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Development of predicted environmental concentrations to prioritize the occurrence of pharmaceuticals in rivers from Catalonia

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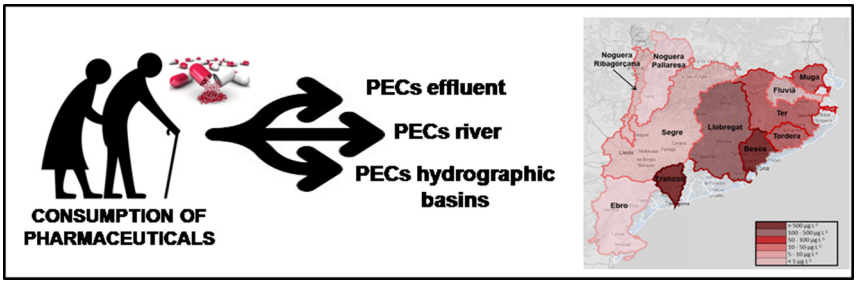
HIGHLIGHTS

- Consumptions of 165 pharmaceuticals used by elderly people have been reported.
- The mean total consumption of pharmaceuticals studied between 2013 and 2016 was 623 ± 3 t year^{-1}.
- Amoxicillin is expected to pose adverse effects for cyanobacteria.
- Metformin pose a small potential for adverse effects to invertebrates and fish.
- Moreover, ibuprofen also poses a small potential for adverse effects to fish.

GRAPHICAL ABSTRACT



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ABSTRACT

The main objective of the present study is to prioritize those pharmaceuticals that have higher chances to be detected in water due to incomplete removal in Wastewater Treatment Plants (WWTPs). To do so, the total consumption of pharmaceuticals in Catalonia (NE Spain) were compiled to calculate the predicted environmental concentrations (PECs) in wastewater effluents and in river water. PECs were estimated using publicly available consumption data in the period of 2013–2016 for a suite of 165 compounds. The selected compounds were based on generic pharmaceuticals with emphasis on drugs consumed by people aged 65 or over as they represent the age group with the highest consumption of pharmaceuticals. The mean total consumption of pharmaceuticals in the period studied was of 623 ± 3 t per year. Paracetamol, metformin and ibuprofen were the most administered drugs although the highest PEC values corresponded to metformin, amoxicillin and metamizole. Finally, predicted environmental levels together with acute and chronic toxicological data allowed estimating the risks of these compounds. Amoxicillin is expected to pose adverse effects for cyanobacteria, whereas metformin and ibuprofen pose a small potential for adverse effects to invertebrates and fish, respectively.

1. Introduction

Nowadays, water pollution represents one of the most serious ecological threats we face. Hence, quality of water has to be preserved to protect the environment and human health from compounds capable of exerting an effect at low levels of concentration. Among other chemicals, pharmaceuticals represent nowadays a relevant class of contaminants because they are continuously released into the aquatic environment and are considered as 'pseudo-persistent' pollutants (Daughton, 2003; Kümmerer, 2009). The first findings of pharmaceuticals in the aquatic environment were reported in the seventies, where the presence of drugs and drug metabolites were detected in sewage water effluent (Hignite and Azarnoff, 1977). Since then, the recurrent and global occurrence of pharmaceuticals in wastewater treatment plants (WWTPs) and surface waters (river, seas, lakes) is reported in

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the range of ng L^{-1} and μg L^{-1} (Hernando et al., 2006; Kümmerer, 2001; Navarro-Ortega et al., 2012a; Navarro-Ortega et al., 2012b; Ternes et al., 2001). Human consumption, animal use, waste disposal and/or manufacturing are the main sources of pharmaceuticals to the environment (Daouk et al., 2015).

Regarding human consumption, the drugbank has 11,901 drugs in its database (Wishart et al., 2018) and the European Medical Agency (EMA) compiles around 2500 active ingredients. Consumption of pharmaceuticals by the global population varies among countries and its use is expected to grow as the population ages and upon polimedication. Virtually every country in the world is experiencing growth in the number and proportion of the elder population. In 2017, 962 million people aged 60 or over were estimated at a global scale, comprising 13% of the global population, and raising to 25% in Europe. This age group is growing at a rate of about 3% per year (United Nations (UN), 2015). Elder population in developed countries have a high consumption of pharmaceuticals (Valderrama Gama et al., 1998), Typical consumption of 5–10 pills/patient/day in residents of senior residences which is translated in a total consumption of pharmaceuticals of hundreds of milligrams per day/person (Lacorte et al., 2017).

Because monitoring of all pharmaceuticals consumed is practically impossible in terms of time and cost, prioritization tools are needed for compounds that deem to pose negative effects in the environment. Predicted environmental concentrations (PECs) is a practical way (Carballa et al., 2008; Franquet-Griell et al., 2015), to estimate the concentrations of drugs expected to be found in the environment based on consumption data. Its use has been reported before for cytostatic (Franquet-Griell et al., 2015; Franquet-Griell et al., 2017) and other drugs (Burns et al., 2018; Guo et al., 2016; Verlicchi et al., 2014) in wastewater and surface waters.

On the other hand, many pharmaceuticals have been reported to be acutely and chronically toxic to aquatic biota with effects varying largely across taxa and among chemical groups (Crane et al., 2006; Fent et al., 2006a; Overturf et al., 2015; Owen et al., 2007; Santos et al., 2010). Acute toxicity values (immobilization or mortality, algae growth within 48–96 h and the half-maximum effective concentration or lethal concentration, EC_{50}/LC_{50}, value) of pharmaceuticals to algae, aquatic plants, *Daphnia magna* and fish species have been generally reported in the order of mg L^{-1}. Moreover, in terms of chronic toxicity, most individual pharmaceuticals (such as antibiotics, antibacterial drugs, anti-inflammatory drugs, non-steroidal anti-inflammatory drugs) induce reproductive toxicity in fish and crustaceans at low or environmentally relevant concentrations (ng L^{-1}-μg L^{-1}) (Crane et al., 2006; Fent et al., 2006a; Overturf et al., 2015; Owen et al., 2007; Santos et al., 2010). In addition, the combination of different drugs sharing a common mechanism of action could produce additive effects that would be enough to enhance toxicity (Cleuvers, 2004; Fent et al., 2006b).

Taking into account the large amount and diversity of pharmaceuticals consumed and discharged to the environment, the aim of this study was to prioritize and evaluate their environmental risk by calculating PECs according to the consumption in hospitals and pharmacies from 2013 to 2016. The procedure has been optimized considering Catalonia, a region of 7.5 million inhabitants, with an elderly population (≥65 years) of 24.5%. This region suffers from water scarcity and thus, the levels and potential toxic effects of pharmaceuticals can be high. PECs were calculated in 11 river basins according to specific population distribution and dilution factor (DF). In addition, the potential risk for the aquatic environment was studied considering acute and chronic toxicity of different aquatic taxa for selected pharmaceuticals with highest PEC_{river}.

2. Material and methods

2.1. Consumption data

Consumption data, being the term "consumption" the dispensation or sales of pharmaceuticals, were obtained from Catalan Health Service (CatSalut) over the period 2013–2016 in pharmacies and hospitals. Compound selection was based on medical prescriptions for the elderly (>65 years) in Catalonia in the last years (http://observatorisalut.gencat.cat) (Generalitat de Catalunya - Catalan Health System Observatory, 2018). A total of 165 drugs belonging to 13 different Anatomical Therapeutic Classification (ATC) groups (A, B, C, D, G, H, J, L, M, N, R, S and V) were included. More than 60% of the pharmaceuticals presented in this study are included in the top 200 worldwide sales and prescriptions realized by Njardarson et al. (McGrath et al., 2010; Njardarson, 2010). Table SI1 (Supplementary Information) shows the ATC and the most relevant physico-chemical properties of target compounds. This information does not include consumption through mutual insurance companies, as this data was not available for the public health system. Hospital data was given as the number of pills, capsules or any formulation of each active pharmaceutical ingredient dispensed (called activities). From the composition and the number of activities of each pharmaceutical, the total consumption (in kg $year^{-1}$) was calculated (Table SI2). The consumptions of the pharmaceuticals in pharmacies were directly provided in mg $year^{-1}$ by the "Pharmaceutical and Medication Management" of CatSalut.

