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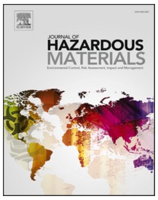

Research Paper

Selection of pharmaceuticals of concern in reclaimed water for crop irrigation in the Mediterranean area

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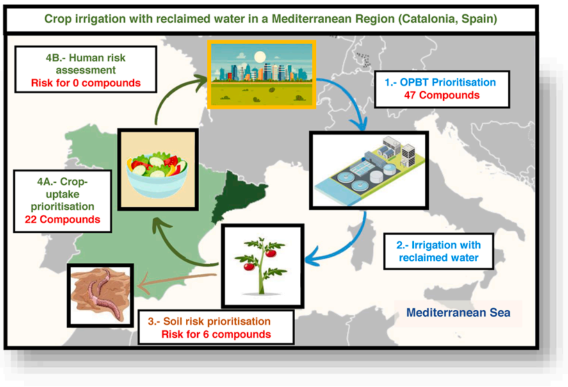
HIGHLIGHTS

- The concentration of 148 pharmaceuticals in wastewater from Catalonia was used as the data source.
- There were 47 pharmaceuticals selected as concerning for the aquatic environment.
- Three antibiotics, iopromide, ibuprofen and metoprolol acid posed a risk to the soil.
- Five psychiatric drugs and two analgesics were often detected in the edible parts of the crops.
- No human risk was foreseen from the consumption of edible crops.

GRAPHICAL ABSTRACT



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ABSTRACT

The reuse of reclaimed water in agriculture is being fostered in areas suffering from water scarcity. However, water pollutants can compromise food safety and pose a risk for the environment. This study aims to select the pharmaceutical compounds worth monitoring and investigating when reclaimed water is used for tomato and lettuce irrigation. A comprehensive study was first conducted to identify the pharmaceuticals frequently detected in secondary wastewater effluents in Catalonia (Northeast Spain). Priority pharmaceuticals were further selected based on their occurrence in secondary effluents, persistence (removal in conventional treatment), bioaccumulation potential, toxicity for aquatic organisms, and the risks they pose to the terrestrial environment and human health (through the consumption of crops). Out of the 47 preselected priority compounds, six could pose a risk to organisms living in soil irrigated with reclaimed water and seven could be potentially taken up by the crops. Nonetheless, no human risk for human consumption was foreseen.

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1. Introduction

As the world's population continues to grow and freshwater resources become increasingly scarce, one of the strategies to cope with this issue is the reuse of water. Therefore, the (re)use of reclaimed water for agriculture purposes has become a common practice in many parts of the world and it is also promoted, for example, in the recent European directive (EU) 2020/741 for water reuse in agriculture [28]. While this practice offers many benefits, such as reduced pressure on freshwater resources and increased food production, secondary effluent water might still contain a high concentration of pathogens, suspended solids, and other regulated and non-regulated contaminants. Polishing treatments (e.g. rapid sand filtration followed by UV disinfection, advanced oxidation processes or nature-based solutions) are usually required after secondary treatments to meet the water quality standards.

There is a great interest in the occurrence of contaminants of emerging concern [19], which include Pharmaceutically Active Compounds (PhACs) and personal care products. Monitoring such contaminants is crucial in water reuse practice; especially of those compounds persisting after water treatment and/or those posing a risk for the environment and human health. The target pollutants can be selected through different prioritisation approaches but, usually, a wide list of compounds is preselected in the first step according, for example, to available previous real monitoring data and/or legislation [34,42]. Afterwards, different prioritisation models can be applied, with the most simple being the one based on contaminant concentration in the environment. Occurrence data can either be measured environmental concentration (MEC) (e.g. [17,69]) or predicted environmental concentration (PEC), [31,60]. Other prioritisation models consider the PEC or MEC together with the toxicity of the compound (PNEC) through the calculation of the corresponding hazard quotient (HQ), [77]. Depending on the source of the toxicity data, different assessment factors are applied, generally in the range of 10 to 1000 [26]. The hazard quotient model is the most applied prioritisation approach, but it only considers occurrence (O) and toxicity (T), omitting other relevant aspects such as persistence (P) and bioaccumulation (B). Compounds that exhibit high persistence might become a threat for the ecosystems because of the continuous exposure of aquatic organisms to their presence [37]. On the other hand, potential uptake and tissue bioaccumulation of these compounds could affect the full trophic chain [33]. The OPBT approach does cover the persistence and bioaccumulation potential of a compound (besides occurrence and toxicity) and therefore might provide a more accurate list of relevant compounds to be considered. The sum of all the 4 scores (one for each of the 4 OPBT parameters) leads to a final score of the compound, as calculated by [74] or [23] in their studies.

While the OPBT procedure was developed to select priority compounds as a potential threat for the aquatic environment, other parameters should also be considered to identify compounds of priority in the specific case of reclaimed water use for irrigation. In the first place, the impact for the organisms living in arable soils (e.g. earthworms) should be considered [49]. The EU guidelines in this field [13] suggest a procedure based on the HQ in soil, calculated by dividing the measured (MEC_{soil}) or predicted concentrations in the soil-water mixture (PEC_{soil}) by the predicted no-effect concentrations in the same matrix ($PNEC_{soil}$). Compounds with HQ equal to or higher than 1 could represent a threat for the soil organisms which are essential for the crop's growth [35].

In the second place, the potential of the crop to uptake the residual pharmaceuticals in the reclaimed water should be evaluated. Several studies over the years have reported not only the uptake but also the accumulation of the residual pharmaceuticals present in the reclaimed water used for irrigation in the different parts of the crops, especially in leafy vegetables such as lettuce. In this context, it is reported that the potential of a pharmaceutical to be taken up by the crop mainly depends on three parameters: pharmaceutical molecular weight, electrochemical charge and polarity [9,40]. In recent years, some studies have predicted the risk related to the ingestion of pharmaceuticals through crops irrigated with reclaimed water. Some of the studies assessed the risk by the calculation of the acceptable daily intake (ADI), if the data are available [7,44,62,64], otherwise by means of the threshold of toxicological concern (TTC), based on the decision tree defined by Cramer et al. [21]. Then, the amount of edible crop to be ingested in order to reach the ADI or TTC is calculated considering the highest detected concentration in the edible part of the crop [54].

Most of the prioritisation studies focus on the so-called parent compounds and do not take into consideration their transformation products (TPs). These compounds can be generated by the human metabolism and/or in the wastewater treatment plants and, sometimes, can have higher toxicities [48] or persistence [66] than the corresponding parent compound and thus can be environmentally relevant [27].

