



Pharmaceuticals and trace metals in the surface water used for crop irrigation: Risk to health or natural attenuation?

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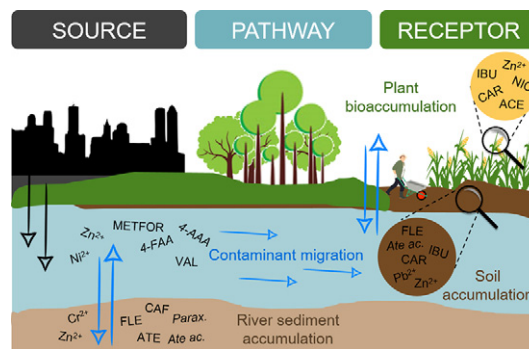
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HIGHLIGHTS

- Pharmaceuticals and TMs occurrence in water-sediment-soil-plant system is addressed.
- Microcontaminants' uptake by maize under real field-scale conditions is assessed.
- Total Hazard Quotient for TMs confirm the absence of potential risk for consumers.
- Pharmaceutical intake through corn consumption do not pose a threat to human health.
- Considering all environmental matrices is key to assess contaminant fate.

GRAPHICAL ABSTRACT



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ABSTRACT

The use of surface water impacted by wastewater treatment plant (WWTP) effluents for crop irrigation is a form of unplanned water reuse. Natural attenuation processes can buffer contamination spreading. However, this practice can promote the exposure of crops to contaminants of emerging concern, such as pharmaceuticals, trace metals (TMs) and metalloids, posing a risk to health. This research aimed to evaluate the presence of 50 pharmaceuticals, some transformation products, 7 TMs and a metalloid in the water-sediment-soil-plant system, and their potential to be bioaccumulated into edible parts of plants, as a result of the unplanned water reuse. The study site consists of an extensive agricultural land downstream Madrid city (Spain) where surface water, strongly impacted by WWTP effluents, is applied through gravity-based systems to cultivate mainly maize. Sampling campaigns were conducted to collect WWTP effluent, surface and irrigation water, river sediments, agricultural soils and maize fruits. Results demonstrate the ubiquitous presence of several pharmaceuticals. The concentration pattern in irrigation water did not resemble the pattern of contents in soils and plants. The

Abbreviations: BCF, bioconcentration factor; BW, body weight; CAM, Community of Madrid; CEC, contaminant of emerging concern; C/N, carbon-to-nitrogen ratio; COD, chemical oxygen demand; DI, daily intake; DO, dissolved oxygen; DW, dry weight; EC, electrical conductivity; ECC, equivalent CaCO₃; EDI, estimated daily intake; EQS, environmental quality standards; ESI, electrospray ionization; HDPE, high density polyethylene; HQ, hazard quotient; IC, inorganic C; ICP-MS, inductively coupled plasma mass spectrometry; ISQGs, interim sediment quality guidelines; LC-MS/MS, liquid chromatography tandem mass spectrometry; LODi, instrumental limit of detection; LOQi, instrumental limit of quantification; MQL, method quantification limits; MRM, multiple reaction monitoring; OM, organic matter; OMC, organic microcontaminant; PP, polypropylene; QQQ, triple quadrupole; R, recovery; RAJ, Real Acequia del Jarama; RfD, reference dose; RGV, reference generic values; RSD, relative standard deviation; RV90, 90th percentile reference values; S/N, signal-to-noise ratio; SPE, solid-phase extraction; TC, total C; THQ, total HQ; TM, trace metal; TOC, total organic C; TP, transformation product; TRV, toxic reference value; TSS, total suspended solids; TTC, threshold of toxicological concern; WWTP, wastewater treatment plant; WW, wet weight.

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pharmaceuticals included in the EU surface water watch lists were quantified in the lowest concentration range (macrolide antibiotics, ciprofloxacin) or were not detected (most of the hormones). Therefore, hormones do not represent an emerging risk in our scenario. The TMs and the metalloid in water and agricultural soils should not arise any concern. Whereas, their presence in the river sediments may have an adverse impact on aquatic ecosystems. Only acetaminophen, ibuprofen, carbamazepine, nicotine, Zn, Cu and Ni were quantified in corn grains. Calculated parameters to assess bioaccumulation and health risk indicate that neither pharmaceuticals nor TMs pose a threat to human health due to consumption of maize cultivated in the area. Results highlight the need to include different environmental matrices when assessing contaminant fate under real field-scale conditions.

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1. Introduction

Water and food security are of global concern and key to achieve sustainable development goals (UN, 2019). However, some contaminants are taken up by plants through different pathways, mostly still under research, and they accumulate in the food chain, compromising the safety of the food consumed by both humans and animals (Tóth et al., 2016). According to the review by Damania et al. (2019), globally, 65% of all irrigated croplands within 40 km downstream of urban areas rely heavily on treated wastewater flows, potentially exposing some 885 million urban residents to possible health risks.

Despite the progress of the treatment technology, wastewater treatment plants (WWTPs) are not able to fully remove contaminants of emerging concern (CECs), such as pharmaceuticals, trace metals (TMs) and metalloids that are frequently found in environmental samples of urban and periurban areas at large distance from the source of pollution (Krzeminski et al., 2019). Given the worldwide disparity on specific consumption patterns and technological solutions adopted (Fekadu et al., 2018), it is difficult to establish an absolute and global dimension of the problem (i.e. tons of substances into receiving water each year). However, specific researches have demonstrated that the occurrence of pharmaceuticals, TMs and metalloids in the environment is not negligible and is increasing in time as a consequence of their growing consumption and use (Elgallal et al., 2016). For instance, antibiotic consumption expressed as daily doses hits 34.8 billion in 2015 and it shows an increase of 65% since 2000 (Klein et al., 2018). Apparently related with the higher antibiotic consumption, aquatic concentrations of ciprofloxacin in the typical (median) ecoregion increased at an average of 16% per year across the period 1995–2015 (Oldenkamp et al., 2019).

Once in the environment, pharmaceuticals, TMs and metalloids can undergo natural attenuation processes (such as biodegradation, sorption or dilution, among others) that reduce their concentrations in water or soil or, as already mentioned, they can be taken up by plants. In the case of pharmaceuticals, transformation products (TPs) resulting from these processes are, more often than not, more soluble and polar than the parent compound and, therefore, more mobile (García-Galán et al., 2010). In this context, the European Medicine Agency declares that any TP that exceeds the concentration of the original compound by 10% needs to be investigated to determine the possible effects on ecosystems (EMA, 2006). The unintentional use of water strongly impacted by WWTP effluents is defined as unplanned water reuse (European Commission, 2017). In the context of agricultural activities, such as crop irrigation, and within the limits established by law in Spain (RD 1620/2007, n.d. establishing the legal regime for treated wastewater reuse), recipients of the contaminant load are agricultural land, the crop itself, and underlying groundwater. Therefore, when crops are intended for human or animal consumption, the risk translates into the possible introduction into the food chain of undesirable substances, which health effects in the case of pharmaceuticals are still unknown as well as their effects when combined with TMs. Moreover, the formation and propagation of the so-called “antibiotic

resistance genes (ARGs)” has recently aroused great concern due to the evidence of their uptake by food crops and, therefore, their introduction in the food chain.

In recent years, numerous studies have been carried out, especially at the laboratory scale under controlled and simplified conditions, which demonstrate how the transfer of a contaminant from water and/or soil to different parts of the plant depends on several factors such as the physico-chemical properties of the soil, the plant species and the characteristics of the contaminant itself (Christou et al., 2019; Li et al., 2019). Despite the importance of these findings, Christou et al. (2019) point out the need to study plant uptake of contaminants under real agricultural practices, where plants are under field water conditions and contaminants are in the environment as multicomponent mixtures. In this sense, Margenat et al. (2019) evaluated the risk to human health of the bioaccumulation of several contaminants (including carbamazepine and its TPs, and TMs) in various vegetables. They concluded that it is of paramount importance to continue conducting studies, including substances belonging to different therapeutic groups, different types of plants, and evaluating the fate of these contaminants in the different environmental compartments involved, such as water, soil and plants. Because of the above referred mobility of these substances and their TPs, research studies cannot consider the potential downstream and legacy effect as negligible (Aymerich et al., 2017; Pereda et al., 2019), but should factor in migration distance and natural attenuation in the analyses.

The general objective of this study is to evaluate the presence of 50 pharmaceuticals of different therapeutic groups, some of their TPs, 7 TMs and a metalloid in the water-sediment-soil-plant system, and their potential to be incorporated and bioaccumulated into edible parts of plants, as a result of the unplanned water reuse by gravity-based irrigation. To this end, a study area has been selected downstream from the city of Madrid, which land use is almost entirely dedicated to intensive agricultural practices, mainly maize, the cereal with the highest worldwide production (38%; calculated with data from FAOSTAT, 2017). In Spain, maize crops accounted for 6% of cereal land (MAPA, 2018), with yields of >11 t/ha (EUROSTAT, 2018). The study site constitutes an excellent scenario to carry out such a research because of its representative water-sediment-soil-plant system. The novelty of this research lies on the fact that WWTP effluent, surface water, irrigation water, sediment, agricultural soil and fruit samples are taken *in situ*, thus are representative of the real unplanned water reuse. Under these conditions, it will be assessed whether the irrigation of crops with water impacted by effluents from WWTPs poses a risk to health or if natural attenuation processes mitigate the spread of contamination. To our knowledge, studies investigating such a pool of environmental compartments for occurrence and fate of pharmaceuticals and TPs are not reported in the literature yet. Even though there are many factors that influence in the uptake of contaminants in food crops under real field conditions (irrigation water quality, irrigation system, proximity to traffic roads, industrial runoff and fertilizer applications among others), results can be extrapolated to other Mediterranean regions, considered a very vulnerable scenario in climate change forecasts, with significant and increasing risks for water, ecosystems,

food, health and security interconnected domains (EEA, 2017; Cramer et al., 2018; IPCC, 2019).