2.2. PEC calculations (effluent, river and basins)

To calculate the predicted environmental concentrations in WWTP effluents (PEC_{eff}) and surface waters (PEC_{river}) in μg L^{-1}, the following equations adapted from Besse et al. (2008) were used:

$$PEC_{eff}\left(\frac{\mu g}{L}\right) = \frac{consumption \times F_{exc} \times \left(1 - F_{wwtp}\right)}{W \times inhab} \times 10^6 \quad (1)$$

$$PEC_{river}\left(\frac{\mu g}{L}\right) = \frac{consumption \times F_{exc} \times \left(1 - F_{wwtp}\right)}{W \times inhab \times DF} \times 10^6 \quad (2)$$

Consumption (g day^{-1}) is the quantity of each pharmaceutical consumed in Catalonia; *Fexc* is the excreted fraction of the unchanged drug, considering both urine and feces. Values were extracted from the Drugbank database (Wishart et al., 2018). For those drugs whose values could not be found, a default value of 0.5 was applied, considering that a pharmaceutical will not be totally excreted as parental compound; *Fwwtp* is the removal fraction in WWTP. Here, when no data was obtained from the bibliography, a default value of 0.5 was used. Then, 1-*Fwwtp*, is the fraction of pharmaceutical's emission from WWTPs to surface waters; *W* (L $inhab^{-1}$ d^{-1}) is the mean water consumption per person per day (about 130.9 L $inhab^{-1}$ d^{-1} in Catalonia). This value was calculated from the mean total urban water consumption in Catalonia in the period studied and the number of inhabitants (IDESCAT, 2017). *Inhab* is the number of inhabitants in a defined zone (in Catalonia, a mean value of 7,446,487 during the period of 2013–2016). In the calculation of PECs, there are several uncertainties which are related to the input parameters of the PEC formula. These uncertainties can produce a bias in the PEC calculation and can alter the results obtained, and thus, their applicability. Among all parameters used in the PEC calculation, the two most significant in the variability of the results are: F_{exc} and F_{wwtp}. In the case of excretion rate, several publications are available on the metabolism of pharmaceuticals and different excretion factors are reported for each drug. The observed differences are probably explained by genomically distinct metabolizing capacities, as well as differences in the routes of administration, sex, age, and health status of the studied subjects (Wishart et al., 2018). On the other hand, removal rates of pharmaceuticals in WWTPs are largely dependent on hydrophobicity and persistence characteristics of the substances. Persistent hydrophilic substances will be present to a greater extent in the treated liquid effluent, hydrophobic ones in the sludge. Expectable removals in WWTPs can thus be inferred to some extent from the substances degradation rates and K_{ow} or K_{oc} values (Lindim et al., 2016). Removal efficiency values can vary between 10 and 90% and

thus, it is important to use the most accurate value in a given site (Estrada-Arriaga et al., 2016; Gros et al., 2017; Gros et al., 2010; Kasprzyk-Hordern et al., 2009; Lajeunesse et al., 2012; Lin et al., 2009; Rosal et al., 2010). The values can be different in WWTP locations according to the served population, capacity, the configuration and type of treatment, in operating parameters and in hydraulic and solid retention times. Other factors such as meteorological conditions, sampling procedure (grab, composite or flow-proportional (Ort et al., 2010) and sampling period (seasonality) can also affect the empirical F_{wwtp}. In the present study, WWTP removals have been selected following previous published papers, and in the case that no removal values were founded, a 50% of removal was used. Removal efficiencies can range from 9 to 100%.

Finally, *DF* is the dilution factor used from WWTP effluents to surface waters. Changes in this value can vary the results >100-fold (Franquet-Griell et al., 2017). In 2006, EMA recommended the use of a default value of 10 (EMA, 2006). However, a more accurate value has been proposed considering the dilution factor of each country, and a value of 25 as the median of the DFs for Spain (Keller et al., 2014). Initially, PEC_{river} values in the present study were calculated using this DF.

However, to obtain more accurate PECs, DFs for the main hydrographic basins in Catalonia were calculated to obtain a better representation of the contamination levels, taking into account the specific characteristics of flow and population. Studied basins were Muga and Fluvià, Ter, Besòs, Llobregat, Francolí, Tordera, Ebro, Segre (a tributary of Ebro), and Noguera Pallaresa and Ribagorçana (tributaries of Segre), which cover most of the area. Table 1 shows geographical information of each river studied, including the population, the river basin area, the length, the water use (L/inhab/day) and the mean, minimum and maximum DF calculated. These new DFs were calculated adapting the formula from Keller et al. (2014) (Keller et al., 2014):

$$DF = \frac{Q_r \times 31536000}{inhab\ basin \times W_{basin}} \quad (3)$$

where,

Qr (m^3/s) is the river flow of each river. The flow data were collected from the hydrographic confederations of each basin and considered geographic and seasonal variability along the basin. Maximum, minimum and mean river flows were used to better estimate PEC variability. The flow data reflect the withdrawal of water in each area. $Inhab_{basin}$ is the population in the basin area (inhabitants). W_{basin} is the water use per capita in the basin, including domestic and industrial use (m^3 $inhab^{-1}$ $year^{-1}$). If data was not available, water consumption at national scale (130 m^3 $inhab^{-1}$ $year^{-1}$) was used. *31,536,000* are seconds per year used to convert units.

To calculate PEC_{river} for each basin, the DF derived from high, mean and low flows in each river basin were applied to Eq. (1) and consumption of pharmaceuticals was considered to be proportional to the population in the studied area. Finally, the $\sum PEC_{river}$ considering each individual drug represented the global occurrence of these compounds in each basin.

2.3. Acute toxicity and environmental risk assessment (ERA)

The acute toxicity of the prioritize pharmaceuticals was reported from the bibliography. However, in the case of metformin, the acute toxicity was determined in the crustacean *Daphnia magna* following standardized protocols (Organization of Economic Co-operation and Development (OECD) 1981) according to Gómez-Canela et al. (2014). Exposure concentrations were prepared in American Society for Testing Materials (ASTM) water at 20 °C using acetone as a carrier (0.1 mL L^{-1}). Negative controls (no acetone) and acetone controls gave no response. Aging of ASTM water was conducted in the laboratory at 20 °C in the darkness to prevent photolysis. Assays were conducted in 50 mL of test medium with 10 animals, per duplicate, and were started at <24-h-old neonates and ended at 48 h. Lethal median concentration effects were estimated fitting immobility concentration responses to the Hill regression model.