Several regions in the Mediterranean area suffer from water scarcity such as Catalonia, in the North East of Spain [59]. Although a number of studies have been performed in this area which report the environmental presence of emerging pollutants [17,67], no consensus exists about which are the most relevant contaminants to be considered regarding reclaimed water reuse. The objective of the present work is to prioritise the pharmaceuticals of concern; i.e. those that might pose a high risk to the environment and human health when reclaimed water is used to irrigate crops. A wide number of pharmaceuticals, metabolites and TPs were preselected using an OPBT approach with real MEC data retrieved from an in-house database on the area of interest. The preselected pharmaceuticals were then prioritised based on two criteria: (i) the risk they might pose to the organisms living in the soil where crops are irrigated with the reclaimed water and (ii) the likelihood of these compounds of being taken up by two of the most cultivated Mediterranean crops: lettuce and tomato. Finally, the risk of consumption of the edible parts of the crops irrigated with reclaimed water was considered for both adults and toddlers (4-year-old children) using the ADI approach.

2. Materials and methods

2.1. Occurrence data in the case study

The environmental occurrence of PhACs is directly related to their consumption, which is site-specific and might differ between different seasons, countries and even regions. Information about the observed concentrations in raw wastewater as well as in secondary treated effluents in the selected region of Catalonia (Northeast Spain) was extracted from Castaño-Trias et al. [17]. In this previous study of the group, a database provides the occurrence levels of 148 pharmaceutical compounds in 5 different water types: hospital wastewater, urban influent wastewater, treated wastewater (TWW) river and sea water collected from 30 publications from the last 10 years in Catalonia. The mean concentrations of PhACs in TWW were calculated from 13 articles from this database (those providing TWW concentration data) and are considered here together with 1 recent article (Table S1).

2.2. Persistence, toxicity and bioaccumulation data

Data regarding persistence, toxicity and bioaccumulation were gathered for the compounds included in the occurrence database and evaluated as follows.

Persistence (P) was related to the removal efficiency (R) of a compound in a conventional activated sludge treatment plant ($\%P = 100\text{-}\%R$), like in other prioritisation approaches in the literature [23]. The compounds exhibiting lower removal are considered the ones with higher persistence. R was calculated as the mean of the removal values reported in the in-house database (Table S2). If the compound concentration in the influent wastewater was zero, the removal efficiency could not be calculated, and it was obtained from the literature on activated sludge systems (Table S3). Studies performed in the Mediterranean area were considered over those related to other areas.

Bioaccumulation (B) refers to the capacity of a compound to accumulate in an organism, especially in its adipose tissue. This parameter can be expressed by the octanol-water partition coefficient ($\log K_{ow}$), which refers to the proportion of the concentration of one compound in n-octanol and in water [43]. Higher proportion values lead to high bioaccumulation potential. Experimental values were extracted from ChemSpider, (http://www.chemspider.com). When no experimental data were available, the value was calculated through the EPI Suite software KOWWIN (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface).

Toxicity (T) was assessed from the predicted no effect concentration (PNEC), as for example, in [29]. When available, real experimental data coming from the NORMAN database (https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php) were considered (as in [74] or [70]). When no data were available for any compound, toxicity was calculated using the EPI Suite ECOSAR software (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface) as in [22] or [39]. Selected toxicity was the lowest available value (acute or chronic) in the three different levels of the trophic chain (algae, daphnia and fish).

2.3. Preselection procedure

In order to allow comparison of the values of the different parameters, a normalisation step was carried on by means of applying discrete scores in the same scale (Table 1). For each parameter, the score varies from 1 to 5, 1 being the lowest concern and 5 the highest, as established in [74]. When no removal data could be retrieved, either because the compound was not detected in the influent wastewater, or because no removal efficiency was available from the literature, the given score was 3. Compound's scores without reported data are thus neither boosted in the prioritisation list, as in the case of the approach adopted by [74] (who applied the maximum score of 5), nor disregarded, as in the case of the approach applied by [23] (who applied the minimum score of 1).

It was assumed that each score had the same weight. Equally weighing occurrence, persistence, toxicity and bioaccumulation is one of the most common approaches to select compounds relevant for the environment [10]. In some cases, in the literature, the experimental data are weighed over predicted values. For instance, [23] modified the scores obtained from predicted data by multiplying them by 0.66. The final scores of many compounds (those with no experimental data available) were thus lowered and many were eventually excluded from their final prioritisation list. In our work, the objective is to select the pharmaceuticals that could pose a risk to the environment in a worst-case scenario. Therefore, the scores obtained from predicted data were not modified and the final score was obtained by totalling the scores of the four OPBT criteria. Compounds obtaining 60% of the maximum score (12 out of 20) were considered of high concern and were thus preselected for the further prioritisation steps (Fig. 1).

Table 1
Thresholds for score assignment, NA (Not Applicable) refers to compounds for which no removal data were available.

Score	Concentration effluent (ng/L)	Removal (%)	PNEC (µg/L)	$\log K_{ow}$
5	> 1000	$< 20\%$	< 0.1	> 4.5
4	500–1000	20–40%	0.1–1	3–4.5
3	100–500	40–60%	1–10	2–3
2	50–100	60–80%	10–100	1–2
1	< 50	$> 80\%$	> 100	< 1
3		NA		

2.4. Prioritisation methodology

2.4.1. Selection of priority compounds for organisms living in soils irrigated with TWW

The compounds obtaining a score (determined as indicated in Section 2.3) equal to or higher than 12, were further evaluated in terms of risk for organisms living in the soil (Fig. 1). The hazard quotient (HQ) of the compounds in soil was calculated by Eq. 1:

$$HQ(soil) = \frac{PEC(soil)}{PNEC(soil)} \tag{1}$$

where PEC is the predicted environmental concentration of the compound in the soil and PNEC its predicted no-effect concentration. If the ratio is ≥ 1, the risk is high; if it is between 1 and 0.1, the risk is medium; and if it is ≤ 0.1, the risk is low according to [35] and [51]. Compounds with HQ ≥ 1 are considered of priority interest from the soil perspective.

PEC was calculated according to the Technical Guidance Document on Risk Assessment (TGDRA) [13] by means of Eq. 2:

$$PEC(soil) = \frac{V \times C \times d}{D \times \rho} \tag{2}$$

where V is the volume of water required for the crops per day and surface unit (L/d·m^2), C the concentration of the pharmaceutical in the treated water used for the irrigation of the crops (expressed in µg/L), d the number of days required for the crops to be harvested (d), D the depth (m) of the considered fraction of soil and ρ the density of the soil (expressed in kg/m^3). The assumed values in the current study are reported in Table 2 together with the corresponding references.

