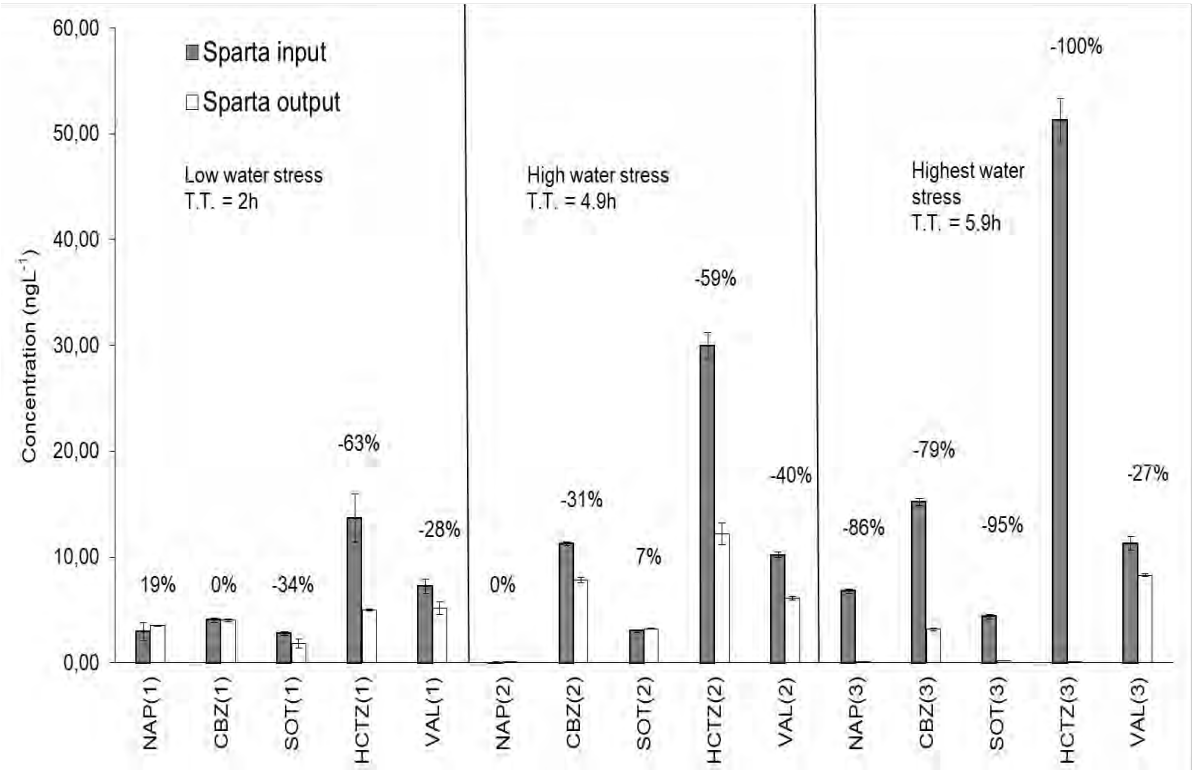

Figure 4. Natural attenuation of individual PhAC concentrations at the Sparta waterbody segment (input-output) with the corresponding water travel time (T.T. / h) in each sampling campaign: 1) July 2015 (low water stress), 2) June 2016 (high water stress) and 3) September 2016 (highest water stress). Note: NAP (Naproxen), CBZ (Carbamazepine), SOT (Sotalol), HCTZ (Hydrochlorothiazide) and VAL (Valsartan). Percentages are depicting the proportion of increase (positive values) or decrease (negative values) of each PhACs per sampling period, while error bars show standard deviation.

4. Discussion

Urban wastewaters were the main source of pollution from PhACs in the Evrotas River. This was indicated by the significant correlations between the score values of each first principal component (physicochemical variables and PhACs families) and urban land use proportions. The lower concentration range of PhACs in the Evrotas River can be attributed to the small resident population in the basin, in comparison with other basins in Greece (Stasinakis, 2012; Stamatis et al., 2013), since concentrations of PhACs were comparable with those detected in small rivers in rural regions with relatively small resident populations (Lindquist, 2005; Kasprzyk-Hordern et al., 2008; Bartelet-Hunt et al., 2009; Morasch, 2013; Chiffre et al., 2016). However, concentrations increased downstream reaching the highest values in the “Sparta” site, located 20km downstream of

the local WWTP. This pattern suggests that the WWTP was the main point source of PhACs and nutrients, as similar studies indicate (Gros et al., 2007, Vieno et al., 2005; Gros et al., 2007; Conley et al., 2008). However, some PhACs such as analgesics/anti-inflammatories, antibiotics, and antihypertensives were also frequently detected in the upstream sampling sites, possibly from untreated wastewaters of the small local settlements.

Fluctuations in river flow influenced the water chemistry of the river. Water regime and weather conditions (Kasprzyk-Hordern et al., 2008) influenced the concentrations of target analytes, nutrients, and physicochemical parameters, which were higher during lower flows (June and September 2016) and were reduced considerably during higher water flows (July 2015). Lower river flows and associated lower dilution accounted for the overall higher total concentrations of detected PhACs and nutrients in 2016. Similarly, high concentrations and high detection frequencies of PhACs as a result of low-flow conditions have also been reported elsewhere (Gros et al., 2007; Fernández et al., 2010; Osorio et al., 2012; Osorio et al., 2016).

Pharmaceutical product concentrations attenuated within the river segment. In-stream attenuation mechanisms are still incompletely understood (Kunkel and Radke, 2011) and could not be clearly established with our approach. However, our results show that increased water travel time (and consequently longer residence time) during dry periods may account for the higher attenuation of most PhACs, and that other factors related to the chemical structure, environmental conditions (e.g. temperature, light intensity, sediment type, turbidity, humic substances, nitrate), and biotic and abiotic processes, such as biodegradation, photodegradation, volatilization and sorption (Vieno et al. 2005; Osorio et al., 2012; Osorio et al., 2016), could also contribute to the attenuation of PhACs. Though, amongst these, environmental conditions such as the seasonal variability of the river flow has shown to be a critical factor affecting the in-stream PhACs concentrations in the Evrotas River (Johnson, 2010; Matamoros and Rodríguez, 2017; Hanamoto et al. 2018). Dilution of surface water can be due to the input of small creeks and/or inputs of groundwater into the river. The different in-stream chemical-biological attenuation processes of the contaminants can also be related to the water travel time within the river segment (Lindqvist et al., 2005; Vieno et al., 2005; Kunkel and Radke, 2012); longer travel times in June and September 2016 within the Sparta River segment resulted in generally higher elimination rates of PhACs. The decrease of PhACs within a

water segment, such as the Sparta segment, depends on the rates at which the natural in-stream attenuation processes operate, as well as on the chemical structure and physicochemical properties of the PhACs and their distribution in the various compartments of the environment (Petrovic et al., 2007).

Table 2. Physicochemical properties of individual PhACs.

Analyte	*Water solubility (mg L^{-1})	**Charge at pH 7	*pK_{a1}	*pK_{a2}	*Log K_{ow}	Log D_{ow} at pH7.4	K_{biol} (L gSS^{-1} d^{-1})	Photolysis rate constant (h^{-1})
Naproxen	15,9	Negative	4,2	n.a.	3,18	-0.16 [d]	<0,2-9 [a]; 1,0-1,9, 0,4-0,8; 0,08-0,4 [c]	0,49[f]
Carbamazepine	17,7	Neutral	13,9	n.a.	2,45	2.77 [d]	≤0,1 [b]; <0,03-<0,06 [a]; <0,005-, <0,008 [c]	0,02 - 0,08[g]
Sotalol	137000	Positive	9,4	10,7	0,24	-1.62 [d]	0,40-0,43 [b]	n.a.
Hydrochlorothiazide	722	Negative	7,9	9,8	-0,07	-0.58 [d]	n.a.	1,61[h]
Valsartan	23,4	Pos./Neut.	4,4	7,4	5,8**	-0.89 [e]	n.a.	n.a.

Notes: D_{ow} –octanol/water distribution ratio; K_{ow} – octanol/water partition coefficient; pK_a – acid dissociacion constant; K_{biol} – biodegradation rate constant; (*) data obtained from (Acuña et al., 2014b); ** values were obtained with Marving software (Chemaxon Ltd.); ([a])data obtained from (Suárez et al.,2010); ([b])data obtained from (Wick et al.,2009); ([c]) data obtained from (Abegglen et al., 2009); ([d])data obtained from (Li et al., 2016); ([e])data obtained from ChemSpider (www.chemspider.com); ([f]) data obtained from (Lin and Reinhard, 2005); ([g])data obtained from (Matamoros et al.,2009); ([h]) data obtained from (Baena-Nogueras et al., 2017); n.a. – not available.

So far, octanol-water partition coefficient (Kow) and octanol-water distribution coefficient (Dow) have been used in order to evaluate the tendency of a substance to stay in the water phase. However, the pH at which measurements are made for evaluating Kow is also a crucial parameter. Wells (2006) reported that Kow does not properly describe environmental partitioning and dynamic in the environment of polar and ionizable compounds, such as PhACs, and that for them the coefficient Dow is more adequate, as it is pKa dependent at the pH of the environment. High Kow (or Dow) (Log Kow > 4) values mean that PhACs tend to sorb onto suspended particles and end up in the sediment, whereas compounds with low Kow (Log Kow < 2.5) and high water solubility are expected to remain in the water phase. Therefore, due to its moderate hydrophilic character (Dow >2.5), low water solubility (17.7 mg L^{-1}) and poor biodegradability (Kbiol< 0.1 L gSS^{-1} d^{-1}), the overall sorption tendency is fairly considerable for carbamazepine. Acuña et al. (2014b) also reported that sorption, rather than biotransformation and photodegradation processes, was the main mechanism driving the in-stream attenuation of carbamazepine. In contrast, hydrophilic compounds with low Dow (< 2.5) and high water solubility (>100 mg L^{-1}) are expected to remain in the aqueous phase and, therefore, to undergo different in-

stream attenuation processes, such as biodegradation and photodegradation (Acuña et al., 2014b; Kunkel and Radke, 2011). Consequently, high attenuation rates of sotalol and especially hydrochlorothiazide, in the present study, in comparison with other analytes could be explained by their overall low Dow (< 2.5) and high water solubility (> 700 mg L^{-1}), while the increase of their attenuation rates, especially in June and September 2016 at low flows could be attributed to their tendency for photodegradation (Kunkel and Radke, 2012; Li et al., 2016; Baena-Nogueras et al., 2017). On the other hand, naproxen and valsartan with their generally low Dow (< 2.5) may be considered as moderately biodegradable PhACs (0.5 < Kbiol < 1 L gSS^{-1} d^{-1}). Though, in the case of naproxen, direct phototransformation resulting in short half-lives (< 3h) has been also proposed as another potential in-stream attenuation pathway beside biodegradation (Lin and Reinhard, 2005; Fono et al., 2006; Lin et al., 2010). Variation in environmental conditions (i.e. temperature, UV radiation) may also affect the in-stream dynamics and fate of PhACs (Osorio et al., 2012). For example, increased water temperatures may decrease sorption, while simultaneously increasing biodegradation (Hulscher and Cornelissen, 1996). However, in the case of the Sparta waterbody segment, the small temperature differences between the sampling periods did not allow finding statistically significant relationships ($p > 0.005$) between water temperature and the in-stream decrease of the PhACs.

Finally, since PhACs do not occur as single compounds in the environment but as a mixture of different transformation products, active substances, and their metabolites, their effects on the aquatic organisms might be stronger than those corresponding to single compounds (Cleuvers, 2003). Also, during drought, when the highest concentration levels of PhACs occur, aquatic biota of temporary rivers are jointly exposed to pollution and water stress, characterized by habitat shrinkage, water quality deterioration and increased competition for limited resources, which in turn can result in severe deleterious effects (Arenas-Sánchez et al., 2016; Karaouzas et al., 2017).

5. Concluding remarks

Concentrations of PhACs, nutrients and physicochemical parameters were considerably higher downstream the WWTP of Sparta city. These concentrations were the highest during low flow conditions in June and September 2016, when increased water travel time accounted for the higher attenuation of most PhACs in the Sparta waterboy segment. The average proportion of decrease for PhACs increased from 22% in July 2015

up to 25% and 77% in June and September 2016. However, the PhACs with the highest average concentration decrease throughout the sampling campaigns was hydrochlorothiazide, followed by sotalol, carbamazepine, valsartan, and naproxen. Our results emphasize that in rivers submitted to strong hydrological stress, such as the Evrotas River, in-stream attenuation mechanisms represent an important contributing factor to the reduced rates of PhACs.

Conflicts of interest

We declare no conflicts of interest. The submitted manuscript contains original data and it is not under review in any other scientific journal. All the authors and relevant institutions have read the submitted version of the manuscript, accept responsibility for it, declare no competing financial interest, and approve its submission.

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3. GENERAL DISSCUSSION

This thesis links the urban origin of chemical contamination (e.g. PhACs) with other stressors especially in the light of water scarcity issues (Chapter 1, 2 and 3). The research has been performed in one Alpine (Chapter 1) and two Mediterranean river basins (Chapter 2 and 3) in order to capture different situations of hydrological stress and water quality degradation.

3.1. Contamination sources of the PhACs in the river ecosystems

3.1.1. Contamination sources and contribution of urban wastewater discharges

Even though PhACs may enter freshwater systems by both, point and non-point sources, WWTPs effluents represent the principal and the most important route of an entrance (Daughton and Ternes, 1999; Buerge et al., 2006b). The results of this thesis showed that urban wastewaters (treated and untreated) were the main source of PhACs pollution (Chapter 1, 2 and 3). Higher concentrations of PhACs occurred in the sites situated downstream from wastewater (treated and untreated) discharge. The detected concentrations of PhACs in wastewater were within the ranges reported in the literature (Verlicchi et al., 2012), being non-steroidal anti-inflammatory drugs (NSAIDs) the most ubiquitous compounds in both treated and untreated wastewater (Chapter 2). These products are available as non-prescription OTC drugs, and the widespread practice of self-medication (Verlicchi et al., 2012; Ortiz de García et al., 2013; Papageorgiou et al., 2016) accounts for their ubiquity. However, and in comparison with the untreated wastewater, the profile and concentration levels of detected PhACs in treated wastewaters differed from the PhACs determined in the raw wastewater. A lower concentration levels of PhACs in treated WWTP effluents, and especially NSAIDs (e.g. ibuprofen, acetaminophen, salicylic acid, naproxen and indomethacin) is related to their generally high elimination rates in the WWTPs (60%-100%, Gros et al., 2010; Verlicchi et al., 2012; Richardson and Ternes, 2014) (Chapter 2). Still, the incomplete removal in conventional WWTPs explains the presence of some PhACs (e.g. diclofenac, Chapter 1) in higher concentrations (Castiglioni et al., 2006; Jelic et al., 2011; Al Aukidy et al., 2014). The treatment process and operational conditions of WWTP, such as hydraulic and sludge retention time, temperature, pH and type of plant configuration, may affect the removal rates of different PhACs and their occurrence in the aquatic environment (Verlicchi et al., 2012).

The PhACs concentrations were lower at the downstream (impact) sampling sites in all studied river basins in comparison to the discharged wastewater (raw and treated) due to various degrees of dilution in receiving rivers and streams. The analysis of PhACs concentrations in the impact sites revealed the effect of wastewater treatment on the total concentration of PhACs (Chapter 2). The absence of WWTP treatment was associated with the highest concentration levels occurring in the lower Ebro River Basin, (Chapter 2). On the contrary, the lower concentrations were in the sites impacted by treated wastewater, particularly regarding the analgesics/anti-inflammatories, additionally favored by their high removal rates in the WWTPs (Verlicchi et al., 2012). PhACs were frequently detected in the upstream sampling sites of the Evrotas River and in the upstream sites of the tributary streams of the lower Ebro (Chapter 2 and 3). Discharges of untreated wastewater (septic tanks, cesspools) by small and sparse local settlements could be the origin of these occurrences, while frequent detection of analgesic/anti-inflammatories and antibiotics may as well be attributed to the presence of other sources of contamination, such as livestock production (Gustafson and Bowen, 1997; Ison and Rutherford et al., 2014; Paíga et al., 2016). Additional non-point sources of aquatic pollution in the Alpine and Mediterranean rivers may, as well, be attributed to the agricultural and urban runoff.

3.1.2. Touristic activity and PhACs

Some studies explaining the seasonality of the PhAC concentration levels, by more or less intensive human use of those PhACs, have been recently published (Moreno-González et al., 2015). Influents of WWTP have shown hourly and seasonal cycles that were also related to the PhACs consumption (Nelson et al., 2011). However, in this thesis, I have shown the relevance of PhACs seasonality associated with touristic activity in Alpine ecosystems. So far, the impact of tourism on river water quality has mostly been evidenced through physicochemical and microbiological parameters (White et al., 1978; Rodriguez, 1987; Almeida et al.,2007; Rashid and Romshoo, 2013; Bhadula et al., 2014), while studies regarding the occurrence of PhACs have been limited to single events (Gerrity et al., 2011). Our results in the Adige River Basin pointed out tourism as a significant contributor to the overall PhACs pollution of the Alpine aquatic environment (Chapter 1). This was particularly relevant in the region of Val di Sole (tributary Noce River; a popular winter tourism destination characterized by intense winter tourism arrivals), where the highest total concentrations of PhACs were detected. The high

abundance of detected PhACs in Val di Sole could be explained by the increased number of tourist arrivals (76.4% of the total population) during the winter period (Chapter 1). In winter, analgesics/anti-inflammatories and antibiotics were associated with tourism. Ski resorts surrounding the Val di Sole produce wastewater treated at the WWTPs of Tonale and Mezzana, and so forth the most abundant compound was an analgesic/anti-inflammatory diclofenac, a compound typically used in the treatment of the sports injuries, such as joint pain and inflammation (Galer et al., 2000). In comparison with the PhACs, PCPs were not correlated with the tourist arrivals, since they are not only incorporated in cosmetics (and therefore linked to direct human usage), but also occur in the wide range of products such as the plastics, adhesives, rubber, and paint (Molins-Delgado et al., 2015; Ramos et al., 2015). Overall, the results of this thesis highlight the relevance of tourism on river quality and stress the need to consider, in future studies, the seasonal touristic fluxes as a factor impacting chemical pollution.

3.2. Environmental factors affecting the occurrence and distribution patterns of PhACs

3.2.1. Effects of hydrological variability on PhACs pollution

The natural river flow regime is fluctuating during the year, as a direct result of rainfall patterns (Burt 1992). Many studies have linked intra-annual flow patterns of rivers and streams to climatic conditions (Beckinsale, 1969; Wilby, 1993; Harris et al., 2000; Baeza et al., 2005). However, human impacts on water flow regime are both direct (reservoir operation, water abstraction), or indirect such as afforestation, urbanization and agricultural practices. Human impacts on the river flow regime affect, as well the extent of aquatic pollution by emerging pollutants (e.g. PhACs; Petrovic et al., 2011). Even though studies have been performed in order to explore the intra-annual (seasonal) occurrence patterns of PhACs (Gros et al., 2007; Fernández et al., 2010; Osorio et al., 2012; Osorio et al., 2016), knowledge regarding the impact of hydrological variability of the streams and rivers on the spatiotemporal distribution of PhACs is still limited. Also, there is lack of continuous monitoring studies of PhACs to describe long-term trends and seasonal variations (Sacher et al., 2008). The results compiled in this thesis point out at the intra-annual hydrological variability of rivers and streams as one of the most important variables affecting the in-stream concentration levels of PhACs. Though, the variability of the river flow has shown to have different causative mechanisms in different regions.

3.2.1.1. Hydrological variability effects on pharmaceuticals and personal care products (PPCPs) pollution in Alpine rivers

In the high mountainous areas, such as the Alps, the river flow regime is strongly influenced by snow accumulation and snowmelt (Gurtz et al., 1999) (Chapter 1). During the melting period (spring-summer) the total river discharge is mostly due to snowmelt and glacier melt. In the Adige River, the higher river flows and associated higher dilution in summer because of snowmelt resulted in generally lower concentrations of (PPCPs) (Chapter 1). However, lower stream flow together with the smaller dilution in the winter period, as a result of the predominance of solid precipitation, resulted in higher concentrations of detected PPCPs (Chapter 1). Our results have pointed out that the hydrological variability was an important influencing factor on the overall concentration levels of micropollutants in Alpine streams and rivers.

3.2.1.2. Hydrological variability effects on PhACs pollution in Mediterranean rivers

In contrast to the Alpine environment, the hydrological variability of the lower Ebro River in Northeast Spain (Chapter 2) and the Evrotas River (Chapter 3) in South Greece have shown different patterns. These were the typical Mediterranean rivers with large intra-annual hydrological variations characterized by flow reductions in summer and floods in spring and autumn (Gasith and Resh, 1999). Mediterranean river and stream flows vary from perennial to ephemeral (Bejarano et al., 2010). The occurring summer droughts result in the headwater and middle-order streams to become intermittent or even to completely dry out during extended periods (Lake, 2003; Sabater et al., 2008). Temporary Mediterranean streams and rivers are one of the most complex and dynamic aquatic ecosystems, as well as amongst the most fragile ones (Sabater et al., 2008; Larned et al., 2010; Sabater and Tockner, 2010). They are affected by strong water pressures resulting from extensive water abstraction, climate change and river fragmentation (Larned et al., 2010). The water quality pressures are additionally accentuated by nutrient enrichment, organic and microcontaminants pollution (e.g. PhACs) from industrial and urban wastewaters and agricultural activities (Vörösmarty et al., 2010; Petrovic et al., 2011; Cooper et al., 2013). These pressures cause discharged wastewater primarily to depend upon factors, such as stream flow rate conditions and percentage of treated wastewaters in the receiving water bodies. Additional in-stream dilution of surface water

and in-stream PhACs concentrations may occur due to different lateral inputs of small creeks or inputs of groundwater into the river. Even though in-stream attenuation mechanisms could not be clearly established with our approach, our results have shown that low flow periods decrease the dilution of contaminants, but also may prolong the hydraulic residence time of PhACs within the river reach, thus increasing the natural in-stream attenuation processes (Chapter 2 and 3). Similar results were detected in studies performed elsewhere (Gros et al., 2007; Fernández et al., 2010; Osorio et al., 2012; Osorio et al., 2016).

In some cases, intermittent Mediterranean stream and rivers have a significant fraction of the overall flow from municipal and industrial wastewater effluents (Hassan and Egozi, 2001; Poff and Zimmerman, 2010). The effluent-dominated streams may represent the worst-case scenario for PhACs exposure to aquatic ecosystems and human population (Brooks et al., 2006). Our results in the effluent-dominated streams of the lower Ebro (Corbera d´Ebre, Prat de Comte, Bot-Gandesa, Poboleda, and Prades) consistently showed these patterns (Chapter 3). In these systems, during drought periods, the biota of intermittent Mediterranean streams and rivers is not only exposed to periods of low flow and increased water temperature (Robinson et al., 2004), but as well to the exacerbated ecological and ecotoxicological effects of increased concentrations of multiple chemical stressors, such as the PhACs (Ponsati et al., 2016). Finally, PhACs adsorbed to sediments and accumulated during low-flow periods in the Mediterranean streams and rivers may remobilize during flood episodes (Daughton and Ternes, 1999; Loos et al., 20009; Petrovic et al., 2011).

3.2.2. Other environmental factors affecting the natural in-stream attenuation of PhACs

Other important environmental factors apart from dilution and mixing affect the in-stream attenuation rates of PhACs as well. These include the amount of incident sunlight received by a specific waterbody, water temperature, water turbidity, groundwater input, soil/sediment type and the presence of reactive radical species (Vieno et al., 2005, Gurr and Reinhard, 2006; Osorio et al., 2012; Kunkel and Radke 2012; Challis et al., 2014). However, an additional important factor which potentially may affect the in-stream persistence of PhACs in surface waters is the adsorption onto the suspended colloidal organic matter, which in turn can limit their mobility and bioavailability (Maskaoui and

Zhou, 2010). Because environmental parameters vary at different spatial and temporal scales, in-stream attenuation rates of PhACs show, as well increased variability which complicates accurate predictions (Gurr and Reinhard 2006; Fenner et al. 2013). The abiotic degradation processes, such as the hydrolysis, temperature and UV radiation generally predominate over biodegradation and, represent the most important factors affecting the in-stream attenuation of PhACs in the surface waters (Osorio et al., 2012; De Laurentiis et al., 2013). For example, fluoroquinolones are easily degradable under UV light despite their low sensitivity to temperature and hydrolysis (Thiele-Bruhn, 2003). Also, NSAIDs like diclofenac and naproxen are highly photodegradable under the sun (Kunkel and Radke, 2012; Hanamoto et al., 2014). Therefore, low detection frequencies of PhACs highly susceptible to photolysis (e.g. diclofenac, ketoprofen etc.) during water scarcity periods may additionally be attributed to the generally higher insolation of the surface water during summer months (Chapter 2 and 3). Vieno et al. (2005) reported that the photolysis process is not effective during winter due to ice and snow cover. The high concentrations of detected PhACs in the Adige River during winter months may, as well, be attributed to decreased sunlight exposure and low surface water temperatures (Chapter 1). However, photolysis is predominately restricted to the uppermost parts of surface waters (Bartels and von Tümpling, 2007), and its importance decreases in the turbid waters (Robinson et al., 2007). Furthermore, some PhACs do not degrade by photolysis at all, because they do not have an absorbing ability towards the UV-A or UV-B radiation or they are not efficiently photo transformed (Borren et al, 2003). Consequently, biodegradation may become more important in-stream attenuation process in these cases, also occurring at solid-liquid interfaces (i.e. sediments). However, once PhACs reach the sediments, their environmental persistence generally decreases, possibly because different aerobic and anaerobic biodegradation processes (Fritsche and Hofrichter, 2008; Mrozik, 2003) occurring there (Al-Rajab et al., 2010; Yu et al., 2013; Radke and Maier 2014). Additional important factors influencing the biodegradation in sediments may be attributed to the exposure time to biomass, availability of co-substrates (for compounds degraded co-metabolically), and the fraction of inert matter. Lower temperatures may as well account for generally higher concentration levels of PhACs detected in winter sediments of Adige River (Chapter 1).

Even though increased water temperatures may decrease sorption while simultaneously increasing biodegradation (Hulscher and Cornelissen, 1996), this was not the case in our study performed on the Evrotas River and the tributary streams of lower Ebro (Chapter 2 and 3). The small water temperatures differences between sampling

periods did not allow finding a statistically significant relationship between water temperature and the in-stream decrease of the PhACs concentrations. However, increased rates of biodegradation, as a result of increased surface water temperatures, have been observed in studies performed elsewhere (Viento et al., 2005; Osorio et al., 2012). Additionally, physical properties of PhACs, such as the vapor pressure, water solubility, and Henry's law constant, together with the deposition, can as well be strongly dependent on environmental conditions, such as high water temperatures (Petrovic and Barceló, 2007).

3.3. Natural in-stream attenuation of PhACs according to their physicochemical properties

Limited knowledge is available regarding the PhACs fate in rivers and the in-stream attenuation mechanisms related to their elimination (Kunkel and Radke, 2011). This is mostly due to a fact that most of the available information regarding in-stream attenuation of PhACs comes from few single stream segment field studies with limited number of compounds and due to difficulties in transferring laboratory-derived knowledge to the real aquatic ecosystems (Kunkel and Radke, 2011; Kunkel and Radke 2012; Writer, 2012).

However, in-stream attenuation of PhACs may be predicted to some extent from the chemical structures and physicochemical properties of the products. These include their water solubility, volatility, acidity, Henry's law constant, lipophilicity (expressed as Kow and Koc) and sorption potential. Other factors include their resistance towards biological and abiotic degradation (Gurr and Reinhard 2006; Kunkel and Radke 2008). Due to the fact that the solubility of the majority of PhACs is notably higher than their actual concentrations in the aquatic environment, solubility does not limit their environmental occurrence, while low values of Henry coefficients make volatilization negligible (Larsen et al., 2004). Hydrolysis degradation is generally negligible for environmentally relevant human drugs (except some antibiotics). Sorption represents a key factor affecting the input, transport, and the transformation of PhACs in the aquatic environment (Scheytt et al., 2005), though it is mainly governed by several processes, such as hydrophobic partitioning, ion exchange, complexation, and hydrogen bonding. In the case of ionizable and polar PhACs, the sorption properties cannot be evaluated from the log Kow because partitioning depends on pH and pKa of the compound (Wells, 2006). For these PhACs, the

coefficient log Dow is more adequate, as it is pKa dependent upon the pH of the environment (Kwon and Armbrust, 2008). Our results were consistent with the aforementioned observations and the studies performed elsewhere (Silva et al., 2011), and PhACs with basic characteristics (pKa>7) showed higher tendency to bind to sediments, such as clarithromycin (pKa 8.9), hydrochlorothiazide (pKa 7.9), metroprolol (pKa 14.1) and acetaminophen (pKa 9.38) (Chapter 1). The generally high values of pKa for PhACs detected in sediments indicated that these PhACs were positively charged at pH conditions of river water and other interactions such as cationic interactions, complexation, and hydrogen bonding (Silva et al., 2011). However, our results from the Evrotas River (Chapter 3) pointed out that log Dow was another possible indicator of PhACs fate in the aquatic environment. Results showed that the hydrophilic PhACs with low log Dow (< 2.5; e.g. hydrochlorothiazide, naproxen, sotalol, valsartan) may rather remain in the aqueous phase and therefore undergo different in-stream attenuation processes (Chapter 3). Besides physicochemical properties, molecular properties (functional groups and their positioning) may as well lead to ionic, ion paring and complexation reactions with the particulate matter and microorganisms, which in turn may contribute to the PhACs partitioning between the aqueous and solid phase. Therefore, PhACs with carboxylic acid functional groups with lower pKa values (<7) are less likely to bind to sediments and solids, while PhACs with functional groups such as the π-conjugated systems, heteroatoms, and nitro, phenolic and naphthoxyl groups, are more prone to photolysis, and oxidative loses by reactions with mineral and humic substances in sediments and soils (Fatta-Kassinos et al., 2011). However, in the biological systems, sometimes only left-handed or right-handed forms of the molecules (stereoisomers) may be degraded by microbial organisms (Bagnall et al., 2013). Tadkaew et al. (2011) also reported high removal efficiencies for compounds bearing electron donating functional groups (e.g. hydroxyl, primary amine groups) in their study on the removal of trace organics by membrane bioreactor treatment, while Hebling et al. (2010) observed predominately biotransformation pathway of amid-containing compounds. Even though photolysis represents the predominant process of PhACs degradation, there is still limited knowledge regarding the toxicity of photolytic by-products compared to the parent compounds (Petrovic and Barceló, 2007). However, besides direct photolysis, indirect photolysis may as well lead to the formation of •OH which in turn can magnify the in-stream degradation rates of some PhACs (e.g. venlafaxine) (Rúa-Gómez and Püttmann, 2013). Robinson et al. (2007), Marotta et al. (2013) and Passananti et al. (2014) have

reported inhibiting and enhancing effects of dissolved organic matter and reactive oxygen species such as $^1O_2$ on the in-stream attenuation of PhACs as well.

4. CONCLUSIONS

1. The occurrence and spatiotemporal distribution of PPCPs in an Alpine aquatic environment were associated with intra-annual hydrological variability and fluctuation of human impacts in touristic areas.
2. Water samples taken near important tourist resorts, the analgesic/anti-inflammatories have shown the highest abundance amongst all studied PhACs, while the most abundant PCPs in water was octyl-dimethyl-p-aminobenzoic acid.
3. Measurements indicated that the accumulation of PPCPs in sediments was moderate in comparison to water samples. The most frequently detected PhACs in sediments from both sampling campaigns were antibiotics, while amongst PCPs in sediments, octocrylene showed the highest concentration in both sampling campaigns.
4. The occurrence and spatiotemporal distribution of PhACs in Mediterranean streams was strongly associated with the seasonal variation of the stream flow
5. PhACs in treated and untreated wastewater were positively and significantly correlated with the resident population, thus confirming the urban origin of wastewater.
6. Significant differences in the total PhACs concentrations (sum of all compounds) between upstream and downstream sampling sites in the Mediterranean streams pointed out wastewater discharges as an important source of aquatic contamination.
7. Generally, the highest concentration levels of PhACs were detected in effluent-dominated streams due to low stream flow and little-to-no upstream dilution; the lowest concentrations were detected in the downstream sites impacted by treated wastewater.
8. NSAIDs were the most frequently detected PhACs in both downstream sites impacted by treated and untreated wastewater.
9. Apart from dilution and chemical-biochemical degradation processes, different distances from the wastewater discharge point to the downstream (impact) sampling site and related with their specific hydraulic travel time showed to be an important factor affecting the in-stream attenuation of PhACs.
10. Concentration levels of PhACs and nutrients were considerably higher downstream the WWTP Sparta, thus confirming the urban origin of wastewaters in the Evrotas River.
11. Occurrence and distribution patterns of PhACs and nutrients in the Evrotas River were associated with the intra-annual hydrological variability of the river flow.