After calculating PECs in surface water (PEC_{river}), risk assessment was performed to determine if these predicted concentrations could cause hazard in the aquatic environment. The guidelines recommends performing a risk assessment when PEC_{river} are higher than 0.01 μg L^{-1} (EMA, 2006). Herein, ERA has been calculated for pharmaceuticals with PEC_{river} values higher than 0.2 μg L^{-1} in 2016 because of the low toxicity of pharmaceuticals with PEC_{river} values between 0.01 and 0.2 μg L^{-1}. The risk quotient (RQ) was calculated using the following equation (Eq. (4)), depending on the available data (Gómez-Canela et al., 2014):

$$RQ = \frac{PEC}{PNEC} \approx \frac{PEC}{NOEC/f_1} \approx \frac{PEC}{LC_{50}/f_2} \quad (4)$$

where, PEC is the predicted concentration for a specific basin only in 2016 (described in the previous section) and PNEC is the predicted no-effect concentration. PNEC was estimated using the chronic toxicity NOEC (no-observed effect concentration) and a security factor f_1 of 10 (OECD, 2002). If NOEC was not available, we took LOEC values as a NOEC proxy. When chronic toxicity NOEC/LOEC were not available, PNEC were estimated using $E(L)C_{50}$, and a security factor f_2 of 1000 (OECD, 2002). For metformin, experimental acute toxicity results in *Daphnia magna* and zebrafish embryos were obtained following existing guidelines OECD 202 (OECD, 2004) and OECD 236 (OECD, 2013) used to estimate PNEC. For data interpretation, the maximum probable risk for ecological effects from contaminated water was followed as recommended by Wentsel et al. (1996):

RQ < 1.0 indicates no significant risk;

1.0 ≤ RQ < 10 indicates a small potential for adverse effects;

Table 1
Main hydrographic basins in Catalonia (Spain), territory information with population inhabiting in each basin, area, water use and calculated dilution factors (DF) using mean, maximum and minimum flows. All values have been extracted from www.idescat.cat (Statistical Institute of Catalonia (IDESCAT), 2008). *This length only represents the part of the river along the Catalonia territory.

	Population	Area	Length	Water use	River flow (m^3/s)		DF	
	Inhab.	km^2	km	L/inhab/day	Mean	Min-max	Mean	Min-max
Muga	21,195	854	58	231	2	0.1–4	11	1–21
Fluvià	59,099	1125	97	188	7	1–11	26	4–40
Ter	583,673	3010	208	142	17	4–20	18	5–23
Tordera	157,865	894	55	244	5	1–9	10	2–19
Besòs	1,587,862	1038	18	121	4	0.1–16	2	0.05–7
Llobregat	2,090,971	4948	175	129	19	0.2–124	7	0.1–100
Francolí	313,892	838	85	177	1	0.1–5	2	0.2–8
Ebre	180,855	3340	120*	159	173	150–199	521	452–600
Segre	211,772	22,579	265	143	16	12–22	32	24–43
Noguera Ribagorçana	96,252	2046	133	163	9	8–11	50	42–61
Noguera Pallaresa	31,125	2820	154	223	19	17–24	237	218–304

10 ≤ RQ < 100 indicates significant potential for adverse effects;
RQ ≥ 100 indicates that potential adverse effects should be expected.

3. Results and discussion

3.1. Consumption of pharmaceuticals: the case study of Catalonia

The mean total consumption of 165 pharmaceuticals in the four years studied (2013–2016) was 623 ± 3 t per year (Table SI2). In 2013, the total consumption of these pharmaceuticals was 599 t year^{-1}, increasing up to 638 t year^{-1} in 2016, showing a 6.5% increase. ATC groups N (nervous system), A (alimentary tract and metabolism) and M (musculo-skeletal system) showed the highest consumptions with values between 47 and 318 t year^{-1} respectively. Fig. 1 displays the consumption trends for all pharmaceuticals compiled ordered by their ATC codes from high to low values. Analyzing the period 2013–2016, the pharmaceuticals belonging to ATC groups N, A, J, H and G have increased their consumption in 2016 with respect to 2013. However, the pharmaceuticals belonging to ATC groups M, S, R and L decreased their consumption in 2016 regard to 2013 (see Fig. 1).

A- Alimentary tract and metabolism: The 24 pharmaceuticals for which consumption data was requested had a mean total annual consumption of 182 t year^{-1} (Table SI2). Metformin, the first-line medication for the treatment of type 2 diabetes, is the most consumed drug in this family with levels between 156 and 164 t year^{-1}, increasing its consumption along the years. The next most consumed drugs were lactulose, omeprazole and ranitidine with levels from 2.3 to 11 t year^{-1} (Table SI2). The other compounds were consumed at levels <2 t year^{-1}. Many of these drugs are consumed by the elderly population.

B- Blood and blood forming organs: In this group, the 11 drugs showed a slight decreasing consumption from 18.8 to 17.4 t year^{-1} was observed (Fig. 1). Acetylsalicylic acid (also known as aspirin) is a medication used to treat pain, fever, or inflammation and was consumed up to 15.9 t year^{-1} (Table SI2). It was followed by clopidogrel, tranexamic acid and ferrous glycine sulfate. The consumptions of these drugs varied from 0.6 (in 2013) to 1.5 t (in 2016). The remaining seven drugs were below 0.19 t in 2016 (Table SI2).

C- Cardiovascular system: Thirty different drugs administered in Catalonia had a mean total annual consumption of 28.6 t. The highest consumptions in this ATC group corresponded to pentoxifylline, valsartan, simvastatin, enalapril, hydrochlorothiazide, furosemide, atorvastatin, losartan and atenolol with levels between 1.5 and 6.2 t year^{-1} in the period studied (see Table SI2). The consumptions remained constant all the period, except for pentoxifylline that decreased from 6.2 t (2013) to 4.5 t (2016), while valsartan and losartan increased their consumptions from 3.2 t (2013) to 5.5 (2016) and from 1.8 t (2013) to 2.2 t (2016), respectively. Herein, the case of furosemide is curious because its values remained slightly constant in the years 2013 (1.8 t), 2014 (1.9 t) and 2016 (2.1 t), but in 2015 its consumption decreased considerably to 0.4 t (Table SI2).

D- Dermatologicals: Among 7 drugs for which consumption data was requested, ketoconazole and clotrimazole were the most consumed pharmaceuticals. Levels in this group were low compared to other ATC groups varied from 0.002 (gentamicin) to 0.32 t year^{-1} (ketoconazole).

G- Genito urinary system and sex hormones: Only ciproterone, tamusoline and finasteride were the pharmaceuticals compiled for this ATC group. Consumptions increasing along the period studied with values between 0.011 t year^{-1} and 0.035 t year^{-1}, attributed mainly to finasteride (used for hair loss treatments) which its consumption increased from 27 kg in 2013 up to 36 kg in 2016 (Table SI2). However, overall consumptions are low.

H- Systemic hormonal preparations, excl. sex hormones and insulins: Five different drugs of this ATC group (dexamethasone, methylprednisolone, prednisone, triamcinolone and glucagon) were consumed in Catalonia. The mean total annual consumption of these drugs was 0.3 t in the period studied. The highest consumption was for prednisone, a synthetic corticosteroid used to certain inflammatory diseases and some types of cancer, ranging from 0.24 t in 2013 and 0.29 t in 2016 (see Table SI2).

J- Antiinfectives for systemic use: Twelve drugs belong to this group were dispensed, with consumptions between 30.3 t (in 2013) and 33.5 t (in 2015) (Fig. 1). The slight decreasing between 2015 and 2016 (32.9 t) could be due to the awareness campaign against the inappropriate use of antibiotics promoted by the World Health Organization (WHO) (WHO, 2018). Amoxicillin, used for the treatment of a number of bacterial infections, was the most consumed pharmaceutical accounting for more than the 87% of the total consumption in this ATC group.