The PNEC values were estimated (according to [13] and also [74]), by means of Eq. 3:

$$PNEC_{soil} = PNEC_{water} \times K_{OC} \times f_{OC} \times 10^{-3} \tag{3}$$

where the $PNEC_{water}$ values are the same as those used for the preselection of analytes (Table S3); K_{OC} is the carbon-water partition coefficient (compound-specific, [10]) extracted from KOCWIN (EPI Suite, https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface), and f_{OC} is the fraction of organic carbon and is soil-dependent. According to [15] f_{OC} was equal to 0.016 for the arable crops in Catalonia.

2.4.2. Selection of relevant compounds to be taken up by the crops irrigated with TWW

The compounds obtaining a score (determined as indicated in Section 2.3) equal to or higher than 12, were further evaluated in terms of likelihood to be taken up by crops (Fig. 1). According to [9,40], the compound uptake by the plants mainly depends on 3 variables:

1. **Molecular weight**: compounds with low molecular weights (under 1,000 g/mol) are easier to be taken up by the roots and translocated to the plant.

1. **Charge**: due to the electrostatic interactions in the roots, acidic compounds are more easily located in them, while neutral or basic compounds are more likely to be found in the aerial part of the plant. This variable is measured by pKa.

1. **Hydrophobicity or hydrophilicity**: this characteristic is expressed by the pH dependant octanol-water distribution coefficient ($LogD$) defined by Eq. 4 (for acidic compounds) and 5 (for basic compounds).

$$Log \quad D = Log \quad K_{ow} + Log \frac{1}{1 + 10^{pH - pK_a}} (\text{acidic compounds}) \tag{4}$$

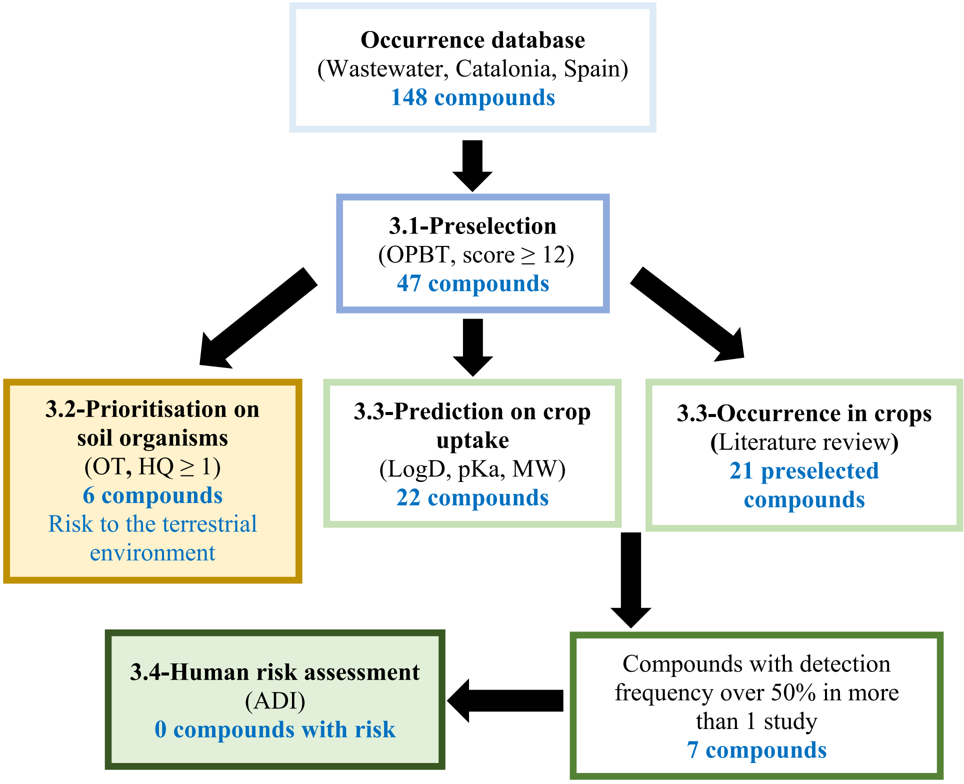

Fig. 1. Workflow for the selection of pharmaceuticals of concern for soil and crops irrigated with reclaimed wastewater. The blue text refers to the number of compounds in each prioritisation step.

Table 2
Values of the parameters occurring in Eq. 2 to estimate concentrations of pharmaceuticals in soils.

Parameter	Value	Extracted from
V	2.67 L/d·m^2 for lettuce 1.08 L/d·m^2 for tomato	[2,78]
C	Depends on compound	This work: Table S1
d	35 days for lettuce, 49 for tomato	[45,55,57]
D	0.2 m (for any crop)	[13,56,73]
ρ	1700 kg/m^3	[13,56,73]

$$Log\quad D = Log\quad K_{ow} + Log\frac{1}{1+10^{pK_a-pH}}(\text{basic compounds}) \tag{5}$$

For neutral pharmaceuticals, the two previous equations converge into Eq. 6:

$$Log\quad D = Log\quad K_{ow} \tag{6}$$

Compounds with Log$D$ under 1 are highly hydrophilic and have a low tendency to translocate in the plant, according to [74]. Compounds with values between 1 and 4 could be taken up and translocated to the plant. Finally, if the values are higher than 4, the compound is considered strongly hydrophobic and thus potentially accumulated in the soil and roots.

Therefore, compounds are considered of priority if they comply with the three following conditions which may favour their uptake by plants: low molecular weight, non-acidic pKa, and Log$D$ values between 1 and 4.

2.4.3. Literature data on compounds present in crops

Since no prediction model is available for the calculation of concentration of pollutants in plants, data on the levels of the 47 OPBT preselected compounds were extracted from the literature. The review was conducted in Scopus using the keywords “Pharmaceutical” AND “Crop” AND “Uptake”. The first 100 publications (based on relevance) were overviewed, and the 18 publications (Table 3) that reported data about the 47 OPBT prioritised compounds were selected. Studies had to clearly report the methodology used for the determination of the concentration of PhACs, the number of samples and the frequency of sampling. In the case of review papers, data quality had to be ensured. Studies had to have sufficient collected data to support their discussions.

2.4.4. Human health risk assessment due to ingestion of crops irrigated with reclaimed water

The potential risk for humans through the consumption of edible crops was assessed for the preselected compounds (for their likelihood to be taken up by crops, Section 2.4.1) and/or with enough information in terms of plant uptake from the literature (Section 2.4.2). The risk was only assessed for the compounds investigated in more than 1 study and with detection frequencies (in the edible part of the crops) higher than 50%. The latest criterion gives more reliability to the data and limits the attention to more frequently detected compounds [10]. The studies where contaminants were spiked in the irrigation water were excluded.