2. Materials and methods

2.1. Study area

The study area is located in the Jarama river subbasin (Tagus river basin), that runs across the southeast of the metropolitan area of Madrid, in central Spain (Fig. 1). Approximately 100 km² of agricultural land is irrigated with water diverted from the Jarama river and distributed by a network of ditches, an infrastructure called the “Real Acequia del Jarama” (hereinafter the RAJ; RAJ, 2017) the construction of which began at the end of the 16th century. Nowadays, the RAJ has a length of approximately 72 km and it extends from the “Presa del Rey” dam (hereinafter the dam; Rivas-Vaciamadrid, Madrid) to the municipality of Mocejón (Toledo, Castilla-La Mancha). About 700 m upstream from

the dam, the Jarama river meets its tributary Manzanares river. Before this confluence, both rivers run throughout urban settlements. The Manzanares river, in particular, runs throughout the city of Madrid and receives effluents from the largest WWTPs of the city. This urban river is strongly affected by anthropic activity that alters its hydrodynamic and sediment geochemistry (de Miguel et al., 2005). At the watershed scale (8544 km²), the annual discharge of WWTP effluents (535 hm³) (CHT, 2019) constitutes almost half of the annual accumulated runoff (1332 hm³) (calculated according to the Integrated System for Rainfall-Runoff Modelling - SIMPA) (Estrela Monreal and Quintas Ripoll, 1996). The relative importance of the treated wastewater volume discharged to the receiving waters is exacerbated at more local scale. Indeed in the watershed of the Manzanares river (1245 km²), the contribution of effluent discharges almost doubles the accumulated runoff (156.9 hm³) (CHT, 2019). This implies that the majority of the river flow consists of treated wastewater, a common condition in rivers of the Mediterranean region where effluents of WWTPs are essential to

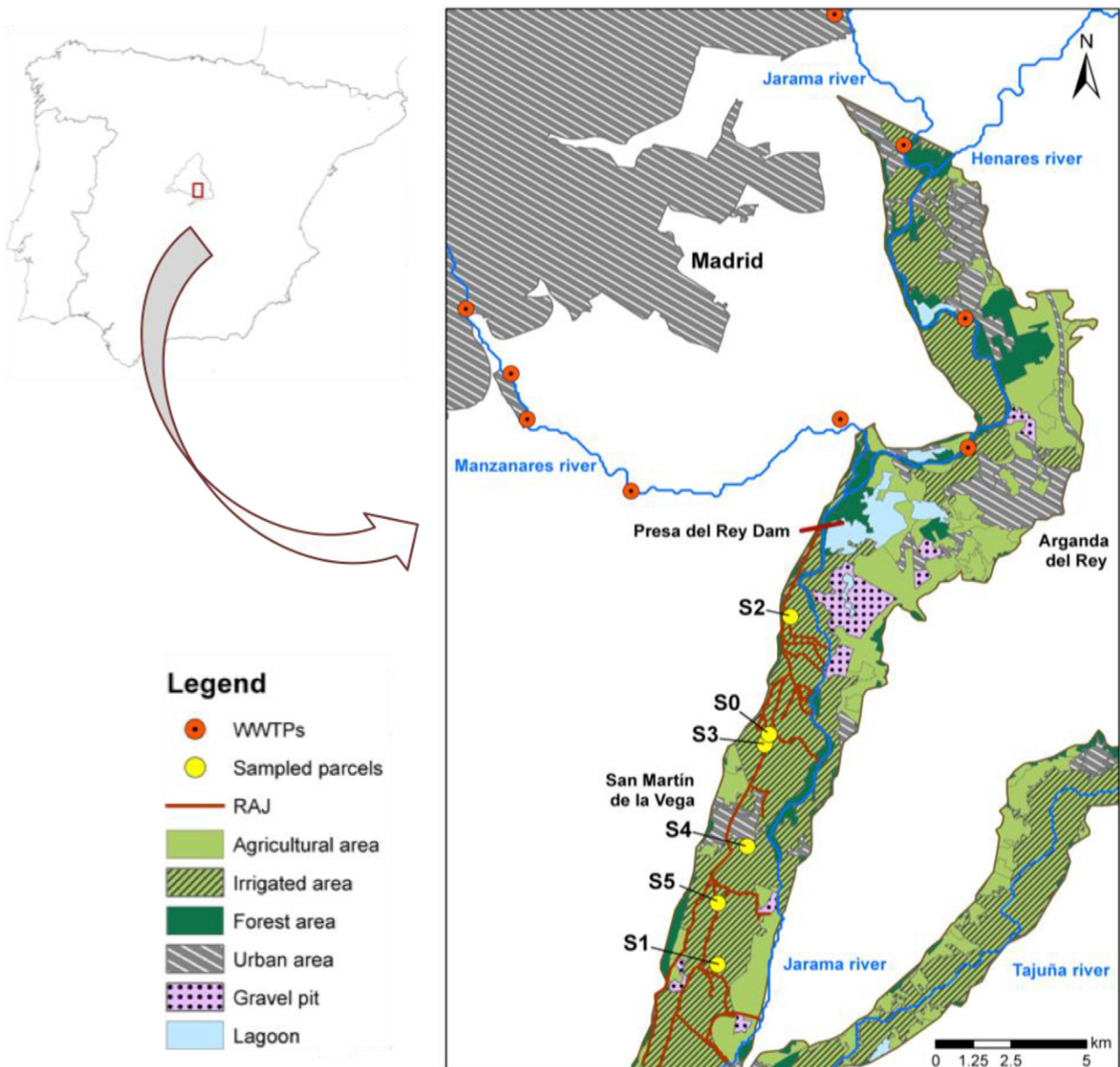


Fig. 1. Map of the study area. S0–S5: soil sampling points.

maintain ecological flows (European Commission, 2017). Climate change is expected to exacerbate the scarcity context across this area, according to Mediterranean forecasts.

The six agricultural parcels sampled in this study are located between the dam and the confluence of the Jarama river and the Tajuña river (Fig. 1). Most abundant crops in the area are maize (34%), wheat (16%) and alfalfa (8%), while approximately 22% are left fallow (data from Irrigation User Community of the RAJ). For the present study, maize was selected because of its high production both in the study area and worldwide. Water requirements of crops are satisfied following the provisions established by the Tagus river Basin Authority. Farmers are associated into a public law corporation (Irrigation User Community of the RAJ) that is in charge of its self-management with the aim to distribute efficiently and equitably water resources among its members. Approximately 15,000 m³ ha⁻¹ are allocated each year to these agricultural fields by gravity-based irrigation, that occurs mainly during summer. Traditionally, much of the irrigation practised in Europe has consisted of gravity-fed systems, and in sizeable areas of the southern Member States including Portugal and Spain, this has represented the dominant form of irrigation until modernisation plans led by EU commitments at the 2000s that facilitated the change from surface irrigation to drip irrigation (Baldock et al., 2000; Sese-Minguez et al., 2017). Currently, gravity-based irrigation still accounts for 24% (ca. 1 million ha) of irrigable area in Spain (MAPA, 2018).

2.2. Sampling strategy

In 2018, sampling campaigns were carried out to collect five environmental matrices: i) WWTP effluent (W1), ii) surface water from the Manzanares river (W2) and irrigation water from the RAJ main channel (W3), iii) river sediments (Sd1-Sd2), iv) agricultural soils (S0-S5), and v) maize fruits (*Zea mays* L.) (C1-C5).

The WWTP effluent, surface water and irrigation water were collected in June, July and September during the irrigation period. River sediments were retrieved concomitantly to WWTP effluent and surface water sampling. Soils and maize fruits have been sampled along a representative area of about 40 km² that extends from the dam and the confluence of the Tajuña river with the Jarama river (Fig. 1), in the northern part of the meadow. Soil sampling has been performed before the beginning of the irrigation period and after approximately 10 days from the last irrigation event. Maize fruits were collected concomitantly to the second soil sampling.

2.2.1. Water sampling

One of the major WWTPs of Madrid has been selected for its effluent collection (W1). The selection was based mainly on two criteria: i) the volume of treated wastewater, and ii) the accessibility to the effluent. The selected WWTP is equipped with a preliminary treatment (coarse screening and grit removal) and a primary sedimentation tank. The treatment is followed by an activated sludge secondary system and a phosphorous precipitation process with ferric chloride. The tertiary treatment consists of flocculation, sand filtration and chlorine disinfection. Although the exhaustive characterization of the contaminant loads released by Madrid WWTPs is beyond the scope of this study, collected effluent samples can be considered sufficiently representative due to the similarity of the treatment technology among Madrid WWTPs. Surface water (W2) was collected from the Manzanares river in Southeast Regional Park, near Rivas-Vaciamadrid city, before its confluence with the Jarama river and therefore upstream the dam. The irrigation water (W3) was sampled at the head of the main ditch channel immediately after the dam.

During each sampling, temperature, pH, and dissolved oxygen (DO) were measured *in situ*. Approximately 6 L of water were collected for analysis of: i) standard physico-chemical parameters, ii) total and soluble TM and metalloids, and iii) pharmaceutical and TPs. Samples for the detection of soluble TM and metalloid content were acidified *in situ* with

HNO₃ (to a pH of 2–3) after filtration through a 0.45 µm filter, whereas, for total contents the samples were not filtered. All material used was made of high-density polyethylene (HDPE) or polypropylene (PP) to avoid a possible sorption of TMs. Water aliquots used for pharmaceutical and TP determinations were collected in amber glass bottles. When analyses were not performed immediately after sampling, samples were stored at –20 °C.

2.2.2. River sediment sampling

Concomitantly to water sampling (W1 and W2), river sediment samples from the Manzanares river were taken (Sd1 and Sd2, respectively). Approximately 0.25 kg of sediment samples were taken from the upper 5 cm at each sampling point for analysis of: i) physico-chemical parameters, ii) total TM and metalloids, and iii) pharmaceutical and TPs. In Sd1 samples (closely downstream the WWTP), numerous artefacts such as for example crystals, tissues and feminine hygiene towels were found, showing that sediments are very anthropized. In the laboratory, macroscopic artefacts were removed and samples were air-dried at room temperature, passed through a 2-mm sieve, stored in HDPE bottles and: i) frozen at –80 °C and lyophilized (Coolvacuum LyoMicron Technologies, S.L., Spain, at –75 °C with 0.05 bar vacuum over 3 days) for pharmaceutical and TP determinations, or ii) preserved in the fridge at 4 °C for the other analyses.

2.2.3. Soil sampling

Soil samples were retrieved from six agricultural parcels distributed in the study area (Fig. 1) for analysis of: i) physico-chemical parameters, ii) total TM and metalloids, and iii) pharmaceuticals and TPs. Five of selected parcels were cultivated with maize (S1 to S5) whereas one parcel was left fallow (S0) at the time of sampling and it was used as a reference. In each parcel, approximately a total of 6 kg of soil were collected up to a depth of 30 cm using a manual auger at three different points located along the main diagonal. Prior to analysis, samples were air-dried, gently crushed and passed through a 2-mm sieve. A representative aliquot for the analyses was obtained by quartering the pre-processed composite soil sample and stored in HDPE bottles. When the analyses could not be performed after sieving, the soil aliquots were frozen and lyophilized, for pharmaceutical and TP determinations, or were refrigerated for the other analyses.

2.2.4. Plant sampling

Corn samples (C1–C5) were collected beside soil sampling points in cultivated parcels, obtaining a total of 6 fruits per parcel for determination of: i) total TMs and metalloids and ii) pharmaceuticals and TPs. Once in the laboratory, corns were weighed to obtain the biomass. Subsequently, they were shelled and, for each parcel, an aliquot of a composite corn grain sample was dried in an oven at 105 °C for moisture measurements. Part of the corn grain sample was frozen and lyophilized (for analysis of pharmaceuticals and TPs) and the other part was preserved at room temperature (for determination of TMs and metalloid) in HDPE bottles.

2.3. Selection of trace metals, metalloid, pharmaceuticals and transformation products

Arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), nickel (Ni), lead (Pb), and zinc (Zn) have been selected based on: 1) data from previous screening carried out in the Manzanares river (de Miguel et al., 2005) and in the Tagus river basin (Arenas-Sánchez et al., 2019); 2) data reporting TM contents in Mediterranean agricultural soils and crops (de Santiago-Martín et al., 2015); 3) the list of priority substances in surface waters published in the Directive 2013/39/EU, 2013 amending other legislative acts regarding priority substances in the field of water policy; 4) the list of TMs included in soil regulations (Directive 86/278/EEC on the protection of the environment, and in particular of the soil, when sewage sludge is used in

agriculture; Order 2770/2006/CAM, n.d. establishing reference levels for heavy metals and TM in contaminated soils within the regional area); and 5) the TMs considered by the European Union in cereal foodstuffs (Commission Regulation (EC) 1881/2006 setting maximum levels for certain contaminants in foodstuffs).