L- Antineoplastic and immune modulating agents: Antineoplastic drugs, also called cytostatic drugs, are pharmaceutical used in the cancer treatments. In this study, only megestrol was requested as data for other cytostatics has been previously published (Franquet-Griell et al., 2015; Franquet-Griell et al., 2017). Megestrol, a progestin with antiandrogen activity, is mainly used as an appetite stimulant and sometimes in the

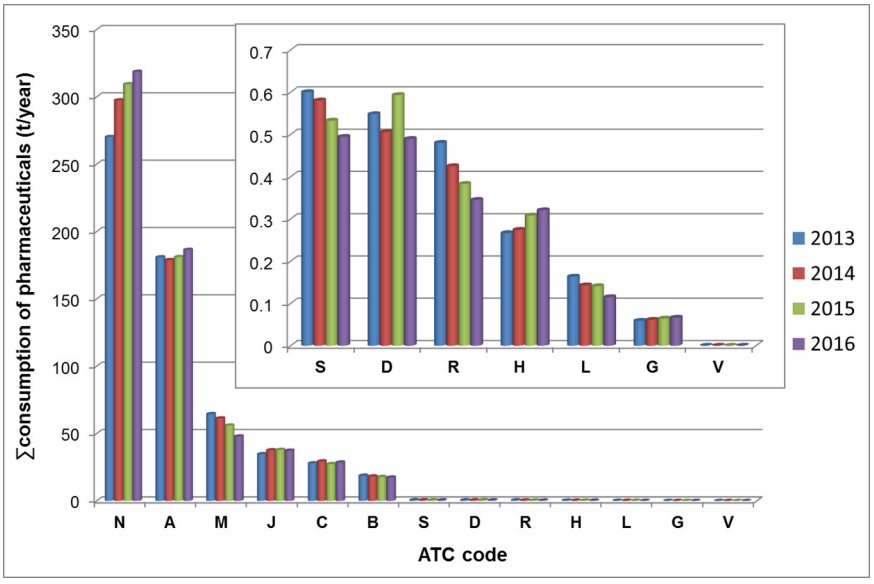

Fig. 1. Consumption of pharmaceuticals (in t year^{-1}) ordered by their ATC codes.

treatment of breast and endometrial cancers. Levels of megestrol have been decreasing along the years and its consumption has changed from 0.16 t year^{-1} in 2013 to 0.11 t year^{-1} in 2016 (see Table SI2).

M- Musculo-skeletal system: Among 7 drugs for which information was requested, ibuprofen was the pharmaceutical with the highest values followed by allopurinol and diclofenac. The total levels of these 8 drugs were in the range of 64.5 t year^{-1} (in 2013) decreasing to 47.8 t year^{-1} (in 2016). In this case, ibuprofen represented approximately the 88% of the total consumption in this ATC group (Table SI2), followed by diclofenac, whose levels decreased considerably along the last years (Table SI2). This lower consumption for ibuprofen in 2016 could be related to the fact that EMA (2014) started to review the cardiovascular risks with systemic ibuprofen medicines (such as those taken by mouth but not topical medicines like creams and gels). The cardiovascular risks being evaluated concern high-dose ibuprofen (2400 mg per day) taken regularly for long periods (EMA, 2014). As in the case of ibuprofen, in 2013, EMA advised the additional risk to suffer heart attacks using diclofenac at high doses (Baigent et al., 2013; EMA, 2013).

N- Nervous system: This ATC group was the one for which more compounds information was requested, as represent the pharmaceuticals administered mostly to the elder population. Total consumptions of 50 compounds increased from 270 t in 2013 up to 319 t in 2016 (Fig. 1). The most consumed pharmaceuticals were paracetamol (201–235 t year^{-1}), metamizole (13.6–20.9 t year^{-1}), gabapentin (10.9–12.1 t year^{-1}), valproic acid (6.7–6.9 t year^{-1}) and levetiracetam (6.4–8.4 t year^{-1}). The other pharmaceuticals studied in this group had levels between 0.09 and 34.47 t year^{-1}.

R- Respiratory system: In this ATC group, the 8 drugs included had consumptions ranging between 0.48 t in 2013 and 0.34 t in 2016 (Table SI2). Theophylline, a methylxanthine drug used in therapy for respiratory diseases such as asthma, was the most consumed drug with a mean value of 0.29 t year^{-1}. In general, lower levels were reported in comparison to other ATC groups.

S- Sensory organs: Chloramphenicol, norfloxacin, dorzolamide, timolol and latanoprost were the most consumed pharmaceuticals. Among those, norfloxacin, a synthetic chemotherapeutic antibacterial agent, was the most consumed with ranges between 0.57 t year^{-1} (in 2013) and 0.46 t year^{-1} (in 2016).

V- Various: This group comprises many different types of drugs. In the present study, naloxone and flumazenil have been included. These two drugs were the least consumed group (Table SI2).

3.2. PECs of pharmaceuticals in wastewaters and rivers

PECs were calculated for the target pharmaceuticals administered mainly in the elder population from Catalonia. Two different PECs (in μg L^{-1}) were calculated; PEC_{eff}, which represent the estimated levels in WWTP effluents and PEC_{river}, which takes into account the DF from WWTP to surface water and represents the estimated concentration in the rivers. In fact, the value of PEC calculation relies in having precise information on demography, geographical data and water management issues. Using a DF of 25 according to Keller et al. (2014), Table SI3 shows PEC values for 165 pharmaceuticals consumed in Catalonia. Out of 165 drugs, 46 had $PEC_{river} > 0.01$ μg L^{-1}, which is the EMA threshold value for risk assessment. Low PECs were attributed to compounds with low consumption, poor excretion or high degradability in the WWTPs.

Considering $\sum$PECs, values ranged between 148 and 162 μg L^{-1} (PEC_{eff}) and between 5.7 and 6.2 μg L^{-1} (PEC_{river}), observing a slightly increase over the study period. Table 2 shows those drugs with highest PECs obtained (both PEC_{eff} and PEC_{river}), including their consumption during the four years (kg day^{-1}), excretion rate (F_{exc}) and WWTP removal (F_{wwtp}).

Values of predicted concentrations for each drug are explained below, described from higher to lower PEC and according to temporal trends for each compound. In the period analyzed (2013–2016), the pharmaceuticals with highest estimated concentrations in the WWTP effluents and consequently in rivers were metformin, amoxicillin, metamizole, levetiracetam, pentoxifylline and gabapentin, with levels between 5.1 and 46 μg L^{-1} (PEC_{eff}) and between 0.20 and 1.79 μg L^{-1} (PEC_{river}) in 2016 (see Table 2).

Fig. 2 displays the maximum, minimum, the 75% quartile and the 25% quartile of the PEC_{eff} (μg L^{-1}) of all pharmaceuticals evaluated. Only the data of 2016 has been represented because the profiles of the other years are similar. The 6 drugs with the highest PECs and which should be prioritized in monitoring studies are described below.

Metformin, a first-line medication for the treatment of type 2 diabetes, was a highly consumed drug with the highest PEC values. The PEC_{eff} and PEC_{river} were constant among the period 2013–16, ranging from 43.6 to 46.2 μg L^{-1} and from 1.68 to 1.78 μg L^{-1}, respectively (Table 2). It has a high excretion rate of 100% (Wishart et al., 2018) and WWTP removal of 94% (Estrada-Arriaga et al., 2016). Little information is available on metformin in waters. Carmona et al. (2017) detected metformin in influent, effluent and river water from Turia River (Spain) at 5.927, 1.252 and 0.013 μg L^{-1}, respectively.