The ADI was calculated from the lowest daily therapeutic dose (LDTD) in the literature with an assessment factor of 1000 [62] and a body weight of 70 kg (Eq. 7). The amount of the crop to be ingested to reach the ADI was then obtained considering the maximum MEC in the edible parts of the crop in the literature and the consumer weight (Eq. 8).

$$ADI\left(\frac{\mu g}{kg-d}\right) = \frac{LDTD\quad\left(\frac{mg}{d}\right)\times 1000(conversion\quad of\quad mg\quad to\quad \mu g)}{1,000(assessment\quad factor)\times 70kg} \tag{7}$$

Table 3
Studies investigating the uptake of the preselected pharmaceuticals in lettuce and tomato irrigated with reclaimed water.

Publication	Studied crop	Part of the crop	Number of compounds	Spiked*	Country	Soil Irrigation Period
[4]	Tomato	Fruits	6	No	Israel	2 years
[18]	Tomato	Fruits	3	No	Cyprus	3 years
[61]	Tomato	Fruits	40	No	Saudi Arabia	1.5–3 months
[5]	Tomato	Leaves and fruits	7	No	Israel	2 years
[30]	Tomato	Leaves and fruits	13	No	Israel	9–14 weeks
[54]	Tomato	Leaves and fruits	60	No	Spain	2 years
[12]	Tomato	Roots, leaves and fruits	30	Yes	Spain	3 months
[72]	Tomato	Fruit	56	No	Spain	Not available
[19]	Tomato, lettuce	Leaves and fruits	60	No	Mediterranean area (review)	2 months
[6]	Tomato, lettuce	Leaves and fruits	3	No	Israel	6–14 weeks
[76]	Lettuce, tomato	Roots and tomato leaves	18	No	USA	2 weeks
[3]	Lettuce	Leaves	3	No	Spain	Not available
[38]	Lettuce	Leaves	9	Yes	USA	Not available
[50]	Lettuce	Leaves	13	Yes	France	46 weeks
[53]	Lettuce	Leaves	74	No	Spain	1.5–3 months
[58]	Lettuce	Leaves	48	No	Spain	55 days
[71]	Lettuce	Leaves	18	No	Spain	Not available
[32]	Lettuce	Leaves and roots	2	No	Spain	8 weeks

*Studies spiking PhACs in the irrigation water were considered to determine the frequency of detection in the edible parts of the crops. Nonetheless, these studies were not considered when determining the maximum MEC.

$$Crop\ \ consumption\ \ to\ \ reach\ \ ADI\left(\frac{kg}{day}\right) = \frac{ADI\ \left(\frac{\mu g}{kg-d}\right)\times consumer\ \ weight(kg)}{Maximum\ \ MEC\ \ in\ \ the\ \ crop\left(\frac{\mu g}{kg}\right)} \tag{8}$$

Since a person of a lower weight might be at a higher risk for ingestion, a low weight (3rd percentile, meaning that only 3 out of 100 are below this weight and 97 are above) was considered, as a worst-case scenario, for two different types of consumers, i.e. adults and 4-year-old toddlers. The applied value for the toddlers in Catalonia region was 12.2 kg [24]. For the adults, the 3rd percentile for Catalonia was not available and the value for Spain was used instead: 56.6 kg [16].

3. Results and discussion

The workflow followed for the selection of priority pharmaceuticals is shown in Fig. 1 and each step is further discussed below (Sections 3.1 to 3.4).

3.1. Preselection of analytes

The list of 148 compounds initially considered, together with their corresponding data of occurrence, persistence, bioaccumulation and toxicity is reported in Table S3. Experimental data were not available for all compounds and were thus predicted using different prediction models and software:

1. Occurrence: concentration in TWW of the initial 148 compounds (in-house database, Table S1).
2. Persistence: the removal efficiency in wastewater treatment plants (WWTPs) was calculated either from Table S1 (99 compounds) or obtained from the literature (37 compounds). No data were available for the remaining 12 compounds and therefore with an assigned default score of 3 (Table 1).
3. Bioaccumulation: logK_{ow} values were obtained from experimental data (41 compounds) or calculated through KOWWIN (from EPISUITE) software as indicated in Section 2.2 (107 compounds).
4. Toxicity: real experimental toxicity data (PNEC values) was only available for 54 compounds, while for the remaining 94 compounds the PNEC values were calculated using the ECOSAR (from EPISUITE) software, as indicated in Section 2.2.

Bioaccumulation was the parameter with fewer available experimental values (41 compounds) whereas occurrence data were available for all studied compounds (148 PhACs). Only 16 compounds had experimental data available for the 4 OPBT parameters. Table S4 and Fig. 2 show the compounds with experimental data for the four parameters.

Table S5 reports the scores assigned to each of the 148 compounds for each of the 4 OPBT parameters (maximum score 5), following the criteria indicated in Table 1. The sum of the scores allowed to rank the compounds from the most relevant (score 19) to the less relevant (score 4). The highest score was obtained for diclofenac, with the maximum score (5) in all categories except in occurrence (score 4, with concentration lower than 1000 ng/L). Final scores equal to or higher than 12 were obtained for 47 compounds, including 3 TPs. They are reported in Table S5 in descending order according to the final score, together with the corresponding therapeutic class. The distribution of these preselected 47 compounds, grouped by the same final score and therapeutic class, is shown in Fig. 3 and Figure S1. Scores for analgesics and anti-inflammatories (9 prioritised compounds) and psychiatric drugs (14 prioritised compounds) ranged between the maximum (19) and the minimum (12), whereas the compounds belonging to other therapeutic classes achieved lower scores in general.

The median of the compound scores for occurrence, persistence, bioaccumulation and toxicity evaluated were 1, 3, 2 and 3, respectively (Table S5). These data suggest that the parameters with more weight over the final scores were persistence and toxicity. Nonetheless, each therapeutic class showed different trends. Fig. 4 compares the therapeutic class profile of the 47 preselected compounds with that of the initial 148. On the one hand, only 7 out of 65 antibiotics in the database were preselected; although they have high toxicities, most of them had low occurrence, persistence, or bioaccumulation values. On the other hand, out of the 19 psychiatric drugs considered in the initial list, 14

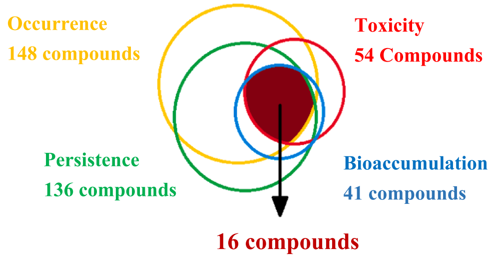

Fig. 2. Number of compounds with real OPBT data, based on Table S4.