The 50 pharmaceuticals investigated in this study, including some TPs, belong to different therapeutic classes (Table 1). The selection

considered their inclusion in the EU monitoring program, their consumption level and previous monitoring data. Indeed, pharmaceuticals mentioned in the watch lists published in 2015 and 2018 (Commission Implementing Decisions (EU) 2015/495 and 2018/840 (n.d.) have been included in the study. The two watch lists differ in the exclusion of the anti-inflammatory diclofenac and the inclusion of the antibiotic amoxicillin in the more recent one. Data about national

Table 1

Pharmaceuticals and transformation products (in italics) selected in this study.

Compound	ATC code	Pharmacological subgroup description		CAS number
Alimentary tract and metabolism				
Omeprazole ^b	A02BC01	Peptic ulcer and gastro-oesophageal reflux	Proton pump inhibitors	73590-58-6
Metformin ^b	A10BA02	Blood glucose lowering drugs, excl. Insulins	Biguanides	1115-70-4
Cardiovascular system				
Flecainide	C01BC04	Antiarrhythmics, class I and III	Antiarrhythmics, class Ic	54143-55-4
Furosemide ^b	C03CA01	High-ceiling diuretics	Sulfonamides	54-31-9
Atenolol	C07AB03	Beta blocking agents	Beta blocking agents, selective	29122-68-7
<i>Atenolol acid</i>				
Enalapril ^b	C09AA02	ACE inhibitors	ACE inhibitors	56392-14-4
Valsartan	C09CA03	Angiotensin II receptor blockers	Angiotensin II receptor blockers	75847-73-3
Atorvastatin ^b	C10AA05	Lipid modifying agents	Angiotensin II receptor blockers	138402-11-6
Gemfibrozil	C10AB04		HMG CoA reductase inhibitors	134523-00-5
			Fibrates	25812-30-0
Sex hormones				
Testosterone	G03BA03	Androgens	3-oxoandrostene (4) derivatives	58-22-0
17 β -Estradiol (E2)	G03CA03	Estrogens	Natural and semisynthetic estrogens	50-28-2
Estril (E3)	G03CA04		Natural and semisynthetic estrogens	50-27-1
Estrone (E1)	G03CA07		Natural and semisynthetic estrogens	53-16-7
17 α -Ethinylestradiol (EE2)	G03CA01		Natural and semisynthetic estrogens	57-63-6
Progesterone	G03DA04	Progestogens	Pregnen (4) derivatives	57-83-0
Anti-infectives for systemic use				
Amoxicillin ^a	J01CA04	β -lactam antibacterials	Penicillins with extended spectrum	26787-78-0
Trimethoprim	J01EA01	Sulfonamides and trimethoprim	Trimethoprim and derivatives	738-70-5
Sulfamethoxazole	J01EC01		Intermediate-acting sulfonamides	723-46-6
<i>N4-acetylsulfamethoxazole (N4ACE)</i>				
	-			21312-10-7
Erythromycin ^a	J01FA01	Macrolides, lincosamides and streptogramins	Macrolides	114-07-08
Clarithromycin ^a	J01FA09		Macrolides	81103-11-9
Azithromycin ^a	J01FA10		Macrolides	83905-01-5
Lincomycin	J01FF02		Lincosamides	7179-49-9
Ofloxacin	J01MA01	Quinolones	Fluoroquinolones	82419-36-1
Ciprofloxacin	J01MA02		Fluoroquinolones	85721-33-1
Metronidazole	J01XD01	Others	Imidazole derivatives	443-48-1
Musculo-skeletal system				
Ibuprofen ^b	M01AE01	Non-steroids anti-inflammatories	Propionic acid derivatives	15687-27-1
Naproxen	M01AE02		Propionic acid derivatives	22204-53-1
Ketoprofen	M01AE03		Propionic acid derivatives	22071-15-4
Diclofenac ^a	M01AB05		Acetic acid derivatives	15307-86-5
Nervous system				
Codeine	N02AJ09	Opioids	Opioids	76-57-3
<i>Benzoylcegonine^c</i>				
	-	Anesthetics	Esters of benzoic acid	519-09-5
Metamizole (Antipyrine)	N02BB02	Other analgesics and antipyretics	Pyrazolones	5907-38-0
<i>4-Aminoantipyrine (4-AA)</i>				
	-			83-07-8
<i>4-Acetamidoantipyrine (4-AAA)</i>				
	-			83-15-8
<i>4-Dimethylaminoantipyrine (4-DAA)</i>				
	-			58-15-1
<i>4-Formylaminoantipyrine (4-FAA)</i>				
	-			1672-58-8
Acetaminophen (Paracetamol) ^b	N02BE01		Anilides	103-90-2
Carbamazepine	N03AF01	Antiepileptics	Carboxamide derivatives	298-46-4
<i>Carbamazepine epoxide</i>				
	-			36507-30-9
Lorazepam ^b	N05BA06	Anxiolytics	Benzodiazepine derivatives	846-49-1
Citalopram	N06AB04	Antidepressants	Selective serotonin reuptake inhibitors	59729-33-8
Venlafaxine	N06AX16		Other antidepressants	99300-78-4
Caffeine ^c	N06BC01	Psychostimulants	Xanthine derivatives	58-08-2
<i>Paraxanthine^c</i>				
	-			611-59-6
Nicotine ^c	N07BA01	Addictive disorders	Drugs used in nicotine dependence	54-11-5
Cotinine ^c	-			486-56-6
Respiratory system				
Salbutamol ^b	R03AC02	Adrenergics	Selective beta-2-adrenoreceptor agonists	51022-70-9
Loratadine	R06AX13	Antihistamines	Other antihistamines for systemic use	79794-75-5

^a Watch lists (2015/495/EU, 2018/840/EU).

^b National Health System (Sistema Nacional de Salud, 2016) and Spanish Pharmaceutical Observatory (Observatorio del Medicamento, 2016).

^c Life-style compounds of drugs of abuse.

consumption, calculated from medical prescriptions and provided by the National Health System (*Sistema Nacional de Salud*, 2016) and the Spanish Pharmaceutical Observatory (*Observatorio del Medicamento*, 2016), were also taken into account. On the other hand, a research group of IMDEA Water carried out in 2019 a screening of surface water in the Tagus River Basin where a set of CECs, including pharmaceuticals, were identified (Rico et al., 2019). Results from the mentioned research were also considered when selecting pharmaceuticals for this study. Finally, due to the growing interest in TPs, the analysis of those that have been frequently detected in previous studies of our research group (Martínez-Hernández et al., 2014, 2018), such as carbamazepine epoxide (from carbamazepine), atenololic acid (from atenolol), paraxanthine (from caffeine), and 4-FAA, 4-AAA, 4-AA, 4-DAA (from metamizole), among others, were also included. Of the 50 investigated compounds in water samples, the 25 with the highest concentrations in the irrigation water were selected for river sediment, soil and plant sample analysis.

2.4. Analytical procedures

2.4.1. Reagents and chemicals

Chemicals were obtained from analytical grade from Merck (Germany), Sigma-Aldrich (USA) and Scharlau (Spain), and FisherScientific (USA) (more details in the Supplementary Material). All TM and metalloid standards were certified reference materials (TraceCERT®) for ICP analysis solutions prepared in HNO₃ (1000 mg L⁻¹). Working standard solutions were prepared by dilution in HNO₃ 1% except for Hg solutions which were diluted in a mixture HNO₃ 1%:HCl 0.5%. The reference standards (purity ≥98–99%) for the quantitative analysis of all compounds listed in Table 1 were purchased from Sigma-Aldrich, except for citalopram (97.2% purity), which was provided by the Centre of Applied Chemistry and Biotechnology of the University of Alcalá (Spain). Isotopically labelled compounds were used as internal standards. Individual standard solutions of targeted compounds were prepared at the concentration level of 2000 mg L⁻¹ in MeOH and stored in amber glass vials at -20 °C in the dark. High purity water was obtained from a Milli-Q water purification Millipore system (USA).

2.4.2. Physico-chemical analysis

Water samples were analysed *in situ* for pH (Crison pH 25) (UNE-EN-ISO 10523:2012) and DO (Crison OXI 45P). In the laboratory, the following standard analysis were performed: electrical conductivity (EC) (Crison MM-41) (UNE-EN-27888:1994), total suspended solids (TSS) using glass fiber filters (UNE-EN 872:2006), total organic C (TOC), total C (TC) and inorganic C (IC) by combustion and infrared spectrophotometry (Shimadzu TOC-VCSH analyser with an autosampler ASI-V) (UNE-EN-ISO 5814), chemical oxygen demand (COD) by the dichromate method (UNE-77004:2002) (Merck Spectroquant TR420 and Spectroquant Pharo 100 Spectrophotometer), and dissolved major anions and cations using a 930 Compact Ion Chromatography Flex (autosampler 858 Professional Sample Processor) coupled to a Titrando 809 (autosampler 814 USB Sample Processor) for HCO₃⁻ ions (Metrohm).

Sediment and soil samples were analysed for pH and EC in a 1:5 solid to water ratio (UNE-ISO 10390:2012 and UNE 77308: 2001, respectively), particle-size distribution by the Bouyoucos method (UNE 103102:1995), organic matter (OM) by the loss-on-ignition method at 360 °C for 24 h, total N by the Kjeldahl method (Bloc Digest 6 for mineralization and automatic Pro-Nitro A distillation unit, Selecta) (UNE 77318:2001), equivalent CaCO₃ (ECC) by the Bernard calcimeter method (UNE 77317:2001) and total P and Fe after microwave acid digestion and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) quantification (detailed in Section 2.4.3 for TMs and metalloid).

2.4.3. Trace metals and metalloid analysis

All samples were subjected to a treatment by microwave digestion prior to analysis of TMs and metalloid, at 190 °C over 10 min (Microwave Digestion System Ethos One, Milestone, Bergamo, Italy), with a mixture of: i) HNO₃:HCl (4:1) for As, Cd, Cr, Cu, Hg, Ni, Pb, and Zn in water samples, and ii) HNO₃:HCl (3:1) for Hg and HNO₃-H₂O₂ (4:1) for As, Cd, Cr, Cu, Ni, Pb, and Zn in the case of sediment, soil and corn grain samples. Samples for the detection of the soluble content of TMs and metalloid were not digested. The concentration of TMs and metalloid in the corresponding solutions was quantified with a 7700× series ICP-MS equipment (with a PFA cross flow nebulizer) from Agilent Technologies (USA). Plasma conditions were 1550 w (forward power), 15 L min⁻¹ (gas flow rate), 0.9 L min⁻¹ (auxiliary gas flow rate) and 1.0 L min⁻¹ (nebulizer gas flow rate). All analyses were performed in triplicate. All material used was pre-washed with an aqueous solution of 1% HNO₃ over 24 h and rinsed with Milli-Q water. Analytical quality parameters (LODi, LOQi) are provided in Table S1 in the Supplementary Material.