12. Increased water travel time and, therefore, the longer residence time in the river during low flows accounted for the higher in-stream attenuation of most studied PhACs.

13. Generally, PhACs with short half-life times showed higher in-stream attenuation rates in comparison with the PhACs showing longer half-life times.

14. Frequent detection of analgesics/anti-inflammatories and antibiotics in the upstream sampling sites may be attributed to the presence of other sources of contamination in the river basin, such as the livestock production.

15. The effects of multiple stress conditions may be amplified under water scarcity and result in the increased concentrations levels of PhACs in river water and sediments.

16. Increased water travel time and simultaneously longer residence time of PhACs within the river stretch or waterbody during low flow conditions in the intermittent Mediterranean rivers and streams contributes considerably to the generally higher in-stream attenuation of PhACs.

5. OUTLOOOK

Our results stress the role the hydrological variability of Alpine and Mediterranean streams and rivers represents in influencing emerging pollutant concentrations (e.g. PhACs, PCPs etc.). These highlight the ecotoxicological hazard especially in water-scarce situations. Precisely, the variability of river water flow should be a priority issue in the future environmental policies regarding the potential impacts of contaminants to freshwater ecosystems. In-stream attenuation processes (i.e. biotransformation, sorption, photolysis, and volatilization) should be better investigated in field conditions and explicitly included in river water quality models in order to determine the in-stream concentrations and loads of PhACs. Since PhACs usually appear as mixtures (parent compounds and metabolites) in the aquatic environment, ecotoxicological studies are required in order to elucidate the short and long-term effects of PhACs mixtures. The fragility of river ecosystems calls for a more detailed investigation of the way these stressors combine when co-occurring. Limitations in water policies ask for the development and implementation of innovative and versatile management strategies.

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ANNEX

SUPPLEMENTARY INFORMATION (CHAPTER 1)

1S. The minimum and maximum river flows with the corresponding occurrence seasons (sampling sites on the Adige and Noce rivers).

Site	Max. Q (m^3/s)	Month Max.	Min. Q (m^3/s)	Month Min.	Average Q (m^3/s)
1	7.56	5	0.247	4	0.592
2A/2B	21.8	9	0.797	2	2.40
3A/3B	88.2	10	5.92	2	11.2
4	204	11	5.04	2	9.71
5	246	11	42.5	4	35.7
6	1135	6	68.4	2	134
7A/7B/7C/7D	1543	6	115	2	210

Note: [Max. Q (m^3/s)] = maximum discharge; [Month max.] = month when maximum occurs; [Min. Q (m^3/s)] = minimum discharge; [Month Min.] = month when minimum occurs; [Average Q (m^3/s)] = average discharge.

Table 2S. Water supply, average daily WWTP outflows (February 15^{th}-17^{th} and July 3^{rd}-5^{th}, 2015) and treatment processes for the main waste water treatment plants in the associated sampling sites.

Name/ Sampling site	Potential water supply A.E.	Average discharge (m^3/d) (February 15^{th}-17^{th}, 2015)	Average discharge (m^3/d) (July 3^{rd} -5^{th}, 2015)	Treatment
Tonale (2A, 2B)	10000	1657	1211	Oxidation, secondary settlement.
Mezzana (3A, 3B)	30000	6015	5141	Denitrification, oxidation, secondary settlement.
Spormaggiore (4)	1500	Disabled	Disabled	Oxidation, secondary settlement.
Fai della Paganella (5)	5200	479	351	Oxidation, secondary settlement.
Salorno(6)	4500	846	730	Desanding, oxidation, secondary settlement.

Trento Sud (7A, 7B, 7C, 7D)	100000	12909	11251	Primary settlement, oxidation, secondary settlement, anaerobic digestion.
Romagnano (7A, 7B, 7C, 7D)	1500	Disabled	Disabled	Oxidation, secondary settlement.

Note: Sources (https://adep.provincia.tn.it/Agenzia-per-la-Depurazione-ADEP; http://www.provincia.bz.it/agenzia-ambiente/acqua/cartine-schede.asp); n.a. = not applicable.

Table 3S. Measured physico-chemical properties of water.

Physico-chemical characteristics	SAMPLING LOCATIONS												Season
	1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Temp [°C]	1.30	3.70	3.40	3.60	5.30	7.65	5.40	6.30	5.05	5.85	6.26	10.8	Winter
EC Abs [µS/cm]	67.0	130	140	88.4	87.0	202	203	182	205	202	205	259	
Turb. [FNU]	0	1.20	3.50	2.30	2.00	3.50	6.25	3.60	3.50	2.90	3.00	2.80	
Vel [m/s]	1.70	1.25	1.10	2.70	2.00	1.30	1.86	2.40	2.70	2.70	2.70	2.70	
Temp [°C]	13.7	13.0	12.6	9.80	13.1	14.8	13.7	15.2	15.8	16.0	16.1	16.1	Summer
EC Abs [µS/cm]	125	132	132	59.6	77.3	180	174	160	170	172	174	174	
Turb. [FNU]	4.61	3.14	2.39	55.0	70.0	4.00	4.21	70.0	72.5	70.0	70.0	70.0	
Vel [m/s]	n.a.	0.70	1.00	2.20	1.90	1.30	n.a.	1.80	1.60	1.40	1.80	1.90	

NOTE: [°C] = Water temperature; [µS/cm] = EC Abs – Actual conductivity; [FNU] = [NTU] = Turbidity; Vel [m/s] = Velocity; n.a. = not applicable

Table 4S. Pairwise correlation coefficients between the variables: (tourist arrivals - sum of compounds in each familiy of comounds) and (resident population - sum of compounds in each familiy of compounds) for each sampling location. Significant Pearson's r values for ($p < 0.01$) are marked in **bold**, for ($p < 0.05$) in *italics* and <u>underlined</u> for ($p < 0.1$).

Group	Familiy	WINTER CAMPAIGN				SUMMER CAMPAIGN			
		Tourist arrivals		Resident population		Tourist arrivals		Resident population	
		r	N	r	N	r	N	r	N
Pharmaceutically active compounds WATER	Analgesics/anti-inflammatories	*0.897*	5	0.337	7	0.112	5	**0.887**	7
	Lipid regulators	0.833	4	0.608	6	n.a.	0	n.a.	0
	Psychiatric drugs	0.871	4	0.442	6	-0.150	4	<u>0.950</u>	4
	β - Blocking agents	0.619	4	<u>0.774</u>	6	0.060	4	0.859	3
	Diuretic	0.835	4	0.477	6	0.104	4	*0.905*	6
	Antihypertensives	0.556	4	*0.815*	6	0.080	4	*0.891*	6
	Antihelminitics	n.a.	2	n.a.	2	n.a.	0	n.a.	0
	Calcium channel blockers	n.a.	2	n.a.	2	n.a.	0	n.a.	0
	Antibiotics	*0.960*	4	0.017	6	0.797	4	<u>0.872</u>	5
	Antidiabetic	n.a.	0	n.a.	0	n.a.	0	n.a.	0
Pharmaceutically active compounds SEDIMENT	Analgesics/anti-inflammatories	n.a.	1	n.a.	1	n.a.	1	n.a.	1
	Lipid regulators	n.a.	0	n.a.	0	n.a.	0	n.a.	0
	Psychiatric drugs	n.a.	0	n.a.	0	n.a.	0	n.a.	0
	β - Blocking agents	n.a.	1	n.a.	1	n.a.	1	n.a.	1
	Diuretic	0.696	3	0.313	3	n.a.	0	n.a.	0
	Antihypertensives	n.a.	0	n.a.	0	n.a.	0	n.a.	0
	Antihelminitics	n.a.	0	n.a.	0	n.a.	0	n.a.	0

	Calcium channel blockers	n.a.	0	n.a.	0	n.a.	0	n.a.	0
	Antibiotics	0.960	3	-0.167	6	0.633	3	-0.054	4
	Antidiabetic	0.161	3	n.a.	2	n.a.	0	n.a.	0
Personal care products WATER	Benzophenones	0.772	3	-0.171	3	-0.294	5	**0.995**	7
	Camphor	n.a.	1	n.a.	1	n.a.	0	n.a.	0
	PABA derivatives	0.045	5	-0.021	7	n.a.	2	n.a.	2
	Benzotriazoles	-0.187	4	-0.043	7	-0.404	5	**0.950**	7
	Fragrances	n.a.	2	n.a.	2	n.a.	0	n.a.	0
	Preservative	0.895	4	0.320	4	n.a.	0	n.a.	0
Personal care products SEDIMENT	Benzophenones	n.a.	0	n.a.	0	n.a.	2	n.a.	2
	Camphor	-0.369	3	*0.959*	4	n.a.	1	n.a.	1
	Crylene	0.586	3	0.473	5	n.a.	2	n.a.	2
	PABA derivatives	-0.300	5	*0.973*	5	n.a.	1	n.a.	1

Notes: n.a. = not applicable; N = number of pairs; r = Pearson moment correlation factor

Table 5S. The isotopically labeled internal standards assigned for their quantification: A) Pharmaceutically active compounds (organized according to therapeutic groups) and B) Personal care products (organized according to their group).

A) Pharmaceutically active compounds

Therapeutic groups	Analyte	Number	CAS number	Corresponding internal standard
Analgesics/anti-inflammatories (14)	Ketoprofen	1	22071-15-4	Ibuprofen-d3
	Naproxen	2	22204-53-1	Ibuprofen-d3
	Ibuprofen	3	15687-27-1	Ibuprofen-d3
	Indomethacine	4	53-86-1	Indomethacine-d4
	Acetaminophen	5	103-90-2	Acetaminophen-d4
	Salicylic acid	6	69-72-7	Acetaminophen-d4
	Diclofenac	7	15307-79-6	Ibuprofen-d3
	Phenazone	8	60-80-0	Phenazone-d3
	Propyphenazone	9	479-92-5	Phenazone-d3
	Piroxicam	10	36322-90-4	Meloxicam-d3
	Tenoxicam	11	59804-37-4	Meloxicam-d3
	Meloxicam	12	71125-39-8	Meloxicam-d3
	Oxycodone	13	124-90-3	Carbamazepine-d10
	Codeine	14	76-57-3	Carbamazepine-d10
Lipid regulators and cholesterol lowering statin drugs (5)	Bezafibrate	15	41859-67-0	Bezafibrate-d6
	Gemfibrozil	16	25812-30-0	Gemfibrozil-d6
	Pravastatin	17	81131-70-6	Gemfibrozil-d6
	Fluvastatin	18	93957-54-1	Gemfibrozil-d6
	Atorvastatin	19	134523-03-8	Gemfibrozil-d6

Psychiatric drugs (15)	Carbamazepine	20	298-46-4	Carbamazepine-d10
	2-Hydroxycarbamazepine[a]	21	68011-66-5	Carbamazepine-d10
	10.11-Epoxycarbamazepine[a]	22	36507-30-9	Carbamazepine-d10
	Acridone[a]	23	578-95-0	Carbamazepine-d10
	Sertraline	24	79559-97-0	Fluoxetine-d5
	Citalopram	25	59729-32-7	Citalopram-d4
	Venlafaxine	26	99300-78-4	Venlafaxine-d6
	Olanzapine	27	132539-06-1	Carbamazepine-d10
	Trazodone	28	25332-39-2	Fluoxetine-d5
	Fluoxetine	29	56296-78-7	Fluoxetine-d5
	Norfluoxetine[a]	30	83891-03-6	Fluoxetine-d5
	Paroxetine	31	110429-35-1	Fluoxetine-d5
	Diazepam	32	439-14-5	Diazepam-d5
	Lorazepam	33	846-49-1	Diazepam-d5
	Alprazolam	34	28981-97-7	Diazepam-d5
Histamine H1 and H2 receptor antagonists (5)	Loratadine	35	79794-75-5	Cimetidine-d3
	Desloratadine[a]	36	100643-71-8	
	Ranitidine	37	66357-59-3	
	Famotidine	38	76824-35-6	
	Cimetidine	39	51481-61-9	
β -Blocking agents (6)	Atenolol	40	29122-68-7	Atenolol-d7
	Sotalol	41	959-24-0	
	Propranolol	42	318-98-9	
	Metoprolol	43	56392-17-7	
	Nadolol	44	42200-33-9	
	Carazolol	45	57775-29-8	
Diuretic (3)	Hydrochlorothiazide	46	58-93-5	Hydrochlorothiazide-d2

	Furosemide	47	54-31-9	Furosemide-d5
	Torasemide	48	56211-40-6	Furosemide-d5
Antidiabetic (1)	Glibenclamide	49	10238-21-8	Glyburide-d3
Antihypertensives (4)	Amlodipine	50	111470-99-6	Amlodipine-d4
	Losartan	51	124750-99-8	Valsartan-d8
	Irbesartan	52	138402-11-6	
	Valsartan	53	137862-53-4	
Antiplatelet agent (1)	Clopidogrel	54	135046-48-9	Glyburide-d3
Prostatic hyperplasia (1)	Tamsulosin	55	106463-17-6	Sulfamethoxazole-d4
To treat asthma (1)	Salbutamol	56	18559-94-9	Atenolol-d7
Anticoagulant (1)	Warfarin	57	81-81-2	Warfarin-d5
Antihelmintics (3)	Albendazole	58	54965-21-8	Ronidazole-d3
	Thiabendazole	59	148-79-8	
	Levamisole	60	16595-80-5	
Synthetic glucocorticoid (1)	Dexamethasone	61	50-02-2	Dexamethasone-d4
Sedation and muscle relaxation (1)	Xylazine	62	23076-35-9	Xylazine-d6
Tranquilizer (2)	Azaperone	63	1649-18-9	Azaperone-d4
	Azaperol[a]	64	2804-05-9	
Antibiotics (13)	Erythromycin	65	59319-72-1	Erythromycin-N.N13C2
	Azithromycin	66	83905-01-5	Azithromycin-d3
	Clarithromycin	67	81103-11-9	Azithromycin-d3
	Tetracycline	68	64-75-5	Sulfamethoxazole-d4
	Ofloxacin	69	82419-36-1	Ofloxacin-d3
	Ciprofloxacin	70	85721-33-1	Ofloxacin-d3
	Sulfamethoxazole	71	723-46-6	Sulfamethoxazole-d4
	Trimethoprim	72	738-70-5	Sulfamethoxazole-d4
	Metronidazole	73	443-48-1	Ronidazole-d3

	Metronidazole-OH[a]	74	4812-40-2	Ronidazole-d3
	Dimetridazole	75	551-92-8	Ronidazole-d3
	Ronidazole	76	7681-76-7	Ronidazole-d3
	Cefalexin	77	15686-71-2	Sulfamethoxazole-d4
Calcium channel blockers (3)	Diltiazem	78	42399-41-7	Carbamazepine-d10
	Verapamil	79	152-11-4	Verapamil-d6
	Norverapamil[a]	80	67812-42-4	Verapamil-d6

[a]Metabolites

B) Personal care products

Group	Analyte	Number	CAS Number	Internal Standard
Benzophenone UV filterss	2.4-Dihydroxybenzophenone; Benzophenone 1, BP1[a]	1	131-56-6	Benzophenone 3 -d5
	2-Hydroxy-4-methoxybenzophenone; Benzophenone 3, BP3	2	131-57-7	Benzophenone 3 -d5
	2.2'-Dihydroxy-4-methoxybenzophenone, DHMB[a]	3	131-53-3	Benzophenone 3 -d5
	4-Hydroxybenzophenone, 4HB[a]	4	1137-42-4	Benzophenone 3 -d5
	4.4'-Dihydroxybenzophenone, 4DHB[a]	5	611-99-4	Benzophenone 3 -d5
Cinnamate UV filters	2-Ethylhexyl-trans-4-methoxycinnamate, EHMC	6	5466-77-3	4-Methylbenzylidene camphor-d3
Camphors UV filters	3-(4'-Methylbenzylidene) camphor, 4MBC	7	36861-47-9	4-Methylbenzylidene camphor-d4
Crylenes UV filters	2-Ethylhexyl-2-cyano-3.3-diphenylacrylate; Octocrylene, OC	8	6197-30-4	4-Methylbenzylidene camphor-d4
PABA derivatives UV filters	Octyl-dimethyl-p-aminobenzoic acid, ODPABA	9	58817-05-3	4-Methylbenzylidene camphor-d4
	Ethyl-p-aminobenzoic acid, Et-PABA	10	94-09-7	4-Methylbenzylidene camphor-d4
Benzotriazoles UV-blockers	1-H-benzotriazole, BZT	11	95-14-7	1-H-benzotriazole-d4
	5-Methyl-benzotriazole, MeBZT	12	136-85-6	1-H-benzotriazole-d4

	5.6-Dimethyl-1-H-benzotriazole, DMeBT	13	4187-79-6	1-b-menzotriazole-d4
	2-(5-Tert-butyl-2-hydroxyphenyl) benzotriazole. TBHPBT	14	3147-76-0	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2-(2-Hydroxy-5-methylphenyl) benzotriazole, UV-P	15	2440-22-4	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2-(2'-Hydroxy-3'.5'-di-tert-butylphenyl) benzotriazole, UV320	16	3846-71-7	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2-Tert-butyl-6-(5-chloro-2H-benzotriazol-2-yl)-4-methylphenol, UV326	17	11/5/3896	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2.4-Di-tert-butyl-6-(5-chloro-2H-benzotriazol-2-yl) phenol, UV327	18	3864-99-1	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2-(2H-Benzotriazol-2-yl)-4.6-di-tert-pentylphenol, UV328	19	25973-55-1	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
	2-(2H-Benzotriazol-2-yl)-4-(1.1.3.3-tetramethylbutyl) phenol, UV329	20	3147-75-9	2-(2H-Benzotriazol-2-yl)-4-methyl-6-(2-propenyl)phenol
Fragrances	1-(3.5.5.6.8.8-Hexamethyl-5.6.7.8-tetrahydronaphthalen-2-yl) ethanone; 6-Acetyl-1.1.2.4.4.7-hexamethyltetralin; Tonalide, AHTN	21	21145-77-7	Tonalide-d3
	1.3.4.6.7.8-Hexahydro-4.6.6.7.8.8.-hexamethyl-cyclopenta[g]benzopyran; Galaxolide, HHCB	22	1222-05-5	Tonalide-d3
	1-(6-Tert-butyl-1.1-dimethyl-2.3-dihydro-1H-inden-4-yl) ethanone; Celestolide, ADBI	23	13171-00-1	Tonalide-d3
Preservatives	Methyl p-hydroxybenzoate; Methyl Paraben, MPB	24	99-76-3	Benzyl Paraben-d4
	Ethyl p-hydroxybenzoate; Ethyl Paraben, EPB	25	120-47-8	Benzyl Paraben-d4

[a]Metabolites

Table 6S. Method performance parameters: recoveries (%), relative standard deviation (RSD% for n=3), limits of detection (LOD, water ngL^{-1}; sediment ngg^{-1}) limits of quantification (LOQ, water ngL^{-1}; sediment ngg^{-1}) for pharmaceutically active compounds.

Therapeutic groups	Analyte	WATER				SEDIMENT			
		LOD (ngL^{-1})	LOQ (ngL^{-1})	Recovery (%) (n=3)	RSD (%) (n=3)	LOD (ngg^{-1})	LOQ (ngg^{-1})	Recovery (%) (n=3)	RSD (%) (n=3)
Analgesics/anti-inflammatories	Codeine	1.0	3.3	87	4.6				
	Oxycodone	3.1	10.4	70	8.2				
	Piroxicam	0.2	0.5	39	4.8				
	Indomethacine	1.0	3.3	102	3.9	0.5	1.5	29	4.7
	Ketoprofen	7.3	24.5	96	2.3	1.0	3.2	63	4.3
	Acetaminophen	0.4	1.3	39	6.9	0.1	0.4	18	3.2
	Ibuprofen	1.8	6.1	85	4.8	0.6	2.0	56	8.8
	Salicylic acid	1.2	3.9	113	5.2				
	Diclofenac	5.2	17.4	91	4.9	0.9	3.0	60	7.0
	Propyphenazone	0.1	0.5	83	2.5				
	Phenazone	0.1	0.4	111	2.2	0.2	0.6	98	4.8
	Naproxen	0.9	2.9	88	4.2	0.6	2.0	67	5.1
	Tenoxicam	0.1	0.5	72	9.9				
	Meloxicam	1.9	6.2	84	12.3				
Lipid regulators and cholesterol lowering statin drugs	Bezafibrate	0.1	0.5	102	3.6	0.05	0.2	113	6.3
	Atorvastatin	0.5	1.6	38	4.1				
	Fluvastatin	0.2	0.6	94	6.3				
	Gemfibrozil	1.0	3.4	97	1.3	0.1	0.2	66	6.9
	Pravastatin	1.2	3.9	87	11.6				
Psychiatric drugs	Diazepam	2.9	9.8	93	3.6	0.1	0.4	101	2.2
	Carbamazepine	1.5	5.0	88	7.0				

	2-hydroxyCBZ	20.1	67.2	95	6.3				
	10.11-epoxyCBZ	22.2	74.1	99	5.5				
	Sertraline	5.8	19.4	16	3.4				
	Olanzapine	0.2	0.8	44	4.0				
	Fluoxetine	1.6	5.2	48	8.4				
	Lorazepam	1.2	4.0	101	1.5	0.4	1.2	116	0.5
	Citalopram	0.1	0.4	92	2.8				
	Norfluoxetine	0.6	2.0	25	5.7				
	Venlafaxine	0.4	1.5	92	1.4				
	Acridone	0.8	2.5	76	6.3				
	Alprazolam	0.8	2.5	100	7.6				
	Trazodone	0.2	0.6	59	5.4				
	Paroxetine	1.4	4.6	61	11.8				
Histamine H1 and H2 receptor antagonists	Ranitidine	0.1	0.3	26	7.7				
	Famotidine	0.1	0.2	33	8.0	0.01	0.03	32	4.5
	Cimetidine	0.1	0.3	30	5.1	0.01	0.04	21	2.0
	Desloratadine	0.1	0.5	23	3.0				
	Loratadine	1.2	4.1	103	11.4				
β - Blocking agents	Nadolol	0.3	0.9	76	3.0	0.1	0.2	59	0.9
	Propranolol	1.5	4.9	127	2.5				
	Atenolol	0.4	1.3	32	7.2	0.04	0.1	27	1.0
	Sotalol	0.8	2.7	39	10.9	0.02	0.1	23	4.8
	Carazolol	0.05	0.18	63	2.4				
	Metoprolol	0.2	0.8	80	3.4	0.05	0.156	44	5.9
Diuretic	Hydrochlorothiazide	0.1	0.3	84	0.8	0.1	0.2	102	3.0
	Furosemide	10.6	35.3	80	12.4	1.9	6.5	55	6.6
	Torasemide	1.0	3.3	81	11.1				
Antidiabetic	Glibenclamide	8.9	29.5	105	3.1	0.02	0.1	76	5.1

Antihypertensives	Losartan	2.7	9.1	61	12.2				
	Irbesartan	0.1	0.2	74	6.3				
	Amlodipine	0.6	1.9	18	5.7				
	Valsartan	0.4	1.2	95	2.1				
Antiplatelet agent	Clopidogrel	0.4	1.4	104	3.0				
Prostatic hyperplasia	Tamsulosin	0.7	2.2	101	3.0				
To treat asthma	Salbutamol	0.2	0.6	52	7.5				
Anticoagulant	Warfarin	0.2	0.5	103	2.1				
Antihelminitics	Thiabendazole	0.1	0.2	82	2.1				
	Levamisole	0.1	0.2	69	7.5				
	Albendazole	0.6	2.1	37	3.8				
Synthetic glucocorticoid	Dexamethasone	0.4	1.4	97	8.1				
Sedation and muscle relaxation	Xylazine	1.3	4.5	102	0.8				
Tranquilizer	Azaperol	0.3	0.8	70	8.1				
	Azaperone	0.8	2.7	83	3.9				
Calcium channel blockers	Dilitiazem	0.6	1.9	100	8.2				
	Verapamil	0.9	2.8	88	18.7				
	Norverapamil	0.2	0.7	99	4.3				
Antibiotics	Cefalexin	0.4	1.2	30	1.9				
	Trimethoprim	0.1	0.2	97	2.1	0.02	0.08	70	1.3
	Metronidazole - OH	8.4	28.2	33	8.0				
	Ronidazole	1.2	4.0	68	1.9				
	Erythromycin	1.5	5.1	103	4.3	0.6	2.0	72	5.9
	Sulfamethoxazole	0.2	0.8	98	5.0				
	Clarithromycin	0.9	3.1	74	2.5	0.2	0.57	99	0.8
	Tetracycline	20.0	66.5	67	9.1				
	Dimetridazole	6.5	21.6	44	12.4				
	Ofloxacin	1.1	3.7	41	4.9				

	Azithromycin	0.1	0.3	12	5.4				
	Ciprofloxacin	10.4	34.8	47	2.9				
	Metronidazole	0.8	2.6	33	4.0	0.1	0.4	20	1.5

Table 7S. Method performance parameters: recoveries (%), relative standard deviation (RSD% for n=3), limits of detection (LOD, water ngL^{-1}; sediment ngg^{-1}) and limits of quantification (LOQ, water ngL^{-1}; sediment ngg^{-1}) for personal care products.

Group	Analyte	Water				Sediment			
		LOD (ngL^{-1})	LOQ (ngL^{-1})	Recovery (%) (n=3)	RSD (%) (n=3)	LOD (ngg^{-1})	LOQ (ngg^{-1})	Recovery (%) (n=3)	RSD (%) (n=3)
Benzophenone UV filterss	BP1	0.4	1.3	n.a.	n.a.	0.05	0.2	78	10
	BP3	0.2	1	n.a.	n.a.	0.01	0.03	95	10
	DHMB	0.2	1	n.a.	n.a.	0.01	0.04	85	12
	4HB	0.4	1.4	n.a.	n.a.	0.01	0.04	114	18
	4DHB	1.2	3.8	n.a.	n.a.	0.01	0.05	104	15
Cinnamate UV filters	EHMC					0.03	0.1	103	19
Camphors UV filters	4MBC	0.3	1	n.a.	n.a.	0.02	0.07	44	6
Crylenes UV filters	OC					0.02	0.08	125	22
PABA derivatives UV filters	ODPABA	0.5	1.8	n.a.	n.a.	0.02	0.05	53	8
	Et-PABA	0.3	1	n.a.	n.a.	0.01	0.04	95	19
Benzotriazoles UV-blockers	BZT	0.5	1.5	n.a.	n.a.	0.01	0.02	113	15
	MeBZT	0.3	1	n.a.	n.a.	0.01	0.05	112	9
	DMeBT	0.4	1.5	n.a.	n.a.	0.01	0.03	89	15
	TBHPBT	0.5	1.6	n.a.	n.a.	0.01	0.04	98	14

	UV-P	0.3	1.1	n.a.	n.a.	0.01	0.03	89	14
	UV320					0.001	0.02	131	21
	UV326	1	3.2	n.a.	n.a.	0.01	0.02	93	19
	UV327	0.6	1.8	n.a.	n.a.	0.01	0.04	90	17
	UV328	0.3	1	n.a.	n.a.	0.01	0.02	131	25
	UV329	0.5	1.7	n.a.	n.a.	0.02	0.05	72	12
Fragrances	AHTN	0.3	1.1	n.a.	n.a.	0.01	0.02	n.a.	n.a.
	HHCB	0.5	1.7	n.a.	n.a.	0.01	0.04	n.a.	n.a.
	ADBI	0.3	1.1	n.a.	n.a.	0.01	0.02	n.a.	n.a.
Preservatives	MPB	4.1	15	n.a.	n.a.	0.02	0.06	n.a.	n.a.
	EPB	10.1	34.7	n.a.	n.a.	0.01	0.03	n.a.	n.a.

Notes: n.a. = not applicable

Table 8S. Concentrations and detection frequencies (D.F.) of individual compounds detected in water samples (pharmaceutically active compounds and personal care products; ngL^{-1}): A) Winter sampling campaign and B) Summer sampling campaign.