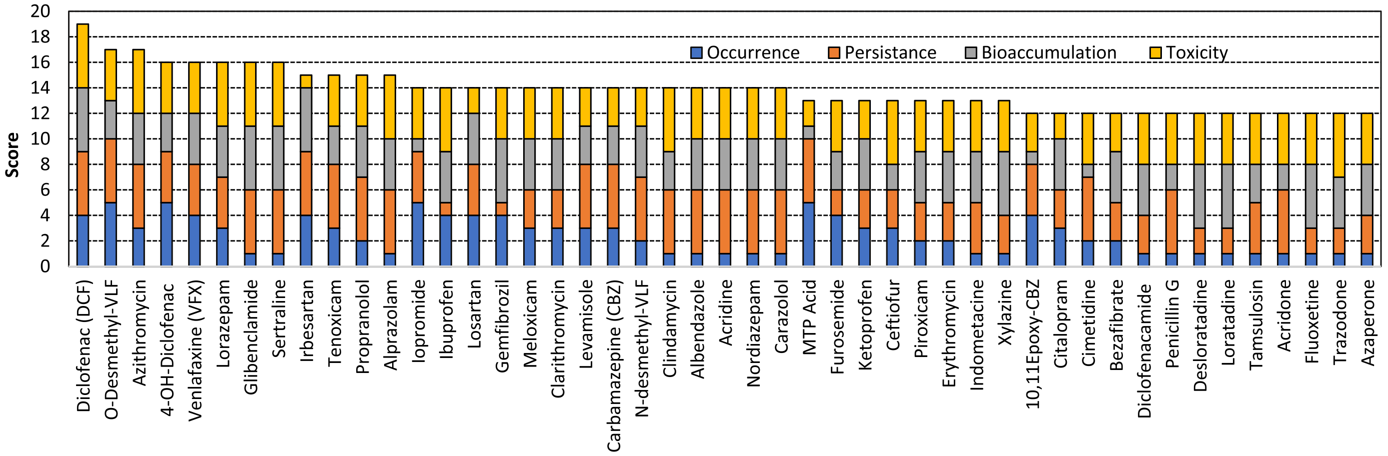

Fig. 3. Contribution of each OPBT parameter (occurrence, persistence, bioaccumulation, toxicity) to the final score for the 47 preselected compounds (score equal to or higher than 12). Each parameter has a maximum score of 5.

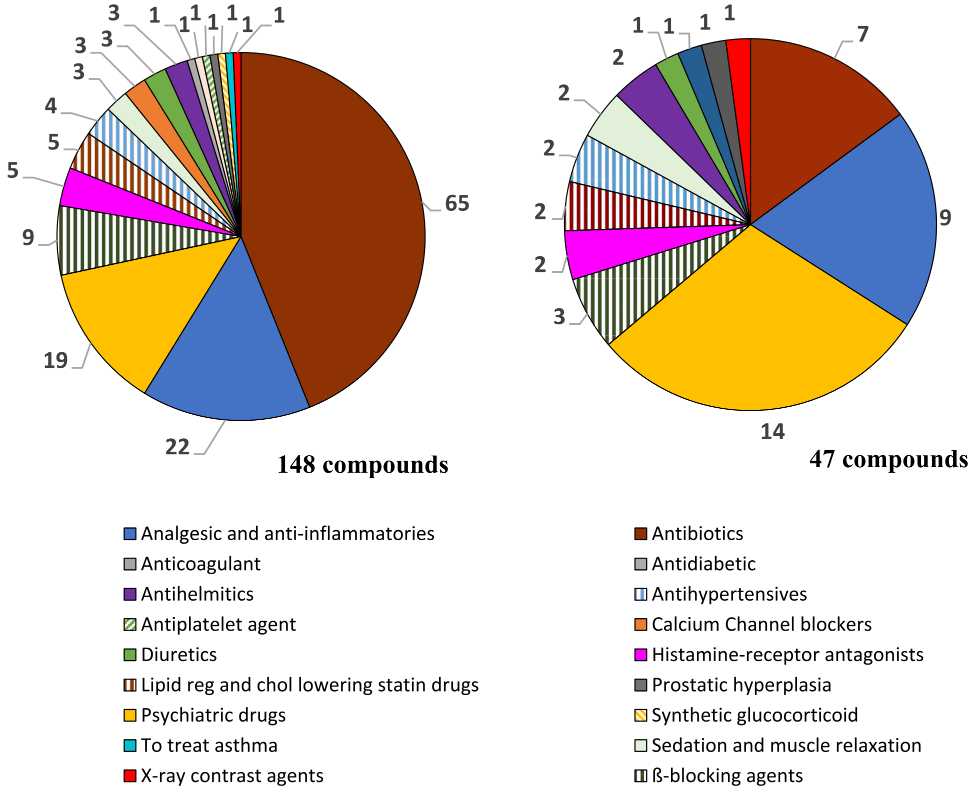

Fig. 4. Number of compounds per therapeutic class in the initial list (left) and in the list of OPBT preselected compounds (right).

were preselected (score > 12). While these compounds have low scores in the occurrence in the secondary effluents, their persistence, bioaccumulation potential and toxicity make them of high relevance for the environment. In contrast, occurrence was the main contributor in the case of the analgesic and anti-inflammatories class, another therapeutic class with high representation in the final list (i.e. 9 compounds preselected out of the initial 22). In the case of the 3 preselected β-blockers, all obtained a score of 5 in persistence.

A comparison can be performed between the 47 OPBT preselected compounds and the 47 compounds at the highest TWW concentrations, as only occurrence is considered in some prioritisation studies [17]. Despite their high concentrations, up to 21 compounds in the occurrence list were not prioritised by OPBT, half of them being analgesics and anti-inflammatories. Among them, the ibuprofen metabolites carboxy-ibuprofen (with a OPBT score of 11) and 2-hydroxy-ibuprofen, which were in the top positions of the occurrence list. Other compounds with high ranking in the occurrence list but not in the OPBT selection were atenolol and sotalol (ß-blocking agents), ranitidine (histamine-receptor antagonist), 2-hydroxy-carbamazepine, norfluoxetine and paroxetine (psychiatric drugs), valsartan (antihypertensive) and hydrochlorothiazide (diuretic). Out of the 10 antibiotics included in the occurrence list, only 5 were also preselected based on the OPBT criteria: azithromycin, clarithromycin, ceftiofur, erythromycin and cimetidine (whereas cefotaxime, ciprofloxacin, sulfamethoxazole, ofloxacin and trimethoprim were excluded).

In contrast, 21 compounds not included in the top 47 based on their occurrence were relevant in the OPBT classification, most of them being psychiatric drugs (8 compounds) such as N-desmethyl-venlafaxine, sertraline or alprazolam. Other examples are glibenclamide (antidiabetic), loratadine, desloratadine (histamine receptor antagonists), albendazole (anthelmintic), carazolol (ß-blocking agent), azaperone (sedation and muscle relaxation) and the antibiotics clindamycin and penicillin G.