Second, amoxicillin had a consumption slightly increasing in the period 2013–15, but suffered a decrease in 2016. Its maximum PEC_{eff} and PEC_{river} were 37.8 μg L^{-1} and 1.46 μg L^{-1}, respectively in 2016 (Table 2). These values are in the order of the levels of amoxicillin in effluents from Girona WWTP that ranged between 0.216 and 0.258 μg L^{-1} (Gros et al., 2013).

The following drug with higher values of PEC was metamizole. This pharmaceutical increased its PEC_{eff} and PEC_{river} values from 9.5 and 0.36 μg L^{-1} in 2013 up to 14.8 and 0.57 μg L^{-1} in 2016, respectively (Table 2). Metamizole, a pharmaceutical used as a painkiller, spasm and fever reliever, is excreted partially (Wishart et al., 2018) and thus, it is expected to be found in aquatic environments. Guedes-Alonso et al. (2013) reported levels of 13 pharmaceuticals in WWTPs from Gran Canaria Island (Spain), detecting concentrations of metamizole between 0.24 and 8.25 μg L^{-1} (Guedes-Alonso et al., 2013). However, not many studies have published the presence of metamizole in waste and river waters from Spain because its rapid degradation to the metabolite 4-acetamidoantipyrine (Huntscha et al., 2012).

Levetiracetam, a medication used to treat epilepsy, is excreted via urine around a 66% of the total drug consumed (Wishart et al., 2018). Its PEC_{eff} and PEC_{river} slightly increased from 5.8 to 7.8 μg L^{-1} and from 0.23 to 0.30 μg L^{-1}, respectively (Tables 2 and SI3). The presence of levetiracetam in Spanish waters has never been studied. However, this compound was detected in influents and effluents from a WWTP from Dresden (Germany) with a concentrations higher than 1 μg L^{-1} (Gurke et al., 2015).

Gabapentin, a medication used to treat partial seizures, neuropathic pain, hot flashes, and restless legs syndrome, was estimated in WWTP effluents at concentrations between 4.6 μg L^{-1} (2013) and 5.1 μg L^{-1} (2016), and in catalan rivers between 0.17 and 0.20 μg L^{-1} in the period studied. Gabapentin has also been detected in European rivers at levels of low μg L^{-1} (Klančar et al., 2018).

Finally, pentoxifylline, is a xanthine derivative used as a drug to treat muscle pain in people with peripheral artery disease and is the 6th drug with the highest PECs. PECs ranged between 5.1 and 6.9 μg L^{-1} (PEC_{eff}), and between 0.20 and 0.27 μg L^{-1} (PEC_{river}), see Tables 2 and SI3. Pentoxifylline has not been detected in Spanish waters but Vanderford et al. (2003) detected this drug at 0.0022 μg L^{-1} in waters from Las Vegas (United States).

Other highly consumed drugs had low PEC values because of their high removal efficiency in the WWTPs. This is the case of paracetamol, ibuprofen and acetylsalicylic acid. Paracetamol was the pharmaceutical with highest consumption (Table SI3), however its PEC values were low. Paracetamol can be excreted via urine in a 90% (Wishart et al., 2018) and is completely eliminated in WWTP. Its PEC_{eff} ranged from 0.17 and 0.2 μg L^{-1} in the 2013–2016 period and the PEC_{river} from 0.0065 and 0.0077 μg L^{-1}, following consumption patterns (Table SI3). Many

Table 2
Prioritization of pharmaceuticals according to EMA's threshold >0.01 μg L^{-1} in river. Consumption rates (kg day^{-1}), PEC_{eff} and PEC_{river} values (in μg L^{-1}) using a dilution factor of 25 according to Keller et al. (2014) are indicated during the period 2013–2016, and include excretion rates (Fexc) and removal in WWTP (Fwwtp). PECs from all pharmaceuticals are listed in Table SI3. F_{exc} values were obtained from Drugbank 5.0 database (Wishart et al., 2018) and F_{wwtp} values were obtained from previous published papers. In the case that F_{exc} and F_{wwtp} values were not found, a value of 0.5 were chosen (marked with an asterisk).