A) Winter sampling campaign

Pharmaceutically active compounds	ANALYTE / (STD ±)	WINTER CAMPAIGN / sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Analgesics/anti-inflammatories	Codeine	n.d.	38.7	40.04	<LOQ	<LOQ	9.67	10.75	15.6	30.52	28.1	20.92	24.2	75%
	(STD ±)		2.82	6.42			0.450	1.28	0.901	2.47	5.70	3.06	4.03	
	Oxycodone	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%
	(STD ±)													
	Piroxicam	n.d.	41.7	42.2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		2.63	8.09										
	Indomethacine	n.d.	21.7	28.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		3.73	8.55										
	Ketoprofen	125	152	193	<LOQ	<LOQ	<LOQ	127	117	131	128	104	143	75%
	(STD ±)	15.0	10.6	23.3				12.0	3.46	1.69	17.4	17.3	3.70	
	Acetaminophen	n.d.	114	226	8.11	27.9	13.5	8.33	1.38	2.51	2.15	3.59	2.97	92%
	(STD ±)		6.35	18.8	2.52	0.516	3.29	1.36	0.695	1.93	0.226	0.461	0.212	
	Ibuprofen	15.8	116	87	40.41	45.1	25.6	38.4	36.8	44.4	38.3	26.9	54.6	100%
	(STD ±)	1.58	22.6	16.9	8.79	7.64	2.07	6.62	10.5	4.35	9.84	6.51	2.46	
	Salicylic acid	13.4	15.1	47.8	19.6	20.48	11.1	4.57	6.27	13.9	8.70	9.37	14.5	100%
	(STD ±)	2.06	2.67	17.0	2.70	1.37	6.61	0.402	0.799	6.97	0.681	0.773	0.977	
	Diclofenac	27.7	569	675	120	119	44.5	61.7	117	154	148	109.1	130.2	100%
	(STD ±)	3.1	5.5	12.8	3.11	15.2	1.58	11.4	6.91	4.12	13.4	2.70	4.05	
	Propyphenazone	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%

	(STD ±)													
	Phenazone	n.d.	<LOQ	0.956	<LOQ	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	8%
	(STD ±)			0.149										
	Naproxen	<LOQ	73.1	55.7	29.7	41.0	22.5	32.6	32.8	45.6	40.66	43.2	51.4	92%
	(STD ±)		10.3	5.67	8.92	8.51	3.01	3.11	9.61	6.27	7.86	2.96	1.62	
Lipid regulators and cholesterol lowering statin drugs	Bezafibrate	n.d.	n.d.	n.d.	7.70	7.61	6.95	9.10	8.28	9.78	10.09	9.51	10.32	75%
	(STD ±)				0.973	1.45	0.707	1.91	1.35	1.58	0.874	1.05	1.31	
	Atorvastatin	n.d.	21.7	12.5	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	<LOQ	<LOQ	<LOQ	17%
	(STD ±)		5.09	2.68										
	Gemfibrozil	<LOQ	<LOQ	<LOQ	19.1	18.1	4.5	<LOQ	10.69	12.9	11.7	9.89	11.6	67%
	(STD ±)				3.20	5.12	1.33		1.03	1.85	0.925	2.47	3.30	
	Pravastatin	n.d.	40.89	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	8%
	(STD ±)		1.71											
Psychiatric drugs	Carbamazepine	<LOQ	137	128	36.3	33.9	25.8	28.2	77.2	92.7	98.4	85.1	96.9	92%
	(STD ±)		0.740	7.11	5.21	4.07	3.26	1.55	4.72	9.55	12.0	4.14	3.35	
	Lorazepam	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	0%
	(STD ±)													
	Citalopram	n.d.	93.0	88.1	<LOQ	n.d.	n.d.	n.d.	<LOQ	19.4	23.4	<LOQ	21.5	42%
	(STD ±)		0.273	3.53						0.904	5.78		4.03	
	Venlafaxine	<LOQ	197	191	17.4	12.4	4.69	5.29	36.3	43.3	41.3	37.01	40.35	92%
	(STD ±)		14.2	6.25	1.42	4.24	0.600	0.537	3.96	0.810	5.88	8.02	5.16	
	Acridone	<LOQ	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Trazodone	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Histamine H1 and H2 receptor antagonists	Ranitidine	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Loratidine	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%

	(STD ±)													
β - Blocking agents	Nadolol	n.d.	<LOQ	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Propranolol	n.d.	57.0	52.9	<LOQ	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	17%
	(STD ±)		11.3	3.31										
	Atenolol	n.d.	18.1	2.64	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		1.5	0.46										
	Sotalol	n.d.	3.69	3.29	14.5	15.7	15.5	20.60	31.4	44.9	49.4	39.0	44.6	92%
	(STD ±)		0.349	0.347	0.510	1.27	4.86	4.58	7.19	7.25	3.62	0.346	6.91	
	Metoprolol	n.d.	44.1	57.7	27.4	26.5	18.9	21.2	42.8	34.3	44.7	40.63	47.2	92%
	(STD ±)		7.67	4.21	2.98	3.67	2.58	2.21	7.90	3.71	4.13	3.23	4.63	
Diuretic	Hydrochlorothiazide	<LOQ	181	189.5	129	119.7	115	133	101.5	164	145	135	145	92%
	(STD ±)		11.5	9.23	14.6	17.5	3.19	5.38	5.77	3.18	6.45	11.5	12.5	
	Furosemide	n.d.	359	<LOQ	<LOQ	n.d.	n.d.	<LOQ	n.d.	<LOQ	n.d.	n.d.	n.d.	8%
	(STD ±)		15.4											
	Torasemide	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Antihypertensives	Losartan	n.d.	149	121	<LOQ	<LOQ	n.d.	<LOQ	13.7	11.9	12.3	12.6	13.03	58%
	(STD ±)		6.64	9.03					1.20	1.88	1.64	1.19	1.24	
	Irbesartan	<LOQ	149	128	77.3	54.4	24.7	37.5	80.11	93.8	95.4	85.5	97.8	92%
	(STD ±)		3.69	4.84	6.63	7.19	4.54	2.07	1.25	1.29	6.83	15.7	17.1	
	Valsartan	n.d.	297	237	197	131	219	281	292	344	326	302.2	330	92%
	(STD ±)		29.0	49.3	4.46	2.40	7.72	6.87	10.2	4.75	16.7	20.6	20.4	
Antiplatelet agent	Clopidogrel	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Prostatic hyperplasia	Tamsulosin	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	0%
	(STD ±)													

To treat asthma	Salbutamol	n.d.	<LOQ	<LOQ	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Anticoagulant	Warfarin	<LOQ	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	n.d.	<LOQ	0%
	(STD ±)													
Antihelminitics	Thiabendazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Levamisol	n.d.	6.04	9.44	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	5.38	<LOQ	<LOQ	<LOQ	25%
	(STD ±)		0.135	1.69						0.806				
	Albendazole	<LOQ	<LOQ	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Tranquilizer	Azaperone	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
Calcium channel blockers	Dilitiazem	n.d.	5.28	10.50	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	5.54	<LOQ	<LOQ	<LOQ	25%
	(STD ±)		0.835	1.70						0.0275				
	Verapamil	n.d.	16.5	20.81	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		2.38	1.53										
	Norverapamil	n.d.	65.5	62.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		2.9	3.5										
Antibiotics	Cefalexin	n.d.	17.1	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8%
	(STD ±)		5.50											
	Trimethoprim	<LOQ	176	196	29.8	16.9	9.58	7.75	16.0	25.3	26.2	19.9	40.64	92%
	(STD ±)		9.54	16.0	0.746	0.243	0.559	0.870	1.37	2.36	1.15	0.222	0.269	
	Metronidazole - OH	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Ronidazole	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%
	(STD ±)													
	Erythromycin	n.d.	91.9	70.29	25.5	12.7	7.37	8.72	<LOQ	10.48	<LOQ	<LOQ	10.27	67%
	(STD ±)		15.6	5.18	0.699	0.775	3.23	3.49		1.02			0.369	

	Sulfamethoxazole	<LOQ	106.7	98.1	23.7	27.5	28.9	25.8	34.6	39.4	44.4	38.9	45.1	92%
	(STD ±)		4.61	0.0203	1.11	2.70	1.73	1.17	3.18	0.283	1.09	1.71	3.71	
	Clarithromycin	n.d.	159	146	70.70	140.1	n.d.	n.d.	n.d.	43.6	n.d.	n.d.	n.d.	42%
	(STD ±)		14.0	10.5	0.947	18.6				7.50				
	Tetracycline	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Metronidazole	n.d.	171	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	8%
	(STD ±)		5.80											
Personal care products	ANALYTE / (STD ±)	WINTER CAMPAIGN / sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Benzophenone UV filters	BP1	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%
	(STD ±)													
	BP3	n.d.	12.5	14.3	< LOQ	< LOQ	13.1	< LOQ	< LOQ	< LOQ	1.61	n.d.	n.d.	33%
	(STD ±)													
	DHMB	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%
	(STD ±)													
Camphors UV filters	4MBC	n.d.	n.d.	n.d.	n.d.	n.d.	61.65	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8%
	(STD ±)													
PABA derivatives UV filters	ODPABA	33.2	50.7	116	38.6	38.9	748	39.3	34.03	36.97	37.3	36.3	35.4	100%
	(STD ±)													
	Et-PABA	n.d.	85.3	88.6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	< LOQ	n.d.	17%
	(STD ±)													
Benzotriazoles UV-blockers	BZT	n.d.	n.d.	< LOQ	n.d.	n.d.	n.d.	84.7	n.d.	n.d.	60.3	n.d.	22.05	25%
	(STD ±)													
	MeBZT	n.d.	11.1	11.9	9.41	4.73	1.54	17.7	6.76	24.6	16.6	10.3	8.59	92%
	(STD ±)													
	DMeBZT	n.d.	< LOQ	10.01	n.d.	3.02	< LOQ	16.7	3.90	14.1	11.6	4.96	4.46	67%
	(STD ±)													

	TBHPBT	n.d.	6.65	17.3	n.d.	n.d.	172	< LOQ	n.d.	3.61	n.d.	n.d.	n.d.	33%
	(STD ±)													
	UVP	n.d.	< LOQ	< LOQ	n.d.	n.d.	124	14.2	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)													
	UV328	< LOQ	52.7	154	< LOQ	< LOQ	669	94.8	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	33%
	(STD ±)													
	UV329	n.d.	66.3	139	n.d.	n.d.	553	136	n.d.	43.95	n.d.	n.d.	< LOQ	42%
	(STD ±)													
Fragrances	Celestolide	n.d.	n.d.	8.36	n.d.	n.d.	74.3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)													
Preservative	EPB	n.d.	70.9	77.9	171	84.8	< LOQ	98.2	n.d.	46.7	72.1	61.5	n.d.	67%
	(STD ±)													

Notes: <LOQ = values under limit of quantification; n.d. =not detected

B) Summer sampling campaign

Pharmaceutically active compounds	ANALYTE / (STD ±)	SUMMER CAMPAIGN/ sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Analgesics/anti-inflammatories	Codeine	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Oxycodone	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Piroxicam	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%
	(STD ±)													
	Indomethacine	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%
	(STD ±)													
	Ketoprofen	n.d.	n.d.	67.1	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	8%

	(STD ±)			6.59										
	Acetaminophen	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	9.72	8%
	(STD ±)												0.620	
	Ibuprofen	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Salicylic acid	42.5	60.7	113	47.4	57.6	44.7	24.3	42.99	26.9	244	26.98	190	100%
	(STD ±)	3.09	6.44	10.3	3.64	10.9	5.95	3.07	3.55	1.50	15.7	2.43	12.1	
	Diclofenac	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	0%
	(STD ±)													
	Propyphenazone	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	2.38	n.d.	8%
	(STD ±)											0.0932		
	Phenazone	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%
	(STD ±)													
	Naproxen	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
Lipid regulators and cholesterol lowering statin drugs	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.	0%
	(STD ±)													
	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.	0%
	(STD ±)													
	Gemfibrozil	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%
	(STD ±)													
	Pravastatin	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%
	(STD ±)													
Psychiatric drugs	Carbamazepine	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%
	(STD ±)													
	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.	0%
	(STD ±)													
	Citalopram	n.d.	1.02	n.d.	n.d.	1.65	n.d.	n.d.	<LOQ	n.d.	0.882	<LOQ	<LOQ	25%

	(STD ±)		0.119			0.581								
	Venlafaxine	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	2.28	1.60	2.08	2.24	2.11	42%
	(STD ±)								0.128	0.204	0.402	0.0321	0.0858	
	Acridone	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Trazodone	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%
	(STD ±)													
Histamine H1 and H2 receptor antagonists	Ranitidine	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%
	(STD ±)													
	Loratidine	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	0%
	(STD ±)													
β - Blocking agents	Nadolol	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%
	(STD ±)													
	Propranolol	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Atenolol	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Sotalol	n.d.	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	<LOQ	<LOQ	n.d.	n.d.	0%
	(STD ±)													
	Metoprolol	n.d.	1.79	1.39	n.d.	n.d.	n.d.	<LOQ	1.84	1.47	1.80	1.78	1.79	58%
	(STD ±)		0.0919	0.0525					0.124	0.145	0.171	0.0722	0.141	
Diuretic	Hydrochlorothiazide	n.d.	11.6	10.1	7.11	6.05	5.82	10.8	12.02	14.3	14.7	14.6	8.09	92%
	(STD ±)		0.318	0.213	0.537	0.209	0.0945	0.300	1.06	0.968	1.21	0.830	0.426	
	Furosemide	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	n.d.	<LOQ	n.d.	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Torasemide	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%
	(STD ±)													
Antihypertensives	Losartan	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%

	(STD ±)													
	Irbesartan	n.d.	0.597	0.741	3.72	2.68	1.004	1.54	3.83	3.78	7.64	5.37	4.25	92%
	(STD ±)		0.0527	0.0675	0.902	0.445	0.178	0.486	0.470	0.186	1.73	0.742	0.127	
	Valsartan	n.d.	n.d.	n.d.	3.39	2.27	1.85	2.92	<LOQ	3.54	<LOQ	<LOQ	<LOQ	42%
	(STD ±)				0.262	0.295	0.351	1.01		0.302				
Antiplatelet agent	Clopidogrel	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%
	(STD ±)													
Prostatic hyperplasia	Tamsulosin	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
To treat asthma	Salbutamol	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%
	(STD ±)													
Anticoagulant	Warfarin	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
Antihelminitics	Thiabendazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Levamisol	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	0%
	(STD ±)													
	Albendazole	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%
	(STD ±)													
Tranquilizer	Azaperone	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%
	(STD ±)													
Calcium channel blockers	Dilitiazem	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%
	(STD ±)													
	Verapamil	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%
	(STD ±)													
	Norverapamil	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
Antibiotics	Cefalexin	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%

	(STD ±)													
	Trimethoprim	n.d.	1.0096	0.955	<LOQ	<LOQ	0.815	<LOQ	<LOQ	1.17	<LOQ	<LOQ	<LOQ	33%
	(STD ±)		0.214	0.179			0.0601			0.358				
	Metronidazole - OH	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%
	(STD ±)													
	Ronidazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	0%
	(STD ±)													
	Erythromycin	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%
	(STD ±)													
	Sulfamethoxazole	n.d.	7.077	6.78	n.d.	n.d.	n.d.	1.13	0.853	1.038	1.502	1.54	2.0076	67%
	(STD ±)		0.0498	0.830				0.165	0.129	0.587	0.191	0.396	0.798	
	Clarithromycin	n.d.	17.96	9.104	<LOQ	<LOQ	n.d.	<LOQ	n.d.	<LOQ	n.d.	n.d.	n.d.	17%
	(STD ±)		0.803	1.80										
	Tetracycline	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	73.8	n.d.	n.d.	n.d.	8%
	(STD ±)									11.7				
	Metronidazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.83	8%
	(STD ±)												1.07	
Personal care products	ANALYTE / (STD ±)	SUMMER CAMPAIGN/ sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Benzophenone UV filters	BP1	n.d.	n.d.	n.d.	0.008	<LOQ	2.6	n.d.	n.d.	n.d.	n.d.	n.d.	2.03	25%
	(STD ±)													
	BP3	38.8	87.8	63.8	41.5	36.9	38.7	31.4	30.5	71.7	4950	243	5720	100%
	(STD ±)													
	DHMB	n.d.	22.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	18.8	n.d.	n.d.	n.d.	17%
	(STD ±)													
Camphors UV filters	4MBC	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%
	(STD ±)													
PABA derivatives UV filters	ODPABA	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%

	(STD ±)													
	Et-PABA	n.d.	6.22	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6.29	9.38	13.4	33%
	(STD ±)													
Benzotriazoles UV-blockers	BZT	1.07	n.d.	66.7	32.4	7.84	110	9.29	151	30.6	79.8	38.6	239	92%
	(STD ±)													
	MeBZT	3.27	n.d.	23.8	17.0	7.46	17.2	11.3	26.9	30.6	32.4	37.8	26.5	92%
	(STD ±)													
	DMeBZT	n.d.	n.d.	n.d.	32.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8%
	(STD ±)													
	TBHPBT	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%
	(STD ±)													
	UVP	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%
	(STD ±)													
	UV328	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%
	(STD ±)													
	UV329	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%
	(STD ±)													
Fragrances	Celestolide	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%
	(STD ±)													
Preservative	EPB	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%
	(STD ±)													

Notes: <LOQ = values under limit of quantification; n.d. =not detected

Table 9S. Concentrations and detection frequencies (D.F.) of individual compounds detected in sediment samples (both pharmaceutically active compounds and personal care products; ngg^{-1}): A) Winter sampling campaign and B) Summer sampling campaign.

A) Winter sampling campaign

Pharmaceutically active compounds	ANALYTE / (STD ±)	WINTER CAMPAIGN / sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Analgesics/anti-inflammatories	Acetaminophen	n.d.	1.34	1.85	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		0.269	0.257										
	Ibuprofen	n.d.	2.044	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	8%
	(STD ±)		0.274											
Lipid regulators and cholesterol lowering statin drugs	Gemfibrozil	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
β - Blocking agents	Sotalol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	<LOQ	n.d.	0%
	(STD ±)													
	Metoprolol	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	0.164	n.d.	8%
	(STD ±)											0.0355		
Diuretic	Hydrochlorothiazide	n.d.	0.371	0.451	n.d.	n.d.	<LOQ	n.d.	0.319	n.d.	<LOQ	0.484	n.d.	33%
	(STD ±)		0.154	0.0698					0.0287			0.110		
Antidiabetic	Glibenclamide	n.d.	2.799	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	15.3	n.d.	0.335	0.513	33%
	(STD ±)		0.206							3.68		0.233	0.344	
Antibiotics	Trimethoprim	n.d.	18.8	15.8	0.208	0.318	n.d.	n.d.	0.193	n.d.	0.0948	0.456	n.d.	58%
	(STD ±)		2.74	1.30	0.0366	0.0170			0.0489		0.00413	0.0375		
	Erythromycin	n.d.	<LOQ	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Clarithromycin	n.d.	58.1	44.1	4.31	2.57	1.11	1.45	1.05	n.d.	1.75	2.45	1.61	83%

	(STD ±)		9.42	4.17	0.901	0.838	0.130	0.277	0.461		0.506	0.410	0.382	
Personal care products	ANALYTE / (STD ±)	WINTER CAMPAIGN / sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Benzophenone UV filters	4HB	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%
	(STD ±)													
Camphors UV filters	4MBC	n.d.	n.d.	0.31	n.d.	n.d.	n.d.	0.91	0.92	< LOQ	2.48	1.48	0.55	50%
	(STD ±)													
Crylenes UV filters	OC	n.d.	3.92	7.60	0.68	n.d.	n.d.	2.50	3.16	n.d.	4.44	4.76	n.d.	58%
	(STD ±)													
PABA derivatives UV filters	ODPABA	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%
	(STD ±)													
	ETPABA	0.41	n.d.	n.d.	0.21	0.23	0.27	n.d.	0.42	0.17	1.39	n.d.	0.82	67%
	(STD ±)													

Notes: <LOQ = values under limit of quantification; n.d. =not detected

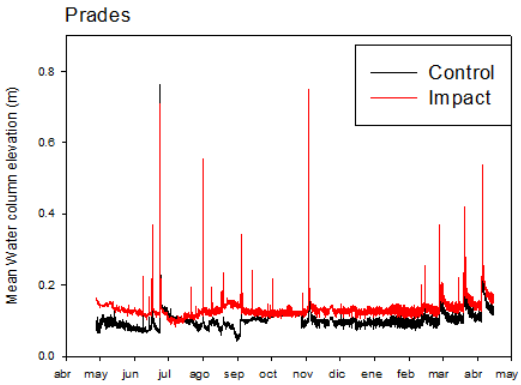
B) Summer sampling campaign

Pharmaceutically active compounds	ANALYTE / (STD ±)	SUMMER CAMPAIGN/ sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Analgesics/anti-inflammatories	Acetaminophen	n.d.	0.658	0.613	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)		0.0636	0.0344										
	Ibuprofen	n.d.	<LOQ	<LOQ	n.d.	n.d.	<LOQ	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	0%
	(STD ±)													
Lipid regulators and cholesterol lowering statin drugs	Gemfibrozil	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%
	(STD ±)													
β - Blocking agents	Sotalol	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0%
	(STD ±)													

	Metoprolol	n.d.	n.d.	n.d.	n.d.	n.d.	0.185	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8%
	(STD ±)						0.0721							
Diuretic	Hydrochlorothiazide	n.d.	<LOQ	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	0%
	(STD ±)													
Antidiabetic	Glibenclamide	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	0%
	(STD ±)													
Antibiotics	Trimethoprim	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%
	(STD ±)													
	Erythromycin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<LOQ	n.d.	n.d.	n.d.	0%
	(STD ±)													
	Clarithromycin	n.d.	1.56	1.71	<LOQ	0.667	0.751	<LOQ	<LOQ	<LOQ	n.d.	0.656	n.d.	42%
	(STD ±)		0.464	1.38		0.125	0.255					0.0157	0.382	
Personal care products	ANALYTE / (STD ±)	SUMMER CAMPAIGN/ sampling locations												D.F.
		1	2A	2B	3A	3B	4	5	6	7A	7B	7C	7D	
Benzophenone UV filters	4HB	26.1	n.d.	n.d.	39.5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	17%
	(STD ±)													
Camphors UV filters	4MBC	n.d.	n.d.	11.1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	8%
	(STD ±)													
Crylenes UV filters	OC	n.d.	n.d.	633	n.d.	n.d.	n.d.	n.d.	n.d.	87.7	n.d.	n.d.	n.d.	17%
	(STD ±)													
PABA derivatives UV filters	ODPABA	<LOQ	n.d.	<LOQ	<LOQ	<LOQ	<LOQ	n.d.	n.d.	n.d.	<LOQ	<LOQ	n.d.	0%
	(STD ±)													
	ETPABA	n.d.	n.d.	n.d.	1.4	n.d.	n.d.	n.d.	n.d.	<LOQ	<LOQ	n.d.	n.d.	8%
	(STD ±)													

Notes: <LOQ = values under limit of quantification; n.d. =not detected

SUPPLEMENTARY INFORMATION (CHAPTER 2)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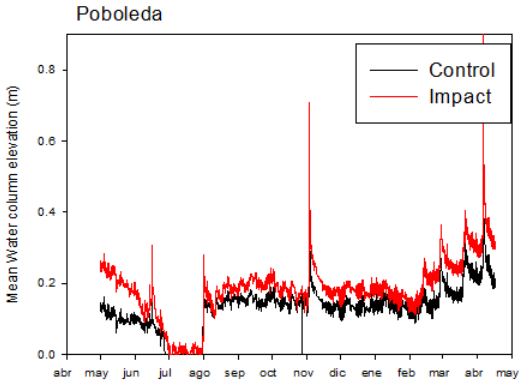
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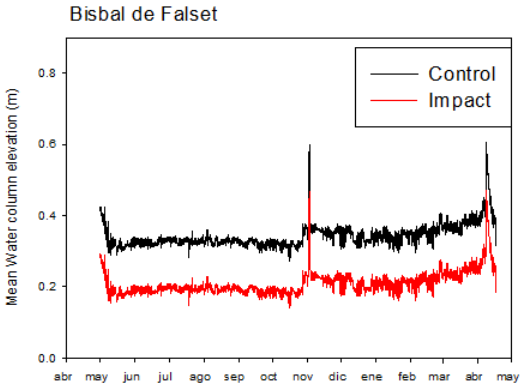
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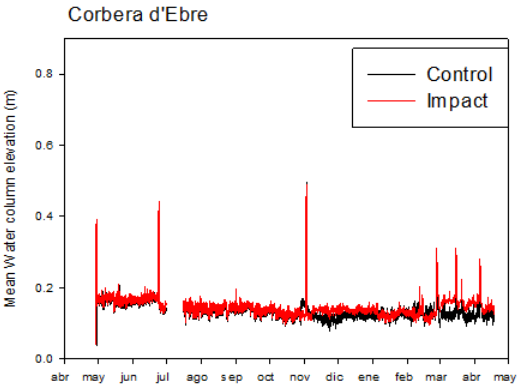
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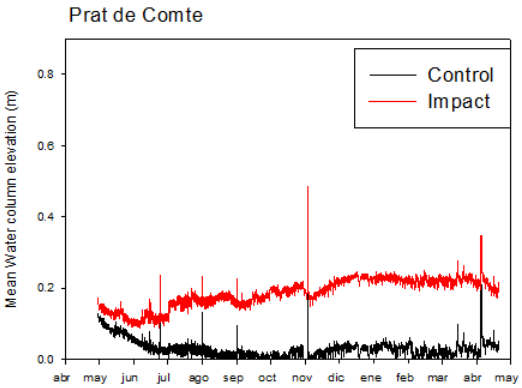
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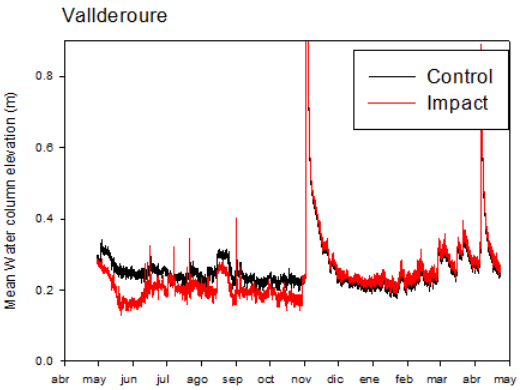
Vallderoure
Control
Impact
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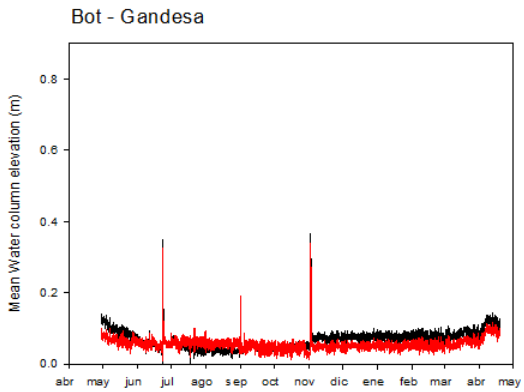
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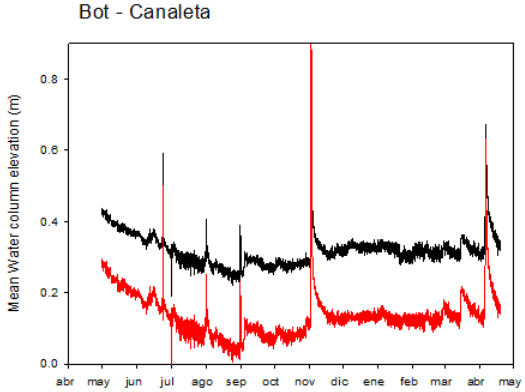
0.8
abr may jun jul ago sep oct nov dic ene feb mar abr may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Mean Water column elevation (m)
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0.4
0.6
0.8
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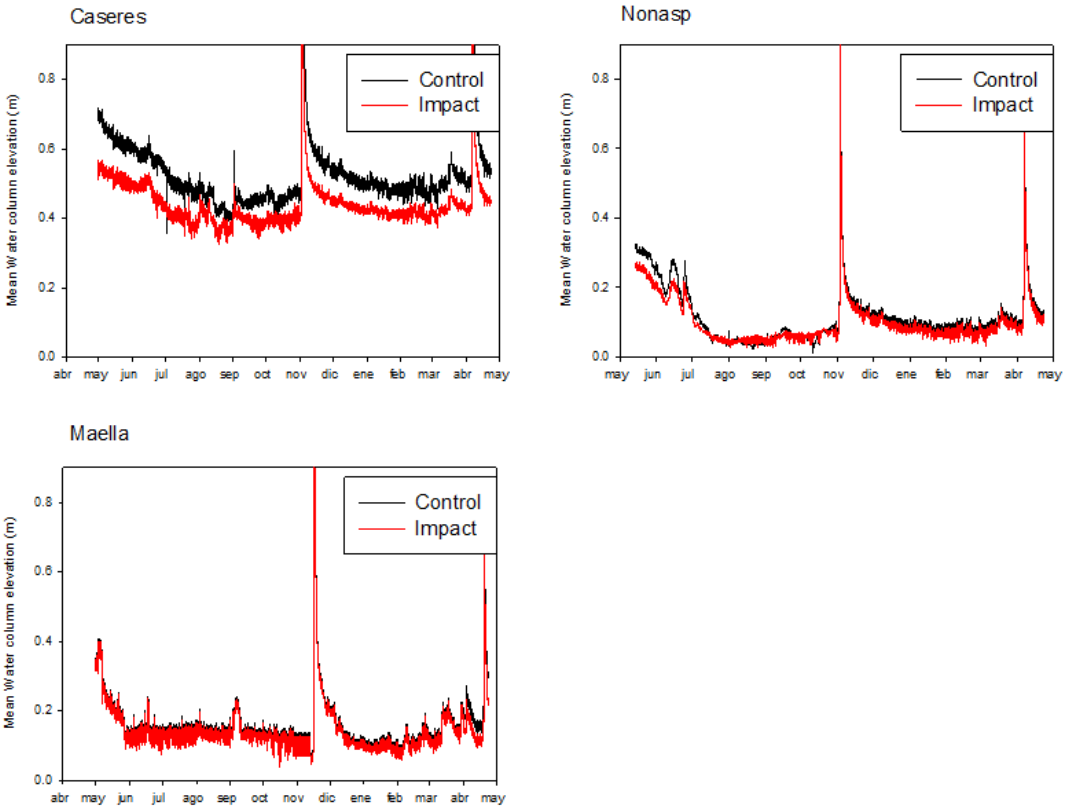

Figure 1S. Mean stream water level (m) at each studied site from May 2015 to May 2016.

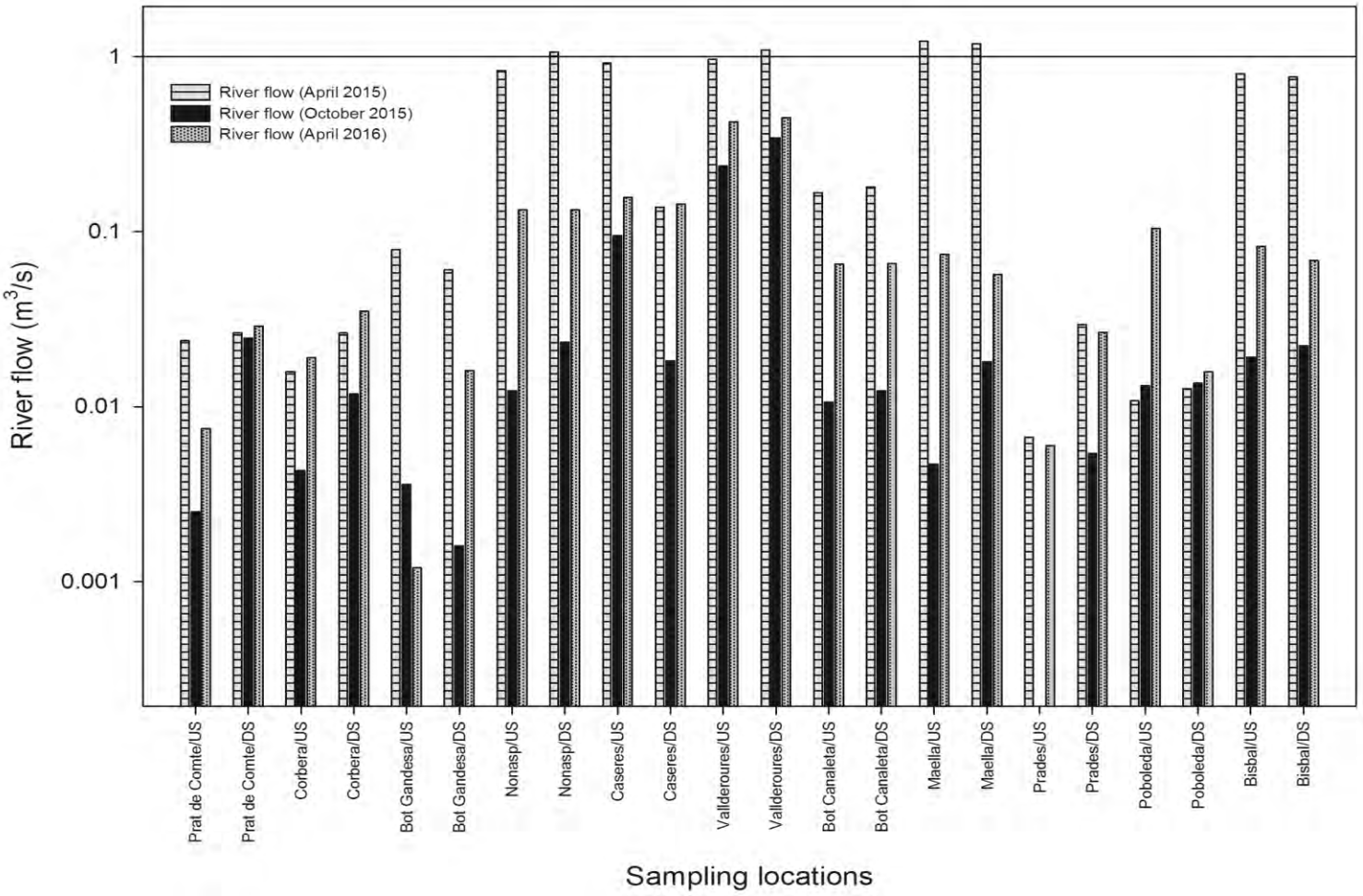

Figure 2S. River and stream flow (m^3s^{-1}) measured during the sampling day and at different control and impact sampling sites (respectively upstream and downstream from the wastewater discharge point) (campaigns April 2015, October 2015 and April 2016). Notice the logarithmic scale of the ordinate.

Table 1S. Water supply, average monthly WWTP outflows (April 2015, October 2015 and April 2016) and treatment processes for the main wastewater treatment plants in the associated sampling sites.

Sampling site	Prades	Poboleda	Bisbal de Falset
Potential water supply A.E.	3650	775	541
Average monthly discharge (April 2015)	2524 m3/d	63.6 m3/d	18.9 m3/d
Average monthly discharge (October 2015)	747 m3/d	49.1 m3/d	12.9 m3/d
Average monthly discharge (April 2016)	1198 m3/d	53.6 m3/d	17.6 m3/d
Treatment	Biological with nitrogen and phosphorus removal (activated sludge, centrifugal dehydration)	Biological with nitrogen removal (activated sludge)	Biological with nitrogen removal (activated sludge)

Note: Sources (http://aca-web.gencat.cat/aca/appmanager/aca)

Table 2S. Measured physicochemical properties of the river water and corresponding sampling sites coordinates.