The transformation products considered in this study presented, in most cases, higher PNEC than the corresponding parent compounds. For instance, ibuprofen had a PNEC of 0.011 μg/L, lower than its transformation products (10.6 μg/L, 7.9 μg/L and 5.6 μg/L for 1-OH-ibuprofen, 2-OH-ibuprofen and carboxy-ibuprofen, respectively). Only sulfamethazine had a PNEC of 30 μg/L, two orders of magnitude lower (0.2 μg/L) than its transformation product N-acetyl-sulfamethazine.

While toxicity and bioaccumulation are inherent to each specific compound, occurrence and persistence can differ from one geographic area to another. The OPBT criteria to select compounds of concern for the aquatic environment (Table 1 and Section 2.3) was also applied to occurrence data of Spain, Portugal, Italy and South Africa, gathered by [74] (table S6), though only to the 69 pharmaceuticals in common with the present study. The number of compounds with scores ≥ 12 was 61 if all the countries were considered, 45 if only data from Spain was considered, and 37 if considering the database collected in the present work in Catalonia, an area representing around 16% of Spain's population. The observed variations depending on the area of the study show that prioritisation studies need to be performed that are specific to each region or country. These differences in the scores obtained between Catalonia and Spain are attributed to the literature sources (14 papers in the present work and 18 in the database from Spain of Verlicchi), as no large differences in the usage of the pharmaceuticals nor in terms of removal in both areas are expected. In fact, both databases only have 3 articles in common.

3.2. Selection of priority compounds for the soil

The selection of the most relevant compounds of the terrestrial ecosystem is based not only on the PNEC values [74] but also on PEC values, i.e. HQs, which are calculated using both toxicity and occurrence data, allow the risk posed for the contaminants to be assessed and the contaminants to be prioritised. The predicted concentration in soil (PEC_{soil}) of the OPBT preselected compounds (Table S7) was calculated based on their concentration in TWW and other parameters related to the chosen crops (lettuce and tomato, Section 2.4.1). The maximum PEC_{soil} was obtained for iopromide: 1.77 ng/g and 1.00 ng/g for lettuce and tomato soils, respectively, with the difference attributable to the differences in the irrigation parameters (Table 2). Regarding $PNEC_{soil}$, the values ranged from $4.88 \cdot 10^{-5}$ ng/g for iopromide up to $8.65 \cdot 10^{3}$ ng/g for irbesartan, respectively (Table S7).

Based on the ratio HQ=PEC/PNEC, out of the 47 OPBT preselected compounds, only 6 exhibited HQ ≥ 1 (high risk) for at least one of the soils growing either tomato or lettuce irrigated with treated water (Table S7): iopromide, penicillin G, ceftiofur, metoprolol-acid, azithromycin and ibuprofen. As in other studies, the antibiotics were determined as the most concerning class in terms of risk for the organisms living in the soil [14]. These 6 compounds also had PNECs under 0.1 ng/g (threshold for compound prioritisation in soil, according to [74]). On the other hand, some compounds with PNECs under 0.1 ng/g (lorazepam, clindamycin, clarithromycin and trazodone) exhibited a HQ below 1 for both lettuce and tomato soils, due to their low predicted soil concentrations, and they were not considered of concern.

Diluting the secondary effluent by a 1:161 factor would decrease all the HQs for lettuce soils to values lower than 1, except for iopromide, which would require a much higher dilution (1:37,000). Lower dilution (1:91 for all compounds except for iopromide (1:21000)) would be necessary in the case of tomato to reach the same conditions. The risk regarding iopromide was also flagged up in other studies in soil [14]. Other authors also prioritised the relevance of emerging contaminants in soil ecosystems using the HQ. As an example, in Lyu et al. [47] PEC values were calculated with a HYDRUS-1D software whereas PNEC values with Eq. 3, which are restricted to acute values (EC50 values with an assessment factor of 1000). The priority PhACs selected by Lyu et al. [47] were the antibiotics erythromycin, ciprofloxacin and sulfadiazine as well as carbamazepine and metoprolol. None of them was selected in the current work, highlighting the influence of the chosen scenarios and countries (China for Lyu et al. [47] and Catalonia in the present study) on occurrence and/or persistence and, therefore, on the final list of prioritised compounds.

3.3. Selection of relevant compounds for crop uptake

3.3.1. Predicted compounds for crop uptake

All the compounds preselected in Section 3.1 had a molecular weight lower than 1000 g/mol, complying with the first criterion to be taken up by the roots and eventually be translocated to the aerial part of the plants (Section 2.4.2). Regarding the two additional criteria (not acidic pKa and LogD between 1 and 4) four different scenarios are possible (Table 4):

1. The compound does not comply with any of the conditions: the compound is not expected to be taken up by the aerial part of the plants (scenario 1).
2. The compound complies with one condition but not the other one: the compound is not predicted to be taken up by the crops, or at a lower degree, and could be considered in further investigations (scenarios 2 and 3).
3. The compound complies with both conditions: the compound can be taken up by the plant and is potentially of concern (scenario 4).

The criteria here considered for plant uptake (scenario 4) was fulfilled by 18 compounds: levamisole, carbamazepine, alprazolam, azaperone, carazolol, acridone, N-desmethyl-venlafaxine, clindamycin, clarithromycin, azithromycin, erythromycin, sertraline, propranolol, desloratadine, fluoxetine, trazodone, albendazole and meloxicam. Four extra compounds had LogD close to 1 and 4: citalopram (0.96), 10,11-epoxy-carbamazepine (0.95), venlafaxine (0.78) and xylazine (4.19) and were also selected (as a precautionary approach), leading to a list of 22 predicted compounds. Table S8 reports the list of compounds with the values of the three parameters. In addition, compounds with acidic pKa and LogD higher than 4 would have been selected as priority for the uptake and accumulation of the compound in the roots (following the criteria explained in Section 2.4.2), but none of the compounds here investigated fell into this category. Figure S2 depicts the regions the different compounds belong to, depending on the fulfilment of the criteria. The detailed list is reported in Table S9.

3.4. Literature data on compounds taken up by crops

The potential uptake of contaminants can be assessed as in Section 3.3.1 [74]. However, no accurate concentrations can be calculated following this approach, and thus, occurrence data were collected from the literature. The literature review was carried out in SCOPUS using the keywords "Pharmaceutical" AND "Crop" AND "Uptake". The 100 most relevant publications were overviewed, and of them, only 18

Table 4
Possible prioritisation scenarios for PhACs crop uptake.