ATC code	Name	F_{exc}	F_{wwtp}	2013			2014			2015			2016		
				kg/day	PEC_{eff}	PEC_{river}	kg/day	PEC_{eff}	PEC_{river}	kg/day	PEC_{eff}	PEC_{river}	kg/day	PEC_{eff}	PEC_{river}
A10BA02	Metformin	1	0.9 (Estrada-Arriaga et al., 2016)	429	44	1.68	440	45	1.72	450	46	1.76	455	46	1.79
J01CA04	Amoxicillin	0.8	0.5	83.1	34	1.30	92.5	38	1.45	93.0	38	1.46	91.6	37	1.44
N02BB02	Metamizole	0.5	0.5	37.4	10	0.37	45.1	11	0.44	51.5	13	0.51	58.2	15	0.57
N03AX14	Levetiracetam	0.66	0.5	17.5	5.9	0.23	19.5	6.5	0.25	21.4	7.2	0.28	23.3	7.8	0.30
N03AX12	Gabapentin	0.5*	0.85 (Lin et al., 2009)	30.1	4.6	0.18	32.3	4.9	0.19	33.2	5.1	0.20	33.7	5.1	0.20
C04AD03	Pentoxifylline	1	0.23 (Kasprzyk-Hordern et al., 2009)	16.9	6.9	0.27	15.2	6.2	0.24	13.7	5.6	0.22	12.6	5.1	0.20
N03AX16	Pregabalin	0.9	0.5	7.6	3.5	0.13	8.1	3.7	0.14	8.3	3.8	0.15	8.6	3.9	0.15
A02BC01	Omeprazole	0.23	0.09 (Rosal et al., 2010)	14.7	3.1	0.12	14.7	3.1	0.12	14.3	3.0	0.12	14.0	3.0	0.11
N04BA02	Levodopa	0.5*	0.53 (Rosal et al., 2010)	7.9	2.0	0.08	8.3	2.1	0.08	8.6	2.2	0.08	8.8	2.2	0.09
N05AN01	Lithium	0.5*	0.5	7.7	2.0	0.08	7.9	2.0	0.08	7.9	2.0	0.08	8.0	2.0	0.08
A11CC05	Cholecalciferol	0.5*	0.5	4.5	1.1	0.04	0	0	0	0	0	0	7.5	1.9	0.07
M04AA01	Allopurinol	0.2	0.5	17.1	1.7	0.07	17.6	1.8	0.07	17.6	1.8	0.07	17.3	1.8	0.07
N01BB02	Lidocaine	0.5*	0.5	2.3	0.6	0.02	3.6	0.9	0.03	5.0	1.3	0.05	6.7	1.7	0.07
J01MA02	Ciprofloxacin	0.5*	0.55 (Wishart et al., 2018)	6.9	1.6	0.06	6.5	1.5	0.06	6.5	1.5	0.06	6.4	1.5	0.06
J01MA12	Levofloxacin	0.9	0.5	2.6	1.2	0.05	2.9	1.3	0.05	3.1	1.4	0.05	3.0	1.4	0.05
C03AA03	Hydrochlorothiazide	0.5*	0.53 (Gros et al., 2017)	6.1	1.5	0.06	6.0	1.4	0.06	5.8	1.4	0.05	5.6	1.3	0.05
N02AX02	Tramadol	0.3	0.4 (Lin et al., 2009)	6.3	1.1	0.04	6.9	1.2	0.05	7.1	1.3	0.05	7.1	1.2	0.05
N06AX05	Trazodone	0.5*	0.5	3.9	1.0	0.04	4.2	1.1	0.04	4.5	1.1	0.04	4.8	1.2	0.05
C03CA01	Furosemide	0.9	0.74 (Estrada-Arriaga et al., 2016)	5.1	1.1	0.04	5.4	1.1	0.04	1.2	0.2	0.01	5.7	1.2	0.05
M01AE01	Ibuprofen	0.1	0.91 (Rosal et al., 2010)	151	1.4	0.05	146	1.3	0.05	121	1.1	0.04	111	1.0	0.04
C09CA01	Losartan	0.35	0.5	4.8	0.8	0.03	5.2	0.9	0.04	5.4	1.0	0.04	5.6	1.0	0.04
N03AX11	Topiramate	0.7	0.5	2.6	0.9	0.04	2.6	0.9	0.04	2.6	0.9	0.04	2.6	0.9	0.04
B01AC04	Clopidogrel	0.5	0.5	4.0	1.0	0.04	3.9	1.0	0.04	3.7	0.9	0.04	3.6	0.9	0.03
C07AB03	Atenolol	0.5*	0.59 (Rosal et al., 2010)	4.6	1.0	0.04	4.5	0.9	0.04	4.3	0.9	0.03	4.0	0.8	0.03
B01AC06	Acetylsalicylic acid	0.5*	0.96 (Gros et al., 2010)	43.6	0.9	0.03	42.5	0.9	0.03	41.5	0.8	0.03	40.5	0.8	0.03
A02BA02	Ranitidine	0.3	0.66 (Rosal et al., 2010)	6.3	0.7	0.03	6.4	0.7	0.03	6.6	0.7	0.03	6.8	0.7	0.03
N05CM02	Clomethiazole	0.5*	0.5	2.4	0.6	0.02	2.6	0.7	0.03	2.7	0.7	0.03	2.7	0.7	0.03
D11AX18	Diclofenac	0.65	0.58 (Lajeunesse et al., 2012)	4.2	1.2	0.05	3.2	0.9	0.03	2.6	0.7	0.03	2.3	0.6	0.03
A10BB09	Gliclazide	0.35	0.5	2.8	0.5	0.02	3.0	0.5	0.02	3.3	0.6	0.02	3.4	0.6	0.02
C01BD01	Amiodarone	0.5*	0.5	2.3	0.6	0.02	2.4	0.6	0.02	2.4	0.6	0.02	2.3	0.6	0.02
C10AA01	Simvastatin	0.13	0.5	9.4	0.6	0.02	9.4	0.6	0.02	9.2	0.6	0.02	8.8	0.6	0.02
A07AA11	Rifaximin	0.95	0.5	0.7	0.3	0.01	0.8	0.4	0.02	1.0	0.5	0.02	1.2	0.6	0.02
B03AA01	Ferrous glycine sulfate	0.5*	0.5	1.6	0.4	0.02	1.9	0.5	0.02	1.8	0.5	0.02	1.9	0.5	0.02
M01AE17	Dexketoprofen	0.8	0.5	0.9	0.4	0.01	0.9	0.4	0.01	1.0	0.4	0.02	1.0	0.4	0.02
B02AA02	Tranexamic acid	0.5*	0.5	1.5	0.4	0.01	1.5	0.4	0.02	1.6	0.4	0.02	1.6	0.4	0.02
A06AD11	Lactulose	0.03	0.5	30.1	0.5	0.02	27.8	0.4	0.02	25.0	0.4	0.01	26.1	0.4	0.02
N06AB03	Fluoxetine	0.5*	0.36 (Gros et al., 2010)	1.2	0.4	0.01	1.2	0.4	0.01	1.2	0.4	0.01	1.2	0.4	0.01
N05BA01	Diazepam	0.5*	0 (Kasprzyk-Hordern et al., 2009)	0.7	0.3	0.01	0.7	0.4	0.01	0.7	0.4	0.01	0.7	0.4	0.01
C07AA05	Propranolol	0.5*	0.33 (Lin et al., 2009)	0.9	0.3	0.01	0.8	0.3	0.01	0.8	0.3	0.01	0.9	0.3	0.01
N06AB04	Citalopram	0.23	0.27 (Gros et al., 2010)	1.8	0.3	0.01	1.9	0.3	0.01	1.9	0.3	0.01	1.8	0.3	0.01
N06AX16	Venlafaxine	0.05	0.19 (Gros et al., 2010)	6.8	0.3	0.01	7.0	0.3	0.01	7.1	0.3	0.01	7.2	0.3	0.01
N07BB01	Disulfiram	0.5*	0.5	1.1	0.3	0.01	1.2	0.3	0.01	1.1	0.3	0.01	1.2	0.3	0.01
N05AH02	Clozapine	0.5	0.5	0.9	0.2	0.01	1.0	0.2	0.01	1.0	0.3	0.01	1.1	0.3	0.01
N03AB02	Phenytoin	0.5*	0.44 (Lajeunesse et al., 2012)	1.1	0.3	0.01	1.1	0.3	0.01	1.0	0.3	0.01	0.9	0.3	0.01

studies have reported the presence of paracetamol in rivers of around the world (Carmona et al., 2017). Paracetamol was detected at mean concentration of 0.98 μg L^{-1} and with 45.5% detection frequency in a monitoring studied carried out in 2014 along the Guadalquivir River (Jaén, South Spain) (Robles-Molina et al., 2014). In another study, López-Roldán et al. detected paracetamol at 0.034 μg L^{-1} in the Llobregat River (Catalonia, Spain) (López-Roldán et al., 2010), highly approaching the PECs calculated in this study. Although paracetamol is predicted to be present at very low levels, its high consumption and the high frequency of detection in waters justifies its inclusion in monitoring studies related to water quality. Ibuprofen, a well-known antiinflamatory drug, has a very high consumption (mean = 47.8 t $year^{-1}$) but taking into account that only 10% is excreted (Wishart et al., 2018), PEC values were low (see Table SI3). Ibuprofen has been recurrently monitored in waste and surface waters (Hedgespeth et al., 2012; Lindberg et al., 2014). In Catalonia, ibuprofen was detected in influent waters (0.172–4.21 μg L^{-1}) and effluent waters (0.03–0.95 μg L^{-1}) from sewage treatment plants (Pedrouzo et al., 2011). Recently, ibuprofen was detected at concentrations up to 2.66 μg L^{-1} in sites impacted by raw wastewater in Ebro river (Mandaric et al., 2018). In another study, López-Serna et al. studied the occurrence of 95 pharmaceuticals and transformation products in the metropolis of Barcelona, including Besòs River. Authors reported concentrations of ibuprofen at 0.061 μg L^{-1} (López-Serna et al., 2013). Ibuprofen was also detected in Llobregat river at 0.152 μg L^{-1} (López-Roldán et al., 2010).