Variable	Site	Reach	Apr-15	Oct-15	Apr-16	Variable	Apr-15	Oct-15	Apr-16
%days without flow	Bisbal	Control	0	0	0	Mean depth (m)	0.327	0.125	0.064
		Impact	0	0	0		0.4	0.388	0.075
	Bot Canaleta	Control	0	0	0		0.127	0.081	0.097
		Impact	0.07	0	0		0.17	0.132	0.209
	Bot Gandesa	Control	0	0	0		0.069	0.046	0.028
		Impact	0	0	0		0.066	0.045	0.052
	Caseres	Control	0	0	0		0.319	0.553	0.519
		Impact	0	0	0		0.12	0.326	0.551
	Corbera Ebre	Control	0	0	0		0.167	0.102	0.088
		Impact	0	0	0		0.28	0.073	0.081
	Maella	Control	0	0	0		0.383	0.068	0.065
		Impact	0	0	0		0.331	0.085	0.259
	Nonasp	Control	0	0	0		0.476	0.078	0.179
		Impact	0	0	0		0.265	0.057	0.179
	Poboleda	Control	7.63	0.07	0		0.19	0.272	0.285
		Impact	0.28	0	0		0.109	0.203	0.235
	Prades	Control	0	0	0		0.054	0.098	0.153
		Impact	0	0	0		0.068	0.12	0.13
	Prat de Comte	Control	0.07	16.53	4.65		0.074	0.045	0.04
		Impact	0	0	0		0.175	0.118	0.137
	Vallderoures	Control	0	0	0		0.462	0.311	0.18
		Impact	0	0	0		0.183	0.142	0.392
Mean velocity m/s	Bisbal	Control	0.4069	0.0561	0.3003	Width (m)	6	2.75	4.3
		Impact	0.213	0.119	0.4559		9	14.00	2
	Bot Canaleta	Control	0.2183	0.0483	0.1723		6	2.70	3.9
		Impact	0.1762	0.0929	0.2239		6	1.00	1.4
	Bot Gandesa	Control	0.6371	0.1568	0.0295		1.8	0.50	1.5
		Impact	0.5121	0.0892	0.2386		1.8	0.40	1.3
	Caseres	Control	0.3613	0.0123	0.0189		8	14.00	16
		Impact	0.3602	0.0046	0.0211		3.2	12.20	12.4
	Corbera Ebre	Control	0.0525	0.011	0.0599		1.8	3.80	3.6
		Impact	0.0587	0.1793	0.2711		1.6	0.90	1.6
	Maella	Control	0.2287	0.0362	0.1334		14	1.90	8.5
		Impact	0.1987	0.1067	0.0398		18	2.00	5.5
	Nonasp	Control	0.1456	0.1218	0.2478		12	1.30	3
		Impact	1.0314	0.1838	0.2478		3.9	2.25	3
	Poboleda	Control	0.0159	0.0114	0.0609		3.6	4.25	6
		Impact	0.0529	0.028	0.0292		2.2	2.40	2.3
	Prades	Control	0.0547	0.00033333	0.0247		2.25	1.20	1.6

		Impact	0.1737	0.0224	0.0785		2.5	2.00	2.6
	Prat de Comte	Control	0.0642	0.0374	0.0663		5	1.50	2.8
		Impact	0.0419	0.1045	0.1004		3.6	2.00	2.1
	Vallderoures	Control	0.2207	0.0764	0.3321		9.5	10.00	7.1
		Impact	0.4964	0.2203	0.1814		12	11.00	6.3
Tº	Bisbal	Control	14.5	15	15.8	pH	7.945	7.94	8.71
		Impact	14.5	15	12.8		8.04	7.7	8.32
	Bot Canaleta	Control	12.2	15.4	11.9		7.857	7.73	8.26
		Impact	10.8	14.3	12.5		7.849	7.65	8.22
	Bot Gandesa	Control	14.7	11.7	14.1		7.891	7.81	8.53
		Impact	15.5	13.2	13.5		7.971	7.64	8.28
	Caseres	Control	17.1	15.7	14.4		8.194	8.19	8.69
		Impact	16.1	15.5	13		8.2	7.79	8.61
	Corbera Ebre	Control	15.9	14	18		8.1	7.88	9.08
		Impact	16.5	14.6	17.4		8.034	7.94	8.85
	Maella	Control	14.7	16.6	17.8		8.02	8.04	8.81
		Impact	15.1	15	19.6		8.174	7.6	9.17
	Nonasp	Control	18.6	15.3	18.2		8.083	7.94	8.53
		Impact	18	16.5	15.5		8.068	7.31	8.54
	Poboleda	Control	13.6	15.4	14.5		7.497	7.84	8.72
		Impact	13.6	15.8	14		7.568	7.54	8.29
	Prades	Control	9.1	12.4	11.6		7.905	7.24	8.52
		Impact	9.8	13.9	11.3		7.388	7.25	7.96
	Prat de Comte	Control	13.3	14.3	14.3		8.105	7.97	8.37
		Impact	13.3	15.8	15.4		8.04	7.85	8.22
	Vallderoures	Control	15.7	15.4	13.6		8.183	7.99	8.92
		Impact	12.7	15.4	12.3		8.07	8.06	8.79
EC	Bisbal	Control	427	507	316	DO (mg/L)	9.23	7.66	9.53
		Impact	430	511	308.6		9.51	7.37	6.24
	Bot Canaleta	Control	905	1103	476		9.12	7.11	8.27
		Impact	981	1309	525		8.87	7.54	6.4
	Bot Gandesa	Control	1694	3020	1564		9.51	9.01	8.28
		Impact	1698	2690	1552		9.31	6.14	8.67
	Caseres	Control	707	835	374		10.23	n.a.	7.63
		Impact	767	827	373.1		9.41	n.a.	8.61
	Corbera Ebre	Control	2190	2540	1777		9.45	8.01	7.71
		Impact	2220	2280	1846		8.01	4.85	6.47
	Maella	Control	711	752	389.1		10.05	n.a.	6.79
		Impact	717	1155	424		10.66	n.a.	9.33
	Nonasp	Control	736	1327	522		9.5	n.a.	7.33
		Impact	740	1374	502		10.07	n.a.	7.08
	Poboleda	Control	762	891	520.2		8.39	7.25	7.86
		Impact	763	922	526.1		8.5	6.03	7.81
	Prades	Control	565	600	381.2		10.21	5.15	7.7

		Impact	514	610	354.5		8.46	3.82	5.81
	Prat de Comte	Control	1157	1623	1087		10.3	7.83	8.17
		Impact	1170	1554	1550		9.5	0.42	5.53
	Vallderoures	Control	531	454	287.8		10.12	9.21	8.21
		Impact	556	490	288.4		10.3	6.64	8.79
Coordinates (X UTM/Y UTM)	Bisbal	Control	31T 309185 4571869						
		Impact	31T 309208 4571701						
	Bot Canaleta	Control	31T 280024 4542234						
		Impact	31T 280441 4542333						
	Bot Gandesa	Control	31T 280701 4543139						
		Impact	31T 280639 4542977						
	Caseres	Control	31T 268872 4546528						
		Impact	31T 268314 4546983						
	Corbera Ebre	Control	31T 288636 4550464						
		Impact	31T 288726 4550520						
	Maella	Control	31T 259833 4555794						
		Impact	31T 260225 4557245						
	Nonasp	Control	31T 270356 4565074						
		Impact	31T 270119 4565576						
	Poboleda	Control	31T 318944 4566736						
		Impact	31T 318802 4566786						
	Prades	Control	31T 330728 4575556						
		Impact	31T 330654 4575771						
	Prat de Comte	Control	31T 282917 4539609						
		Impact	31T 282028 4539645						
	Vallderoures	Control	31T 259681 4528211						
		Impact	31T 259345 4528757						

Notes: n.a. = not applicable

2. Materials and Methods

2.3.2. Analytical method

Mobile phase and gradient elution in positive and negative electrospray ionization:
For the analysis in positive electrospray ionization, the optimized separation conditions were as follows: solvent (A) methanol, solvent (B) 10 mM formic acid/ammonium formate (pH 3.2) at a flow rate of 0.5 mL/min. The gradient elution was: initial conditions 5% A; 0–4.5 min, 5–95% A; 4.5–4.6 min, 100% A; 4.6–6.0 min, 100% A; from 6.0 to 6.1 return to initial conditions; 6.1–6.7, equilibration of the column. The analysis in negative electrospray ionization was performed by using acetonitrile (A) and 5 mM ammonium acetate/ammonia (pH = 8) (B) at a flow rate of 0.6 mL/min. The gradient elution was: 0–1.5 min, 0–60% A; 1.5–2.0 min, 100% A; 2.0–3.0 min, 100% A; 3.20 min return to initial conditions; 3.20–3.70 min, equilibration of the column.

Table 3S. Target compounds organized according to their therapeutic groups and the isotopically labeled internal standards assigned for their quantification.

Therapeutic groups	Analyte	Number	CAS number	Corresponding internal standard
Analgesics/anti-inflammatories (14)	Ketoprofen	1	22071-15-4	Ibuprofen-d3
	Naproxen	2	22204-53-1	Ibuprofen-d3
	Ibuprofen	3	15687-27-1	Ibuprofen-d3
	Indomethacine	4	53-86-1	Indomethacine-d4
	Acetaminophen	5	103-90-2	Acetaminophen-d4
	Salicylic acid	6	69-72-7	Acetaminophen-d4
	Diclofenac	7	15307-79-6	Ibuprofen-d3
	Phenazone	8	60-80-0	Phenazone-d3
	Propyphenazone	9	479-92-5	Phenazone-d3
	Piroxicam	10	36322-90-4	Meloxicam-d3
	Tenoxicam	11	59804-37-4	Meloxicam-d3
	Meloxicam	12	71125-39-8	Meloxicam-d3
	Oxycodone	13	124-90-3	Carbamazepine-d10
	Codeine	14	76-57-3	Carbamazepine-d10
Lipid regulators and cholesterol lowering statin drugs (5)	Bezafibrate	15	41859-67-0	Bezafibrate-d6
	Gemfibrozil	16	25812-30-0	Gemfibrozil-d6
	Pravastatin	17	81131-70-6	Gemfibrozil-d6
	Fluvastatin	18	93957-54-1	Gemfibrozil-d6
	Atorvastatin	19	134523-03-8	Gemfibrozil-d6
Psychiatric drugs (11)	Carbamazepine	20	298-46-4	Carbamazepine-d10
	Acridone[a]	21	578-95-0	Carbamazepine-d10
	Sertraline	22	79559-97-0	Fluoxetine-d5
	Citalopram	23	59729-32-7	Citalopram-d4
	Venlafaxine	24	99300-78-4	Venlafaxine-d6
	Trazodone	25	25332-39-2	Fluoxetine-d5
	Fluoxetine	26	56296-78-7	Fluoxetine-d5
	Norfluoxetine[a]	27	83891-03-6	Fluoxetine-d5
	Paroxetine	28	110429-35-1	Fluoxetine-d5
	Diazepam	29	439-14-5	Diazepam-d5
	Alprazolam	30	28981-97-7	Diazepam-d5
Histamine H1 and H2 receptor antagonists (5)	Loratadine	31	79794-75-5	Cimetidine-d3
	Desloratadine[a]	32	100643-71-8	Cimetidine-d3
	Ranitidine	33	66357-59-3	Cimetidine-d3
	Famotidine	34	76824-35-6	Cimetidine-d3
	Cimetidine	35	51481-61-9	Cimetidine-d3
β -Blocking agents (6)	Atenolol	36	29122-68-7	Atenolol-d7
	Sotalol	37	959-24-0	Atenolol-d7
	Propranolol	38	318-98-9	Atenolol-d7
	Metoprolol	39	56392-17-7	Atenolol-d7

	Nadolol	40	42200-33-9	Atenolol-d7
	Carazolol	41	57775-29-8	Atenolol-d7
Diuretic (1)	Furosemide	42	54-31-9	Furosemide-d5
Antidiabetic (1)	Glibenclamide	43	10238-21-8	Glibenclamide-d3
Antihypertensives (4)	Amlodipine	44	111470-99-6	Amlodipine-d4
	Losartan	45	124750-99-8	Valsartan-d8
	Irbesartan	46	138402-11-6	Valsartan-d8
	Valsartan	47	137862-53-4	Valsartan-d8
Antiplatelet agent (1)	Clopidogrel	48	135046-48-9	Gibenclamide-d3
Prostatic hyperplasia (1)	Tamsulosin	49	106463-17-6	Sulfamethoxazole-d4
To treat asthma (1)	Salbutamol	50	18559-94-9	Atenolol-d7
Anticoagulant (1)	Warfarin	51	81-81-2	Warfarin-d5
Antihelmintics (3)	Albendazole	52	54965-21-8	Ronidazole-d3
	Thiabendazole	53	148-79-8	Ronidazole-d3
	Levamisole	54	16595-80-5	Ronidazole-d3
Synthetic glucocorticoid (1)	Dexamethasone	55	50-02-2	Dexamethasone-d4
Sedation and muscle relaxation (1)	Xylazine	56	23076-35-9	Xylazine-d6
Antibiotics (9)	Erythromycin	57	59319-72-1	Erythromycin-N.N13C2
	Ofloxacin	58	82419-36-1	Ofloxacin-d3
	Sulfamethoxazole	59	723-46-6	Sulfamethoxazole-d4
	Trimethoprim	60	738-70-5	Sulfamethoxazole-d4
	Metronidazole	61	443-48-1	Ronidazole-d3
	Metronidazole-OH[a]	62	4812-40-2	Ronidazole-d3
	Dimetridazole	63	551-92-8	Ronidazole-d3
	Ronidazole	64	7681-76-7	Ronidazole-d3
	Cefalexin	65	15686-71-2	Sulfamethoxazole-d4
Calcium channel blockers (3)	Diltiazem	66	42399-41-7	Carbamazepine-d10
	Verapamil	67	152-11-4	Verapamil-d6
	Norverapamil[a]	68	67812-42-4	Verapamil-d6

[a]Metabolites

Table 4S. Target compounds and their optimized UPLC-QqLIT-MS/MS parameters by negative and positive ionization mode.

			Quantification		Confirmation		
Compounds	**Rt (min)**	**Precursor ion (m/z)**	**Q3**	**DP/CE/CXP**	**Q3**	**DP/CE/CXP**	**Ion ratio (±SD) n=5**
Compounds analyzed under PI mode							
Metronidazole-OH	0.96	187 $[M+H]^+$	126	51/23/18	123	51/19/16	1.2 (±0.05)
Sotalol	1.10	273 $[M+H]^+$	255	51/17/12	133	51/37/12	1.2 (±0.13)
Salbutamol	1.20	240 $[M+H]^+$	148	46/27/18	122	46/15/10	1.7 (±0.27)
Atenolol-d_7 (IS)	1.20	274 $[M+H]^+$	145	61/37/10	-	-	-
Ronidazole	1.22	201 $[M+H]^+$	140	46/17/14	-	-	-
Atenolol	1.22	267 $[M+H]^+$	145	91/27/18	190	91/37/14	1.3 (±0.03)
Ronidazole-d_3 (IS)	1.23	204 $[M+H]^+$	143	46/17/18	-	-	-
Metronidazole	1.24	172 $[M+H]^+$	128	56/35/10	82	56/21/10	1.1 (±0.09)
Ranitidine	1.24	315 $[M+H]^+$	176	66/25/24	130	66/35/12	1.1 (±0.07)
Famotidine	1.24	338 $[M+H]^+$	189	61/29/22	259	61/17/12	1.1 (±0.07)
Cimetidine-d_3 (IS)	1.26	256 $[M+H]^+$	95	81/39/14	-	-	-
Cimetidine	1.28	253 $[M+H]^+$	159	41/21/24	95	41/37/12	1.1 (±0.04)
Codeine	1.36	300 $[M+H]^+$	152	61/87/12	115	61/101/16	1.2 (±0.16)
Oxycodone	1.45	316 $[M+H]^+$	298	71/27/10	241	71/41/18	3.5 (±0.23)
Levamisol	1.46	205 $[M+H]^+$	178	41/31/14	91	41/59/14	1.1 (±0.02)
Dimetridazole	1.48	142 $[M+H]^+$	96	61/23/14	95	61/31/14	1.0 (±0.06)
Trimethoprim	1.73	291 $[M+H]^+$	230	91/33/12	261	91/35/10	1.4 (±0.05)
Cefalexin	1.74	348 $[M+H]^+$	158	31/15/24	106	31/43/12	1.7 (±0.17)
Nadolol	1.88	310 $[M+H]^+$	254	81/25/12	201	81/31/16	2.3 (±0.13)
Ofloxacin-d_3 (IS)	1.90	365 $[M+H]^+$	321	96/27/12	-	-	-
Ofloxacin	1.90	362 $[M+H]^+$	318	86/27/12	261	86/39/12	1.2 (±0.12)
Sulfamethoxazole-d_4 (IS)	1.96	258 $[M+H]^+$	160	101/23/18	-	-	-
Sulfamethoxazole	1.98	254 $[M+H]^+$	92	81/37/12	156	81/23/12	1.1 (±0.03)
Phenazone-d_3 (IS)	2.04	192 $[M+H]^+$	59	41/51/8	-	-	-
Phenazone	2.05	189 $[M+H]^+$	77	76/57/10	56	76/53/10	1.2 (±0.07)
Sulfadoxine-d_3 (surrogate)	2.06	314 $[M+H]^+$	156	51/25/12	-	-	-
Xylazine-d_6 (IS)	2.10	227 $[M+H]^+$	90	61/33/14	-	-	-
Xylazine	2.11	221 $[M+H]^+$	90	66/31/10	77	66/83/12	1.4 (±0.09)
Metoprolol	2.20	268 $[M+H]^+$	133	86/35/12	121	111/33/18	1.3 (±0.04)
Thiabendazole	2.33	202 $[M+H]^+$	175	76/37/28	131	76/45/10	1.1 (±0.05)
Tamsulosin	2.45	409 $[M+H]^+$	228	86/33/16	200	86/45/32	1.2 (±0.04)
Sulfadimethoxine-d_6 (surrogate)	2.49	317 $[M+H]^+$	162	61/33/8	-	-	-
Carazolol	2.52	299 $[M+H]^+$	116	66/27/14	222	66/29/10	2.4 (±0.21)
Trazodone	2.63	372 $[M+H]^+$	176	86/35/14	148	86/35/14	1.8 (±0.05)
Venlafaxine-d_6 (IS)	2.74	284 $[M+H]^+$	64	96/61/10	-	-	-
Venlafaxine	2.75	278 $[M+H]^+$	58	66/55/10	260	66/17/12	1.5 (±0.45)
Propranolol	2.86	260 $[M+H]^+$	116	101/25/12	183	76/25/24	1.3 (±0.05)
Citalopram-d_4 (IS)	2.89	329 $[M+H]^+$	113	21/35/14	-	-	-
Citalopram	2.90	325 $[M+H]^+$	109	56/35/16	262	56/27/12	1.4 (±0.06)

Norfluoxetine	2.93	296 $[M+H]^+$	134	61/11/12	-	-	-
Acridone	3.00	196 $[M+H]^+$	166	141/61/14	167	141/47/16	1.1 (±0.03)
Verapamil-d_6(IS)	3.12	461 $[M+H]^+$	165	66/37/22	-	-	-
Norverapamil	3.12	441 $[M+H]^+$	165	101/35/10	150	101/57/12	3.1 (±0.46)
Verapamil	3.13	455 $[M+H]^+$	165	116/37/14	77	116/129/12	2.2 (±0.20)
Diltiazem	3.13	415 $[M+H]^+$	178	91/35/10	109	91/35/10	26.2 (±6.94)
Carbamazepine-d_{10} (IS)	3.16	247 $[M+H]^+$	204	46/31/32	-	-	-
Desloratadine	3.16	311 $[M+H]^+$	259	61/31/12	258	61/53/18	1.1 (±0.03)
Carbamazepine	3.19	237$[M+H]^+$	194	61/29/28	193	61/49/14	1.3 (±0.26)
Propyphenazone	3.20	231 $[M+H]^+$	189	151/31/8	56	151/61/8	1.4 (±0.15)
Amlodipine-d_4 (IS)	3.25	413 $[M+H]^+$	238	61/17/36	-	-	-
Paroxetine	3.26	330 $[M+H]^+$	192	106/29/26	123	101/35/10	2.7 (±0.21)
Erythromycin	3.39	734 $[M+H]^+$	576	116/27/22	158	116/39/14	1.00 (±0.06)
Erythromycin-N,N$^{13}C_2$ (IS)	3.40	736 $[M+H]^+$	578	76/29/24	-	-	-
Alprazolam	3.43	309 $[M+H]^+$	281	86/37/42	205	76/53/20	1.2 (±0.03)
Fluoxetine-d_5 (IS)	3.46	315 $[M+H]^+$	44	76/53/8	-	-	1.7 (±0.08)
Fluoxetine	3.47	310 $[M+H]^+$	44	61/61/8	148	61/13/12	7.3 (±0.35)
Amlodipine	3.53	409 $[M+H]^+$	238	41/15/12	294	41/15/12	1.7 (±0.07)
Sertraline	3.60	307 $[M+H]^+$	159	66/41/16	276	66/17/44	2.1(±0.16)
Albendazole	3.70	266 $[M+H]^+$	234	46/29/12	191	46/47/18	1.4 (±0.09)
Diazepam-d_5 (IS)	3.75	290 $[M+H]^+$	198	101/47/26	-	-	-
Diazepam	3.76	285 $[M+H]^+$	193	86/45/16	154	86/37/20	1.7 (±0.08)
Warfarin-d_5 (IS)	3.78	314 $[M+H]^+$	163	56/21/28	-	-	-
Warfarin	3.79	309 $[M+H]^+$	163	66/21/18	251	66/27/12	1.0 (±0.02)
Glibenclamide	4.00	494 $[M+H]^+$	369	116/21/14	169	116/51/26	1.2 (±0.02)
Glibenclamide-d_3 (IS)	4.00	497 $[M+H]^+$	372	131/23/12	-	-	-
Clopidogrel	4.34	322 $[M+H]^+$	212	81/23/10	184	81/31/16	1.3 (±0.06)
Loratadine	4.37	383 $[M+H]^+$	337	86/33/12	267	86/45/10	2.4 (±0.05)
Compounds analyzed under NI mode							
			Quantification		**Confirmation**		
Compounds	**Rt (min)**	**Precursor ion (m/z)**	**Q3**	**DP/CE/CXP**	**Q3**	**DP/CE/CXP**	**Ion ratio (±SD) n=5**
Acetaminophen-d_4(IS)	0.55	154 $[M-H]^-$	111	-60/ -26/-7	-	-	-
Acetaminophen	0.56	150 $[M-H]^-$	107	-45/ -24/ -15	-	-	-
Salicylic acid	0.59	137 $[M-H]^-$	93	-50/ -20/ -1	-	-	-
Tenoxicam	0.90	336 $[M-H]^-$	152	-60/ -26/ -7	272	-60/ -16/ -11	1.2 (±0.13)
Piroxicam	0.93	330 $[M-H]^-$	146	-65/ -26/ -9	266	-65/ -18/ -11	1.2 (±0.07)
Valsartan	0.95	434 $[M-H]^-$	179	-105/ -30/ -9	350	-105/ -26/ -13	1.1 (±0.17)
Valsartan-d_8(IS)	0.95	442 $[M-H]^-$	179	-105/ -32/-11	-	-	-
Naproxen	0.96	229 $[M-H]^-$	170	-30/ -20/ -9	185	-30/ -10/ -7	1.1 (±0.47)
Furosemide-d_5(IS)	0.96	334 $[M-H]^-$	290	-40/ -22/-11	-	-	-
Furosemide	0.97	329 $[M-H]^-$	285	-95/ -20/ -11	205	-95/ -30/ -15	1.4 (±0.03)
Ketoprofen-d_3(Surrogate)	1.00	256 $[M-H]^-$	212	-30/ -10/ -11	-	-	-
Pravastatin	1.00	423 $[M-H]^-$	321	-100/ -20/ -13	303	-100/ -24/ -13	1.5 (±0.03)
Ketoprofen	1.01	253 $[M-H]^-$	209	-30/ -12/ -11	-	-	-
Meloxicam-d_3(IS)	1.05	353 $[M-H]^-$	289	-60/ -20/ -13	-	-	-
Meloxicam	1.06	350 $[M-H]^-$	146	-65/ -28/ -7	286	-65/ -18/ -15	1.2 (±0.07)
Bezafibrate-d_6(IS)	1.09	366 $[M-H]^-$	280	-15/ -24/ -11	-	-	-

Bezafibrate	1.10	360 $[M-H]^-$	274	-55/ -38/ -9	154	-55/ -22/ -11	2.2 (±0.10)
Losartan	1.17	421 $[M-H]^-$	127	-105/ -40/ -5	179	-105/ -34/ -11	1.2 (±0.04)
Ibuprofen-d_3(IS)	1.17	208 $[M-H]^-$	164	-55/ -10/ -7	-	-	-
Ibuprofen	1.18	205 $[M-H]^-$	161	-60/ -10/ -13	-	-	-
Diclofenac	1.25	294 $[M-H]^-$	250	-65/ -16/ -11	214	-65/ -28/ -11	16.5 (±5.05)
Indomethacine-d_4(IS)	1.26	360 $[M-H]^-$	316	-35/ -14/-13	-	-	-
Indomethacine	1.27	356 $[M-H]^-$	312	-60/ -12/ -13	297	-60/ -26/ -13	3.4 (±0.04)
Irbesartan	1.28	427 $[M-H]^-$	193	-95/ -34/ -11	399	-95/ -26/ -19	7.1 (±0.59)
Dexamethasone	1.35	451 $[M-H]^-$	361	-85/ -24/ -15	307	-85/ -46/ -13	3.8 (±0.17)
Dexamethasone-d_4(IS)	1.34	395 $[M-H]^-$	363	-5/ -18/ -15	-	-	-
Gemfibrozil-d_6(IS)	1.39	255 $[M-H]^-$	121	-75/ -22/ -15	-	-	-
Gemfibrozil	1.40	249 $[M-H]^-$	121	-65/ -24/ -7	127	-65/ -14/ -9	13.7 (±0.65)
Fluvastatin	1.46	410 $[M-H]^-$	210	-90/ -40/ -9	348	-90/ -22/ -9	1.5 (±0.04)
Atorvastatin	1.52	557 $[M-H]^-$	278	-65/ -42/ -5	397	-65/ -62/ -7	1.2 (±0.03)

DP: Declustering Potential; CE: Collision Energy; CXP: Collision cell exit potential.

Table 5S. Method performance parameters for the pharmaceutically active compounds: recoveries (%), relative standard deviation (RSD% for n=3), limits of detection (LOD; ngL^{-1}) limits of quantification (LOQ; ngL^{-1}).

Therapeutic groups	Analyte	LOD (ngL^{-1})	LOQ (ngL^{-1})	% Recoveries (n=3)	% RSD (n=3)
Analgesics/anti-inflammatories (14)	Ketoprofen	8.9	29.7	118	5.20
	Naproxen	0.8	2.5	91	4.05
	Ibuprofen	4.24	14.1	99	5.53
	Indomethacine	1.2	4.0	90	3.16
	Acetaminophen	1.1	3.8	112	5.47
	Salicylic acid	0.9	3.1	103	3.53
	Diclofenac	2.00	6.66	92	5.48
	Phenazone	0.3	1.1	93	4.79
	Propyphenazone	0.2	0.8	102	5.56
	Piroxicam	0.3	1.1	88	5.08
	Tenoxicam	0.4	1.3	88	2.77
	Meloxicam	0.2	0.7	93	3.42
	Oxycodone	4.1	13.5	97	2.37
	Codeine	0.1	0.3	102	2.13
Lipid regulators and cholesterol lowering statin drugs (5)	Bezafibrate	0.2	0.8	98	5.26
	Gemfibrozil	0.11	0.36	88	4.01
	Pravastatin	0.8	2.7	85	3.61
	Fluvastatin	0.19	0.62	82	5.63
	Atorvastatin	0.03	0.1	85	4.70
Psychiatric drugs (11)	Carbamazepine	0.2	0.68	104	2.51
	Acridone[a]	0.06	0.2	82	3.30
	Sertraline	3.3	10.9	98	1.88
	Citalopram	0.1	0.5	84	3.89

	Venlafaxine	0.06	0.20	100	1.28
	Trazodone	0.2	0.7	89	3.12
	Fluoxetine	0.3	0.9	45	7.42
	Norfluoxetine[a]	0.1	0.5	67	2.62
	Paroxetine	0.4	1.2	52	2.08
	Diazepam	0.2	0.6	97	4.32
	Alprazolam	1.11	3.68	103	3.94
Histamine H1 and H2 receptor antagonists (5)	Loratadine	0.04	0.14	46	6.20
	Desloratadine[a]	0.05	0.16	33	15.1
	Ranitidine	0.03	0.09	44	4.68
	Famotidine	0.07	0.24	52	1.97
	Cimetidine	0.01	0.022	77	3.81
β -Blocking agents (6)	Atenolol	0.03	0.1	62	0.56
	Sotalol	0.1	0.4	49	3.91
	Propranolol	0.08	0.26	60	1.14
	Metoprolol	0.16	0.55	66	3.80
	Nadolol	0.02	0.1	86	8.34
	Carazolol	0.03	0.11	50	5.21
Diuretic (1)	Furosemide	13.8	46.1	89	5.98
Antidiabetic (1)	Glibenclamide	0.2	0.8	97	8.10
Antihypertensives (4)	Amlodipine	0.6	2.1	100	8.78
	Losartan	0.8	2.6	79	8.27
	Irbesartan	0.05	0.2	59	4.38
	Valsartan	0.4	1.36	91	4.37
Antiplatelet agent (1)	Clopidogrel	0.04	0.1	61	4.96
Prostatic hyperplasia (1)	Tamsulosin	0.04	0.1	64	4.81
To treat asthma (1)	Salbutamol	0.03	0.1	73	3.44
Anticoagulant (1)	Warfarin	0.22	0.74	94	3.01
Antihelmintics (3)	Albendazole	0.02	0.1	38	2.84
	Thiabendazole	0.03	0.09	84	4.33
	Levamisole	0.02	0.06	85	6.09
Synthetic glucocorticoid (1)	Dexamethasone	0.5	1.7	106	9.03
Sedation and muscle relaxation (1)	Xylazine	0.2	0.6	79	4.33
Antibiotics (9)	Erythromycin	3.09	10.3	78	3.15
	Ofloxacin	0.9	3.2	60	4.28
	Sulfamethoxazole	0.2	0.8	91	3.88
	Trimethoprim	0.11	0.37	75	4.58
	Metronidazole	0.7	2.2	77	2.61
	Metronidazole-OH[a]	0.57	1.89	15	1.40

	Dimetridazole	2.45	8.16	97	5.21
	Ronidazole	0.2	0.8	87	4.89
	Cefalexin	0.5	1.8	23	1.09
Calcium channel blockers (3)	Diltiazem	0.04	0.1	92	3.11
	Verapamil	0.1	0.3	88	6.31
	Norverapamil[a]	0.1	0.5	99	5.98

[a]Metabolites

Table 6S. Results summary of the multivariate analysis of variance (MANOVA): A) Multivariate Tests and B) Tests of Between-Subjects Effects

A)

Effect		F	Hypothesis df	Error df	Sig.	Observed Power[d]
Intercept	Pillai's Trace	262.181[b]	9.000	13.000	.000	1.000
	Wilks' Lambda	262.181[b]	9.000	13.000	.000	1.000
	Hotelling's Trace	262.181[b]	9.000	13.000	.000	1.000
	Roy's Largest Root	262.181[b]	9.000	13.000	.000	1.000
Treatment	**Pillai's Trace**	**18.943[b]**	**9.000**	**13.000**	**.000**	**1.000**
	Wilks' Lambda	18.943[b]	9.000	13.000	.000	1.000
	Hotelling's Trace	18.943[b]	9.000	13.000	.000	1.000
	Roy's Largest Root	18.943[b]	9.000	13.000	.000	1.000
Effluent dominance	**Pillai's Trace**	**22.822[b]**	**9.000**	**13.000**	**.000**	**1.000**
	Wilks' Lambda	22.822[b]	9.000	13.000	.000	1.000
	Hotelling's Trace	22.822[b]	9.000	13.000	.000	1.000
	Roy's Largest Root	22.822[b]	9.000	13.000	.000	1.000
Season	**Pillai's Trace**	**2.164**	**18.000**	**28.000**	**.032**	**.900**
	Wilks' Lambda	2.351[b]	18.000	26.000	.023	.919
	Hotelling's Trace	2.516	18.000	24.000	.018	.929
	Roy's Largest Root	4.796[c]	9.000	14.000	.005	.961
Treatment * Effluent dominance	Pillai's Trace	1.483[b]	9.000	13.000	.251	.441
	Wilks' Lambda	1.483[b]	9.000	13.000	.251	.441
	Hotelling's Trace	1.483[b]	9.000	13.000	.251	.441
	Roy's Largest Root	1.483[b]	9.000	13.000	.251	.441
Treatment * Season	Pillai's Trace	.811	18.000	28.000	.673	.405
	Wilks' Lambda	.977[b]	18.000	26.000	.511	.479
	Hotelling's Trace	1.128	18.000	24.000	.385	.537

	Roy's Largest Root	2.521[c]	9.000	14.000	.059	.721
Effluent dominance * Season	Pillai's Trace	.753	18.000	28.000	.732	.374
	Wilks' Lambda	.818[b]	18.000	26.000	.666	.397
	Hotelling's Trace	.870	18.000	24.000	.614	.411
	Roy's Largest Root	1.835[c]	9.000	14.000	.149	.557
Treatment * Effluent dominance * Season	Pillai's Trace	.506	18.000	28.000	.932	.246
	Wilks' Lambda	.477[b]	18.000	26.000	.946	.226
	Hotelling's Trace	.448	18.000	24.000	.958	.206
	Roy's Largest Root	.705[c]	9.000	14.000	.696	.218

Notre: Significant Pillai's Trace values for ($p < 0.05$) are marked in **bold**.