Condition	Scenario 1	Scenario 2	Scenario 3	Scenario 4
MW < 1000 g/mol	Yes	Yes	Yes	Yes
Neutral and basic compounds	No	No	Yes	Yes
LogD between 1 and 4	No	Yes	No	Yes
Result	Disregarded	To be further investigated		Predicted

publications reported data about the occurrence of the 47 OPBT prioritised compounds (Table 3). Out of the 47 selected compounds by OPBT criteria, information in the literature was available for 21 compounds including 13 out of the 22 predicted to be taken up by crops (Table S9, Table S10). Six out of the 13 compounds were investigated in more than 1 study and with detection frequencies (in the edible part of the crops) equal to or higher than 50%: carbamazepine, epoxy-carbamazepine, venlafaxine, fluoxetine, citalopram and propranolol. Nevertheless, propranolol was only detected in one of the 2 studies targeting it, at a low concentration (maximum 0.4 ng/g), and in tomato leaves, which are not considered an edible part of the crop for human health risk assessment, and hence it was disregarded in the following section.

The psychiatric drug carbamazepine and its metabolite epoxy-carbamazepine were always detected in multiple studies in tomato and lettuce leaves (Table S9). According to [65], the presence of the metabolite is not only related to direct uptake from the terrestrial environment irrigated with reclaimed water, but it can also be generated by metabolization of carbamazepine by the plant. Venlafaxine, fluoxetine and citalopram were investigated in few studies (not more than 3 studies each) but all were detected in more than 50% of them (Tables S9, Table S10). Additionally, although diclofenac and ibuprofen were not expected to bioaccumulate (pKa of 4.2 and 4.9, respectively), they were found in crops in more than 50% of the studies performed (Table S9) and, hence, they were added to the list of compounds relevant for crop uptake.

Not enough information was found for some of the compounds expected to be taken up by crops. Clarithromycin, for example, was detected only once in lettuce (130 ng/g, [50]) (Table S9). Furthermore, this compound has a half-life of 0.027 days (calculated with EPI Suite) and might be rapidly degraded. The other priority antibiotics for crop uptake azithromycin, clindamycin and erythromycin were not detected in the crops in the 2 studies targeting them [5,54]. As in the previous scenario, these compounds had concentrations in the water as low as 5 ng/L for clindamycin or under the limit of detection for azithromycin. Similarly, insufficient occurrence data were available for alprazolam, desloratadine and N-desmethyl-VLF. No studies targeted other compounds predicted to be taken up: acridone, albendazole, azaperone, carazolol, levamisole, meloxicam, sertraline, trazodone and xylazine (Table S10).

Finally, some but insufficient information (i.e. detection frequencies of these compounds below 50% either in leaves or tomato fruit) was found in the literature for the following compounds not included in the list of predicted compounds for crop uptake: furosemide, gemfibrozil, ibuprofen, indomethacin, irbesartan, ketoprofen and O-desmethyl-VLF.

Concentrations observed in the leafy parts of the crops were much higher than the concentrations observed in the fruit, in line with the results of the recent study of [19] with more than 29 types of crops.

3.5. Human health risk assessment (HHRA)

The HHRA of the selected PhACs was related to the amount of crop irrigated with reclaimed water that can be safely consumed before reaching their ADI and the detected concentrations of the PhACs in the edible parts of the crops (Eq. 7). In other risk assessment approaches the ingested amount of crop is calculated for an established geographical area, and in a specific year and/or season. In that case, the calculated amount of vegetable consumed is thus compared with the ADI through the HQ. However, people within the same geographical area might have different consumption habits, and also, they can vary depending on the season of the year. For example, tomato consumption in Spain is higher in the summer period compared to other seasons. Therefore, calculating the amount of crop to be safely consumed (as performed in the present work which is indeed one of the first ones to assess the risk using real toxicity data), instead of calculating a HQ based on an established diet offers a more flexible and wider perspective.

In our work, out of the 7 compounds evaluated for HHRA (Table 5), the maximum amount of crop to be safely consumed was determined by the riskiest compound, i.e. diclofenac, which also presented the highest observed concentration in the studied crops tomato and lettuce (up to 26.9 and 11.6 μg/kg, respectively). These concentrations combined with their reported ADI (1.43 μg/kg-d) determine the threshold amount of vegetable to be safely consumed: 3.01 kg of lettuce and 6.97 kg of tomato for adults, or 0.65 kg of lettuce and 1.50 kg of tomato for toddlers, which is considered unrealistic. The recommended daily intake of lettuce and tomato in Catalonia is under 300 g and 240 g for lettuce and tomato, respectively (regardless the age of the consumer). Data were extracted from Martínez et al. [52].

The remaining 6 compounds posed lower risk to both adults and toddlers. Citalopram was only detected in studies analysing lettuce irrigated with TWW. Despite being detected at a high concentration (20 μg/kg in [58]), the ADI (4.09 μg/kg-d) make the recommended amount of lettuce to consume, as high as 11.56 kg for adults and 2.49 kg for toddlers. Carbamazepine was detected up to 10 μg/kg in lettuce and 4 μg/kg in tomato fruits. The reported ADI for this compound is 2.86 μg/kg-d. The calculated amounts of crops to be ingested to reach these values are 16.17 kg or 40.43 kg of lettuce and tomato, respectively, for adult consumers, and 3.49 kg or 8.71 kg of lettuce and tomato, respectively, for the toddlers. Fluoxetine was detected in both tomato and lettuce (4.3 and 0.03 μg/kg, respectively). The ADI of the compound is 4.71 μg/kg-d, therefore, the amount of lettuce to reach the ADI is lower compared to the previous presented values: 62.05 kg for adults and 13.38 kg for toddlers. In tomato, due to the low concentration, the ADI would be reached at 8894.29 kg of tomato for adults and 1917.14 kg of tomato for toddlers. Ibuprofen could only be considered in tomato and at a low concentration (0.6 μg/kg). This concentration level combined with a high ADI (11.43 μg/kg-d) allowed safe consumption of up to 1078.1 kg and 232.8 kg of tomato for adults and toddlers respectively [52].

Venlafaxine was detected at low concentrations (2.3 and 0.1 μg/kg in tomato and lettuce, respectively) and with an ADI of 7.71 μg/kg-d, the amount of crop to be safely consumed is as high as 189.84 kg of lettuce or 4366.29 kg of tomato for adults, and 40.92 kg of lettuce and 941.14 of tomato for toddlers. Finally, epoxy carbamazepine, was detected at remarkably lower concentrations than the other compounds (only 0.1 and 0.2 μg/kg in tomato and lettuce, respectively). Prosser et al. [64] reported an ADI equal to the value of the parent compound, carbamazepine, therefore, no risk is predicted in the consumption of up to 808.57 kg and 174.29 kg of lettuce for adults and toddlers respectively and 1617.14 kg and 348.57 kg of tomato for adults and toddlers, respectively [52].