Finally, acetylsalicylic acid had constant PEC_{eff} (from 0.89 to 0.82 μg L^{-1}) and PEC_{river} (from 0.034 to 0.032 μg L^{-1}) over the studied period. Acetylsalicylic acid has been detected in water as salicylic acid due to its rapid degradation (Skibinski and Komsta, 2016). In the North Sea, the Scheldt estuary and in Belgian harbours salicylic acid was detected at levels ranging from 0.011 to 0.855 μg L^{-1} between the period May 2007 and June 2009 (Wille et al., 2010). In another study, salicylic acid was detected in influents and effluents of two WWTPs in

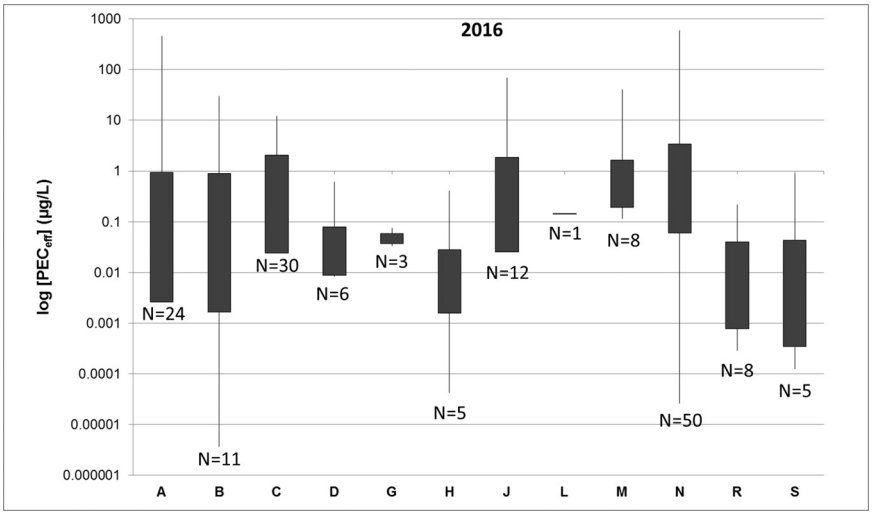

Fig. 2. Boxplot in logarithmic scale of pharmaceuticals PEC_{eff} levels in 2016 for each ATC family. The rest of the years studied have not been represented because they have similar profiles. N indicates the number of pharmaceuticals studied in each family.

Portugal at levels between 1.17 and 61.26 µg L^{-1} (influents) and between 0.11 and 0.30 µg L^{-1} (effluents) and in the receiving water of the Lis River at a concentration range of 0.025 to 0.29 µg L^{-1} (Paíga et al., 2016).

3.3. Application of PECs in hydrographic basins

To obtain more accurate information and due to the important role of DF in the calculation of PECs (Franquet-Griell et al., 2017), DFs were recalculated for the most important hydrographic basin in Catalonia according to the Eq. (3). Mediterranean rivers, are characterized by high flow fluctuations because of seasonal variations linked with the weather and precipitations. Thus, it is important to determine PECs in each river basin considering this flow variability. For that reason, mean flow values from the middle course of the river, and maximum and minimum flows were compiled for each river during 2016 to represent the flow variability (Table 1). Table 3 displays the PEC_{river} ranges in each river basin for these main compounds detected in each basin. To determine the global impact of pharmaceuticals in the different basins, total PEC_{river} ($\sum PEC_{river}$) were calculated considering all compounds using the mean DF of each river basin in 2016. Fig. 3 shows the hydrographic basins studied colored according to their $\sum PEC_{river}$. Among the eleven main Catalan river basins studied, Noguera Pallaresa and Noguera Ribagorçana, Fluvià, Segre and Ebro River (only the part of the river in Catalonia) were the basins with lowest $\sum PEC_{river}$ (between 0.2 and 3.3 µg L^{-1}), due to either high DF values (Table 1) and/or low population. Contrarily, Francolí and Besòs were the basins with the highest $\sum PEC_{river}$ with 50.3 and 66.6 µg L^{-1}, respectively, as these two rivers have the lowest DF of all of them (see Table 1) and, in the case of Besòs river, it is characterized by highly urbanized area. The high variability in the Llobregat river flow (see Table 1) report high $\sum PEC_{river}$ in the time with low flows and lower $\sum PEC_{river}$ values in the time with highest flows (Table 3).

Table SI4 displays all PEC_{river} values for all pharmaceuticals in each hydrographic basin in Catalonia considering the mean DF, and minimum and maximum DFs. In Besòs, Francolí and Llobregat rivers, >90% of the pharmaceuticals compiled had PEC_{river} values higher 0.010 µg L^{-1}, which is the EMA proposed threshold (EMA, 2006). However, in the rest of rivers studied, <47% of the pharmaceuticals had PEC_{river} values higher 0.010 µg L^{-1}. Even so, the levels of PECs reported in the present study are higher in comparison to the predicted environmental concentrations of pharmaceuticals in different studies (Burns et al., 2018; Franquet-Griell et al., 2015; Franquet-Griell et al., 2017; Verlicchi et al., 2014). For instance, in Besòs and Francolí, the most impacted river basins in Catalonia, metformin and amoxicillin had a PEC_{river} of 26.5 and 21.3 µg L^{-1} in Besòs basin, and 20.0 and 16.1 µg L^{-1} in Francolí basin (in 2016). Following, metamizole had 8.5 and 6.4 µg L^{-1}, levetiracetam 4.5 and 3.4 µg L^{-1}, gabapentin 2.9 and 2.2 µg L^{-1} and pentoxifylline acid 2.9 and 2.2 µg L^{-1} respectively for the two basins (Table 3). On the other hand, Nogueres and Ebro, which accounted for the lowest impacted basins, PEC_{river} for metformin was of 0.8–0.12 and 0.08 µg L^{-1} respectively, much lower than values predicted in the other basins. Recently, Lindim et al. (2016) evaluated the emissions and concentrations of 54 pharmaceuticals in Swedish river

Table 3
PEC_{river} (µg L^{-1}) ranges in each river basin for the 6 pharmaceuticals with the highest PECs. Mean represents PEC values calculated with mean DF, and min and max represent PEC values calculated with high and low DF, respectively (values given in Table 1). Due to the different excretion and WWTP removals, the values of gabapentin and pentoxifylline are similar.

Hydrographic basins	Metformin	Amoxicillin	Metamizol	Levetiracetam	Gabapentin	Pentoxifylline
	Mean (min-max)	Mean (min-max)	Mean (min-max)	Mean (min-max)	Mean (min-max)	Mean (min-max)
Muga	2.4 (1.3–26.9)	2.0 (1.0–21.7)	0.8 (0.4–8.6)	0.4 (0.2–4.5)	0.3 (0.1–3.0)	0.3 (0.1–3.0)
Fluvià	0.8 (0.5–5.2)	0.7 (0.4–4.2)	0.3 (0.2–1.7)	0.1 (0.09–0.9)	0.09 (0.06–0.6)	0.09 (0.06–0.6)
Ter	2.3 (1.8–8.2)	1.8 (1.4–6.6)	0.7 (0.6–2.6)	0.4 (0.3–1.4)	0.3 (0.2–0.9)	0.25 (0.2–0.9)
Tordera	2.7 (1.5–13.9)	2.2 (1.2–11.2)	0.9 (0.5–4.4)	0.5 (0.2–2.3)	0.3 (0.2–1.5)	0.3 (0.2–1.5)
Besòs	26.5 (7.6–1061)	21.3 (6.1–853)	8.5 (2.4–339)	4.5 (1.3–179)	2.9 (0.8–118)	2.9 (0.8–117)
Llobregat	7.4 (0.5–496)	6.0 (0.4–399)	2.4 (0.2–158)	1.2 (0.1–84)	0.8 (0.05–55)	0.8 (0.05–54.8)
Francolí	20.0 (4.5–181)	16.1 (3.6–145)	6.4 (1.4–58)	3.4 (0.8–30.4)	2.2 (0.5–20.1)	2.2 (0.5–19.9)
Ebre	0.08 (0.07–0.09)	0.06 (0.05–0.07)	0.03 (0.02–0.03)	0.013 (0.011–0.15)	0.009 (0.008–0.01)	0.009 (0.008–0.01)
Segre	1.3 (1.0–1.8)	1.1 (0.8–1.4)	0.4 (0.3–0.6)	0.2 (0.2–0.3)	0.15 (0.1–0.2)	0.15 (0.1–0.2)
Noguera Pallaresa	0.12 (0.10–0.13)	0.1 (0.08–0.11)	0.04 (0.03–0.04)	0.02 (0.016–0.022)	0.013 (0.011–0.014)	0.013 (0.01–0.015)
Noguera Ribagorçana	0.8 (0.6–0.9)	0.6 (0.5–0.7)	0.25 (0.2–0.3)	0.13 (0.010–0.015)	0.09 (0.07–0.10)	0.085 (0.07–0.10)