2.4.4. Pharmaceuticals and transformation product analysis

2.4.4.1. Sample preparation. Water samples were filtered through a 0.7 µm glass fiber filter (Merck Millipore, IRL) and pH was adjusted to 8–9 with NH₄OH (32% v/v). An aliquot (100 mL) of the sample, fortified with 100 µL of a solution of isotope-labelled internal standards of 40 µg L⁻¹, was passed through an Oasis HLB solid phase extraction cartridge (200 mg, 6 mL, Waters, USA), previously conditioned with 6 mL of MeOH, 6 mL of ultrapure water, and 6 mL of basified ultrapure water (pH 8–9). After loading the sample, 10 mL of ultrapure water was added and then, the cartridge was dried under vacuum (5 bar) to eliminate residual water. Analytes were eluted with three aliquots of 4 mL of MeOH. The organic extract was evaporated to dryness at 45 °C, 0.2 Torr using a Speed Vac concentrator (ThermoScientific, USA), and then reconstituted in 500 µL of MeOH:water (10:90, v/v) and vortex stirring for 1 min. Reconstituted samples were centrifuged for 5 min at 13,000 rpm (MiniSpin centrifuge, Eppendorf, USA) and transferred to an amber glass vial prior to analysis.

Freeze-dried sediment and soil samples were grinded to obtain a more homogeneous sample with an agate mortar. Sample extraction procedure was based on the EPA Method 1694 with some modifications (USEPA, 2007). Briefly, 1 g of sample was weighed and joined with 200 µL of a solution of isotope-labelled internal standards of 40 µg L⁻¹. Then, the samples were placed in a fume hood overnight to allow the evaporation of methanol, achieving a concentration of 8 ng g⁻¹ for each pharmaceutical. The sample was well mixed and left to dryness during a night in a fridge 4 °C. A triplicate sequential extraction was carried out adding 20 mL MeCN and sonicating the mixture in an ultrasonic bath for 30 min (Fisherbrand Model FB11201, Fisher Scientific, USA). Previous to the second extraction, a 15 mL of phosphate buffer at pH 2 was added to the soil and vortexed to resuspend soils. Supernatants were then separated by centrifugation (3000 rpm, 5 min) (centrifuge, 5810R Eppendorf™, USA) and concentrated to a volume of 10 mL. Then, 250 mg of Na₂EDTA·2H₂O was added and the extract was brought to a volume of 100 mL with ultrapure water. The solution was subjected to a solid-phase extraction (SPE) process using Oasis HLB cartridges (1 g, 20 mL), previously conditioned with 20 mL of MeOH, 6 mL of ultrapure water, and 6 mL of acidified ultrapure water adjusted to pH = 2.0 ± 0.5 with HCl. After the acid aqueous sample was loaded, the cartridge was washed with 20 mL of ultrapure water and dried under vacuum for 5 min. Retained analytes were eluted with two aliquots of 10 mL of MeOH. The organic extract was evaporated to dryness and reconstituted in 4 mL of MeOH:H₂O (10:90, v/v). Finally, 1 mL aliquots were centrifuged for 5 min at 13,000 rpm and transferred to an amber glass vial prior to analysis.

Freeze-dried corn grain samples (1 g) were weighed into a 50 mL PP centrifuge tube and 200 µL of a solution of isotope-labelled internal

standards of $40 \mu\text{g L}^{-1}$ was added. Then, the samples were placed in a fume hood overnight, achieving a concentration of 8 ng g^{-1} for each pharmaceutical. For the extraction, 30 mL of MeOH and a mixture of 4 g of MgSO_4 , 1 g of NaCl, 1 g of $\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O}$ and 0.5 g of $\text{C}_6\text{H}_6\text{Na}_2\text{O}_7 \cdot 1.5 \text{ H}_2\text{O}$ were added and the tube was shaken (1 min) and sonicated (15 min) in an ultrasonic bath. The extract was centrifuged for 15 min at 4000 rpm and the supernatant was collected. A double extraction was performed by adding 30 mL of MeOH. Both supernatants were evaporated to dryness. Analytes were reconstituted in 25 mL of ultrapure water containing 25 mg of EDTA, and subjected to a SPE process using the protocol specified in the treatment of water samples. Finally, the organic extract was evaporated to dryness, reconstituted in 4 mL of MeOH:water (10:90, v/v) and vortex stirring for 1 min. An aliquot of 1 mL was centrifuged for 5 min at 13,000 rpm and transferred to an amber glass vial for further analysis.

2.4.4.2. Pharmaceuticals and transformation products quantification by LC-MS/MS. The quantification of pharmaceuticals and TPs in the extracts obtained from different matrices was carried out using a liquid chromatograph (1200 series, Agilent Technologies, USA) coupled to a triple quadrupole (QQQ) mass spectrometer (6495A, Agilent Technologies), equipped with an electrospray ionization (ESI) interface, in positive and negative mode. Ions were generated using an electrospray ion source with Agilent Jet Stream Technology. Instrumental parameters and chromatographic separations used in Liquid chromatography tandem mass spectrometry (LC-MS/MS) method are summarized in Table S2.

The performance of the analytical methodology was studied in terms of selectivity, sensitivity, linearity and accuracy. The quantification of target compounds was carried out in multiple reaction monitoring (MRM) mode. Instrumental limits of quantification (LOQ_i) were determined as the lowest compound concentration with a signal-to-noise ratio (S/N) = 10, and instrumental limits of detection (LOD_i) were determined as the minimum detectable amount of analyte with a S/N = 3, maintaining abundance criteria between MRM transitions. The linearity for each compound was established from the corresponding LOQ_i level to a maximum concentration of $20 \mu\text{g L}^{-1}$, using external standards over two concentration ranges; for low levels (100 ng L^{-1}) and high levels of quantification ($20 \mu\text{g L}^{-1}$). The standard regression line was obtained as the mean of three injections of each calibration point, which had a regression coefficient (R^2) > 0.99. The method to extract pharmaceuticals and TPs in was developed for water, soil, sediment and corn samples. Taking into account the large number of pharmaceuticals and TPs included in this study and their different properties, it was necessary to evaluate and optimize the extraction efficiency for target compounds in all matrices. For water samples (W1, W2 and W3), accuracy ($n = 3$) of the method were evaluated as recovery (R) and relative standard deviation (RSD) percentages using fortified samples. The selection of the spiking levels was based on the amounts of pharmaceuticals generally found in each one of the matrices under study, according to a preliminary quantitative analysis. Water samples were prepared by adding a mixture of target compounds at $0.1 \mu\text{g L}^{-1}$ (for lower levels) or at $1 \mu\text{g L}^{-1}$ (for high background levels). Method quantification limits (MQLs) were determined taking into account the pre-concentration factor (LOQ_i/200) applied in SPE protocol and achieved absolute recoveries. Recoveries (%) and RSD (%) in soil, sediment and corn grain samples were evaluated at concentration levels of 8 ng g^{-1} (for soil and sediment) and 5 ng g^{-1} (for corn grain samples). The MQLs were determined taking into account methodological recoveries. Analytical quality parameters (LOD_i, LOQ_i, methodological recoveries and RSD) are provided in Tables S2–S5. In order to control and minimize the presence of interferences for achieving a reliable quantification, possible matrix effects were assessed by different strategies: the addition of isotope-labelled internal standards, the validation of recovery percentages in each matrix, and the dilution of pre-concentrated SPE extracts.

2.5. Bioconcentration factor and health risk assessment

The soil-to-grain bioconcentration factor (BCF) was calculated as the TM, metalloid, pharmaceutical, or TP content in the fruit in dry weight (DW) divided by its content in soil after the irrigation period, for each parcel.

The potential risk to human health from the consumption of grain corn containing TMs and metalloid was estimated through the Hazard Quotient (HQ) (Margenat et al., 2019). Briefly, the HQ was calculated as the Estimated Daily Intake (EDI, $\mu\text{g kg}^{-1}$ body weight (BW) per day) divided by the Reference dose (RfD). Oral RfD values are maximum tolerable daily intake by oral administration ($\mu\text{g kg}^{-1}$ BW day⁻¹). The EDI was calculated as the Daily Intake (DI, g day⁻¹) per C_M (TM or metalloid concentration, mg kg⁻¹ wet weight, WW) divided by the BW (70 kg for European adults, according to EFSA Scientific Committee, 2012). The DI was taken from the maize food consumption in Europe between 2016 and 2018 (26.85 g day^{-1}) and the projections for 2028 (27.67 g day^{-1}) (OECD/FAO, 2019). The total HQ (THQ) was calculated as the sum of the HQs for all TMs and metalloid detected in corn grains.

The approach of the Threshold of Toxicological Concern (TTC) was applied to estimate the human health risk related to the intake of pharmaceuticals when consuming maize. Pharmaceuticals detected in edible parts of plants have been assigned to the corresponding category (Class I, II and III) by using the decision tree of Cramer et al. (1976) implemented in the software Toxtree (Patlewicz et al., 2008, v. 2.6.13). Categories are defined according to criteria about the substance structural data and the known toxicity of chemicals with similar structure characteristics (Kroes et al., 2004). The TTC values were selected according to Kroes et al. (2004) with values of 30.0, 9.0 and $1.5 \mu\text{g kg}^{-1}$ BW day⁻¹ for Class I, II and III, respectively. The daily consumption (DC, kg day⁻¹) by an adult or a toddler (BW: 12 kg, according to EFSA Scientific Committee, 2012) to reach the TTC was calculated according to Margenat et al. (2019) replacing in this study the 95th percentile value with maximum concentrations measured in the corn (C_{max}, ng g^{-1} WW). Therefore, DC derives from multiplying the TTC and the BW, and subsequently dividing the product by the maximum concentrations detected in the corn.

2.6. Statistical analysis

The significance of the differences in mean values of contaminant concentrations among water matrices was investigated by means of one-way analysis of variance (ANOVA) using a post-hoc test (Tukey). The homogeneity of variances was verified by the Levene test. The significance of differences in the mean values of contaminant contents in cultivated soils before and after irrigation was investigated with a Student's *t*-test. These analyses were done using the open source software PSP (Free Software Foundation, Inc.).

3. Results and discussion

3.1. Physico-chemical properties of environmental matrices

During sampling campaigns, physico-chemical parameters of the two water matrices (WWTP effluent – W1, and surface and irrigation water – W2, W3) were stable (Table 2). Average temperature ranged between 23.9 and 25.4 °C. Surface water pH was 7.6, whereas pH of the WWTP effluent was slightly lower (6.9). Average EC was 818, 948 and $1071 \mu\text{S cm}^{-1}$ for W1, W2 and W3, respectively. All collected water samples were oxidic ($\text{DO} > 3 \text{ mg L}^{-1}$). However, DO concentrations were generally lower in W3 probably due to the effect of the dam on the river flow dynamic.

From data obtained measuring standard physico-chemical parameters, it is very clear that the WWTP effluent differs from surface water samples collected in the Manzanares river (W2) and the irrigation channel (W3). Whereas, W2 and W3 have very similar characteristics.

Table 2
Physico-chemical parameters and nutrients (mean \pm standard error) in WWTP effluent (W1), surface water upstream the dam (W2), and irrigation water (W3).