Design: Intercept + Treatment + ED + Season + Treatment * ED + Treatment * Season + ED * Season + Treatment * ED * Season

b. Exact statistic

c. The statistic is an upper bound on F that yields a lower bound on the significance level.

d. Computed using alpha = .05

B)

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Observed Power[j]
Corrected Model	Analgesics	16.243[a]	11	1.477	20.989	.000	1.000
	Lipid	15.450[b]	11	1.405	10.596	.000	1.000
	Psychiatric	9.451[c]	11	.859	2.678	.025	.866
	Histamine	7.806[d]	11	.710	4.194	.002	.981
	Blocking	12.908[e]	11	1.173	7.744	.000	1.000
	Diuretic	9.560[f]	11	.869	1.499	.204	.573
	Antihypertensives	10.910[g]	11	.992	2.743	.023	.876
	Antihelmintics	2.810[h]	11	.255	1.609	.168	.610
	Antibiotics	8.692[i]	11	.790	1.845	.110	.684
Intercept	Analgesics	150.652	1	150.652	2141.445	.000	1.000
	Lipid	38.235	1	38.235	288.448	.000	1.000
	Psychiatric	28.993	1	28.993	90.369	.000	1.000
	Histamine	2.834	1	2.834	16.750	.001	.974
	Blocking	23.121	1	23.121	152.580	.000	1.000
	Diuretic	47.669	1	47.669	82.224	.000	1.000
	Antihypertensives	60.150	1	60.150	166.354	.000	1.000
	Antihelmintics	3.681	1	3.681	23.186	.000	.996
	Antibiotics	16.260	1	16.260	37.969	.000	1.000
Treatment	**Analgesics**	**11.567**	**1**	**11.567**	**164.419**	**.000**	**1.000**
	Lipid	**2.143**	**1**	**2.143**	**16.169**	**.001**	**.969**
	Psychiatric	.851	1	.851	2.652	.118	.343
	Histamine	1.297	1	1.297	7.667	.012	.752
	Blocking	.428	1	.428	2.825	.108	.361
	Diuretic	.147	1	.147	.254	.619	.077

	Antihypertensives	1.831	1	1.831	5.064	.035	.574
	Antihelmintics	.022	1	.022	.141	.711	.065
	Antibiotics	.238	1	.238	.556	.464	.110
Effluent dominance	**Analgesics**	**4.459**	**1**	**4.459**	**63.385**	**.000**	**1.000**
	Lipid	**12.159**	**1**	**12.159**	**91.728**	**.000**	**1.000**
	Psychiatric	1.979	1	1.979	6.170	.022	.659
	Histamine	1.348	1	1.348	7.969	.010	.768
	Blocking	**8.990**	**1**	**8.990**	**59.326**	**.000**	**1.000**
	Diuretic	4.878	1	4.878	8.415	.009	.790
	Antihypertensives	**3.663**	**1**	**3.663**	**10.130**	**.004**	**.859**
	Antihelmintics	**1.730**	**1**	**1.730**	**10.895**	**.003**	**.882**
	Antibiotics	1.061	1	1.061	2.478	.130	.324
Season	Analgesics	.678	2	.339	4.820	.019	.736
	Lipid	.565	2	.282	2.129	.144	.387
	Psychiatric	1.842	2	.921	2.871	.079	.501
	Histamine	1.170	2	.585	3.457	.050	.583
	Blocking	1.227	2	.613	4.047	.033	.656
	Diuretic	1.703	2	.851	1.468	.253	.278
	Antihypertensives	1.419	2	.710	1.963	.165	.360
	Antihelmintics	.219	2	.109	.689	.513	.150
	Antibiotics	3.509	2	1.755	4.097	.031	.661
Treatment * Effluent dominance	Analgesics	.088	1	.088	1.258	.275	.188
	Lipid	.742	1	.742	5.600	.028	.617
	Psychiatric	.876	1	.876	2.729	.113	.351
	Histamine	.409	1	.409	2.416	.135	.317
	Blocking	.417	1	.417	2.749	.112	.353
	Diuretic	.099	1	.099	.171	.683	.068
	Antihypertensives	.386	1	.386	1.068	.313	.167
	Antihelmintics	.060	1	.060	.376	.546	.090
	Antibiotics	.002	1	.002	.006	.940	.051
Treatment * Season	Analgesics	.077	2	.038	.546	.587	.128
	Lipid	.503	2	.252	1.898	.175	.349
	Psychiatric	.099	2	.049	.154	.858	.071
	Histamine	.643	2	.322	1.901	.174	.350
	Blocking	.408	2	.204	1.345	.282	.258
	Diuretic	.581	2	.291	.501	.613	.121
	Antihypertensives	1.851	2	.926	2.560	.101	.455
	Antihelmintics	.057	2	.029	.181	.836	.074
	Antibiotics	.357	2	.178	.417	.665	.109
Effluent dominance * Season	Analgesics	.128	2	.064	.912	.417	.186
	Lipid	.087	2	.043	.327	.725	.095
	Psychiatric	.048	2	.024	.075	.928	.060
	Histamine	.389	2	.195	1.150	.336	.225
	Blocking	.137	2	.068	.450	.643	.114
	Diuretic	.473	2	.236	.408	.670	.107
	Antihypertensives	.978	2	.489	1.352	.280	.259

	Antihelmintics	.020	2	.010	.062	.940	.058
	Antibiotics	.559	2	.279	.652	.531	.145
Treatment * Effluent dominance * Season	Analgesics	.071	2	.036	.508	.609	.122
	Lipid	.041	2	.021	.155	.857	.071
	Psychiatric	.767	2	.383	1.195	.322	.233
	Histamine	.258	2	.129	.763	.479	.162
	Blocking	.013	2	.007	.043	.958	.056
	Diuretic	.959	2	.479	.827	.451	.172
	Antihypertensives	.061	2	.031	.085	.919	.061
	Antihelmintics	.185	2	.093	.583	.567	.134
	Antibiotics	.000	2	.000	.000	1.000	.050
Error	Analgesics	1.477	21	.070			
	Lipid	2.784	21	.133			
	Psychiatric	6.737	21	.321			
	Histamine	3.553	21	.169			
	Blocking	3.182	21	.152			
	Diuretic	12.175	21	.580			
	Antihypertensives	7.593	21	.362			
	Antihelmintics	3.334	21	.159			
	Antibiotics	8.993	21	.428			
Total	Analgesics	274.261	33				
	Lipid	82.245	33				
	Psychiatric	57.265	33				
	Histamine	16.519	33				
	Blocking	51.168	33				
	Diuretic	89.528	33				
	Antihypertensives	116.348	33				
	Antihelmintics	11.370	33				
	Antibiotics	41.724	33				
Corrected Total	Analgesics	17.720	32				
	Lipid	18.233	32				
	Psychiatric	16.189	32				
	Histamine	11.359	32				
	Blocking	16.090	32				
	Diuretic	21.735	32				
	Antihypertensives	18.503	32				
	Antihelmintics	6.144	32				
	Antibiotics	17.685	32				

Notre: Significant values with applied Bonferroni correction ($p < 0.0055$) are marked in **bold** and underlined.

a. R Squared = .917 (Adjusted R Squared = .873)

b. R Squared = .847 (Adjusted R Squared = .767)

c. R Squared = .584 (Adjusted R Squared = .366)

d. R Squared = .687 (Adjusted R Squared = .523)

e. R Squared = .802 (Adjusted R Squared = .699)

f. R Squared = .440 (Adjusted R Squared = .146)

g. R Squared = .590 (Adjusted R Squared = .375)

h. R Squared = .457 (Adjusted R Squared = .173)

i. R Squared = .492 (Adjusted R Squared = .225)

j. Computed using alpha = .05

Table 7S. Detection frequencies, minimum, maximum and individual concentrations of PhACs (ngL^{-1}) in three sampling campaigns in: A) untreated wastewater and B) treated wastewater.

A)

Analyte	1st SAMPLING CAMPAIGN (April 2015)									2nd SAMPLING CAMPAIGN (October 2015)									3rd SAMPLING CAMPAIGN (April 2016)									MIN	MAX	AVE. D.F.
	SAMPLING LOCATIONS								D.F.	SAMPLING LOCATIONS								D.F.	SAMPLING LOCATIONS								D.F.			
	1	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8				
Analgesics/anti-inflammatories																														
Ketoprofen	577	<LOQ	580	384	2034	240	<LOQ	744	75%	933	53.5	1383	727	166	523	226	104	100 %	374	<LOQ	540	465	687	566	149	209	88%	<LOQ	2034	88%
STD ±	51.9		13.6	30.9	164	0.175		8.30		0.296	1.14	64.2	14.2	4.50	2.38	7.05	0.432		1.93		20.2	2.69	11.5	8.03	13.3	9.01				
Naproxen	3721	<LOQ	2267	2118	3156	4363	246	3926	88%	4392	2259	4181	2909	3259	6439	259	3877	100 %	4410	228	2447	2248	3394	5502	85.8	3376	100 %	<LOQ	6439	96%
STD ±	189		81.6	57.4	90.7	222	11.8	532		569	308	188	180	407	416	1.32	246		122	2.31	270	90.4	325	102	2.24	192				
Ibuprofen	5472	3267	3102	2293	3448	9536	906	3051	100 %	8777	3427	5757	3625	8658	13572	1287	3033	100 %	6302	3427	2714	2427	4618	11394	1060	3931	100 %	906	13572	100 %
STD ±	584	382	317	182	323	359	22.7	506		611	265	271	285	320	1863	52.0	153		472	247	117	158	281	1325	7.41	82.9				
Indomethacine	331	N.D.	N.D.	281	N.D.	79.4	N.D.	N.D.	38%	72.1	46.1	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	25%	172	336	N.D.	271	N.D.	N.D.	N.D.	N.D.	38%	N.D.	336	33%
STD ±	16.2			5.11		1.85				1.10	1.87								0.921	11.3		1.75								
Acetaminophen	7779	5040	10491	6403	12082	14378	8336	6156	100 %	9351	7592	6436	7406	15468	17546	6540	8126	100 %	7534	5247	11752	6663	12950	15828	7504	6332	100 %	5040	17546	100 %
STD ±	343	291	115	242	92.2	907	403	951		324	468	104	357	155	1481	438	166		419	269	212	275	131	1442	189	186				
Salicylic acid	2218	282	978	714	503	111	2318	221	100 %	3335	559	282	755	3297	558	1502	2662	100 %	2824	140	763	331	4659	174	2670	169	100 %	111	4659	100 %
STD ±	114	3.40	10.6	48.6	4.66	29.03	329	1.13		559	29.8	13.4	94.6	60.1	10.98	211	198		86.5	2.31	49.2	49.01	28.8	6.92	134	10.05				
Diclofenac	853	<LOQ	488	958	282	405	386	437	88%	600	135	280	792	249	286	309	297	100 %	445	96.3	278	938	124	181	209	353	100 %	<LOQ	958	96%
STD ±	52.2		11.4	11.7	22.6	9.19	16.7	24.3		1.14	4.46	3.25	59.6	9.20	8.75	12.3	15.8		20.4	1.45	18.9	36.5	5.07	8.62	12.2	34.9				
Phenazone	50.2	<LOQ	27.4	203	325	10.9	26.5	N.D.	75%	80.9	9.76	40.98	18.7	108	4.53	N.D.	N.D.	75%	9.57	20.1	29.2	7.21	9.46	9.52	13.3	5.01	100 %	N.D.	325	83%
STD ±	7.03		1.62	13.4	7.55	0.108	1.51			2.27	0.681	2.32	1.05	11.2	0.214				0.297	4.63	1.02	0.356	0.647	0.504	1.74	0.114				
Propyphenazone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Piroxicam	4.33	N.D.	2.63	3.89	3.29	3.63	<LOQ	8.71	75%	41.1	16.3	90.2	7.57	13.8	31.4	254	39.8	100 %	N.D.	102	48.99	21.8	N.D.	52.6	<LOQ	36.8	63%	N.D.	254	79%
STD ±	0.0777		0.188	0.168	0.136	0.363		1.41		4.07	1.22	6.18	1.01	0.178	3.87	5.99	4.38			2.65	2.31	0.851		11.01		2.49				
Tenoxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%

STD ±																													
Meloxicam	N.D.	N.D.	13.3	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	N.D.	<LOQ	N.D.	N.D.	5.29	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	3.90	N.D.	N.D.	13%	N.D.	13.3	13%
STD ±			0.932												0.478									0.137						
Oxycodone	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	130	N.D.	<LOQ	N.D.	N.D.	N.D.	13%	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	130	4%
STD ±												6.92																		
Codeine	243	N.D.	336	281	331	117	34.2	495	88%	740	6.53	324	539	41.3	239	71.1	92.6	100 %	959	23.1	436	139	11.4	508	3.79	99.5	100 %	N.D.	959	96%
STD ±	19.8		15.8	24.1	45.6	8.06	5.05	11.4		13.4	0.377	10.2	1.80	3.41	11.3	8.24	10.1		23.7	0.452	14.5	7.21	0.152	11.3	0.233	9.02				
Lipid regulators and cholesterol lowering statin drugs																														
Bezafibrate	N.D.	N.D.	N.D.	655	N.D.	N.D.	N.D.	N.D.	13%	N.D.	N.D.	2.95	925	N.D.	27.9	10.3	N.D.	50%	N.D.	N.D.	N.D.	473	N.D.	N.D.	N.D.	N.D.	13%	N.D.	925	25%
STD ±				30.2								0.0767	36.02		1.43	1.09						25.02								
Gemfibrozil	1093	1665	1002	653	1436	135	536	1388	100 %	2512	1535	1785	71.6	704	745	771	1908	100 %	2031	1693	261	254	143	903	126	2380	100 %	71.6	2512	100 %
STD ±	34.8	360	60.9	42.3	69.5	6.38	5.56	112		29.7	67.3	54.1	2.07	4.998	7.11	72.9	142		95.6	22.5	5.59	11.8	5.87	76.9	6.59	118				
Pravastatin	163	N.D.	854	934	429	529	291	808	88%	224	13.99	910	1451	63.4	300	723	377	100 %	326	148	1525	1516	115	511	515	346	100 %	N.D.	1525	96%
STD ±	4.10		8.69	48.5	27.01	26.3	14.7	98.2		5.27	1.95	31.9	54.5	5.61	1.99	10.7	2.51		13.3	0.906	32.1	19.2	5.001	0.462	17.9	2.35				
Fluvastatin	N.D.	N.D.	N.D.	N.D.	4.22	7.13	N.D.	N.D.	25%	N.D.	N.D.	7.86	N.D.	3.79	23.3	10.7	N.D.	50%	N.D.	N.D.	N.D.	N.D.	21.5	43.2	N.D.	N.D.	25%	N.D.	43.2	33%
STD ±					0.305	0.539						0.594		0.351	2.21	0.944							0.931	2.04						
Atorvastatin	222	N.D.	247	343	431	88.2	46.8	675	88%	105	30.9	457	168	38.2	82.7	179	107	100 %	21.5	140	220	104	22.8	121	15.6	197	100 %	N.D.	675	96%
STD ±	6.41		10.4	35.6	14.9	5.10	2.36	21.2		5.61	0.631	8.69	7.89	5.97	4.32	0.177	3.98		1.81	1.90	8.95	8.11	2.62	10.96	0.411	14.6				
Psychiatric drugs																														
Carbamazepine	8.48	<LOQ	104	118	130	54.0	233	31.95	88%	115	8.24	552	187	14.8	234	544	54.4	100 %	109	24.9	129	380	120	303	903	72.3	100 %	<LOQ	903	96%
STD ±	1.33		9.11	8.94	14.7	2.10	5.42	1.76		3.60	0.277	13.04	8.76	1.11	6.11	4.38	2.29		4.89	3.67	0.761	6.82	5.42	17.5	17.97	3.43				
Acridone[a]	N.D.	N.D.	4.67	N.D.	30.6	N.D.	8.32	10.3	50%	2.80	1.29	18.2	<LOQ	<LOQ	<LOQ	8.27	1.63	63%	N.D.	N.D.	N.D.	N.D.	N.D.	17.4	20.05	N.D.	25%	N.D.	30.6	46%
STD ±			0.183		6.99		0.984	1.38		0.115	0.129	2.62				0.238	0.0902							1.30	1.55					
Sertraline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Citalopram	561	11.02	134	N.D.	587	69.02	20.3	123	88%	355	63.7	152	89.1	320	69.7	912	203	100 %	145	50.2	236	136	95.4	184	64.5	293	100 %	N.D.	912	96%
STD ±	23.99	1.45	15.5		24.5	2.02	0.176	18.6		0.454	2.17	3.46	2.79	6.91	2.73	6.77	9.05		12.03	0.667	4.84	18.7	3.74	6.33	2.48	19.9				
Venlafaxine	247	1.92	153	163	307	46.4	247	21.3	100 %	111	207	143	91.5	285	38.1	330	95.2	100 %	225	106	157	438	651	79.7	835	183	100 %	1.92	835	100 %
STD ±	5.44	0.101	7.04	4.39	20.5	0.801	0.640	2.95		0.427	6.38	7.80	3.94	7.18	0.186	2.22	1.13		6.11	4.67	5.95	9.92	3.06	3.10	7.02	3.23				
Trazodone	N.D.	N.D.	188	88.7	152	21.2	8.78	N.D.	63%	4.34	2.84	75.5	20.5	52.2	60.3	269	1.45	100 %	N.D.	N.D.	61.7	87.7	58.3	185	11.8	N.D.	63%	N.D.	269	75%
STD ±			10.2	3.33	17.5	0.485	0.301			0.23	1.74	5.59	4.23	4.94	4.30	11.6	0.301				0.640	5.40	2.19	0.678	0.308					

										4																			
Fluoxetine	<LOQ	N.D.	14.8	<LOQ	42.3	N.D.	12.1	N.D.	38%	16.4	N.D.	N.D.	N.D.	8.63	N.D.	N.D.	N.D.	25%	10.7	N.D.	28.6	N.D.	<LOQ	12.7	51.1	N.D.	50%	N.D.	51.1	38%
STD ±			1.36		11.4		0.551			1.76				0.170					0.552		1.26			1.11	3.29					
Norfluoxetine[a]	<LOQ	<LOQ	<LOQ	<LOQ	38.3	<LOQ	12.6	<LOQ	25%	16.1	N.D.	N.D.	N.D.	10.7	N.D.	N.D.	N.D.	25%	23.2	N.D.	46.2	N.D.	N.D.	N.D.	69.8	N.D.	38%	N.D.	69.8	29%
STD ±					10.4		0.0611			0.585				0.526					2.20		1.32				5.30					
Paroxetine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Diazepam	<LOQ	<LOQ	7.41	N.D.	N.D.	N.D.	<LOQ	N.D.	13%	8.95	3.28	11.2	6.83	9.51	N.D.	3.84	2.04	88%	9.64	43.7	9.03	N.D.	2.21	N.D.	11.4	7.38	75%	N.D.	43.7	58%
STD ±			0.709							0.752	0.0580	0.882	0.486	0.767		0.171	0.192		0.806	2.57	0.671		0.126		0.0749	0.235				
Alprazolam	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	16.97	<LOQ	<LOQ	7.09	N.D.	N.D.	N.D.	<LOQ	25%	9.82	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	13%	N.D.	17	13%
STD ±										1.001			0.697						0.565											
Histamine H1 and H2 receptor antagonists																														
Loratadine	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	0%	N.D.	N.D.	3.85	N.D.	N.D.	N.D.	2.55	N.D.	25%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	3.85	8%
STD ±												0.0949				0.437														
Desloratadine[a]	N.D.	N.D.	2.44	N.D.	11.4	N.D.	N.D.	N.D.	25%	N.D.	3.85	2.87	N.D.	N.D.	N.D.	N.D.	N.D.	25%	N.D.	N.D.	13.3	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	13.3	21%
STD ±			0.789		0.00843						0.479	0.138									0.298									
Ranitidine	2.10	N.D.	87.7	50.5	20.5	5.66	90.6	497	88%	27.01	1.27	187	379	55.1	83.6	551	25.1	100%	8.75	7.20	64.8	854	4.74	89.5	81.7	<LOQ	88%	N.D.	854	92%
STD ±	0.135		4.29	2.88	7.10	0.601	13.6	67.03		0.816	0.147	3.42	1.81	4.83	2.02	22.4	1.54		0.168	0.644	4.94	26.2	0.346	2.62	3.11					
Famotidine	N.D.	N.D.	22.4	N.D.	N.D.	72.1	N.D.	N.D.	25%	N.D.	N.D.	97.4	N.D.	N.D.	52.4	N.D.	N.D.	25%	N.D.	N.D.	11.6	N.D.	N.D.	31.1	N.D.	N.D.	25%	N.D.	97.4	25%
STD ±			1.30			7.63						3.94			3.97						4.37			3.04						
Cimetidine	N.D.	N.D.	N.D.	0.820	N.D.	46.1	N.D.	N.D.	25%	N.D.	N.D.	1.24	2.62	N.D.	8.15	N.D.	N.D.	38%	<LOQ	N.D.	<LOQ	N.D.	<LOQ	19.6	<LOQ	N.D.	13%	N.D.	46.1	25%
STD ±				0.0281		3.75						0.0468	0.329		0.310									1.04						
β -Blocking agents																														
Atenolol	990	23.6	67.01	1947	935	195	88.5	2134	100%	587	1071	74.4	1837	221	461	463	2165	100%	759	60.6	555	828	572	700	161	2808	100%	23.6	2808	100%
STD ±	26.8	2.004	0.694	40.1	6.55	24.6	2.11	66.9		1.61	22.2	7.002	19.1	1.53	9.67	14.3	263		5.30	4.12	3.17	87.6	2.85	34.1	4.12	81.9				
Sotalol	N.D.	N.D.	N.D.	N.D.	2.14	N.D.	N.D.	N.D.	13%	N.D.	N.D.	1.18	N.D.	N.D.	290	N.D.	N.D.	25%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	4.74	13%	N.D.	290	17%
STD ±					0.205							0.707			9.74											0.330				
Propranolol	8.67	<LOQ	N.D.	N.D.	5.42	4.31	N.D.	N.D.	38%	10.5	N.D.	N.D.	30.7	1.61	8.48	N.D.	N.D.	50%	8.84	N.D.	N.D.	101	N.D.	N.D.	13.8	N.D.	38%	N.D.	101	42%
STD ±	1.29				0.592	0.0451				0.506			4.49	0.102	0.282				0.0331			7.08			0.443					
Metoprolol	18.2	N.D.	28.2	152	75.6	23.7	18.5	N.D.	75%	19.9	N.D.	37.3	171	15.2	9.33	33.1	6.73	88%	N.D.	N.D.	N.D.	780	21.6	N.D.	N.D.	N.D.	25%	N.D.	780	63%
STD ±	4.18		0.995	0.0968	7.71	1.79	0.337			1.30		1.37	2.49	1.32	0.373	0.637	0.810					53.96	1.02							
Nadolol	N.D.	N.D.	N.D.	N.D.	54.3	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	23.01	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	207	N.D.	N.D.	N.D.	13%	N.D.	207	13%
STD ±					16.1									1.85									12.8							
Carazolol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														

Diuretic																													
Furosemide	2459	<LOQ	1420	2656	1642	2100	<LOQ	3491	75%	2233	<LOQ	3140	3347	1471	2768	866	2331	88%	2875	<LOQ	4430	2286	614	2355	<LOQ	3510	75%	<LOQ	4430	79%
STD ±	25.9		203	202	128	80.4		445		5.07		208	394	10.3	323	107	88.01		43.999		237	237	122	66.3		316				
Antidiabetic																													
Glibenclamide	42.3	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	23.6	N.D.	N.D.	N.D.	N.D.	N.D.	5.35	5.23	38%	<LOQ	12.3	N.D.	N.D.	<LOQ	N.D.	21.7	<LOQ	25%	N.D.	42.3	25%
STD ±	0.849									0.693						0.433	0.255			0.969					1.01					
Antihypertensives																													
Amlodipine	100	N.D.	N.D.	N.D.	207	58.4	353	N.D.	50%	28.2	N.D.	14.1	15.6	33.9	26.6	158	68.3	88%	23.5	N.D.	55.9	92.7	26.7	47.9	57.5	123	88%	N.D.	353	75%
STD ±	17.2				9.28	8.95	18.8			0.237		2.36	2.69	3.03	0.511	11.5	2.13		1.27		3.20	12.7	0.0884	3.45	2.47	5.30				
Losartan	25.9	967	128	770	251	45.6	878	<LOQ	88%	377	455	374	934	61.5	152	1026	22.5	100%	234	975	177	1013	178	251	1096	59.3	100%	<LOQ	1096	96%
STD ±	2.14	27.4	1.51	17.5	16.2	0.885	59.4			13.7	2.11	14.99	8.17	3.43	8.38	55.6	2.55		15.03	29.8	0.648	18.4	2.16	12.4	32.04	2.66				
Irbesartan	N.D.	321	286	236	697	185	1.92	1.47	88%	39.3	91.4	913	265	922	356	3.78	25.4	100%	49.2	329	979	502	566	243	N.D.	11.8	88%	N.D.	979	92%
STD ±		21.1	11.7	46.6	18.2	12.6	0.119	0.0854		1.71	2.08	36.8	14.6	21.3	7.88	0.343	1.19		2.87	43.5	23.8	6.93	6.09	2.59		0.815				
Valsartan	2521	521	4833	1242	4107	868	15.9	932	100%	3174	699	4208	918	4149	947	216	505	100%	3804	69.9	2550	1284	4732	661	366	662	100%	15.9	4833	100%
STD ±	189	31.2	238	114	379	24.9	4.81	215		36.4	7.73	617	46.5	147	13.6	3.54	3.43		6.94	6.92	73.3	42.8	606	28.3	13.61	10.4				
Antiplatelet agent																													
Clopidogrel	0.442	0.805	3.87	0.858	9.84	1.27	N.D.	N.D.	75%	2.06	6.51	4.36	1.12	2.61	2.95	N.D.	1.54	88%	N.D.	139	N.D.	N.D.	2.28	N.D.	N.D.	3.38	38%	N.D.	139	67%
STD ±	0.0751	0.0602	0.189	0.0599	3.58	0.163				0.147	0.220	0.365	0.152	0.302	0.329		0.0704			4.62			0.141			0.269				
Prostatic hyperplasia																													
Tamsulosin	10.5	<LOQ	2.50	N.D.	12.5	1.45	2.03	3.96	75%	8.75	7.22	5.11	3.49	5.55	2.65	N.D.	3.30	88%	2.64	N.D.	8.30	14.3	6.25	6.37	5.26	8.21	88%	N.D.	14.3	83%
STD ±	1.05		0.293		3.81	0.162	0.236	1.91		0.132	0.209	0.300	0.438	0.277	0.167		0.0598		0.123		0.487	2.04	0.255	0.0277	0.219	0.403				
To treat asthma																													
Salbutamol	N.D.	N.D.	2.25	9.21	9.60	N.D.	N.D.	5.36	50%	2.45	4.19	15.2	8.01	1.40	9.96	47.1	N.D.	88%	<LOQ	N.D.	3.32	8.92	<LOQ	<LOQ	<LOQ	6.20	38%	N.D.	47.1	58%
STD ±			0.0740	0.324	2.74			0.455		0.141	0.170	1.83	0.634	0.0659	0.368	2.75					0.00997	0.474				0.165				
Anticoagulant																													
Warfarin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Antihelmintics																													
Albendazole	N.D.	N.D.	N.D.	2.87	N.D.	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	2.87	4%
STD ±				0.720																										
Thiabendazole	1.56	0.995	2.63	0.846	1.06	1.99	1.16	<LOQ	88%	<LOQ	<LOQ	39.7	<LOQ	<LOQ	N.D.	N.D.	N.D.	13%	N.D.	<LOQ	N.D.	8.36	<LOQ	<LOQ	17.4	N.D.	25%	N.D.	39.7	42%
STD ±	0.196	0.193	0.3001	0.0166	0.361	0.373	0.158					1.80										0.228			0.998					
Levamisole	14.9	N.D.	66.02	342	391	44.2	8.24	7.52	88%	22.3	0.768	44.5	153	140	93.9	7.33	10.4	100%	18.5	N.D.	41.9	422	338	17.6	20.6	N.D.	75%	N.D.	422	88%

STD ±	0.414		8.81	25.2	15.8	0.626	0.972	1.97		0.762	0.0324	2.36	9.69	9.53	3.17	0.351	0.633		1.07		1.79	21.1	14.9	1.80	1.22					
Synthetic glucocorticoid																														
Dexamethasone	N.D.	N.D.	14.3	<LOQ	N.D.	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	14.3	4%
STD ±			0.446																											
Sedation and muscle relaxation																														
Xylazine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Antibiotics																														
Erythromycin	53.5	N.D.	N.D.	N.D.	170	N.D.	N.D.	N.D.	25%	360	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	69.01	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	360	17%
STD ±	0.669				11.3					7.40									12.8											
Ofloxacin	52.6	<LOQ	520	<LOQ	118	645	<LOQ	37.6	63%	546	238	1158	102	38.9	172	1133	19.8	100 %	296	285	1138	116	88.3	326	174	205	100 %	<LOQ	1158	88%
STD ±	15.2		85.1		16.3	32.2		2.64		5.23	23.9	67.5	1.48	5.01	4.42	120	1.91		11.03	8.83	161	7.14	4.13	20.1	4.28	17.2				
Sulfamethoxazole	<LOQ	N.D.	39.1	N.D.	N.D.	37.04	N.D.	N.D.	25%	3.27	8.92	726	N.D.	79.97	5.95	N.D.	<LOQ	63%	28.99	180	N.D.	N.D.	26.6	58.6	N.D.	N.D.	50%	N.D.	726	46%
STD ±			3.22			1.91				0.875	0.0312	0.947		5.67	0.794				1.62	12.6			2.15	4.60						
Trimethoprim	<LOQ	<LOQ	16.7	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	13%	14.8	N.D.	186	N.D.	35.02	17.9	N.D.	N.D.	50%	23.2	168	<LOQ	<LOQ	13.9	11.4	N.D.	N.D.	50%	N.D.	186	38%
STD ±			0.758							0.699		10.5		2.89	1.20				0.413	10.9			1.24	6.42						
Metronidazole	551	N.D.	N.D.	N.D.	N.D.	261	N.D.	N.D.	25%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	145	N.D.	N.D.	N.D.	13%	N.D.	551	13%
STD ±	25.6					17.1																	9.40							
Metronidazole-OH[a]	16.1	N.D.	N.D.	N.D.	N.D.	180	N.D.	N.D.	25%	N.D.	N.D.	24.5	27.2	N.D.	N.D.	N.D.	N.D.	25%	N.D.	N.D.	N.D.	N.D.	26.8	N.D.	N.D.	N.D.	13%	N.D.	180	21%
STD ±	1.83					8.91						5.39	0.926										1.14							
Dimetridazole	N.D.	N.D.	N.D.	N.D.	N.D.	79.6	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	45.2	N.D.	N.D.	13%	N.D.	79.6	8%
STD ±						2.78																		1.75						
Ronidazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														
Cefalexin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Calcium channel blockers																														
Diltiazem	20.1	N.D.	222	66.3	259	27.1	5.94	7.41	88%	6.44	N.D.	158	81.8	61.98	77.9	N.D.	46.9	75%	N.D.	N.D.	262	98.5	50.4	88.5	N.D.	48.8	63%	N.D.	262	75%
STD ±	0.173		16.5	5.92	19.6	0.141	0.180	0.574		0.231		3.61	7.55	1.93	2.65		4.09				1.75	11.2	2.77	1.27		2.77				
Verapamil	N.D.	N.D.	22.2	N.D.	13.9	20.04	N.D.	N.D.	38%	8.65	N.D.	6.74	N.D.	35.5	7.50	N.D.	N.D.	50%	N.D.	N.D.	15.6	N.D.	N.D.	10.3	N.D.	N.D.	25%	N.D.	35.5	38%
STD ±			1.48		3.87	0.273				0.329		0.0252		1.67	0.536						0.854			0.947						
Norverapamil[a]	N.D.	N.D.	8.97	N.D.	12.98	23.2	N.D.	N.D.	38%	N.D.	N.D.	N.D.	N.D.	N.D.	7.65	N.D.	N.D.	13%	N.D.	N.D.	16.4	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	23.2	21%
STD ±			0.619		3.28	1.78									0.522						0.424									

Notes: D.F. (detection frequency); AVE.D.F. (average detection frequency in all sampling campaigns); MIN (minimal concentration detected); MAX (maximal concentration detected); N.D. (not detected); <LOQ (below limit of quantification); [a] metabolites; Sampling sites (1-Corbera , 2- Caseres, 3-Nonasp, 4- Bot Gandesa, 5-Maella, 6-Vallderoures, 7-Prat del C., 8-Bot Canaleta).