Other prioritisation studies raised concern on contaminants of emerging concern when reclaimed wastewater is used for irrigation, through the calculation of risk quotients for environmental and human risk assessment (e.g. [47] in China and [25], in Italy). Several differences are spotted depending on the area of interest. While erythromycin (also predicted to be taken up) and sulfamethoxazole (not OPBT preselected) were prioritised in both lists, some were only considered of priority in one country: ofloxacin [47], metoprolol [47] and clarithromycin [25]. None of these compounds were preselected in our work in Spain, remarking the necessity to perform studies to determine the compounds of priority for the different areas and regions.

4. Conclusions and future prospects

The present work has prioritised the pharmaceuticals posing a higher concern for the environment and human health when reclaimed water is used for irrigation of crops. To achieve this objective, occurrence data of 148 PhACs in wastewater effluents in Catalonia (Northeast of Spain) were gathered with their persistence, toxicity and bioaccumulation data, and used to preselect the 47 compounds of higher concern.

Since the consumption of pharmaceuticals differs from one country

Table 5
Human risk assessment of the selected PhACs in real samples of tomato and lettuce, ordered by increasing lettuce consumption to reach ADI. Maximum daily intake calculated for an adult and a toddler in Spain. Studies with irrigation water spiked with PhACs were not considered for the selection of the highest MEC.

Compound (Prioritised, Freq. Det. ≥ 50%)	Age	Diclofenac	Citalopram	Carbamazepine	Fluoxetine	Ibuprofen	Venlafaxine	10,11-epoxy-CBZ
Highest MEC in lettuce leaf (ng/g)	-	26.9[a]	20[b]	10[c]	4.3[a]	No data	2.3[b]	0.2[d]
Highest MEC in tomato fruit (ng/g)	-	11.6[e]	No data	4[f]	0.03[g]	0.6[h]	0.1[i]	0.1[i]
LDTD (mg/d) for an adult of 70 kg	-	100[j]	286[k]	200[j]	330[l]	800[j]	540[k]	200[j]
ADI (µg/kg-d)	-	1.43	4.09	2.86	4.71	11.43	7.71	2.86
lettuce consumption to reach ADI (kg/d)	Adult	3.01	11.56	16.17	62.05	No data	189.84	808.57
tomato consumption to reach ADI (kg/d)		6.97	No data	40.43	8,894.29	1,078.10	4,366.29	1,617.14
lettuce consumption to reach ADI (kg/d)	Toddler	0.65	2.49	3.49	13.38	No data	40.92	174.29
tomato consumption to reach ADI (kg/d)		1.50	No data	8.71	1,917.14	232.38	941.14	348.57

[a] [71], [b] [53], [c] [5], [d] The value was calculated from [6] assuming a percentage of water in the leaf of 95%,), [e] [18] [f] [4], [g] [72] The water content in the tomato fruit was assumed to be 95%, [h] [30], [i] [54], [j] [64], [k] extracted from https://www.drugs.com, [l] [11].

to another, the selected compounds might differ when occurrence data specific to each country is used in prioritisation studies. Therefore, more prioritisation studies are required to spot the compounds that could pose a higher risk in the different countries. Additionally, there is a need for more OPBT experimental data for several PhACs to more accurately carry-on further prioritisations.

Preselected compounds were further prioritised by the risk they can pose for the soil organisms and the potential uptake by the crops (lettuce and tomato) when the reclaimed water is reused for irrigation. It emerged that 6 were of possible concern for soil organisms: iopromide, penicillin G, ceftiofur, MTP acid, azithromycin and ibuprofen. In the case of crops, 22 compounds were predicted to be taken up by lettuce and tomato. Upon comparison with real experimental data, the ubiquitous presence of diclofenac, citalopram, fluoxetine, ibuprofen, venlafaxine, carbamazepine and one of its transformation products (10,11-epoxycarbamazepine) in the crops of interest in this study was confirmed. However, the compounds detected in the edible parts of the crops were at concentrations that should not pose a risk for consumption by adults and toddlers. Nonetheless, information on PhAC concentrations in the edible part of crops is largely lacking in the literature and more field studies are necessary to gather more real data and to reach a more accurate risk assessment.

While toxicity and bioaccumulation are intrinsic properties, occurrence and persistence depend on the population's consumption habits and wastewater treatment trains and allow some measures to be taken to mitigate the environmental risk posed by these compounds. Several possibilities can be considered to achieve this goal, such as limiting the consumption of the drugs of concern or using alternative compounds posing lower environmental/human risk. In parallel, another solution might be to adopt alternative secondary wastewater treatments and/or tertiary polishing treatments. Among treatment technologies, nature-based solutions such as constructed wetlands (CW) could be implemented. In fact, for example venlafaxine and carbamazepine, compounds with low removal in wastewater treatment plants (32% and 6%, respectively, Table S3) are reported to reach removals as high as 74% in a subsurface flow CW [68] and 94% in full-scale aerated sub-surface flow hybrid CW [1], respectively. Another option could be the adoption of an ozonation step as an end-of-pipe treatment. This treatment does not only allow a removal of around 84% and 57% for carbamazepine and venlafaxine, respectively, from the secondary effluents but also iopromide (relevant for the soil) at 68% [46]. Additionally, it also might reduce the concentration of 10,11-epoxy-CBZ between 70–90%, according to Kharel et al. [41]. Nonetheless, ozonation treatment might generate toxic transformation products and, therefore, a post treatment based on granular activated carbon to eliminate residual contaminants could be a good option [36,75]. Finally, another tertiary treatment that could be considered is UV that, even though not designed for the removal of PhACs, could still improve the removal of certain compounds from the TWW, such as metoprolol, up to 40% [20].

A holistic assessment of other contaminants is recommended to find possible adverse effects that could still be unspotted including other contaminants of emerging concern apart from pharmaceuticals, such as plasticizers, pesticides, metals or hormones as well as bacteria and antibiotic resistance genes [8] and bacteria [63], in order to cope with the spread of multidrug resistance. Moreover, to have a more realistic risk assessment it is necessary to consider the effects of mixtures of contaminants, rather than simply evaluating the effects of multiple individual compounds.

Environmental Implications

In a world suffering from water stress, the search for alternative water sources is gaining importance. Among them, reclaimed water is a promising option for irrigation purposes, but its safe usage must be ensured. In the present manuscript, the authors elaborate a list of waterborne pharmaceuticals considered of concern based on the assessment of their risk to the environment and human health in a specific scenario: reclaimed water used to irrigate tomato and lettuce in a Mediterranean region. Monitoring and evaluating the presence of these priority pharmaceuticals contributes to a safer use of reclaimed water.

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.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.133538.

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