Parameters	Units	W1	W2	W3
T	°C	24.1 \pm 0.1	25.4 \pm 0.1	23.9 \pm 0.0
pH		6.9 \pm 0.2	7.6 \pm 0.0	7.6 \pm 0.1
EC	$\mu\text{S cm}^{-1}$	818 \pm 176	948 \pm 76	1071 \pm 63
DO	mg L^{-1}	6.9 \pm 0.4	6.3 \pm 0.5	4.8 \pm 0.4
TSS		0.3 \pm 0.1	14.8 \pm 3.3	16.1 \pm 5.3
TOC		7.5 \pm 0.3	10.3 \pm 0.3	7.7 \pm 0.7
TC		18.0 \pm 2.4	38.1 \pm 1.9	42.9 \pm 1.2
IC		10.5 \pm 2.1	27.8 \pm 1.8	35.1 \pm 1.6
COD		18.6 \pm 0.8	30.3 \pm 0.4	23.2 \pm 1.2
ALK	$\text{mg CaCO}_3 \text{ L}^{-1}$	46.3 \pm 8.6	128.7 \pm 8.7	159.7 \pm 8.2
Cl ⁻	mg L^{-1}	99.7 \pm 5.1	93.2 \pm 6.6	109.3 \pm 7.5
NO ₂ ⁻		0.3 \pm 0.1	2.2 \pm 0.1	1.9 \pm 0.1
NO ₃ ⁻		27.7 \pm 1.4	18.2 \pm 0.8	18.6 \pm 0.9
HPO ₄ ²⁻		1.1 \pm 0.2	0.6 \pm 0.2	0.6 \pm 0.2
SO ₄ ²⁻		74.5 \pm 0.7	162.3 \pm 13.5	192.0 \pm 12.5
NH ₄ ⁺		0.3 \pm 0.0	18.0 \pm 1.9	11.1 \pm 0.6
Na ⁺		64.3 \pm 1.6	72.2 \pm 5.8	82.9 \pm 4.5
K ⁺		20.5 \pm 0.6	18.0 \pm 1.4	14.0 \pm 0.5
Ca ²⁺		33.3 \pm 1.0	58.4 \pm 3.4	81.1 \pm 6.9
Mg ²⁺		8.8 \pm 0.0	16.9 \pm 1.3	23.7 \pm 2.2

T = temperature; EC = electrical conductivity; DO = dissolved oxygen; TSS = total suspended solids; TOC = total organic C; TC = total C; IC = inorganic C; COD = chemical oxygen demand; ALK = alkalinity.

Parameters that remarkably differed between the two water matrix were TSS, nitrogen (N) species, sulfate (SO₄²⁻), bicarbonates (HCO₃⁻) and COD. As expected, TSS were much lower in the WWTP effluent than in surface water, 0.3 vs 15 mg L⁻¹, respectively. On the other hand, N in the effluent was present mainly in its oxidized form (NO₃⁻) whereas the reduced form (NH₄⁺) coexisted with NO₃⁻ in the surface water. The total N (N_T) concentration was much higher than the concentration in the effluent and increased along the flow path, the same occurred for COD. Samples collected in W2 and W3 exhibited a relevant excess of SO₄²⁻ that cannot be explained through gypsum dissolution processes and that might be related to agricultural practices in the surrounding area. When plotting (Ca²⁺ + Mg²⁺) vs (HCO₃⁻) all samples fall along the 1:1 equiline indicating that one of the hydrogeochemical processes controlling the composition of surface water is calcite and dolomite dissolution. In general, surface and irrigation water (W2 and

W3) appeared more mineralized than the WWTP effluent (W1) as a consequence of mineral interaction processes. A parallel work with a higher sampling frequency scheme in this study area in 2019 has confirmed that water quality can be considered homogeneous throughout the irrigation period (unpublished data).

Main physico-chemical characteristics of sediment and soil samples are shown in Table 3. Sediment pHs were moderately basics (7.6–7.7) and the EC was low (0.53–0.60 dS m⁻¹). Textural classes were sandy loam for Sd1 and sand for Sd2, in both classes being sand the predominant fractions. The content of OM, N, P and Fe was different between sampling points, always higher in Sd2 than in Sd1, probably as a consequence of the slowdown of the river flow due to the dam, favouring sedimentation and precipitation processes. In the same way, the ECC content was also higher in Sd2 than in Sd1, as previously reported for this stretch of the Manzanares river (de Miguel et al., 2005).

As shown in Table 3, soil parameter values were those typically found in agricultural soils in the Mediterranean area (Andradas and Martínez, 2001). Soil pHs were basic to moderately alkaline (7.9–8.5) according to the presence of calcareous material, which appeared in variable contents depending on the plot (between 5.3 and 27.5% of ECC). This variability is consistent with the heterogeneity of an alluvial plain, as is the case. The EC varied between 0.14 and 0.19 dS m⁻¹, corresponding to a non-saline soil. The textural class of soils was silty loam (S0–S3 and S5 samples) and loam (S4 sample), the silt fraction ranging from 41.6% to 61.9%. Both textural classes correspond to a medium texture. The OM contents were those usually found in intensive irrigation area in Spain (~2%) and C/N ratios were from normal to medium-high (9.5–12.9). Since parameters related to the organic fraction could be altered after the irrigation campaign, they were analysed before and after the irrigation period. However, no temporal differences were observed beyond those expected by the environmental variability itself. Therefore, Table 3 shows average values of both campaigns. The P and Fe contents ranged from 0.6 to 1.6 g kg⁻¹ and from 13.8 g kg⁻¹ to 21.2 g kg⁻¹, respectively.

3.2. Occurrence and fate of trace metals and metalloids

Data on trace metal in all water matrices (WWTP effluent – W1, surface water – W2, and irrigation water – W3, Fig. 2a, b, c, respectively), showed that Zn and Ni were the elements with the highest concentrations, Cd and Hg with the lowest, and As, Cu, Cr, and Pb with

Table 3
Physico-chemical parameters and nutrients (average contents) in river sediments downstream the WWTP (Sd1) and upstream the dam (Sd2), and agricultural soils (S0–5). Standard errors are in parentheses.

Samples	pH	EC dS m ⁻¹	Sand %	Silt	Clay	Textural class	OM %	TOC	N	C/N	ECC	P g kg ⁻¹	Fe
Sediments													
Sd1	7.7 (0.0)	0.53 (0.08)	70.1	16.2	13.7	Sandy loam	0.9 (0.2)	0.5	0.04 (0.01)	12.1	0.5 (0.1)	0.5 (0.0)	6.2 (0.4)
Sd2	7.6 (0.0)	0.60 (0.02)	90.0	2.5	7.5	Sand	1.8 (0.4)	1.1	0.13 (0.03)	8.0	3.2 (0.4)	1.0 (0.2)	10.9 (2.1)
Soils													
S0	8.1 (0.0)	0.15 (0.02)	28.5	53.8	17.7	Silty loam	2.1 (0.1)	1.2	0.13 (0.0)	9.5	21.8	1.3 (0.0)	17.1 (1.2)
S1	8.5 (0.1)	0.14 (0.02)	27.8	61.9	10.3	Silty loam	2.1 (0.3)	1.2	0.13 (0.1)	10.0	6.3	1.6 (0.7)	21.2 (11.2)
S2	8.2 (0.0)	0.14 (0.02)	32.9	52.6	14.5	Silty loam	1.8 (0.0)	1.0	0.10 (0.1)	10.1	5.3	0.6 (0.0)	20.9 (1.2)
S3	7.9 (0.2)	0.19 (0.0)	27.6	51.4	21.0	Silty loam	1.9 (0.1)	1.1	0.10 (0.0)	10.8	27.5	0.8 (0.1)	13.8 (0.9)
S4	8.0 (0.1)	0.15 (0.02)	38.8	41.6	19.6	Loam	1.9 (0.1)	1.1	0.10 (0.0)	11.2	11.4	0.8 (0.0)	16.6 (0.4)
S5	8.1 (0.1)	0.15 (0.03)	19.6	57.6	22.8	Silty loam	2.0 (0.1)	1.1	0.09 (0.0)	12.9	12.9	0.6 (0.0)	18.6 (0.6)

EC = electrical conductivity; OM = organic matter; TOC = total organic C; ECC = equivalent CaCO₃.

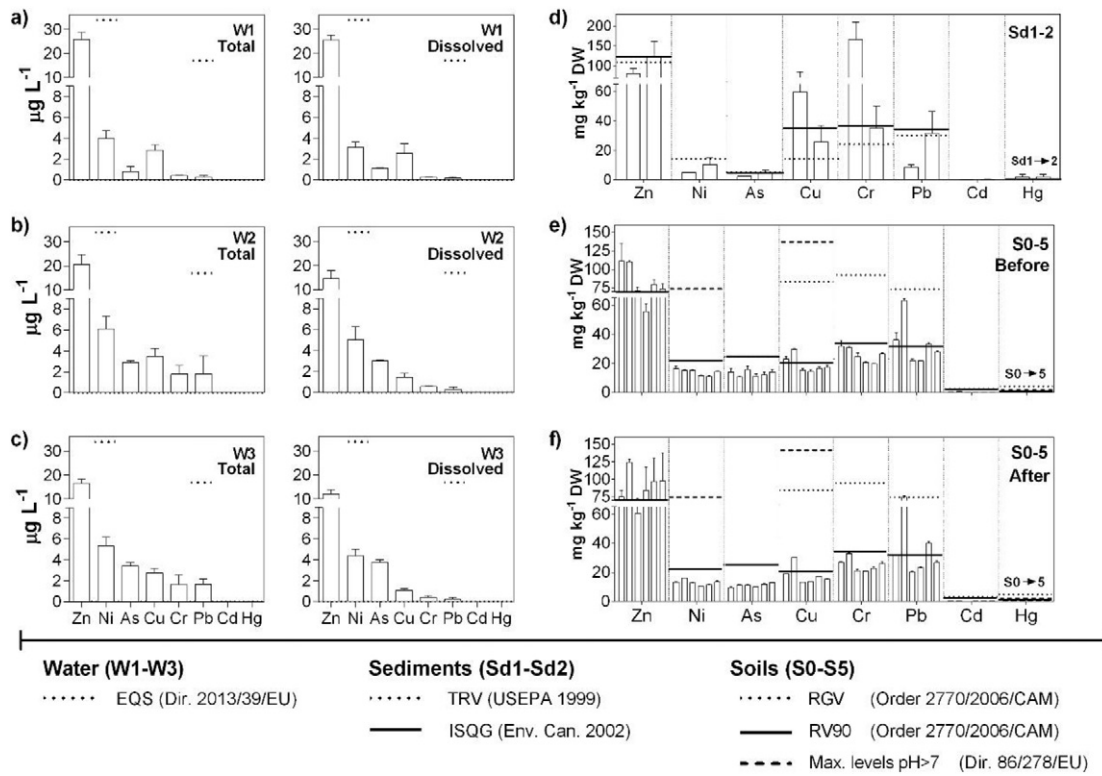


Fig. 2. Total and dissolved average concentrations of trace metals (TMs) and metalloid in: a) WWTP effluent (W1), b) surface water upstream the dam (W2), c) irrigation water (W3), d) sediments downstream the WWTP (Sd1) and upstream the dam (Sd2), and soils (S0–5) e) before and f) after the irrigation period. Error bars are standard deviation. DW = dry weight. Selected quality standards are presented: EQS = Environmental Quality Standards; TRV = Toxic Reference Values; ISQGs = Canadian Interim Sediment Quality Guidelines; RGV = Reference Generic Values; RV90 = 90th percentile reference values.

intermediate concentrations. ANOVA test showed that As concentrations were significantly higher in W3 and W2 than in W1, while Zn was higher in W1. For the rest TMs, no significant differences among matrices were found. Values were generally low and typical for urban rivers (Arenas-Sánchez et al., 2019). With the exception of Cr and Pb, the TMs investigated were mainly in their soluble form (70–90% of soluble fraction). Data of Cd, Pb, Hg and Ni concentrations were compared to the Environmental Quality Standards (EQSs) established for priority substances in inland surface waters (Directive 2013/39/EU, 2013). The EQS levels were never exceeded.