B)

Analyte	1st SAMPLING CAMPAIGN (April 2015)			D.F.	2nd SAMPLING CAMPAIGN (October 2015)			D.F.	3rd SAMPLING CAMPAIGN (April 2016)			D.F.	MIN	MAX	AVE. D.F.
	SAMPLING LOCATIONS				SAMPLING LOCATIONS				SAMPLING LOCATIONS						
	POBOLEDA	BISBAL DE FALSET	PRADES		POBOLEDA	BISBAL DE FALSET	PRADES		POBOLEDA	BISBAL DE FALSET	PRADES				
Analgesics/anti-inflammatories															
Ketoprofen	233	65.03	138	100%	273	30.6	180	100%	232	51.03	159	100%	30.6	273	100%
STD ±	24.4	0.982	27.7		15.5	2.74	12.05		16.2	8.10	28.2				
Naproxen	N.D.	67.6	74.003	67%	41.6	10.7	11.2	100%	N.D.	92.7	62.5	67%	N.D.	92.7	78%
STD ±		7.11	4.48		4.20	1.01	1.33			7.11	1.86				
Ibuprofen	N.D.	N.D.	<LOQ	0%	46.996	N.D.	<LOQ	33%	<LOQ	N.D.	<LOQ	0%	N.D.	46.996	11%
STD ±					6.32										
Indomethacine	N.D.	79.2	<LOQ	33%	N.D.	27.1	29.7	67%	N.D.	16.6	26.1	67%	N.D.	79.2	56%
STD ±		0.430				2.66	3.16			1.97	2.59				
Acetaminophen	184	32.3	57.02	100%	237	122	69.7	100%	203	84.99	59.1	100%	32.3	237	100%
STD ±	15.6	1.72	0.235		12.5	2.87	12.97		36.5	3.48	2.27				
Salicylic acid	23.5	<LOQ	560	67%	201	6.05	622	100%	<LOQ	<LOQ	430	33%	<LOQ	622	67%
STD ±	0.322		32.4		27.4	0.310	62.4				27.1				
Diclofenac	129	37.4	45.3	100%	183	173	142	100%	126	144	53.9	100%	37.4	183	100%
STD ±	9.23	5.36	0.530		10.96	17.3	2.60		2.25	31.6	1.78				
Phenazone	<LOQ	74.6	<LOQ	33%	18.6	76.8	9.30	100%	N.D.	71.3	13.4	67%	N.D.	76.8	67%
STD ±		2.41			1.74	4.01	0.165			1.92	0.64				
Propyphenazone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Piroxicam	N.D.	18.7	N.D.	33%	N.D.	42.9	N.D.	33%	<LOQ	37.8	N.D.	33%	N.D.	42.9	33%
STD ±		1.04				3.19				3.05					
Tenoxicam	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Meloxicam	N.D.	N.D.	N.D.	0%	N.D.	3.29	N.D.	33%	N.D.	4.23	N.D.	33%	N.D.	4.23	22%
STD ±						0.424				0.288					
Oxycodone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Codeine	135	14.5	3.23	100%	181	121	31.1	100%	135	101	15.6	100%	3.23	181	100%
STD ±	5.84	1.68	0.209		4.03	2.24	1.41		9.50	6.79	0.740				
Lipid regulators and cholesterol lowering statin drugs															
Bezafibrate	278	N.D.	104	67%	319	N.D.	18.2	67%	329	N.D.	182	67%	N.D.	329	67%
STD ±	9.34		2.52		16.6		1.63		11.2		4.35				
Gemfibrozil	456	1.49	598	100%	413	N.D.	512	67%	618	N.D.	618	67%	N.D.	618	78%
STD ±	142	0.0216	36.2		34.2		10.9		62.7		22.6				
Pravastatin	N.D.	22.9	N.D.	33%	N.D.	56.2	N.D.	33%	N.D.	36.3	N.D.	33%	N.D.	56.2	33%
STD ±		2.95				2.32				2.43					
Fluvastatin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Atorvastatin	N.D.	1.84	1.72	67%	1.05	11.7	3.08	100%	N.D.	1.93	7.51	67%	N.D.	11.7	78%
STD ±		0.296	0.156		0.183	0.256	0.133			0.103	0.181				
Psychiatric drugs															
Carbamazepine	<LOQ	44.2	16.7	67%	1.28	60.2	41.6	100%	N.D.	52.7	11.7	67%	N.D.	60.2	78%

STD ±		2.93	1.31		0.123	1.69	0.688			6.44	0.361				
Acridone[a]	N.D.	2.67	<LOQ	33%	<LOQ	9.87	1.22	67%	N.D.	N.D.	N.D.	0%	N.D.	9.87	33%
STD ±		0.042				0.265	0.0850								
Sertraline	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Citalopram	<LOQ	32.6	11.6	67%	34.7	37.4	41.5	100%	N.D.	45.9	9.64	67%	N.D.	45.9	78%
STD ±		2.64	0.255		3.54	3.20	1.87			3.44	0.517				
Venlafaxine	1.11	27.3	11.98	100%	48.9	35.7	35.1	100%	N.D.	74.9	33.7	67%	N.D.	74.9	89%
STD ±	0.0918	0.640	0.346		1.29	4.34	1.03			9.05	2.07				
Trazodone	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Fluoxetine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Norfluoxetine[a]	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Paroxetine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Diazepam	N.D.	<LOQ	N.D.	0%	4.51	6.04	1.46	100%	N.D.	2.66	N.D.	33%	N.D.	6.04	44%
STD ±					0.199	0.0997	0.0761			0.306					
Alprazolam	N.D.	10.9	N.D.	33%	<LOQ	24.8	N.D.	33%	N.D.	<LOQ	N.D.	0%	N.D.	24.8	22%
STD ±		0.813				0.790									
Histamine H1 and H2 receptor antagonists															
Loratadine	<LOQ	N.D.	<LOQ	0%	<LOQ	0.489	N.D.	33%	N.D.	N.D.	N.D.	0%	N.D.	0.49	11%
STD ±						0.0397									
Desloratadine[a]	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Ranitidine	N.D.	42.5	3.27	67%	27.1	62.8	11.9	100%	<LOQ	79.6	1.58	67%	N.D.	79.6	78%
STD ±		3.56	0.450		0.161	2.95	0.476			2.76	0.0776				
Famotidine	N.D.	N.D.	N.D.	0%	1.57	N.D.	1.499	67%	N.D.	N.D.	N.D.	0%	N.D.	1.57	22%
STD ±					0.235		0.212								
Cimetidine	N.D.	N.D.	<LOQ	0%	N.D.	11.09	N.D.	33%	<LOQ	18.6	<LOQ	33%	N.D.	18.6	22%
STD ±						0.594				0.557					
β -Blocking agents															
Atenolol	391	134	53.99	100%	477	259	99.8	100%	436	242	57.6	100%	53.99	477	100%
STD ±	26.9	0.246	3.86		90.04	3.92	3.25		4.98	10.6	6.92				
Sotalol	N.D.	1.64	N.D.	33%	N.D.	N.D.	59.5	33%	N.D.	N.D.	N.D.	0%	N.D.	59.5	22%
STD ±		0.142					2.70								
Propranolol	<LOQ	66.8	4.69	67%	N.D.	21.5	7.33	67%	<LOQ	42.6	9.23	67%	N.D.	66.8	67%
STD ±		5.14	0.0737			0.760	0.300			1.60	0.0939				
Metoprolol	<LOQ	75.5	<LOQ	33%	N.D.	49.3	25.9	67%	N.D.	33.1	N.D.	33%	N.D.	75.5	44%
STD ±		1.72				0.560	1.15			0.567					
Nadolol	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	0.534	33%	N.D.	N.D.	N.D.	0%	N.D.	0.53	11%
STD ±							0.0689								
Carazolol	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Diuretic															
Furosemide	366	94.2	265	100%	459	347	470	100%	447	224	333	100%	94.2	470	100%

STD ±	25.9	4.74	11.7		8.11	6.28	14.3		10.6	3.32	11.5				
Antidiabetic															
Glibenclamide	N.D.	55.6	5.62	67%	N.D.	64.6	17.5	67%	N.D.	<LOQ	<LOQ	0%	N.D.	64.6	44%
STD ±		1.05	0.207			4.95	0.702								
Antidiabetic															
Amlodipine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Losartan	<LOQ	47.98	<LOQ	33%	146	62.2	88.7	100%	N.D.	172.6	60.1	67%	N.D.	173	67%
STD ±		5.69			2.23	3.08	7.74			12.3	5.61				
Irbesartan	<LOQ	1.50	11.6	67%	112	2.27	169	100%	N.D.	N.D.	17.3	33%	N.D.	169	67%
STD ±		0.0221	0.0523		1.74	0.185	4.13				0.0737				
Valsartan	291	97.5	166	100%	331	255	107	100%	319	161	197	100%	97.5	331	100%
STD ±	7.79	37.2	0.482		14.3	22.8	11.8		13.8	4.92	5.85				
Antiplatelet agent															
Clopidogrel	<LOQ	N.D.	0.915	33%	19.7	N.D.	10.3	67%	N.D.	N.D.	N.D.	0%	N.D.	19.7	33%
STD ±			0.0696		1.97		0.208								
Prostatic hyperplasia															
Tamsulosin	<LOQ	8.43	<LOQ	33%	2.42	12.4	1.28	100%	N.D.	10.6	N.D.	33%	N.D.	12.4	56%
STD ±		0.119			0.171	0.711	0.0610			0.350					
To treat asthma															
Salbutamol	N.D.	6.28	0.269	67%	2.42	5.30	0.806	100%	N.D.	0.506	<LOQ	33%	N.D.	6.28	67%
STD ±		0.400	0.0438		0.120	0.320	0.0587			0.00843					
Anticoagulant															
Warfarin	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Antihelmintics															
Albendazole	N.D.	1.25	<LOQ	33%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	1.25	11%
STD ±		0.081													
Thiabendazole	N.D.	6.35	2.10	67%	<LOQ	6.48	<LOQ	33%	N.D.	N.D.	N.D.	0%	N.D.	6.48	33%
STD ±		0.399	0.000435			0.534									
Levamisole	0.306	103	16.8	100%	68.4	97.9	18.4	100%	<LOQ	104	10.3	67%	<LOQ	104	89%
STD ±	0.0301	11.2	0.0589		4.92	1.42	0.650			3.57	0.346				
Synthetic glucocorticoid															
Dexamethasone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Sedation and muscle relaxation															
Xylazine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Antibiotics															
Erythromycin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Ofloxacin	26.98	213	44.99	100%	135	149	23.2	100%	<LOQ	169	16.4	67%	<LOQ	213	89%
STD ±	2.80	6.44	4.17		7.02	3.85	0.982			16.7	0.166				
Sulfamethoxazole	19.9	30.7	N.D.	67%	38.03	85.8	9.41	100%	N.D.	<LOQ	N.D.	0%	N.D.	85.8	56%
STD ±	0.342	3.28			2.57	2.90	3.97								
Trimethoprim	<LOQ	8.81	N.D.	33%	4.69	33.97	N.D.	67%	<LOQ	4.63	N.D.	33%	N.D.	33.97	44%
STD ±		0.543			0.166	2.43				0.216					

Metronidazole	N.D.		N.D.		27.1	33%	N.D.		N.D.		N.D.	0%	N.D.		N.D.		45.4	33%	N.D.		45.4		22%								
STD ±					3.77												3.09														
Metronidazole-OH[a]	N.D.		N.D.		10.7	33%	N.D.		N.D.		N.D.	0%	<LOQ		17.2		10.97	67%	N.D.		17.2		33%								
STD ±					1.03										1.38		0.649														
Dimetridazole	N.D.		N.D.		<LOQ	0%	N.D.		N.D.		N.D.	0%	N.D.		N.D.		N.D.	0%	N.D.		<LOQ		0%								
STD ±																															
Ronidazole	<LOQ		<LOQ		<LOQ	0%	N.D.		N.D.		N.D.	0%	N.D.		N.D.		N.D.	0%	N.D.		<LOQ		0%								
STD ±																															
Cefalexin	N.D.		N.D.		N.D.	0%	N.D.		N.D.		N.D.	0%	N.D.		N.D.		N.D.	0%	N.D.		N.D.		0%								
STD ±																															
Calcium channel blockers																															
Diltiazem	2.18		N.D.		3.39	67%	30.95		N.D.		3.19	67%	N.D.		N.D.		2.69	33%	N.D.		30.95		56%								
STD ±	0.247				0.0342		3.28				0.182						0.230														
Verapamil	N.D.		N.D.		N.D.	0%	N.D.		0.557		N.D.	33%	N.D.		N.D.		N.D.	0%	N.D.		0.56		11%								
STD ±									0.106																						
Norverapamil[a]	N.D.		<LOQ		N.D.	0%	1.52		<LOQ		N.D.	33%	N.D.		N.D.		N.D.	0%	N.D.		1.52		11%								
STD ±							0.243																								

Notes: D.F. (detection frequency); AVE.D.F. (average detection frequency in all sampling campaigns); MIN (minimal concentration detected); MAX (maximal concentration detected); N.D. (not detected); <LOQ (below limit of quantification); [a] metabolites

Table 8S. Detection frequencies, minimum, maximum and individual concentrations of PhACs (ngL^{-1}) in three sampling campaigns in upstream (control) sampling sites.

Analyte	1st SAMPLING CAMPAIGN (April 2015)												2nd SAMPLING CAMPAIGN (October 2015)												3rd SAMPLING CAMPAIGN (April 2016)												MIN	MAX	AVE. D.F.
	SAMPLING LOCATIONS												SAMPLING LOCATIONS												SAMPLING LOCATIONS														
	1	2	3	4	5	6	7	8	9	10	11	D.F.	1	2	3	4	5	6	7	8	9	10	11	D.F.	1	2	3	4	5	6	7	8	9	10	11	D.F.			
Analgesics/anti-inflammatories																																							
Ketoprofen	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	96.6	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	96.6	3%
STD ±													3.93																										
Naproxen	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	0%	187	N.D.	<LOQ	<LOQ	4.79	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	18%	136	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	187	9%
STD ±													7.07				0.701								4.71														
Ibuprofen	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	<LOQ	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Indomethacine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	8.52	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	15.3	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	15.3	6%
STD ±													0.113												0.589														
Acetamino	6.16	9.1	24.1	4.19	5.33	5.9	8.6	24.	<L	5.14	<LO	82	8.8	6.7	N.D.	N.	<LO	16.4	9.15	8.77	N.	7.7	<LO	55	11.	<LO	17.	5.8	4.3	15.	25.	<LO	6.0	17.	16.	82	N.	25.	73%

phen		7				1	5	1	OQ		Q	%	7	9		D.	Q				D.	8	Q	%	9	Q	6	3	8	999	5	Q	2	3	8	%	D.	5	
STD ±	0.220	0.237	0.164	0.271	0.462	0.557	4.34	0.113		0.205			0.653	0.619				1.57	0.652	2.89		0.198			0.592		0.851	0.463	0.0773	1.27	2.52		0.475	1.67	1.09				
Salicylic acid	12.2	15.7	18.7	<LOQ	16.4	21.2	21.98	12.3	<LOQ	23.5	46.7	82%	88.05	25.5	18.7	15.6	16.6	65.99	14.4	7.19	38.7	86.9	29.97	10 0%	50.8	<LOQ	<LOQ	<LOQ	38.96	40.6	20.2	21.98	21.1	53.4	25.6	73%	<LOQ	88.1	85%
STD ±	0.848	0.691	0.853		2.44	1.90	1.26	0.395		0.723	7.24		5.95	0.183	0.521	1.05	1.87	5.50	0.0944	5.28	1.96	4.16	29.4		2.01				1.79	2.68	3.52	0.411	1.81	2.08	2.61				
Diclofenac	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	N.D.	15.1	<LOQ	N.D.	N.D.	<LOQ	9%	73.1	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	9%	28.6	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	73.1	9%
STD ±							0.105						6.09												0.662														
Phenazone	5.01	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	13.5	N.D.	<LOQ	1.83	N.D.	N.D.	N.D.	N.D.	2.19	N.D.	N.D.	27%	3.16	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	13.6	15%
STD ±	0.259												0.490			0.101					0.254				0.210														
Propyphenazone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Piroxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Tenoxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Meloxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Oxycodone	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Codeine	4.98	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	1.21	N.D.	18%	4.24	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	2.57	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	9%	N.D.	4.98	12%
STD ±	0.585									0.152			0.370												0.123														
Lipid regulators and cholesterol lowering statin drugs																																							
Bezafibrate	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Gemfibrozil	82.2	0.620	0.559	N.D.	1.90	N.D.	N.D.	1.37	N.D.	<LOQ	0.406	55%	30.5	N.D.	<LOQ	N.D.	N.D.	N.D.	1.11	N.D.	<LOQ	<LOQ	<LOQ	18%	28.7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	82.2	27%
STD ±	5.45	0.228	0.0574		0.174			1.35			0.0198		1.17						0.00400						0.677														
Pravastatin	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Fluvastatin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							

Atorvastatin	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	<LOQ	0%
STD ±																																									
Psychiatric drugs																																									
Carbamazepine	35.3	<LOQ	<LOQ	N.D.	<LOQ	N.D.	<LOQ	N.D.	<LOQ	3.43	<LOQ	18%	43.3	N.D.	<LOQ	N.D.	1.101	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	18%	36.9	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	43.3	15%
STD ±	0.380									0.00537			0.0523				0.0152								1.23																
Acridone[a]	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	1.75	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	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.	0%	N.D.	1.75	3%
STD ±													0.240																												
Sertraline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	N.D.	0%
STD ±																																									
Citalopram	8.73	<LOQ	N.D.	N.D.	N.D.	<LOQ	N.D.	<LOQ	N.D.	<LOQ	N.D.	9%	6.88	<LOQ	N.D.	N.D.	N.D.	<LOQ	0.710	N.D.	N.D.	N.D.	N.D.	18%	3.51	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	8.73	12%
STD ±	0.932												0.232						0.0445						0.0650																
Venlafaxine	26.9	1.89	N.D.	N.D.	1.25	N.D.	0.575	N.D.	N.D.	N.D.	N.D.	36%	27.6	N.D.	<LOQ	N.D.	1.72	1.40	3.73	0.482	N.D.	N.D.	N.D.	45%	19.6	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	27.6	30.30%
STD ±	1.98	0.495			0.00340		0.0217						1.90				0.0645	0.207	0.168	0.309					0.469																
Trazodone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	1.31	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	1.31	3%
STD ±													0.0487																												
Fluoxetine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	N.D.	0%
STD ±																																								
Norfluoxetine[a]	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	<LOQ	0%
STD ±																																								
Paroxetine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	N.D.	0%
STD ±																																								
Diazepam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	N.D.	0%
STD ±																																								
Alprazolam	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																								
Histamine H1 and H2 receptor antagonists																																									
Loratadine	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	<LOQ	0%
STD ±																																								
Desloratadine[a]	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	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.	0%	N.D.	N.D.	0%

STD ±																																							
Ranitidine	0.513	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	0.879	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	9%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	0.88	6%
STD ±	0.0428												0.0490																										
Famotidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Cimetidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.208	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	0.21	3%
STD ±															0.0725																								
β -Blocking agents																																							
Atenolol	2.07	1.01	0.127	0.563	0.170	N.D.	N.D.	<LOQ	N.D.	0.665	0.258	64%	3.60	N.D.	0.392	<LOQ	0.487	0.315	0.233	0.308	0.356	<LOQ	0.352	73%	2.07	4.14	1.52	0.940	<LOQ	<LOQ	<LOQ	1.53	<LOQ	<LOQ	1.03	55%	N.D.	4.14	64%
STD ±	0.265	0.860	0.0297	0.208	0.000124					0.0372	0.00386		0.2833		0.126		0.0116	0.00542	0.0432	0.0521	0.165		0.00847		0.115	0.107	0.0791	0.0371				0.0434			0.0141				
Sotalol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Propranolol	<LOQ	<LOQ	N.D.	N.D.	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	0%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Metoprolol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Nadolol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Carazolol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Diuretic																																							
Furosemide	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	165	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	0%	N.D.	165	3%
STD ±													5.55																										
Antidiabetic																																							
Glibenclamide	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	4.30	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	0%	N.D.	4.30	3%
STD ±													0.268																										
Antihypertensives																																							
Amlodipine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Losartan	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	65.4	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	16.2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	65.4	6%

STD ±													4.28												0.923																
Irbesartan	N.D.	<LOQ	0.827	N.D.	2.19	<LOQ	<LOQ	N.D.	N.D.	<LOQ	<LOQ	18%	43.9	<LOQ	N.D.	N.D.	<LOQ	1.62	N.D.	N.D.	N.D.	0.688	0.576	36%	19.7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	43.9	21%
STD ±			0.0381		0.516								3.17					0.159				0.122	0.164		0.597																
Valsartan	242	<LOQ	9.07	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	N.D.	<LOQ	11.3	27%	173	<LOQ	N.D.	1.43	3.03	5.86	<LOQ	<LOQ	1.43	<LOQ	<LOQ	45%	117	7.64	6.55	5.83	N.D.	<LOQ	N.D.	<LOQ	N.D.	7.46	7.73	55%	N.D.	242	42%
STD ±	18.2		0.100								0.539		8.79			0.413	0.127	0.587			0.565				4.44	0.693	0.451	0.269						0.454	0.623					
Antiplatelet agent																																								
Clopidogrel	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.201	0.199	0.136	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	27%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	0.20	9%
STD ±															0.174	0.013	0.019																							
Prostatic hyperplasia																																								
Tamsulosin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	0.317	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	0.32	3%
STD ±													0.02																											
To treat asthma																																							
Salbutamol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	N.D.	<LOQ	0%	N.D.	<LOQ	0%
STD ±																																								
Anticoagulant																																							
Warfarin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																								
Antihelmintics																																							
Albendazole	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																								
Thiabendazole	1.65	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0985	18%	<LOQ	<LOQ	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	1.65	6%
STD ±	0.264										0.00213																													
Levamisole	4.65	<LOQ	N.D.	0.0782	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0.249	27%	3.74	N.D.	0.284	N.D.	0.242	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	27%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	4.65	18%
STD ±	0.300			0.00248							0.00911		0.0590		0.186		0.0278																							
Synthetic glucocorticoid																																							
Dexamethasone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																								
Sedation and muscle relaxation																																							
Xylazine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																								

Antibiotics																																								
Erythromycin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Ofloxacin	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	19.2	<LOQ	<LOQ	<LOQ	15.8	<LOQ	18%	12.06	3.56	3.46	<LOQ	<LOQ	<LOQ	4.60	9.71	<LOQ	3.96	3.48	64%	9.04	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	9%	N.D.	19.2	30.30%
STD ±						3.26				0.0608			0.552	0.548	0.360				0.459	6.58		0.0706	0.336		0.725														
Sulfamethoxazole	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	14.6	3.23	N.D.	N.D.	<LOQ	12.1	N.D.	<LOQ	<LOQ	N.D.	N.D.	27%	6.74	2.01	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	18%	N.D.	14.7	15%
STD ±													0.720	0.212				1.996							0.124	0.00787													
Trimethoprim	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Metronidazole	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Metronidazole-OH[a]	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	<LOQ	0%
STD ±																																							
Dimetridazole	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Ronidazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							
Cefalexin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Calcium channel blockers																																							
Diltiazem	2.23	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9%	<LOQ	<LOQ	N.D.	N.D.	N.D.	<LOQ	<LOQ	0.131	<LOQ	<LOQ	N.D.	9%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	2.23	6%
STD ±	0.324																			0.00827																				
Verapamil	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																																							
Norverapamil[a]	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																																							

Notes: D.F. (detection frequency); AVE. D.F. (average detection frequency in all sampling campaigns); MIN (minimal concentration detected); MAX (maximal concentration detected); N.D. (not detected); <LOQ (below limit of quantification); [a] metabolites; Sampling sites (1-Corbera , 2- Caseres, 3-Nonasp, 4- Bot Gandesa, 5-Maella, 6-Vallderoures, 7-Prat del C., 8-Bot Canaleta, 9-Poboleda, 10-Bisbal de Falset, 11-Prades).

Table 9S. Detection frequencies, minimum, maximum and individual concentrations of PhACs (ngL^{-1}) in three sampling campaigns in: A) downstream sites impacted by untreated (raw) wastewater and B) downstream sites impacted by treated wastewater.

A)

Analyte	1st SAMPLING CAMPAIGN (April 2015)									2nd SAMPLING CAMPAIGN (October 2015)									3rd SAMPLING CAMPAIGN (April 2016)									MIN	MAX	AVE. D.F.
	SAMPLING LOCATIONS								D.F.	SAMPLING LOCATIONS								D.F.	SAMPLING LOCATIONS								D.F.			
	1	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8				
Analgesics/anti-inflammatories																														
Ketoprofen	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	120	N.D.	<LOQ	55.6	<LOQ	N.D.	69.3	<LOQ	38%	79.6	N.D.	N.D.	108	<LOQ	N.D.	69.3	<LOQ	38%	N.D.	120	25%
STD ±										6.13			1.87			2.94			5.56			4.50			0.856					
Naproxen	152	<LOQ	29.3	931	14.96	18.6	56.96	<LOQ	75%	1039	51.7	179	1447	78.9	143	139	48.4	100 %	612	27.6	78.6	1471	57.3	104	40.5	52.4	100 %	<LOQ	1471	92%
STD ±	25.3		3.35	14.1	0.260	0.379	7.70			104	4.43	4.25	62.7	10.6	5.70	8.07	1.78		31.3	2.03	1.92	5.68	3.14	5.56	1.18	4.03				
Ibuprofen	701	N.D.	650	95.5	N.D.	<LOQ	115	N.D.	50%	2660	<LOQ	1110	1670	155	445	142	41.5	88%	1743	N.D.	586	575	136	346	233	26.1	88%	N.D.	2660	75%
STD ±	5.81		47.8	4.91			14.6			61.3		318	224	8.25	24.1	12.6	8.67		188		5.21	13.03	15.5	4.45	2.84	0.562				
Indomethacine	18.8	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	13%	20.2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	30.3	N.D.	N.D.	18.1	N.D.	N.D.	N.D.	N.D.	25%	N.D.	30.3	17%
STD ±	6.72									1.58									0.960			2.23								
Acetaminophen	2671	267	141	457	89.7	172	7779	380	100 %	3633	130	15.6	1511	16.97	540	6151	986	100 %	2898	225	314	770	63.3	409	6505	632	100 %	15.6	7779	100 %
STD ±	252	27.2	0.576	30.6	2.34	9.34	243	32.6		121	2.50	5.28	34.6	2.83	2.94	128	83.7		83.3	9.94	10.96	42.6	17.9	6.26	122	4.34				
Salicylic acid	471	30.4	136	161	48.8	130	1412	28.8	100 %	623	269	20.6	437	71.4	236	1722	17.2	100 %	52.1	<LOQ	34.8	265	86.7	270	1412	38.1	88%	<LOQ	1722	96%
STD ±	3.47	2.56	9.17	5.42	4.37	19.3	189	1.34		21.97	11.7	2.56	81.1	8.10	10.7	10.4	0.972		1.29		0.947	12.9	2.42	1.60	281	3.61				
Diclofenac	46.5	<LOQ	<LOQ	15.6	N.D.	49.6	52.9	<LOQ	50%	198	<LOQ	35.5	168	64.9	<LOQ	50.6	<LOQ	63%	67.5	<LOQ	N.D.	49.1	<LOQ	38.2	70.6	17.8	63%	N.D.	198	58%
STD ±	15.2			1.97		0.836	7.24			2.86		1.04	1.35	3.75		6.06			1.22			2.31		1.57	4.23	0.175				
Phenazone	5.21	N.D.	N.D.	<LOQ	<LOQ	N.D.	<LOQ	N.D.	13%	28.9	<LOQ	3.93	4.02	7.51	N.D.	N.D.	N.D.	50%	7.33	N.D.	N.D.	N.D.	N.D.	N.D.	5.47	N.D.	25%	N.D.	28.9	29%
STD ±	0.295									1.82		0.302	0.139	0.714					0.127						0.503					
Propyphenazone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Piroxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	7.37	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	84.6	<LOQ	25%	N.D.	N.D.	N.D.	15.4	N.D.	N.D.	<LOQ	N.D.	13%	N.D.	84.6	13%
STD ±										0.362						3.41						1.66								
Tenoxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Meloxicam	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Oxycodone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														
Codeine	20.6	N.D.	3.45	1.60	<LOQ	<LOQ	2.49	<LOQ	50%	112	N.D.	19.95	46.2	35.02	8.18	14.5	<LOQ	75%	63.2	N.D.	1.65	3.92	3.37	1.50	N.D.	<LOQ	63%	N.D.	112	63%
STD ±	4.46		2.90	0.046			0.282			5.97		1.28	3.79	4.17	0.553	0.378			3.89		0.112	0.258	0.240	0.139						