As expected, the highest TM concentrations in the river were found in sediments. The TMs that accumulated the most were Zn, Cu, Cr and Pb (Fig. 2d). Both WWTP effluents and urban runoff can contribute to the accumulation of TMs with a high anthropogenic component along the sediments of the Manzanares river (Vystavna et al., 2012). Values (Fig. 2d) were similar, or even lower (except for Cr), than ranges previously reported for the Manzanares river sediments downstream from the city of Madrid (10–39 As, 30–126 Cr, 62–347 Cu, 0.23–1.24 Hg, 14–36 Ni, 104–371 Pb, 198–591 Zn mg kg^{-1}) (de Miguel et al., 2005). Concentrations of Zn, Ni and Pb were higher in sediments upstream the dam (Sd2), but those of Cu and Cr were higher in sediments downstream the WWTP (Sd1). The higher ECC content found in Sd2 than in Sd1 could explain the highest contents of Zn, Ni and Pb. A high potential of remobilisation of these TMs and a negative environmental impact could be expected, as previously reported for this stretch of the Manzanares river (de Miguel et al., 2005). Considering international regulations about TMs in river sediments, all TMs presented concentrations higher than the threshold established for Canadian Interim Sediment Quality Guidelines (ISQGs) for the Protection of Aquatic Life (Environment Canada, 2002), and also than the Toxic Reference Value (TRV), except for Ni and Cd (USEPA, 1999). This leads to concerns

about possible adverse effects on aquatic ecosystems inhabiting sediments.

In the case of agricultural soils, TM and metalloid concentrations in fallow (S0) and cultivated soils (S1–S5) before (Fig. 2e) and after (Fig. 2f) the irrigation campaign are presented. As for sediments, the most accumulated TMs in soils were Zn, Cu, Cr, and Pb. Zinc, Cu, and Pb showed the highest gradient of content among parcels (56–125, 13–30 and 20–75 mg kg^{-1} DW, respectively). Differences among samples were not explained by soil properties. No significant differences were observed when comparing cultivated soils before and after the irrigation campaign by Student's *t*-test. The TM content was representative to that usually reported for agricultural soils in the Mediterranean area (de Santiago-Martín et al., 2015). In some cases, Zn, Cu, Pb, Cd, and Hg occurred with concentrations higher than the 90th percentile reference values (RV90) of soils of Madrid based on the Order 2770/2006/CAM, n.d. of the Community of Madrid (CAM). The Reference Generic Values (RGV) for contaminated soils reported in this Order and the maximum levels established by the European Union (Directive 86/278/EEC, n.d.) were never exceeded.

3.3. Occurrence and fate of pharmaceuticals and transformation products

3.3.1. Water

Pharmaceuticals and TPs occurred in the WWTP effluent (W1), surface water (W2) and irrigation water (W3) (Fig. 3a, b, c, respectively) with concentrations mainly in the order of ng L^{-1} and only few of them reached values up to $\mu\text{g L}^{-1}$. Indeed, concentrations ranged from non-detectable to 7000 ng L^{-1} . The EQSs to evaluate the chemical status of surface waters cannot be lower than the maximum acceptable limits of detection methods defined in the European watch lists (2015/495 and 2018/840). Therefore, these values will be compared to measured

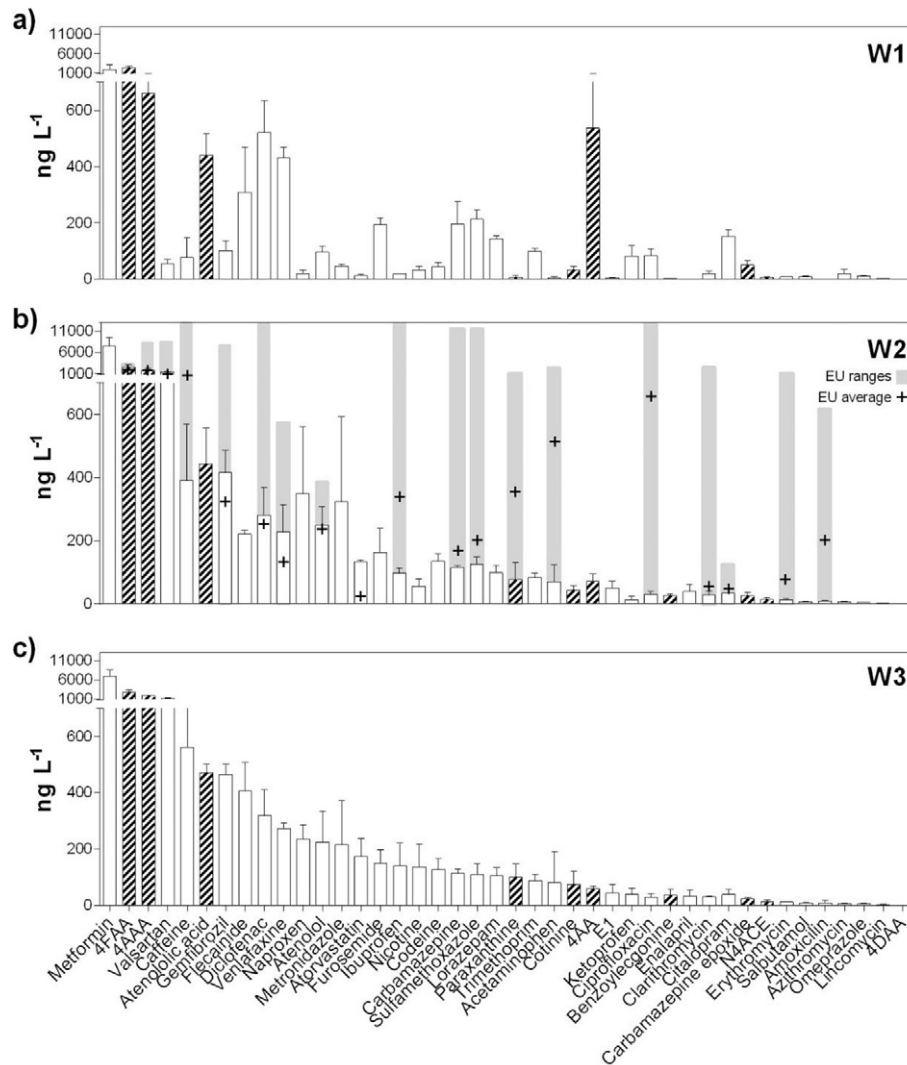


Fig. 3. Pharmaceutical and transformation product (TP) average concentrations in: a) WWTP effluent (W1), b) surface water upstream the dam (W2), and c) irrigation water (W3). A black frame indicates the TPs. Error bars are standard deviation. European concentration ranges and average values in surface waters are presented (Zhou et al., 2019).

concentrations to overcome the absence of EQSs when assessing the water quality in terms of pharmaceuticals. The maximum acceptable limits of detection methods vary from the minimum of 0.035 ng L^{-1} (defined for the hormone 17α -ethinylestradiol (EE2)) to the maximum of 89 ng L^{-1} (defined for the antibiotic ciprofloxacin). Concerning pharmaceuticals mentioned in the watch lists, only the anti-inflammatory diclofenac and the natural estrogen estrone (E1) exceeded the limits established specifically for them by at least one order of magnitude. For the rest of substances, between 16 and 20 pharmaceuticals in W1, W2 and W3 exceeded the highest detection limit mentioned above (89 ng L^{-1}). Of these substances, 12 appeared in all water matrices. Those pharmaceuticals that were never detected ($<1 \text{ ng L}^{-1}$) during the sampling campaigns in water matrices were steroid hormones (17β -estradiol, estriol, 17α -ethinylestradiol, progesterone, testosterone). Such results are encouraging since these substances are highly active compounds that can induce a therapeutic effect even at very low concentrations (Barbosa et al., 2016).

As shown in Fig. 3, detected pharmaceuticals in the bar-charts have been ordered according to their concentration in irrigation water (Fig. 3c), from the highest to the lowest value. This helps to quickly recognize that the composition pattern of the Manzanares river (W2) and irrigation water (W3) are similar, and somehow differ from that of the WWTP effluent (W1). Such a similarity suggests that the dam does

not have an evident impact on the water chemistry in terms of pharmaceutical concentrations and therefore on its natural attenuation, in contrast to what is reported in the literature (Carmona et al., 2014). Contrary to expectations, the quality of surface and irrigation water in terms of pharmaceutical concentration is not fully reflected by the loads from the selected WWTP effluent. With the exception of few substances occurring with the highest concentrations at the three sampling sites, the effluent had even lower concentrations than those detected downstream. Therefore, it seems that dilution processes do not play a key role in the contaminant attenuation likely because WWTP effluents account for a substantial fraction of the river discharge. On the other hand, the difference between effluents and surface water can due to two main reasons both possibly valid at the same time: i) pharmaceutical sorption/desorption onto/from the river sediments; and ii) uncontrolled wastewater discharges and/or runoff along the flow path.

From a more global point of view, the concentrations measured in W2 and W3 are in the low and medium concentration range when compared with data published about selected pharmaceuticals in European surface waters (Zhou et al., 2019). Therefore, results reveal a situation that is consistent with the European panorama regarding the occurrence of common consumed pharmaceuticals and, to some extent, point out even a lower level of contamination of surface water in the

investigated urban and periurban area. The only exception is represented by 4 pharmaceuticals that occur with concentrations $>1000 \text{ ng L}^{-1}$, resembling the highest concentrations detected in rivers across Europe (Zhou et al., 2019). These pharmaceuticals were drugs that act on the metabolism (metformin), the nervous system (4-AAA, 4-FAA) and the cardiovascular system (valsartan). Since investigated crops are exposed exclusively to irrigation water (W3), a more exhaustive discussion about pharmaceutical occurrence and fate will be provided for this matrix (Fig. 3c). Metformin, an oral antidiabetic, was the pharmaceutical that occurred with the highest average concentration (7000 ng L^{-1}), a result that can be correlated to its high consumption in Spain (Sistema Nacional de Salud, 2016). On the other hand, metamizole, one of the most consumed analgesics, was never detected in irrigation water, whereas its TPs (4-AAA and 4-FAA) were found with average concentrations higher than 1800 ng L^{-1} . These results confirm the greater persistence and mobility of the TPs of this analgesic already described in the literature (Leal et al., 2017; Martínez-Hernández et al., 2018). Metformin, 4-FAA, and 4-AAA were also the most concentrated in W1 (Fig. 3a), but instead of valsartan other compounds such as 4-AA (average concentration of 537 ng L^{-1} in W1 respect to $<100 \text{ ng L}^{-1}$ in W2 and W3) or diclofenac (average concentration of 522 ng L^{-1} in W1 respect to 281 ng L^{-1} in W2 and 319 ng L^{-1} in W3) followed the ranking according to concentration values.

In the concentration range between 250 and 1000 ng L^{-1} , compounds such as caffeine (life-style compound), atenolol, gemfibrozil, flecainide (cardiovascular system), diclofenac (musculo-skeletal system) and venlafaxine (nervous system) were found. The presence of some of these compounds in the Manzanares river has been previously reported (González Alonso et al., 2010; Martínez-Bueno et al., 2010). Moreover, it is important to remark that despite the well documented toxicological effect of diclofenac (Schwaiger et al., 2004; Triebkorn et al., 2004; Lonappan et al., 2016), this anti-inflammatory occurred in irrigation water with an average concentration of 319 ng L^{-1} , far above the maximum acceptable method detection limit defined in the first watch list (10 ng L^{-1}). Between 100 and 250 ng L^{-1} , pharmaceuticals acting on similar systems were detected: musculo-skeletal (naproxen, ibuprofen), cardiovascular (atenolol, atorvastatin, furosemide) and nervous systems (codeine, carbamazepine and lorazepam), and the life-style compounds nicotine and paraxanthine (caffeine TP). Atenolol, acid occurred with concentrations higher than atenolol suggesting that under site environmental conditions the transformation of the parent compound is favoured and that the TP is more persistent than his precursor. On the other hand, such behaviour was not observed for paraxanthine (caffeine TP) and cotinine (nicotine TP). In the concentration range of $100\text{--}250 \text{ ng L}^{-1}$, some antibiotics were also detected: metronidazole (nitroimidazole group) was the antibiotic concentrated the most (215.2 ng L^{-1}), followed by sulfamethoxazole (109 ng L^{-1}), an antibiotic belonging to the group of sulfonamides. Metronidazole concentrations were consistent with those previously observed in Spanish rivers and, according to Carvalho and Santos (2016) this compound is usually detected in European aquatic environments despite its reduced consumption and limited percentage of excretion (20%). Sulfamethoxazole is usually administered in combination with trimethoprim (88 ng L^{-1} in W3) with the name co-trimoxazole. One would expect these compounds to be found in higher concentrations in water since: i) sulfonamides are partially excreted unchanged, ii) trimethoprim has a high persistence, and iii) co-trimoxazole is widely consumed (Carvalho and Santos, 2016).

Finally, the rest of pharmaceuticals were encountered with average concentrations lower than 100 ng L^{-1} . As expected, macrolide antibiotics (azithromycin, clarithromycin and erythromycin), β -lactams (amoxicillin) and quinolones (ciprofloxacin), included in the latest watch list (2018/840), have been detected in this range ($<100 \text{ ng L}^{-1}$). On the one hand, according to the irrigation schedule,

the sampling campaign occurred in summer, a period of low antibiotic prescription (Brauer et al., 2016). On the other hand, chemical characteristics of these pharmaceuticals make them not very persistent compounds. Thus, macrolides are poorly water soluble, amoxicillin has an easily hydrolysable β -lactam nucleus under environmental conditions, and ciprofloxacin exhibit poor water solubility at environmental pHs (Carvalho and Santos, 2016). Nevertheless, although at low concentrations, the presence of these antibiotics has been reported as a constant in European surface waters due to their continuous and high consumption (Carvalho and Santos, 2016). This is a major concern as they have been classified as critically important due to the existence of evidence of transmission of microorganisms or resistance genes (AEMPS, 2018).

Concerning the analytical method applied to water matrices, a total of 35 compounds out of 50 (70%) presented recoveries within the 70–120% range (Table S3). Regardless of the recovery level, RSD values $\leq 20\%$ were obtained for the majority of analytes (93%), thus demonstrating good performance of the analytical methodology. The only compound whose quantification may be unreliable (R% $>120\%$ and RSD $>20\%$) is the antibiotic ofloxacin and therefore data about its occurrence are not provided. In conclusion, values presented for the analytical method are considered acceptable given the wide range of compounds with different polarities.

3.3.2. Sediments

Pharmaceutical and TP contents in sediments are shown in Fig. 4. Of the 25 investigated contaminants, 7 could not be analysed due to the complexity of this matrix and the obtained analytical recoveries (Table S4). The content of those pharmaceuticals detected in the sediments were in the order of ng g^{-1} . Only naproxen and furosemide were never detected.

As shown, the pattern of pharmaceutical content in sediments did not correspond to the pattern of concentrations in water. Thus, flecainide, caffeine and its TP paraxanthine, and atenolol and its TP atenolol acid were the compounds that showed the highest contents in sediments indicating that they are likely to be attenuated by sorption processes onto river sediments. Conversely, 4-AAA, 4-FAA and valsartan, detected with the highest average concentrations in water ($>1000 \text{ ng L}^{-1}$), were not the most accumulated in sediments. Unfortunately, metformin, with very high concentrations in irrigation water, could not be analysed in sediments (neither in soils) due to the low recovery obtained in this matrix with the methodology used. Further research is currently under development to optimize the extraction of this pharmaceutical from both sediments and soils.

In general, higher pharmaceutical and TP contents were found in Sd2 sampling point than in Sd1, probably due to the predominance in Sd2 of fractions that have a great influence on sorption processes, such as organic, carbonate, phosphate, and Fe fractions. Interaction in the water-sediment system are also highly regulated by the ionization state, pKa, hydrophobicity (K_{ow}) and molecular weight. With the exception of metronidazole, positively and neutral compounds occurred in higher contents confirming that the ionization state plays a primary role in their sorption. Sorption onto sediments can represent a sink for pharmaceuticals and TPs, however their accumulation in sediments not necessarily result in a reduction of their bioavailability or toxicity since they can be continuously released to the overlying water (Ebele et al., 2017).

3.3.3. Soils

The pharmaceutical and TP content in soils of investigated agricultural plots is shown in Fig. 5. As for sediments, of the 25 compounds selected, 7 could not be analysed (Table S4). Measured concentrations were in the order of ng g^{-1} for all compounds. Valsartan, naproxen and furosemide, out of the 19 analysed, were never detected. Measured contents in soils were generally lower than measured contents in sediments probably due to the continuous contact between sediments and contaminated surface water.

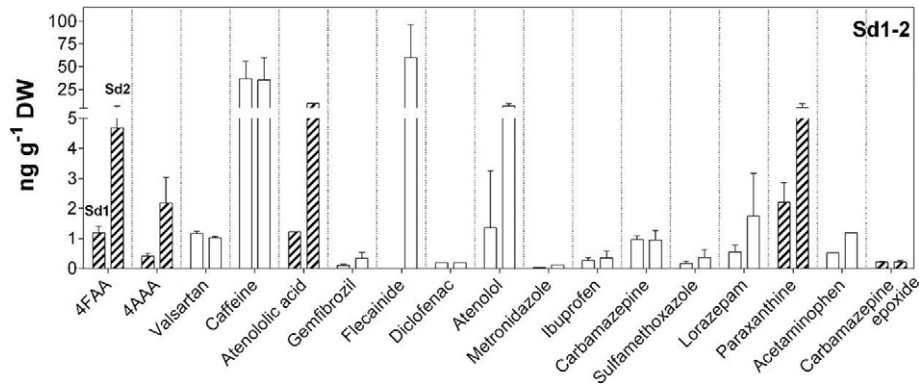


Fig. 4. Pharmaceutical and transformation product (TP) average concentrations in sediments downstream the WWTP (Sd1) and upstream the dam (Sd2). A black frame indicates the TPs. Error bars are standard deviation. DW = dry weight.

As in the case of sediments, the pattern of pharmaceutical content in soil did not correspond to the pattern of concentration in irrigation water. Thus, those pharmaceuticals that were detected in water with high levels were exhibiting lower contents in soils (4-AAA, 4-FAA) or they were even not detected (valsartan). Similar to what observed for sediments, flecainide, caffeine and its TP paraxanthine, and atenolol and its TP atenololic acid showed higher contents in soils. However, unlike sediments, compounds with low concentrations in irrigation water, such as ibuprofen, acetaminophen, and carbamazepine and its TP carbamazepine epoxide, showed higher contents in soils. Previous studies have already shown the persistence of some of these compounds in soils, such as carbamazepine (Carter et al., 2018). These results show that low concentrations of pharmaceuticals in irrigation water can mask high contents in cultivated soils and that, therefore, it is essential to consider all the environmental matrices involved.

When comparing pharmaceutical and TP contents before and after the irrigation period, different patterns were observed: some

compounds increased (4-FAA, 4-AAA, metronidazole, ibuprofen), others decreased (gemfibrozil, flecainide, carbamazepine, lorazepam, acetaminophen, lorazepam), and others remained practically constant along the irrigation season (atenololic acid, sulfamethoxazole, paraxanthine) or varied according to the sampling point (caffeine, diclofenac, atenolol, carbamazepine epoxide). Notables were the cases of: i) ibuprofen, which was practically not detected before irrigation but reached values of up to 13 ng g⁻¹ DW after irrigation, and ii) acetaminophen and carbamazepine epoxide, decreasing after the irrigation period in some cases up to 100%.

It should be noted, however, that there were no differences between the pharmaceutical and TP content in soil of the reference plot (S0), which was fallow during the sampling year, and the rest of the study plots (S1–S5). This could be due to two main reasons: i) soil, despite being fallow, receives continuous contributions of pharmaceuticals due to the slow and progressive degradation of plant debris resulting from the maize harvest with which it has been amended in previous

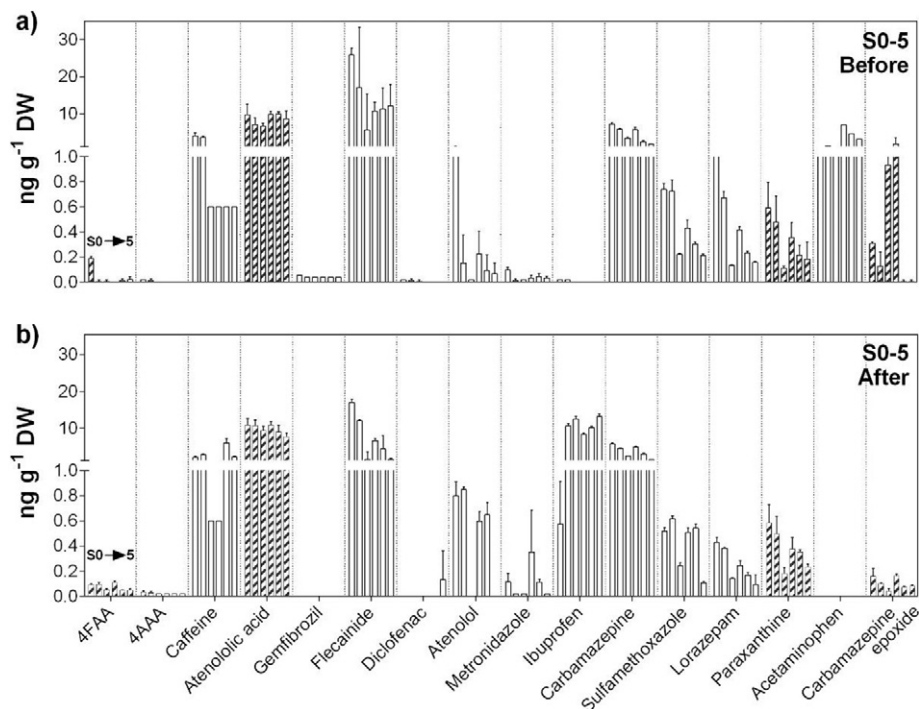


Fig. 5. Pharmaceutical and transformation product (TP) average concentrations in soils (S0–5): a) before and b) after the irrigation period. A black frame indicates the TPs. Error bars are standard deviation. DW = dry weight.

years; ii) the lack of moisture and the absence of vegetation slow down the microbial activity responsible for the biodegradation of compounds. Despite these considerations, causes of the apparent lack of leaching of pharmaceuticals as a result of meteorological precipitation should also be investigated. To confirm this result, it would be necessary to carry out a study with a higher number of fallow soil sampling points that allows statistical comparisons.