				6																									
Lipid regulators and cholesterol lowering statin drugs																													
Bezafibrate	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.994	128	N.D.	2.26	2.89	N.D.	50%	N.D.	N.D.	N.D.	71.7	N.D.	N.D.	N.D.	N.D.	13%	N.D.	128	21%
STD ±												0.157	3.37		0.0815	0.140						0.897							
Gemfibrozil	260	2.16	12.3	1.99	7.69	2.24	31.6	1.49	100 %	192	4.53	32.9	6.79	38.8	8.001	301	26.5	100 %	237	1.52	N.D.	4.37	33.1	2.36	30.3	10.7	88%	N.D.	301	96%
STD ±	39.8	0.321	1.31	0.317	0.0151	0.186	4.30	0.429		90.5	2.33	15.997	0.806	20.6	0.394	8.08	4.74		16.4	0.0672		0.0406	2.63	0.101	0.646	1.45				
Pravastatin	26.4	N.D.	<LOQ	12.7	<LOQ	<LOQ	12.4	<LOQ	38%	32.2	N.D.	23.1	149	N.D.	9.76	20.1	6.32	75%	15.04	N.D.	18.9	89.1	N.D.	<LOQ	55.3	<LOQ	50%	N.D.	149	54%
STD ±	6.55			1.71			0.616			3.93		0.756	2.26		0.452		0.501		1.76		0.485	3.86			4.70					
Fluvastatin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Atorvastatin	2.55	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	13%	13.4	<LOQ	2.27	13.1	7.45	3.37	30.5	0.964	88%	2.72	N.D.	N.D.	1.96	N.D.	0.847	3.50	N.D.	50%	N.D.	30.5	50%
STD ±	0.494									0.264		0.312	2.52	0.491	0.451	1.31	0.144		0.0713			0.173		0.0469	0.109					
Psychiatric drugs																													
Carbamazepine	31.6	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	4.46	<LOQ	25%	78.7	<LOQ	19.08	17.1	26.1	6.39	208	2.01	88%	42.7	N.D.	<LOQ	7.82	3.61	2.27	175	<LOQ	63%	N.D.	208	58%
STD ±	8.18						0.431			4.03		1.58	0.618	1.58	0.202	2.34	0.309		3.06			0.192	0.0707	0.0725	5.52					
Acridone[a]	N.D.	N.D.	<LOQ	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	3.09	<LOQ	1.74	<LOQ	<LOQ	<LOQ	2.71	0.312	50%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	2.47	N.D.	13%	N.D.	3.09	21%
STD ±										0.413		0.180				0.185	0.0588								0.0493					
Sertraline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Citalopram	26.4	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	13%	38.7	<LOQ	0.954	13.8	25.8	4.71	48.4	1.83	88%	22.8	<LOQ	<LOQ	<LOQ	1.45	1.26	17.6	<LOQ	50%	N.D.	48.4	50%
STD ±	5.67									1.95		0.175	1.06	2.19	1.12	2.79	0.0718		0.692				0.117	0.0747	1.003					
Venlafaxine	46.4	1.42	1.92	<LOQ	4.27	1.05	30.9	0.445	88%	42.1	2.66	24.4	23.8	35.2	5.35	102	2.15	100 %	78.2	N.D.	3.31	5.81	4.92	2.71	304	1.20	88%	N.D.	304	92%
STD ±	10.3	0.588	0.0160		0.0313	0.131	0.0640	0.0298		0.565	0.116	0.760	0.675	2.75	0.119	0.427	0.0931		2.64		0.0538	0.303	0.168	0.151	1.53	0.0555				
Trazodone	<LOQ	N.D.	<LOQ	2.13	<LOQ	<LOQ	2.28	N.D.	25%	1.21	N.D.	1.68	7.903	21.1	2.37	9.97	N.D.	75%	N.D.	N.D.	N.D.	3.68	2.12	1.65	6.03	N.D.	50%	N.D.	21.1	50%
STD ±				0.181			0.389			0.0189		0.247	0.520	3.46	0.832	0.507						0.325	0.0901	0.0740	0.110					
Fluoxetine	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	<LOQ	N.D.	0%	4.31	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	41.3	N.D.	13%	N.D.	41.3	8%
STD ±										0.1004															2.70					
Norfluoxetine[a]	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	5.39	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	<LOQ	N.D.	<LOQ	N.D.	N.D.	N.D.	43.4	N.D.	13%	N.D.	43.4	8%
STD ±										0.718															2.12					
Paroxetine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Diazepam	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0.707	0.630	1.24	N.D.	0.926	<LOQ	50%	1.45	N.D.	N.D.	N.D.	<LOQ	N.D.	2.37	N.D.	25%	N.D.	2.37	25%
STD ±												0.0357	0.154	0.0389		0.0937			0.132						0.0674					
Alprazolam	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	4.99	N.D.	<LOQ	N.D.	<LOQ	N.D.	N.D.	N.D.	13%	3.96	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	4.99	8%

STD ±										0.125									0.240										
Histamine H1 and H2 receptor antagonists																													
Loratadine	N.D.	<LOQ	<LOQ	N.D.	<LOQ	N.D.	<LOQ	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.558	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	0.558	4%
STD ±																0.102													
Desloratadine[a]	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																													
Ranitidine	1.47	N.D.	0.280	<LOQ	<LOQ	0.266	1.03	<LOQ	50%	10.4	<LOQ	1.52	35.05	3.69	2.09	226	0.313	88%	<LOQ	<LOQ	<LOQ	56.8	<LOQ	1.90	16.6	<LOQ	38%	N.D.	226	58%
STD ±	0.166		0.0288			0.0463	0.189			0.497		0.00675	5.36	0.379	0.331	9.21	0.0363					4.24		0.103	0.143					
Famotidine	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	4.27	N.D.	N.D.	2.88	N.D.	N.D.	25%	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	4.27	8%
STD ±												0.0618			0.596														
Cimetidine	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	0.177	0.153	N.D.	0.155	N.D.	N.D.	38%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	<LOQ	13%
STD ±												0.0153	0.0117		0.00141														
β -Blocking agents																													
Atenolol	18.8	1.20	0.303	12.9	0.738	1.18	2.59	1.97	100%	115	7.70	0.650	268	19.5	4.61	19.2	13.9	100%	35.6	5.97	1.10	241	4.81	4.75	42.3	13.6	100%	0.303	268	100%
STD ±	5.71	0.142	0.0054	0.184	0.0257	0.293	0.223	0.0519		6.59	0.550	0.0291	10.7	0.636	0.797	0.855	0.292		2.06	0.436	0.0436	15.7	0.127	0.426	0.883	1.03				
Sotalol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																													
Propranolol	<LOQ	<LOQ	N.D.	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	0%	1.48	N.D.	N.D.	4.47	1.35	0.705	N.D.	N.D.	50%	<LOQ	N.D.	<LOQ	5.32	N.D.	<LOQ	5.44	N.D.	25%	N.D.	5.44	25%
STD ±										0.116			0.220	0.0853	0.0740							0.243			0.327					
Metoprolol	N.D.	N.D.	<LOQ	<LOQ	<LOQ	N.D.	N.D.	N.D.	0%	3.33	N.D.	N.D.	11.98	1.21	N.D.	3.50	N.D.	50%	N.D.	N.D.	N.D.	19.8	N.D.	N.D.	N.D.	N.D.	13%	N.D.	19.8	21%
STD ±										0.203			0.787	0.119		0.127						0.395								
Nadolol	N.D.	N.D.	N.D.	N.D.	0.496	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	26.6	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	1.25	N.D.	N.D.	N.D.	13%	N.D.	26.6	13%
STD ±					0.0154									0.667									0.00346							
Carazolol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Diuretic																													
Furosemide	156	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	13%	517	N.D.	76.7	856	56.3	193	196	<LOQ	75%	185	N.D.	N.D.	271	<LOQ	162	<LOQ	<LOQ	38%	N.D.	856	42%
STD ±	0.718									25.5		12.04	36.2	2.80	6.69	18.2			8.51			7.13		14.2						
Antidiabetic																													
Glibenclamide	2.01	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	6.12	N.D.	N.D.	N.D.	N.D.	N.D.	1.59	N.D.	25%	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	<LOQ	N.D.	0%	N.D.	6.12	13%
STD ±	0.0117									0.480						0.0957														
Antihypertensives																													
Amlodipine	<LOQ	N.D.	N.D.	N.D.	<LOQ	<LOQ	<LOQ	N.D.	0%	<LOQ	N.D.	N.D.	6.08	N.D.	N.D.	31.7	<LOQ	25%	N.D.	N.D.	<LOQ	N.D.	N.D.	<LOQ	31.5	<LOQ	13%	N.D.	31.7	13%
STD ±													2.35			1.41									1.70					
Losartan	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	N.D.	29.6	N.D.	13%	147	<LOQ	12.4	111	63.7	5.37	281	N.D.	75%	34.6	<LOQ	N.D.	17.5	N.D.	N.D.	207	N.D.	38%	N.D.	281	42%
STD ±							3.27			5.80		1.12	6.31	1.75	0.576	5.95			2.19			2.52			5.99					
Irbesartan	N.D.	<LOQ	4.44	3.90	2.63	1.75	0.756	N.D.	63%	48.5	3.32	61.2	49.4	4.22	26.5	N.D.	1.28	88%	28.3	N.D.	2.07	11.4	2.96	4.48	N.D.	N.D.	63%	N.D.	61.2	71%
STD ±			0.353	0.656	0.5985	0.125	0.0181			4.50	0.329	8.15	9.52	0.616	1.69		0.131		0.567		0.0528	0.527	0.0662	0.315						

Valsartan	244	24.7	81.1	44.3	10.2	16.3	<LOQ	<LOQ	75%	810	38.7	872	603	90.9	116	14.5	10.8	100 %	245	13.3	432	469	87.95	58.8	23.5	11.8	100 %	<LOQ	872	92%
STD ±	4.33	1.56	1.84	0.271	1.57	1.59				19.3	1.03	50.1	12.1	10.6	5.90	0.604	0.979		30.2	0.0894	15.1	7.49	5.63	0.884	0.724	0.481				
Antiplatelet agent																														
Clopidogrel	0.243	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	13%	0.515	0.362	0.531	0.3004	1.56	0.409	N.D.	<LOQ	75%	N.D.	<LOQ	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	1.56	29%
STD ±	0.0758									0.0252	0.0426	0.0311	0.0505	0.0897	0.0826															
Prostatic hyperplasia																														
Tamsulosin	<LOQ	<LOQ	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	0%	1.16	<LOQ	N.D.	0.767	0.923	<LOQ	N.D.	N.D.	38%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	1.53	N.D.	13%	N.D.	1.53	17%
STD ±										0.106			0.0321	0.0933											0.0408					
To treat asthma																														
Salbutamol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	0.569	N.D.	<LOQ	N.D.	0.301	N.D.	1.06	N.D.	38%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	1.06	13%
STD ±										0.0808				0.00938		0.0368														
Anticoagulant																														
Warfarin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Antihelmintics																														
Albendazole	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Thiabendazole	1.18	N.D.	N.D.	N.D.	N.D.	N.D.	0.185	N.D.	25%	<LOQ	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	0%	N.D.	1.18	8%
STD ±	0.220						0.00486																							
Levamisole	5.10	N.D.	0.202	2.21	0.513	N.D.	0.830	0.0885	75%	7.37	N.D.	2.92	13.5	28.96	1.09	<LOQ	N.D.	63%	2.94	<LOQ	<LOQ	8.78	1.66	<LOQ	4.49	<LOQ	50%	N.D.	28.96	63%
STD ±	1.02		0.0241	0.105	0.0294		0.0264	0.00672		0.422		0.205	0.672	1.70	0.0205				0.0404			0.736	0.0465		0.234					
Synthetic glucocorticoid																														
Dexamethasone	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Sedation and muscle relaxation																														
Xylazine	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														
Antibiotics																														
Erythromycin	<LOQ	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	N.D.	0%	64.998	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	64.998	4%
STD ±										2.64																				
Ofloxacin	17.8	<LOQ	<LOQ	<LOQ	<LOQ	53.7	<LOQ	<LOQ	25%	99.05	20.6	6.58	13.2	9.89	14.1	281	6.63	100 %	39.7	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	32.1	<LOQ	25%	N.D.	281	50%
STD ±	1.37					5.23				5.92	9.35	0.564	0.699	0.426	0.145	16.7	1.49		1.45						0.885					
Sulfamethoxazole	<LOQ	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	11.4	5.14	38.9	N.D.	27.4	7.43	N.D.	<LOQ	63%	5.33	2.18	N.D.	N.D.	1.39	<LOQ	N.D.	N.D.	38%	N.D.	38.9	33%
STD ±										0.818	0.106	3.15		2.70	1.61				0.393	0.0836			0.107							

Trimethoprim	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	1.69	N.D.	18.97	1.41	N.D.	N.D.	38%	1.78	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	13%	N.D.	18.97	17%
STD ±												0.108		1.11	0.573				0.129											
Metronidazole	22.3	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	13%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	22.3	4%
STD ±	0.470																													
Metronidazole-OH[a]	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	<LOQ	N.D.	<LOQ	N.D.	N.D.	0%	<LOQ	N.D.	<LOQ	<LOQ	<LOQ	N.D.	<LOQ	<LOQ	0%	N.D.	<LOQ	0%
STD ±																														
Dimetridazole	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														
Ronidazole	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														
Cefalexin	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±																														
Calcium channel blockers																														
Diltiazem	4.47	N.D.	3.12	N.D.	1.35	N.D.	N.D.	N.D.	38%	<LOQ	N.D.	6.66	15.6	29.9	3.96	N.D.	0.453	63%	N.D.	N.D.	<LOQ	7.38	<LOQ	1.44	N.D.	<LOQ	25%	N.D.	29.9	42%
STD ±	1.10		2.31		0.00539							0.684	1.18	2.40	0.567		0.00484					0.2005		0.0778						
Verapamil	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	2.42	N.D.	N.D.	N.D.	13%	N.D.	N.D.	<LOQ	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	2.42	4%
STD ±														0.167																
Norverapamil[a]	N.D.	N.D.	N.D.	N.D.	N.D.	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	<LOQ	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±																														

Notes: D.F. (detection frequency); AVE. D.F. (average detection frequency in all sampling campaigns); MIN (minimal concentration detected); MAX (maximal concentration detected); N.D. (not detected); <LOQ (below limit of quantification); [a] metabolites; Sampling sites (1-Corbera , 2-Caseres, 3-Nonasp, 4- Bot Gandesa, 5-Maella, 6-Vallderoures, 7-Prat del C.,8-Bot Canaleta).

B)

Analyte	1st SAMPLING CAMPAIGN (April 2015)				2nd SAMPLING CAMPAIGN (October 2015)				3rd SAMPLING CAMPAIGN (April 2016)				MIN	MAX	AVE. D.F.
	SAMPLING LOCATIONS			D.F.	SAMPLING LOCATIONS			D.F.	SAMPLING LOCATIONS			D.F.			
	POBOLEDA	BISBAL DE FALSET	PRADES		POBOLEDA	BISBAL DE FALSET	PRADES		POBOLEDA	BISBAL DE FALSET	PRADES				
Analgesics/anti-inflammatories															
Ketoprofen	55.7	<LOQ	<LOQ	33%	66.5	N.D.	77.5	67%	56.6	<LOQ	45.8	67%	N.D.	77.5	56%
STD ±	1.26				7.76		3.45		3.61		2.58				
Naproxen	N.D.	<LOQ	41.6	33%	12.7	<LOQ	N.D.	33%	N.D.	<LOQ	35.9	33%	N.D.	41.6	33%
STD ±			5.55		1.17						4.27				
Ibuprofen	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	<LOQ	0%	N.D.	N.D.	<LOQ	0%	N.D.	<LOQ	0%
STD ±															
Indomethacine	N.D.	N.D.	N.D.	0%	N.D.	5.37	14.5	67%	N.D.	N.D.	22.8	33%	N.D.	22.8	33%
STD ±						0.402	1.15				1.97				
Acetaminophen	25.7	6.99	16.3	100%	45.9	33.8	26.3	100%	25.99	18.7	33.7	100%	6.99	45.9	100%
STD ±	3.64	0.177	0.305		5.06	6.59	3.21		2.52	0.923	0.710				
Salicylic acid	18.6	27.6	62.1	100%	99.3	88.9	74.8	100%	19.8	79.2	88.2	100%	18.6	99.3	100%
STD ±	1.19	2.90	14.95		3.69	3.61	4.004		0.375	0.597	2.35				

Diclofenac	27.6	<LOQ	26.999	67%	56.4	<LOQ	71.3	67%	20.4	20.6	41.00003	100%	<LOQ	71.3	78%
STD ±	1.99		3.84		5.49		4.94		0.561	1.75	2.73				
Phenazone	<LOQ	<LOQ	<LOQ	0%	5.06	<LOQ	10.5	67%	N.D.	<LOQ	10.95	33%	N.D.	10.9	33%
STD ±					0.215		1.44				0.447				
Propyphenazone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Piroxicam	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Tenoxicam	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Meloxicam	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Oxycodone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Codeine	1.05	1.91	2.56	100%	1.83	1.41	24.4	100%	N.D.	<LOQ	10.9	33%	N.D.	24.4	78%
STD ±	0.193	0.438	0.411		0.115	0.0849	2.40				1.02				
Lipid regulators and cholesterol lowering statin drugs															
Bezafibrate	25.3	N.D.	53.97	67%	31.1	N.D.	8.42	67%	43.4	N.D.	36.4	67%	N.D.	53.9	67%
STD ±	4.17		1.47		7.46		0.806		3.16		3.71				
Gemfibrozil	53.3	<LOQ	34.3	67%	53.2	N.D.	24.6	67%	31.1	N.D.	55.01	67%	N.D.	55.01	67%
STD ±	6.44		3.52		4.99		4.12		9.27		4.19				
Pravastatin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Fluvastatin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Atorvastatin	N.D.	N.D.	0.687	33%	0.143	N.D.	1.62	67%	N.D.	N.D.	5.87	33%	N.D.	5.87	44%
STD ±			0.0178		0.0331		0.0262				0.297				
Psychiatric drugs															
Carbamazepine	<LOQ	3.80	12.6	67%	<LOQ	4.88	23.9	67%	N.D.	13.1	7.93	67%	N.D.	23.9	67%
STD ±		0.511	1.97			0.0427	2.76			0.288	0.773				
Acridone[a]	N.D.	N.D.	<LOQ	0%	<LOQ	<LOQ	0.634	0%	N.D.	N.D.	N.D.	0%	N.D.	0.634	0%
STD ±							0.00675								
Sertraline	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Citalopram	<LOQ	<LOQ	6.02	33%	4.61	0.8007	24.4	100%	N.D.	<LOQ	4.92	33%	N.D.	24.4	56%
STD ±			0.746		0.195	0.123	4.60				0.347				
Venlafaxine	1.93	0.533	7.37	100%	N.D.	3.27	18.2	67%	N.D.	1.52	26.4	67%	N.D.	26.4	78%
STD ±	0.0275	0.025	0.755			0.0846	0.336			0.0158	1.22				
Trazodone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Fluoxetine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Norfluoxetine[a]	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Paroxetine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Diazepam	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%

STD ±															
Alprazolam	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Histamine H1 and H2 receptor antagonists															
Loratadine	<LOQ	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Desloratadine[a]	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Ranitidine	N.D.	N.D.	1.41	33%	0.781	<LOQ	3.15	67%	<LOQ	<LOQ	<LOQ	0%	N.D.	3.15	33%
STD ±			0.182		0.0497		0.476								
Famotidine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.566	33%	N.D.	N.D.	N.D.	0%	N.D.	0.566	11%
STD ±							0.0600								
Cimetidine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	<LOQ	<LOQ	<LOQ	0%	N.D.	<LOQ	0%
STD ±															
β -Blocking agents															
Atenolol	21.1	0.775	26.8	100%	42.02	0.473	30.02	100%	48.9	<LOQ	38.9	67%	<LOQ	48.9	89%
STD ±	2.57	0.119	3.96		6.62	0.0120	3.73		1.75		2.53				
Sotalol	N.D.	N.D.	N.D.	0%	N.D.	N.D.	20.2	33%	N.D.	N.D.	N.D.	0%	N.D.	20.2	11%
STD ±							2.64								
Propranolol	<LOQ	<LOQ	2.35	33%	N.D.	<LOQ	3.57	33%	<LOQ	<LOQ	4.93	33%	N.D.	4.93	33%
STD ±			0.174				0.642				0.0129				
Metoprolol	<LOQ	N.D.	<LOQ	0%	N.D.	<LOQ	13.9	33%	N.D.	N.D.	N.D.	0%	N.D.	13.9	11%
STD ±							2.13								
Nadolol	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.338	33%	N.D.	N.D.	N.D.	0%	N.D.	0.338	11%
STD ±							0.0609								
Carazolol	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Diuretic															
Furosemide	76.6	<LOQ	72.8	67%	51.7	<LOQ	95.4	67%	102	<LOQ	85.5	67%	<LOQ	102	67%
STD ±	6.29		2.67		8.99		2.14		3.66		3.08				
Antidiabetic															
Glibenclamide	N.D.	<LOQ	3.07	33%	N.D.	<LOQ	12.02	33%	N.D.	<LOQ	<LOQ	0%	N.D.	12.02	22%
STD ±			0.264				2.37								
Antihypertensives															
Amlodipine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Losartan	<LOQ	<LOQ	<LOQ	0%	15.8	N.D.	58.6	67%	N.D.	N.D.	6.94	33%	N.D.	58.6	33%
STD ±					1.09		4.54				0.0936				
Irbesartan	<LOQ	<LOQ	8.09	33%	10.3	0.663	92.8	100%	N.D.	N.D.	N.D.	0%	N.D.	92.8	44%
STD ±			0.646		0.419	0.0600	8.45								
Valsartan	15.1	16.9	87.6	100%	56.8	4.93	62.7	100%	23.1	9.04	179	100%	4.93	179	100%
STD ±	3.86	3.11	8.16		3.07	0.507	2.999		3.61	0.450	5.25				
Antiplatelet agent															
Clopidogrel	<LOQ	N.D.	0.484	33%	2.68	N.D.	4.26	67%	N.D.	N.D.	N.D.	0%	N.D.	4.26	33%
STD ±			0.0948		0.101										
Prostatic hyperplasia															
Tamsulosin	<LOQ	N.D.	<LOQ	0%	0.360	N.D.	0.770	67%	N.D.	N.D.	N.D.	0%	N.D.	0.77	22%

STD ±					0.0130		0.126								
To treat asthma															
Salbutamol	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0.266	33%	N.D.	N.D.	<LOQ	0%	N.D.	0.266	11%
STD ±							0.0387								
Anticoagulant															
Warfarin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Antihelmintics															
Albendazole	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Thiabendazole	<LOQ	N.D.	0.931	33%	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	0.931	11%
STD ±			0.118												
Levamisole	0.948	N.D.	10.1	67%	4.33	0.356	11.3	100%	<LOQ	<LOQ	7.49	33%	N.D.	11.3	67%
STD ±	0.113		2.06		0.346	0.0104	0.982				0.398				
Synthetic glucocorticoid															
Dexamethasone	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Sedation and muscle relaxation															
Xylazine	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Antibiotics															
Erythromycin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Ofloxacin	<LOQ	18.6	<LOQ	33%	24.8	4.29	19.3	100%	<LOQ	<LOQ	<LOQ	0%	<LOQ	24.8	44%
STD ±		0.883			0.289	0.676	5.99								
Sulfamethoxazole	N.D.	<LOQ	N.D.	0%	4.13	5.98	1.49	100%	N.D.	<LOQ	N.D.	0%	N.D.	5.98	33%
STD ±					0.171	0.413	0.484								
Trimethoprim	<LOQ	<LOQ	N.D.	0%	1.26	<LOQ	N.D.	33%	N.D.	N.D.	N.D.	0%	N.D.	1.26	11%
STD ±					0.0980										
Metronidazole	N.D.	N.D.	9.78	33%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	33.2	33%	N.D.	33.2	22%
STD ±			2.46								1.48				
Metronidazole-OH[a]	N.D.	N.D.	3.54	33%	N.D.	N.D.	N.D.	0%	<LOQ	<LOQ	11.1	33%	N.D.	11.1	22%
STD ±			0.376								1.14				
Dimetridazole	N.D.	N.D.	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Ronidazole	<LOQ	<LOQ	<LOQ	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															
Cefalexin	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Calcium channel blockers															
Diltiazem	0.623	N.D.	2.18	67%	3.31	N.D.	1.80	67%	N.D.	N.D.	1.68	33%	N.D.	3.31	56%
STD ±	0.0330		0.260		0.0905		0.275				0.133				
Verapamil	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	N.D.	0%
STD ±															
Norverapamil[a]	N.D.	N.D.	N.D.	0%	<LOQ	N.D.	N.D.	0%	N.D.	N.D.	N.D.	0%	N.D.	<LOQ	0%
STD ±															

Notes: D.F. (detection frequency); AVE.D.F. (average detection frequency in all sampling campaigns); MIN (minimal concentration detected); MAX (maximal concentration detected); N.D. (not detected); <LOQ (below limit of quantification); [a] metabolites

SUPPLEMENTARY INFORMATION (CHAPTER 3)

Table 1S. Main characteristics of the treatment process, population served and average monthly WWTP outflows of the Sparta WWTP for the sampling periods of July 2015, June and September 2016.

Name	Sparti
Code	GR254001017
Latitude (φ)	37.070952
Longitude (λ)	22.447718
Settlement	Sparti
Max Population	22000
Operated since	1990
Disposal of treated effluent	Evrotas
Average inflow in WWTP (m3/day)	4634
Average inflow of wastewater (m3/day)	4594
Average inflow of sewage (m3/day)	40
Average inflow load BOD5 (kg/day)	1159
Average monthly outflow of wastewater (m3/d) (July 2015)	3950
Average monthly outflow of wastewater (m3/d) (June 2016)	4163
Average monthly outflow of wastewater (m3/d) (September 2016)	3662
Sewage treatment line	Primary settlement
	Secondary settlement
	N removal
	P removal (biological)
	Disinfection(chlorination)
	Further processing (gravity filters)
Sludge treatment line	Thickening
	Dehydration

Note: sources (Special Water Secretariat, YPEKA: http://astikalimata.ypeka.gr/Services/Pages/View.aspx?xuwcode=GR254001017)

Table 2S. Distance (m) and corresponding water travel times between the input and output of each waterbody segment in all sampling campaigns.

Waterbody segments	Campaign (29/07/2015-30/07/2015)		Campaign (24/06/2016-25/06/2016)		Campaign (31/08-03/09/2016)	
	Distance	Travel time (T.T.) / h	Distance	Travel time (T.T.) / h	Distance	Travel time (T.T.) / h
KolUS INPUT-OUTPUT	3950m	4	3950m	12	3950m	22
KolDS INPUT-OUTPUT	3670m	3	3670m	n.a.	3670m	n.a.
Vivari INPUT-OUTPUT	3610m	2	3610m	n.a.	3610m	6,5
Sparta INPUT-OUTPUT	3700m	2	3700m	4,9	3700m	5,9

Table 3S. The analysis of a land cover map for each sampling site, as retrieved by CORINE product for 2012 (land use, %).

Land uses	Campaign (29/07/2015-30/07/2015)				Campaign (24/06/2016-25/06/2016)				Campaign (31/08-03/09/2016)			
	SAMPLING LOCATIONS											
	KolUS	KolDS	Vivari	Sparta	KolUS	KolDS	Vivari	Sparta	KolUS	KolDS	Vivari	Sparta
Forest (%)	80	60	30	10	80	60	30	10	80	60	30	10
Agriculture(%)	20	40	70	65	20	40	70	65	20	40	70	65
Industrial (%)	0	0	0	0	0	0	0	0	0	0	0	0
Urban (%)	0	0	0	15	0	0	0	15	0	0	0	15

Table 4S. Agricultural and Livestock census of Greece 2009 per each sampling site.

Sampling site	Agricultural area (m^2)				Livestock (number)							
	Annual crops	Tree crops	Vineyards	Grassland - pastures	Cattles	Sheeps	Goats	Pigs	Equines	Rabbits	Poultries	Beehive
KolUS	705.835,3	11.464.426,1	39.400,4	1.510.683,8	-	3.030	4.640	-	31	677	4.329	678
KolDS	801.245,1	13.265.671,1	50.016,6	2.104.902,0	-	3.203	5.102	-	35	729	4.822	709
Vivari	3.541.576,35	43.504.244,80	163.444,70	15.306.288,87	910	8.584	12.767	44	74	1.244	10.667	1.500
Sparta	5.461.108,10	187.592.961,63	401.773,43	34.904.193,01	1.307	28.886	43.381	7.938	154	3.084	111.745	4.238

Table 5S. Measured physicochemical properties of water.

Physicochemical properties	Campaign (29/07/2015-30/07/2015)				Campaign (24/06/2016-25/06/2016)				Campaign (31/08-03/09/2016)			
	SAMPLING SITES											
	KolUS	KolDS	Vivari	Sparta	KolUS	KolDS	Vivari	Sparta	KolUS	KolDS	Vivari	Sparta
K^+ (mgL^{-1})	0.77	0.73	0.7	1.15	0.75	0.75	0.66	2.43	0.8	1.03	0.62	2.3
Cl^- (mgL^{-1})	8.74	8.62	7.06	10.5	10.96	10.7	9.07	13.8	11.3	11.8	9.33	18.3
NO_3^- (mgL^{-1})	0.59	0.62	0.88	1.59	0.35	0.30	0.58	0.71	0.39	0.33	0.64	0.73
NO_2^- (mgL^{-1})	0.00171	0.00155	0.00169	0.00822	0.002	0.003	0.002	0.105	0.001	0.002	0.002	0.04
NH_4^+ (mgL^{-1})	0.0110	0.0077	0.0118	0.0115	0.01	0.042	0.012	0.065	0.007	0.022	0.007	0.249
PO_4^{3-} (mgL^{-1})	0.0009	0.0011	0.0004	0.0522	0.002	0,001	0.002	0.006	0.003	0.013	0.002	0.015
D.O. (mgL^{-1})	9.50	9.00	9.20	9.20	10.8	9.88	10.3	2.99	9.37	9.55	9.98	6.00
Water Temperature (°C)	18.2	21.8	18.8	20.1	23.2	19.4	16.9	25.5	16.6	21.2	18.4	23.4
Conductivity ($\mu ScmL^{-1}$)	465	450	564	605	457	417	520	651	519	447	139	624

Table 6S. Target compounds organized according to their therapeutic groups and the isotopically labeled internal standards assigned for their quantification.

Therapeutic groups	Analyte	Number	CAS number	Corresponding internal standard
Analgesics/anti-inflammatories (10)	Ketoprofen	1	22071-15-4	Ibuprofen-d3
	Naproxen	2	22204-53-1	Ibuprofen-d3
	Ibuprofen	3	15687-27-1	Ibuprofen-d3
	Indomethacine	4	53-86-1	Indomethacine-d4
	Diclofenac	5	15307-79-6	Ibuprofen-d3
	Phenazone	6	60-80-0	Phenazone-d3
	Propyphenazone	7	479-92-5	Phenazone-d3
	Piroxicam	8	36322-90-4	Meloxicam-d3
	Tenoxicam	9	59804-37-4	Meloxicam-d3
	Oxycodone	10	124-90-3	Carbamazepine-d10
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	11	41859-67-0	Bezafibrate-d6
	Gemfibrozil	12	25812-30-0	Gemfibrozil-d6
	Pravastatin	13	81131-70-6	Gemfibrozil-d6
	Fluvastatin	14	93957-54-1	Gemfibrozil-d6
Psychiatric drugs (13)	Carbamazepine	15	298-46-4	Carbamazepine-d10
	2-Hydroxycarbamazepine[a]	16	68011-66-5	Carbamazepine-d10
	10.11-Epoxycarbamazepine[a]	17	36507-30-9	Carbamazepine-d10
	Sertraline	18	79559-97-0	Fluoxetine-d5
	Citalopram	19	59729-32-7	Citalopram-d4

	Olanzapine	20	132539-06-1	Carbamazepine-d10
	Trazodone	21	25332-39-2	Fluoxetine-d5
	Fluoxetine	22	56296-78-7	Fluoxetine-d5
	Norfluoxetine[a]	23	83891-03-6	Fluoxetine-d5
	Paroxetine	24	110429-35-1	Fluoxetine-d5
	Diazepam	25	439-14-5	Diazepam-d5
	Lorazepam	26	846-49-1	Diazepam-d5
	Alprazolam	27	28981-97-7	Diazepam-d5
Histamine H1 and H2 receptor antagonists (3)	Ranitidine	28	66357-59-3	Diazepam-d5
	Famotidine	29	76824-35-6	Diazepam-d5
	Cimetidine	30	51481-61-9	Diazepam-d5
β -Blocking agents (3)	Sotalol	31	959-24-0	Diazepam-d5
	Propranolol	32	318-98-9	Diazepam-d5
	Carazolol	33	57775-29-8	Diazepam-d5
Diuretic (3)	Hydrochlorothiazide	34	58-93-5	Hydrochlorothiazide-d2
	Furosemide	35	54-31-9	Furosemide-d5
	Torasemide	36	56211-40-6	Furosemide-d5
Antidiabetic (1)	Glibenclamide	37	10238-21-8	Glyburide-d3
Antihypertensives (3)	Amlodipine	38	111470-99-6	Amlodipine-d4
	Losartan	39	124750-99-8	Valsartan-d8
	Valsartan	40	137862-53-4	Valsartan-d8
Prostatic hyperplasia (1)	Tamsulosin	41	106463-17-6	Sulfamethoxazole-d4
To treat asthma (1)	Salbutamol	42	18559-94-9	Atenolol-d7
Anticoagulant (1)	Warfarin	43	81-81-2	Warfarin-d5

Antihelmintics (2)	Albendazole	44	54965-21-8	Ronidazole-d3
	Thiabendazole	45	148-79-8	Ronidazole-d3
Synthetic glucocorticoid (1)	Dexamethasone	46	50-02-2	Dexamethasone-d4
Sedation and muscle relaxation (1)	Xylazine	47	23076-35-9	Xylazine-d6
Tranquilizer (2)	Azaperone	48	1649-18-9	Azaperone-d4
	Azaperol[a]	49	5/9/2804	Azaperone-d4
Antibiotics (11)	Erythromycin	50	59319-72-1	Erythromycin-N.N13C2
	Clarithromycin	51	81103-11-9	Azithromycin-d3
	Tetracycline	52	64-75-5	Sulfamethoxazole-d4
	Ofloxacin	53	82419-36-1	Ofloxacin-d3
	Sulfamethoxazole	54	723-46-6	Sulfamethoxazole-d4
	Trimethoprim	55	738-70-5	Sulfamethoxazole-d4
	Metronidazole	56	443-48-1	Ronidazole-d3
	Metronidazole-OH[a]	57	4812-40-2	Ronidazole-d3
	Dimetridazole	58	551-92-8	Ronidazole-d3
	Ronidazole	59	7681-76-7	Ronidazole-d3
	Cefalexin	60	15686-71-2	Sulfamethoxazole-d4
Calcium channel blockers (2)	Verapamil	61	152-11-4	Verapamil-d6
	Norverapamil[a]	62	67812-42-4	Verapamil-d6

[a]Metabolites

Table 7S. Method performance parameters for the PhACs in river water: recoveries (%), relative standard deviation (RSD% for n=3), limits of detection (LOD; ngL^{-1}) limits of quantification (LOQ; ngL^{-1}).