As for sediments, the accumulation of pharmaceuticals in soils depends on their physico-chemical properties, such as the state of ionization and hydrophobicity, and on the properties of the soil such as clay content, OM and hydroxides (Martínez-Hernández et al., 2014; Meffe and de Bustamante, 2014). For example, the sorption of the flecainide antiarrhythmic can be interpreted as the result of its positive ionization and the high value of the octanol/water partition coefficient ($\log K_{ow}$ 3.78) that favours interaction with OM and soil clays. In our study, differences among samples were apparently not related to soil properties.

3.4. Bioaccumulation of contaminants in plants: risk to health?

The concentration of TMs in the corn grains was generally low, in the order of mg kg^{-1} . Only Zn, Cu, and Ni were quantified. Contents of As, Cr, Pb, Cd, and Hg were $< \text{LOQ}$ (Table S1). Cadmium and Pb are the only TMs included in the list of contaminants in cereal foodstuffs (Commission Regulation (EC) 1881/2006) and therefore these data indicate that there is no risk related to the consumption of maize grown in the investigated area. The detected TM concentrations in DW were $1.3\text{--}41.6 \text{ mg kg}^{-1}$ (Zn) $> 0.9\text{--}1.9 \text{ mg kg}^{-1}$ (Cu) $> 0.2\text{--}0.5 \text{ mg kg}^{-1}$ (Ni). Results showed that soil-to-grain BCFs were < 1 in all cases: $0.04\text{--}0.24$ (Zn), $0.05\text{--}0.13$ (Cu), and $0.02\text{--}0.03$ (Ni). This implies that TM translocation to edible parts of maize was very low. In order to determine the health risks associated with the consumption of these cereal, the HQ was calculated considering the TMs detected in corn grains (WW). The oral RfD values used were 300, 400 and $20 \mu\text{g kg}^{-1} \text{ BW day}^{-1}$ for Zn, Cu, and Ni, respectively (Margenat et al., 2019). The average HQ of corn grains from maize plants collected from all parcels were 0.013 (Zn), 0.001 (Cu) and 0.004 (Ni). The THQ ranged from 0.005 to 0.041 (period 2016–2018) or reached a value of 0.042 (projection from 2028 according to OECD/FAO, 2019). In all cases, values were < 1 , so there would be no potential risk for consumers. These findings are consistent with those of Margenat et al. (2019) for food crops in a periurban area of the city of Barcelona, Spain.

The concentration of pharmaceuticals and TPs in the irrigation water did not respond to the bioaccumulation pattern in the fruit of plants, as was the case in sediments and soils. In a similar study in agricultural areas irrigated with pretreated wastewater in Saudi Arabia, Picó et al. (2019) also observed that pharmaceuticals and TPs that accumulated in the soil (atenolol, caffeine, carbamazepine and gemfibrozil) were not exactly the same as those quantified in the different studied vegetables (atenolol, caffeine, carbamazepine epoxide and hydroxy-ibuprofen). In our study, out of the 25 pharmaceuticals analysed in the plants only acetaminophen ($8.4\text{--}27.5 \text{ ng g}^{-1} \text{ DW}$), nicotine ($0.03\text{--}1.2 \text{ ng g}^{-1} \text{ DW}$), ibuprofen ($0.2\text{--}1.1 \text{ ng g}^{-1} \text{ DW}$) and carbamazepine ($0.04\text{--}0.4 \text{ ng g}^{-1} \text{ DW}$) were detected in corn grains. These compounds were in the lowest concentration ranges quantified in water: $< 100 \text{ ng L}^{-1}$ (acetaminophen) and $100\text{--}250 \text{ ng L}^{-1}$ (nicotine, ibuprofen and carbamazepine). Conversely, in soils the contents of acetaminophen (before irrigation), ibuprofen (after), and carbamazepine (before and after) were among the highest values, together with flecainide, atenolol and caffeine. Similar values were obtained by Margenat et al. (2019) studying carbamazepine, among other organic microcontaminants (OMCs), in edible parts of lettuce, tomato, cauliflower and broad beans. Unlike the present study, they detected the TP carbamazepine epoxide in plants. Also, the authors observed that only 10 of the 33 OMCs were detected.

Metformin, caffeine and its TP paraxanthine, gemfibrozil, flecainide, atenolol and its TP atenolol acid, and metronidazole, have been

detected in corn grain samples at a concentration below the MQL (between 0.1 and $1 \text{ ng g}^{-1} \text{ DW}$, except for metformin; $10 \text{ ng g}^{-1} \text{ DW}$). Therefore, its presence was confirmed but a quantitative data cannot be provided. Another very large group of pharmaceuticals and TPs were not detected in the fruit, even if some of them, such as 4-AAA, 4-FAA and valsartan, were present in irrigation water at concentrations higher than 1000 ng L^{-1} .

Concerning the analytical method, the recoveries between 60 and 140% with $\text{RSD} < 20\%$ are considered acceptable for routine analyses of microcontaminant residues in plant samples (European Commission, 2010). In this study, a 52% of compounds meet the criteria of recovery. A 32% of the total presented absolute recoveries between 30 and 60%, and only a 16% of analytes (citalopram, flecainide, metformin and venlafaxine) yielded absolute recoveries $< 30\%$ (Table S5). The number of compounds that presented low recoveries is much higher in comparison to water matrix, thus evidencing the greater complexity of this matrix, probably as a consequence of the high starch content that makes the SPE purifying step not so effective. In trace environmental quantitative analysis, low recovery (with good repeatability) is not an obstacle for a reliable quantification, as high recovery is required only when the sensitivity of the method is poor (Al-Odani et al., 2010).

For ibuprofen and carbamazepine, it has been possible to calculate the soil-to-grain BCF. Whereas this data cannot be provided for acetaminophen since it was not detected in the soil after the irrigation period. For each parcel, the BCF was well below 1 for both contaminants (average values 0.05), indicating their tendency to remain retained in soil and/or in other plant tissues rather than translocate to the fruit. In general, obtained results agree with the description from Christou et al. (2019) that identified maize as a plant with a limited potential uptake of OMCs. These results highlight the necessity to measure the pharmaceutical content in different parts of the maize such as roots, stems and leaves to understand the whole translocation process. In general, the absorption by plants of anionic compounds is lower than that of neutrals due to the repulsion with the electrically charged surface of the root (Christou et al., 2019; Li et al., 2019). Cationic or neutral compounds tend to accumulate in the root, while translocation to the aerial part is diminished. In the present study, the relationship between ionic charge and absorption is not so evident. Carter et al. (2018) concluded that the plant uptake depends on the combination of several factors, such as sorption potential and hydrophobicity, which explained the absorption pattern of benzodiazepines by radish and beet. Likewise, they observed that certain TPs are produced as part of plant metabolism, which deserves future studies.

With the exception of ibuprofen, defined as belonging to Class I (low order of oral toxicity), the contaminants detected and quantified in corn grains (acetaminophen, nicotine, and carbamazepine) belong to Class III that consists of substances that allow no strong initial presumption of safety or may suggest significant toxicity (Cramer et al., 1976; Patlewicz et al., 2008). By applying the TTCs corresponding to the identified classes, the DC values for toddlers (1–3 years) ranged between 0.96 kg d^{-1} for acetaminophen to 60 kg d^{-1} for ibuprofen. Corresponding DC values for adults vary between 5.61 kg d^{-1} and 2333 kg d^{-1} . Calculated DC are far above the typical European DI of maize (26.85 g d^{-1}) and therefore the consumption of the investigated corn would not pose any threat to human health.

4. Conclusions

The present study assessed the occurrence of pharmaceuticals and TPs, TMs and metalloid in the water-sediment-soil-plant system and their potential uptake by maize under real field-scale conditions. Most important findings can be summarized as follows:

- Concentrations of TMs and metalloid in water should not arise any concern. Conversely, TMs tends to accumulate in the river sediments with contents exceeding international threshold values, implying possible adverse effects on the aquatic ecosystems.

- Measured contents of TMs and metalloid in soils are in the range of those reported for Mediterranean agricultural soils. Based on regulation about Cd and Pb in cereal foodstuffs, there is not any risk to human health associated with the consumption of the investigated maize. The THQ for all TMs detected in corn grains were below 1 confirming the absence of any potential risk for consumers.
- A large group of pharmaceuticals, mainly those that act on metabolism and on nervous and cardiovascular systems, were detected in water matrices, generally within the ranges reported for European surface waters. With the exception of the estrogen estrone, hormones were never detected in water. Therefore, in our scenario, this pharmaceutical class does not imply an emerging risk. Macrolide antibiotics, ciprofloxacin and diclofenac (included in the EU watch lists) were not among those contaminants detected with the highest concentration. However, diclofenac, highly exceeded the maximum acceptable method detection limit suggesting the presence of considerable inputs of this contaminant to the environment.
- Results confirm the well-known persistence of the metamizole TPs (4-AAA and 4-FAA) and the atenolol TP (atenololic acid) indicating that pharmaceutical degradation does not necessarily imply a decrease in contamination. Efforts to detect new TPs based on metabolomic studies should be made and supported by the development of analytical techniques.
- The concentration pattern of pharmaceuticals and TPs in irrigation water did not correspond to the pattern of contents in soils and plant fruits. This result highlights the need to include the different environmental compartment when assessing the fate of contaminants under real field-scale conditions.
- Only acetaminophen, nicotine, ibuprofen, and carbamazepine were detected in the corn grains with quite low concentrations, confirming the limited potential uptake of pharmaceuticals by maize. Soil-to-grain BCFs prove that these substances were not easily translocated towards the edible part of the plant. According to the TTCs, the consumption of the corn would not pose any threat to human health in terms of pharmaceutical intake.
- The contaminants discharged by the WWTP effluent seems not to undergo to dilution that lower their concentration because effluents build-up the majority of the river discharge. Attenuation along the flow is therefore not clearly observed. However, there are substances that tends to be accumulated into the soil and sediments, some of them are also taken up by maize. It appears, that the contamination is buffered by attenuation processes such as sorption onto soil and sediments and, to a lower extent, plant uptake.

Finally, the authors would like to highlight that although pharmaceutical, TP, TM and metalloid concentrations found at each of investigated compartments in this study suggest that they are not posing a risk to public health individually, interaction among contaminants within these scenarios should be considered in the future strategy dealing with water quality issues. In this sense, risk assessments still need to be reinforced and performed for the whole spectrum and cocktail effects are likely being masked behind current monitoring procedures and compliance assessments. The difficulty in assessing health impacts of toxic chemicals in wastewater (including TPs and other contaminants), because of the associated long latency period before the appearance of effects, is a suggested cause for this limitation (Bos et al., 2009). Nevertheless, the precautionary principle is still valid and should be maintained so long as scientific information is incomplete or inconclusive. In order to improve policy coherence towards sustainable development, political will is key to foster research and enhance knowledge uptake into practice, to implement synergy measures and cross-sectoral coordination between water, agricultural and public health policies. This is particularly essential in scenarios of potential hotspots downstream

urban wastewater and runoff discharge in densely populated areas and/or under water scarcity contexts.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2019.135825>.

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