Therapeutic groups	Analyte	LOD (ngL^{-1})	LOQ (ngL^{-1})	%Recoveries (n=3)	%RSD (n =3)
Analgesics/anti-inflammatories (10)	Ketoprofen	4.47	14.9	85%	6.2%
	Naproxen	0.59	2.0	98%	6.1%
	Ibuprofen	2.98	9.9	89%	5.8%
	Indomethacine	0.81	2.7	80%	1.7%
	Diclofenac	1.34	4.5	87%	5.0%
	Phenazone	0.18	0.6	107%	1.3%
	Propyphenazone	0.18	0.6	85%	2.3%
	Piroxicam	0.17	0.6	71%	4.0%
	Tenoxicam	0.14	0.5	66%	1.9%
	Oxycodone	2.91	9.7	82%	3.6%
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	0.18	0.6	99%	1.6%
	Gemfibrozil	0.13	0.4	95%	3.1%
	Pravastatin	0.87	2.9	105%	1.3%
	Fluvastatin	0.13	0.4	90%	3.9%
Psychiatric drugs (13)	Carbamazepine	0.07	0.2	94%	1.3%
	2-Hydroxycarbamazepine[a]	0.08	0.3	87%	2.7%
	10.11-Epoxycarbamazpine[a]	0.40	1.3	106%	1.3%
	Sertraline	3.34	11.1	24%	8.1%
	Citalopram	0.09	0.3	90%	5.0%
	Olanzapine	0.03	0.1	66%	8.5%
	Trazodone	0.07	0.2	103%	7.1%
	Fluoxetine	0.61	2.0	93%	2.1%
	Norfluoxetine[a]	0.31	1.0	122%	2.5%

	Paroxetine	0.79	2.6	103%	2.6%
	Diazepam	0.18	0.6	100%	4.8%
	Lorazepam	0.65	2.2	98%	2.6%
	Alprazolam	0.33	1.1	107%	1.2%
Histamine H1 and H2 receptor antagonists (3)	Ranitidine	0.03	0.1	46%	2.3%
	Famotidine	0.05	0.2	95%	4.3%
	Cimetidine	0.02	0.1	83%	4.4%
β -Blocking agents (3)	Sotalol	0.12	0.4	102%	0.9%
	Propranolol	0.09	0.3	58%	5.4%
	Carazolol	0.03	0.1	90%	2.7%
Diuretic (3)	Hydrochlorothiazide	0.07	0.2	99%	3.1%
	Furosemide	4.55	15.2	88%	2.9%
	Torasemide	0.17	0.6	109%	5.3%
Antidiabetic (1)	Glibenclamide	0.68	2.3	79%	3.0%
Antihypertensives (3)	Amlodipine	0.68	2.3	69%	3.8%
	Losartan	0.62	2.1	110%	6.0%
	Valsartan	0.31	1.0	87%	2.3%
Prostatic hyperplasia (1)	Tamsulosin	0.04	0.1	76%	3.8%
To treat asthma (1)	Salbutamol	0.02	0.1	45%	2.4%
Anticoagulant (1)	Warfarin	0.10	0.3	94%	1.9%
Antihelmintics (2)	Albendazole	0.02	0.1	37%	4.0%
	Thiabendazole	0.02	0.1	69%	1.6%
Synthetic glucocorticoid (1)	Dexamethasone	0.45	1.5	95%	1.7%
Sedation and muscle relaxation (1)	Xylazine	0.24	0.8	95%	0.4%
Tranquilizer (2)	Azaperone	0.34	1.1	83%	1.4%
	Azaperol[a]	0.20	0.7	84%	1.6%
Antibiotics (11)	Erythromycin	1.20	4.0	101%	4.1%

	Clarithromycin	0.24	0.8	116%	1.8%
	Tetracycline	5.65	18.8	78%	4.5%
	Ofloxacin	0.28	0.9	55%	9.0%
	Sulfamethoxazole	0.23	0.8	90%	2.2%
	Trimethoprim	0.05	0.2	79%	1.5%
	Metronidazole	0.75	2.5	74%	3.3%
	Metronidazole-OH[a]	0.55	1.8	33%	1.1%
	Dimetridazole	5.79	19.3	94%	1.1%
	Ronidazole	0.17	0.6	95%	3.1%
	Cefalexin	0.07	0.2	16%	5.3%
Calcium channel blockers (2)	Verapamil	0.08	0.3	45%	0.6%
	Norverapamil[a]	0.19	0.6	87%	7.8%

[a]Metabolites

Table 8S. Average concentrations and average detection frequencies (D.F.) of PhACs detected in water samples (ngL^{-1}) at each waterbody segment: 1.1.)1st sampling campaign (29-30/07/2015), 1.2.) 2nd sampling campaign (24-25/06/2016) and 1.3.) 3rd sampling campaign (31/08-03/09/2016); and concentrations of PhACs detected in water samples (ngL^{-1}) at input and output of each waterbody segment: 2.1.)1st sampling campaign (29-30/07/2015), 2.2.) 2nd sampling campaign (24-25/06/2016) and 2.3.) 3rd sampling campaign (31/08-03/09/2016).

1.1.)

Therapeutic groups	Analyte	KolUS	STD ±	KolDS	STD ±	Vivari	STD ±	Sparta	STD ±	D.F.
Analgesics/anti-inflammatories (10)	Ketoprofen	<LOQ		n.d.		n.d.		<LOQ		0%
	Naproxen	n.d.		2.6	0.0056	3.0	0.022	3.2	0.45	75%
	Ibuprofen	n.d.		n.d.		n.d.		n.d.		0%
	Indomethacine	n.d.		n.d.		n.d.		n.d.		0%

	Diclofenac	n.d.		<LOQ		n.d.		<LOQ		0%
	Phenazone	n.d.		n.d.		n.d.		n.d.		0%
	Propyphenazone	n.d.		n.d.		n.d.		n.d.		0%
	Piroxicam	n.d.		n.d.		n.d.		n.d.		0%
	Tenoxicam	n.d.		n.d.		n.d.		n.d.		0%
	Oxycodone	n.d.		n.d.		n.d.		n.d.		0%
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.d.		0%
	Gemfibrozil	n.d.		n.d.		n.d.		n.d.		0%
	Pravastatin	n.d.		n.d.		n.d.		n.d.		0%
	Fluvastatin	n.d.		n.d.		n.d.		n.d.		0%
Psychiatric drugs (13)	Carbamazepine	<LOQ		<LOQ		n.d.		4.0	0.17	25%
	2-Hydroxycarbamazepine[a]	n.d.		n.d.		n.d.		<LOQ		0%
	10.11-Epoxycarbamazpine[a]	n.d.		n.d.		n.d.		2.4	0.065	25%
	Sertraline	n.d.		n.d.		n.d.		n.d.		0%
	Citalopram	n.d.		n.d.		n.d.		n.d.		0%
	Olanzapine	n.d.		n.d.		n.d.		n.d.		0%
	Trazodone	n.d.		n.d.		n.d.		n.d.		0%
	Fluoxetine	n.d.		n.d.		n.d.		n.d.		0%
	Norfluoxetine[a]	n.d.		n.d.		n.d.		n.d.		0%
	Paroxetine	n.d.		n.d.		n.d.		n.d.		0%
	Diazepam	n.d.		n.d.		n.d.		n.d.		0%
	Lorazepam	n.d.		n.d.		n.d.		n.d.		0%
	Alprazolam	n.d.		n.d.		n.d.		n.d.		0%
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.d.		0%
	Famotidine	n.d.		n.d.		n.d.		n.d.		0%
	Cimetidine	n.d.		n.d.		n.d.		n.d.		0%
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		2.3	0.33	25%

	Propranolol	n.d.		n.d.		n.d.		<LOQ		0%
	Carazolol	n.d.		n.d.		n.d.		n.d.		0%
Diuretic (3)	Hydrochlorothiazide	0.84	0.090	0.76	0.12	0.67	0.10	9.4	1.2	100%
	Furosemide	n.d.		n.d.		n.d.		n.d.		0%
	Torasemide	n.d.		n.d.		n.d.		n.d.		0%
Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.d.		0%
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.d.		0%
	Losartan	n.d.		n.d.		n.d.		n.d.		0%
	Valsartan	n.d.		n.d.		n.d.		6.2	0.65	25%
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.d.		0%
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.d.		0%
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.d.		0%
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.d.		0%
	Thiabendazole	n.d.		n.d.		n.d.		n.d.		0%
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.d.		0%
Sedation and muscle relaxation (1)	Xylazine	n.d.		n.d.		n.d.		n.d.		0%
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.d.		0%
	Azaperol[a]	n.d.		n.d.		n.d.		n.d.		0%
Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.d.		0%
	Clarithromycin	n.d.		n.d.		n.d.		n.d.		0%
	Tetracycline	n.d.		n.d.		n.d.		n.d.		0%
	Ofloxacin	n.d.		n.d.		n.d.		n.d.		0%
	Sulfamethoxazole	n.d.		n.d.		n.d.		2.5	0.13	25%
	Trimethoprim	n.d.		n.d.		0.31	0.14	0.60	0.32	50%
	Metronidazole	n.d.		n.d.		n.d.		n.d.		0%
	Metronidazole-OH[a]	n.d.		n.d.		n.d.		n.d.		0%
	Dimetridazole	n.d.		n.d.		n.d.		n.d.		0%
	Ronidazole	n.d.		n.d.		n.d.		n.d.		0%

	Cefalexin	n.d.		n.d.		n.d.		n.d.		0%
Calcium channel blockers (2)	Verapamil	n.d.		n.d.		n.d.		n.d.		0%
	Norverapamil[a]	n.d.		n.d.		n.d.		n.d.		0%

Notes: <LOQ = values below limit of quantification; n.d. =not detected; [a]Metabolites

1.2.)

Therapeutic groups	Analyte	KolUS	STD ±	KolDS	STD ±	Vivari	STD ±	Sparta	STD ±	D.F.
Analgesics/anti-inflammatories (10)	Ketoprofen	<LOQ		<LOQ		<LOQ		39	2.0	25%
	Naproxen	n.d.		n.d.		n.d.		<LOQ		0%
	Ibuprofen	n.d.		n.d.		n.d.		n.d.		0%
	Indomethacine	n.d.		n.d.		n.d.		n.d.		0%
	Diclofenac	n.d.		n.d.		n.d.		n.d.		0%
	Phenazone	n.d.		n.d.		n.d.		n.d.		0%
	Propyphenazone	n.d.		n.d.		n.d.		n.d.		0%
	Piroxicam	n.d.		n.d.		n.d.		n.d.		0%
	Tenoxicam	n.d.		n.d.		n.d.		n.d.		0%
	Oxycodone	n.d.		n.d.		n.d.		n.d.		0%
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.d.		0%
	Gemfibrozil	n.d.		n.d.		n.d.		n.d.		0%
	Pravastatin	n.d.		n.d.		n.d.		n.d.		0%
	Fluvastatin	n.d.		n.d.		n.d.		n.d.		0%
Psychiatric drugs (13)	Carbamazepine	n.d.		n.d.		n.d.		9.5	0.21	25%
	2-Hydroxycarbamazepine[a]	n.d.		n.d.		n.d.		0.40	0.047	25%
	10.11-Epoxycarbamazpine[a]	n.d.		n.d.		n.d.		3.7	0.27	25%
	Sertraline	n.d.		n.d.		n.d.		n.d.		0%
	Citalopram	n.d.		n.d.		n.d.		n.d.		0%
	Olanzapine	n.d.		n.d.		n.d.		n.d.		0%

	Trazodone	n.d.		n.d.		n.d.		n.d.		0%
	Fluoxetine	n.d.		n.d.		n.d.		n.d.		0%
	Norfluoxetine[a]	n.d.		n.d.		n.d.		n.d.		0%
	Paroxetine	n.d.		n.d.		n.d.		n.d.		0%
	Diazepam	n.d.		n.d.		n.d.		n.d.		0%
	Lorazepam	n.d.		n.d.		n.d.		n.d.		0%
	Alprazolam	n.d.		n.d.		n.d.		<LOQ		0%
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.d.		0%
	Famotidine	n.d.		n.d.		n.d.		n.d.		0%
	Cimetidine	n.d.		n.d.		n.d.		n.d.		0%
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		3.1	0.088	25%
	Propranolol	n.d.		n.d.		n.d.		n.d.		0%
	Carazolol	n.d.		n.d.		n.d.		n.d.		0%
Diuretic (3)	Hydrochlorothiazide	n.d.		n.d.		n.d.		21	1.1	25%
	Furosemide	n.d.		n.d.		n.d.		20	2.1	25%
	Torasemide	n.d.		n.d.		n.d.		n.d.		0%
Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.d.		0%
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.d.		0%
	Losartan	n.d.		n.d.		n.d.		n.d.		0%
	Valsartan	n.d.		6.5	0.64	3.5	0.082	8.1	0.21	75%
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.d.		0%
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.d.		0%
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.d.		0%
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.d.		0%
	Thiabendazole	n.d.		n.d.		n.d.		n.d.		0%
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.d.		0%
Sedation and muscle relaxation (1)	Xylazine	n.d.		n.d.		n.d.		n.d.		0%
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.d.		0%

	Azaperol[a]	n.d.		n.d.		n.d.		n.d.		0%
Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.d.		0%
	Clarithromycin	n.d.		n.d.		n.d.		n.d.		0%
	Tetracycline	n.d.		n.d.		n.d.		n.d.		0%
	Ofloxacin	n.d.		n.d.		n.d.		n.d.		0%
	Sulfamethoxazole	n.d.		n.d.		n.d.		<LOQ		0%
	Trimethoprim	n.d.		n.d.		n.d.		n.d.		0%
	Metronidazole	n.d.		n.d.		n.d.		n.d.		0%
	Metronidazole-OH[a]	n.d.		n.d.		n.d.		n.d.		0%
	Dimetridazole	n.d.		n.d.		n.d.		n.d.		0%
	Ronidazole	n.d.		n.d.		n.d.		n.d.		0%
	Cefalexin	n.d.		n.d.		n.d.		n.d.		0%
Calcium channel blockers (2)	Verapamil	n.d.		n.d.		n.d.		n.d.		0%
	Norverapamil[a]	n.d.		n.d.		n.d.		n.d.		0%

Notes: <LOQ = values below limit of quantification; n.d. =not detected; [a]Metabolites

1.3.)

Therapeutic groups	Analyte	KolUS	STD ±	KolDS	STD ±	Vivari	STD ±	Sparta	STD ±	D.F.
Analgesics/anti-inflammatories (10)	Ketoprofen	<LOQ		<LOQ		<LOQ		45	3.3	25%
	Naproxen	n.d.		n.d.		n.d.		6.8	0.22	25%
	Ibuprofen	n.d.		n.d.		n.d.		n.d.		0%
	Indomethacine	n.d.		n.d.		n.d.		n.d.		0%
	Diclofenac	n.d.		n.d.		n.d.		n.d.		0%
	Phenazone	n.d.		n.d.		n.d.		n.d.		0%
	Propyphenazone	n.d.		n.d.		n.d.		n.d.		0%
	Piroxicam	n.d.		n.d.		n.d.		n.d.		0%

	Tenoxicam	n.d.		n.d.		n.d.		n.d.		0%
	Oxycodone	n.d.		n.d.		n.d.		n.d.		0%
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.d.		0%
	Gemfibrozil	n.d.		n.d.		n.d.		n.d.		0%
	Pravastatin	n.d.		n.d.		n.d.		n.d.		0%
	Fluvastatin	n.d.		n.d.		n.d.		n.d.		0%
Psychiatric drugs (13)	Carbamazepine	n.d.		n.d.		n.d.		9.2	0.23	25%
	2-Hydroxycarbamazepine[a]	n.d.		n.d.		n.d.		1.1	0.067	25%
	10.11-Epoxycarbamazpine[a]	n.d.		n.d.		n.d.		5.3	0.076	25%
	Sertraline	n.d.		n.d.		n.d.		n.d.		0%
	Citalopram	n.d.		n.d.		n.d.		n.d.		0%
	Olanzapine	n.d.		n.d.		n.d.		n.d.		0%
	Trazodone	n.d.		n.d.		n.d.		n.d.		0%
	Fluoxetine	n.d.		n.d.		n.d.		n.d.		0%
	Norfluoxetine[a]	n.d.		n.d.		n.d.		n.d.		0%
	Paroxetine	n.d.		n.d.		n.d.		n.d.		0%
	Diazepam	n.d.		n.d.		n.d.		n.d.		0%
	Lorazepam	n.d.		n.d.		n.d.		n.d.		0%
	Alprazolam	n.d.		n.d.		n.d.		<LOQ		0%
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.d.		0%
	Famotidine	n.d.		n.d.		n.d.		n.d.		0%
	Cimetidine	n.d.		n.d.		n.d.		n.d.		0%
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		4.4	0.20	25%
	Propranolol	n.d.		n.d.		n.d.		n.d.		0%
	Carazolol	n.d.		n.d.		n.d.		n.d.		0%
Diuretic (3)	Hydrochlorothiazide	n.d.		n.d.		n.d.		51	2.1	25%
	Furosemide	<LOQ		n.d.		n.d.		n.d.		0%
	Torasemide	n.d.		n.d.		n.d.		n.d.		0%

Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.d.		0%
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.d.		0%
	Losartan	n.d.		n.d.		n.d.		n.d.		0%
	Valsartan	5.2	0.31	9.1	0.95	6.2	0.14	9.8	0.39	100%
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.d.		0%
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.d.		0%
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.d.		0%
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.d.		0%
	Thiabendazole	n.d.		n.d.		n.d.		n.d.		0%
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.d.		0%
Sedation and muscle relaxation (1)	Xylazine	n.d.		n.d.		n.d.		n.d.		0%
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.d.		0%
	Azaperol[a]	n.d.		n.d.		n.d.		n.d.		0%
Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.d.		0%
	Clarithromycin	n.d.		n.d.		n.d.		n.d.		0%
	Tetracycline	n.d.		n.d.		n.d.		n.d.		0%
	Ofloxacin	n.d.		n.d.		n.d.		n.d.		0%
	Sulfamethoxazole	n.d.		n.d.		n.d.		3.8	0.085	25%
	Trimethoprim	n.d.		n.d.		n.d.		n.d.		0%
	Metronidazole	n.d.		n.d.		n.d.		n.d.		0%
	Metronidazole-OH[a]	n.d.		n.d.		n.d.		n.d.		0%
	Dimetridazole	n.d.		n.d.		n.d.		n.d.		0%
	Ronidazole	n.d.		n.d.		n.d.		n.d.		0%
	Cefalexin	n.d.		n.d.		n.d.		n.d.		0%
Calcium channel blockers (2)	Verapamil	n.d.		n.d.		n.d.		n.d.		0%
	Norverapamil[a]	n.d.		n.d.		n.d.		n.d.		0%

Notes: <LOQ = values below limit of quantification; n.d. =not detected; [a]Metabolites

2.1.)

Therapeutic groups	Analyte	KolUS INPUT	STD ±	KolUS OUTPUT	STD ±	KolDS INPUT	STD ±	KolDS OUTPUT	STD ±	Vivari INPUT	STD ±	Vivari OUTPUT	STD ±	Sparta INPUT	STD ±	Sparta OUTPUT	STD ±
Analgesics/ anti-inflammatories (10)	Ketoprofen	n.d.		<LOQ		n.d.		n.d.		n.d.		n.d.		<LOQ		<LOQ	
	Naproxen	n.d.		n.d.		2,55	0,006	n.d.		3,51	0,035	2,41	0,010	2,97	0,871	3,52	0,025
	Ibuprofen	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Indomethacine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Diclofenac	n.d.		n.d.		n.d.		<LOQ		n.d.		n.d.		n.d.		<LOQ	
	Phenazone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Propyphenazone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Piroxicam	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Tenoxicam	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Oxycodone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Gemfibrozil	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Pravastatin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Fluvastatin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Psychiatric drugs (13)	Carbamazepine	<LOQ		<LOQ		<LOQ		n.d.		n.d.		n.d.		4,04	0,205	4,03	0,134
	2-Hydroxycarbamazepine[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		<LOQ		n.d.	
	10.11-Epoxycarbamazpine[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		2,32	0,045	2,46	0,08
	Sertraline	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Citalopram	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Olanzapine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Trazodone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Fluoxetine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Norfluoxetine[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Paroxetine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	

	Diazepam	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.	
	Alprazolam	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Famotidine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Cimetidine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		2,79	0,197	1,84	0,460
	Propranolol	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		<LOQ		n.d.	
	Carazolol	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Diuretic (3)	Hydrochlorothiazide	0,814	0,0007	0,871	0,180	0,821	0,104	0,693	0,144	0,673	0,092	0,674	0,108	13,7	2,26	5,03	0,085
	Furosemide	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Torasemide	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Losartan	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Valsartan	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		7,24	0,692	5,19	0,601
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Thiabendazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Sedation and muscle relaxation (1)	Xylazine	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Azaperol[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	

Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Clarithromycin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Tetracycline	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Ofloxacin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Sulfamethoxazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		2,96	0,091	2,09	0,168
	Trimethoprim	n.d.		n.d.		n.d.		n.d.		0,310	0,140	n.d.		0,610	0,307	0,597	0,330
	Metronidazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Metronidazole-OH[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Dimetridazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Ronidazole	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Cefalexin	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
Calcium channel blockers (2)	Verapamil	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	
	Norverapamil[a]	n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.		n.d.	

Notes: <LOQ = values below limit of quantification; n.d. =not detected; [a]Metabolites

2.2.)

Therapeutic groups	Analyte	KolUS INPUT	STD ±	KolUS OUTPUT	STD ±	KolDS INPUT	STD ±	KolDS OUTPUT	STD ±	Vivari INPUT	STD ±	Vivari OUTPUT	STD ±	Sparta INPUT	STD ±	Sparta OUTPUT	STD ±
Analgesics/ anti-inflammatories (10)	Ketoprofen	<LOQ		<LOQ		<LOQ		n.a.		<LOQ		<LOQ		35,6	0,480	41,9	3,49
	Naproxen	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		<LOQ		<LOQ	
	Ibuprofen	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Indomethacine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Diclofenac	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Phenazone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Propyphenazone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Piroxicam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Tenoxicam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

	Oxycodone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Gemfibrozil	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Pravastatin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Fluvastatin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Psychiatric drugs (13)	Carbamazepine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		11,3	0,185	7,82	0,233
	2-Hydroxycarbamazepine[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		0,398	0,047	<LOQ	
	10.11-Epoxycarbamazpine[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		4,59	0,215	2,84	0,320
	Sertraline	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Citalopram	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Olanzapine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Trazodone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Fluoxetine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Norfluoxetine[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Paroxetine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Diazepam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Lorazepam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Alprazolam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		<LOQ		n.d.	
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Famotidine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Cimetidine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		3,01	0,132	3,22	0,044
	Propranolol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Carazolol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Diuretic (3)	Hydrochlorothiazide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		29,96	1,25	12,2	1,02
	Furosemide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		19,5	2,11	<LOQ	
	Torasemide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Losartan	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Valsartan	n.d.		n.d.		6,45	0,638	n.a.		3,54	0,082	<LOQ		10,2	0,261	6,11	0,154
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Thiabendazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Sedation and muscle relaxation (1)	Xylazine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Azaperol[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Clarithromycin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Tetracycline	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Ofloxacin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Sulfamethoxazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		<LOQ		<LOQ	
	Trimethoprim	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Metronidazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Metronidazole-OH[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Dimetridazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Ronidazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Cefalexin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Calcium	Verapamil	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

channel blockers (2)	Norverapamil[a]	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

Notes: <LOQ = values below limit of quantification; n.d. =not detected;n.a. =not applicable [a]Metabolites

2.3.)

Therapeutic groups	Analyte	KolUS INPUT	STD ±	KolUS OUTPUT	STD ±	KolDS INPUT	STD ±	KolDS OUTPUT	STD ±	Vivari INPUT	STD ±	Vivari OUTPUT	STD ±	Sparta INPUT	STD ±	Sparta OUTPUT	STD ±
Analgesics/ anti-inflammatories (10)	Ketoprofen	<LOQ		<LOQ		<LOQ		n.a.		<LOQ		<LOQ		58,5	3,11	31,2	3,55
	Naproxen	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		6,79	0,215	<LOQ	
	Ibuprofen	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Indomethacine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Diclofenac	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Phenazone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Propyphenazone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Piroxicam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Tenoxicam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Oxycodone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Lipid regulators and cholesterol lowering statin drugs (4)	Bezafibrate	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Gemfibrozil	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Pravastatin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Fluvastatin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Psychiatric drugs (13)	Carbamazepine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		15,2	0,344	3,18	0,119
	2-Hydroxycarbamazepine a	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		1,15	0,067	<LOQ	
	10.11-Epoxycarbamazpinea	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		5,34	0,076	<LOQ	
	Sertraline	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Citalopram	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Olanzapine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Trazodone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

	Fluoxetine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Norfluoxetinea	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Paroxetine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Diazepam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Lorazepam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Alprazolam	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		<LOQ		n.d.	
Histamine H1 and H2 receptor antagonists (3)	Loratadine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Famotidine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Cimetidine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
β -Blocking agents (3)	Sotalol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		4,38	0,203	<LOQ	
	Propranolol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Carazolol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Diuretic (3)	Hydrochlorothiazide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		51,2	2,06	<LOQ	
	Furosemide	<LOQ		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Torasemide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antidiabetic (1)	Glibenclamide	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antihypertensives (3)	Amlodipine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Losartan	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Valsartan	<LOQ		5,22	0,314	9,10	0,945	n.a.		4,04	0,050	8,44	0,234	11,3	0,666	8,27	0,112
Prostatic hyperplasia (1)	Tamsulosin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
To treat asthma (1)	Salbutamol	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Anticoagulant (1)	Warfarin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antihelmintics (2)	Albendazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Thiabendazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Synthetic glucocorticoid (1)	Dexamethasone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Sedation and muscle	Xylazine	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

relaxation (1)																	
Tranquilizer (2)	Azaperone	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Azaperola	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Antibiotics (11)	Erythromycin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Clarithromycin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Tetracycline	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Ofloxacin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Sulfamethoxazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		3,77	0,085	<LOQ	
	Trimethoprim	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Metronidazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Metronidazole-OHa	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Dimetridazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Ronidazole	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Cefalexin	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
Calcium channel blockers (2)	Verapamil	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	
	Norverapamila	n.d.		n.d.		n.d.		n.a.		n.d.		n.d.		n.d.		n.d.	

Notes: <LOQ = values below limit of quantification; n.d. =not detected;n.a. =not applicable [a]Metabolites

Figure 1S. Principal components analysis (PCA) including nutrients and physicochemical variables. The vector length and direction reflects the importance of each variable's contribution to each of the two axes. Percentage of variance explained by each PC (F) in parenthesis. In blue are the four sites; Numbers 1-3 next to to the site name indicate the three sampling campaigns (July 2015, June 2016 and September 2016).

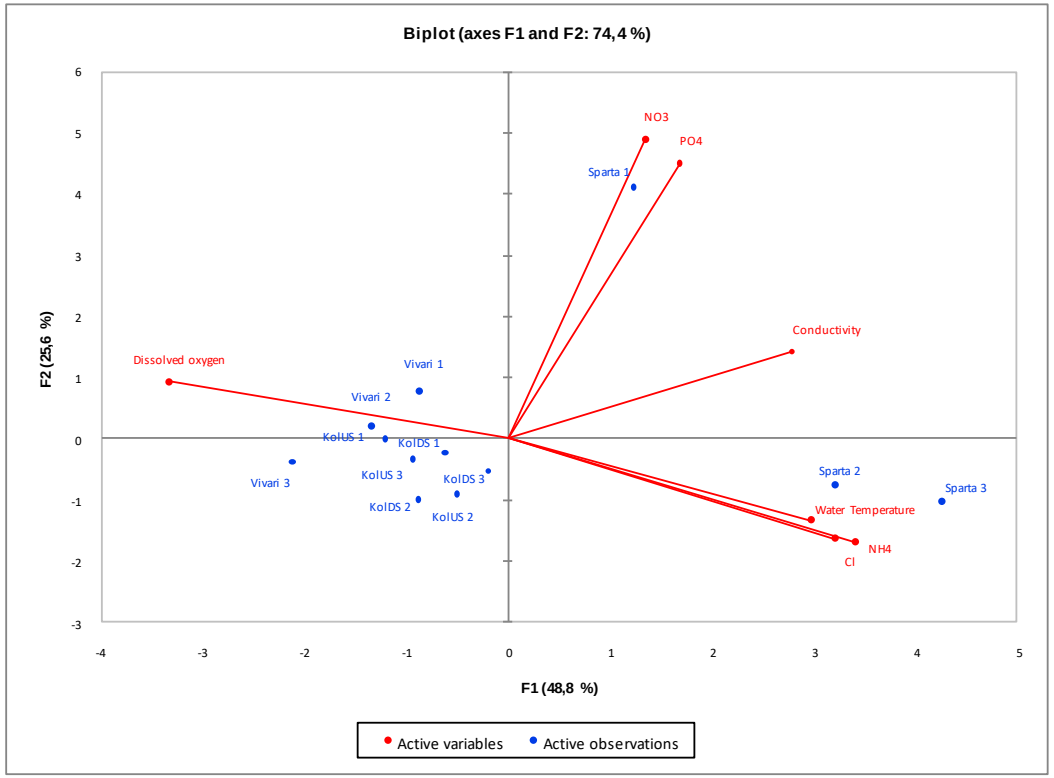

Figure 2S. Principal components analysis (PCA) with the PhACs families. The vector length and direction reflects the importance of each variable's contribution to each of the two axes. Percentage of variance explained by each PC (F) in parenthesis. In blue are the four sites; Numbers 1-3 next to the site name indicate the three sampling campaigns (July 2015, June 2016 and September 2016).