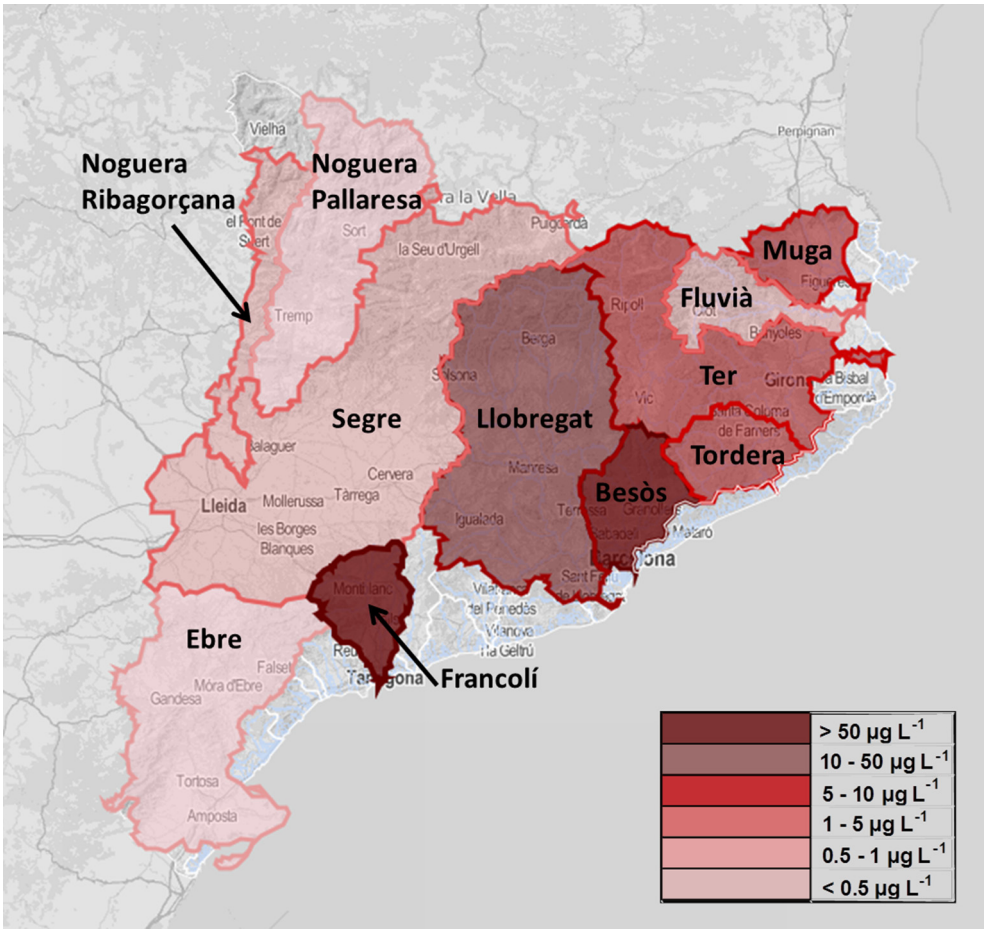

Fig. 3. $\sum PEC_{river}$ of pharmaceuticals in the main hydrographic basins of Catalonia in 2016.

basins, reporting that metformin, gabapentin and atenolol were the pharmaceuticals with the highest emissions. The prioritized pharmaceuticals for monitoring (metformin, amoxicillin, metamizole, levetiracetam, gabapentin and pentoxifylline) would always be detected in low river flow conditions (low values of DF). In this scenario, Llobregat would also be impacted by high concentrations of pharmaceuticals whereas in Muga, Fluvià, Ter, Tordera, Ebro, Segre and Nogueres the PEC_{river} values would be lower (Tables 3 and SI4). Thus, because the studied rivers have high variable flow, the use of specific DFs which consider the seasonal variability of water flows can provide a better characterization of the presence of pharmaceuticals in a specific river basin and thus, a more accurate risk assessment.

3.4. Environmental risk assessment (ERA) of pharmaceuticals: the case study of Catalonia

For the six pharmaceuticals having the highest PECs, we calculated the environmental risks using the worst river scenario (Besòs river), which has the lowest dilution factor of the studied rivers and hence the highest PECs. We also included paracetamol, ibuprofen and acetylsalicylic acid due to their highly prescription rate and usage in Spain. Reported concentration effects from acute and chronic toxicity studies for at least three different aquatic phyla were considered (i.e. algae or plant, vertebrate, invertebrate) to estimate predicted non-effect concentrations (PNECs). Assessment factors of 10 and 1000 were used to determine PNECs from chronic and acute concentration effects, respectively. Toxicity data was obtained from toxicological databases (DrugBank, EPA), chemical suppliers (Sigma-Aldrich) and selected publications and experimental test for metformin. When more than one concentration effect was reported within a given toxicity source, chemical and species, its median was considered. Environmental risks were obtained using the risk quotient approach depicted in Eq. (4). Results reported in Table 4 reflect the reported known scarcity for chronic toxicity data on pharmaceuticals, which in most cases was limited to a single species (Fent et al., 2006a). For three chemicals, levetiracetam, gabapentin and pentoxifylline there was no toxicological information and for metamizole, toxicological information was limited to a single study. Table 4 also evidenced the great disparity of toxicological information within and among species, which in several cases expanded several orders of magnitude (Santos et al., 2010). For the antibiotic amoxicillin cyanobacteria species were about three orders of magnitude more sensitive than the rest of species, which is in line with previous studies (Andreozzi et al., 2004). Paracetamol acute toxicity data was the most variable within a given species (over 4 orders of magnitude for *Danio rerio* LC_{50}) and ibuprofen showed the greatest differences between acute and chronic toxicity responses (350 fold in *Danio rerio*) and among algae species (85 fold). Disparity of results within species for metformin and acetylsalicylic acid were within an order of magnitude. When outlier values from Table 4 were not considered, *Daphnia* and algae species were about 10 fold more sensitive than fish to paracetamol and acetylsalicylic acid and fish were up to 300 fold more sensitive to metformin and ibuprofen than *Daphnia* and algae. The above mentioned lack of consistence in species sensitivity across the studied pharmaceuticals agrees with previous reported toxicological information (Santos et al., 2010) but partly disagrees with the argument claiming that pharmaceuticals should affect to greater extent fish than algae or invertebrates due to the presence of more biological targets in fish (Fent et al., 2006a; Gunnarsson et al., 2008).

Table 4
Acute and chronic toxicity and risk assessment for pharmaceuticals in Besòs River (2016, calculated with the mean flow) for pharmaceuticals with $PEC_{river} > 0.1\ \mu g\ L^{-1}$ indicate in Table 2 and include also paracetamol, ibuprofen and acetylsalicylic acid which are highly consumed despite having low PECs. RQ: Risk Quotient based on an assessment factor of 1000 except for * which as 10 (OECD, 2002).

ATC code	Name	PEC_{river} Besòs (2016) ($mg\ L^{-1}$)	Organism	Specie	End-point	Response	Reference	EC_{50}/LC_{50} ($mg\ L^{-1}$)	PNEC	RQ
N02BE01	Paracetamol	1.1e−4	Algae	*Not indicated*	*Not indicated*	Growth	(Osorio et al., 2016)	134	0.13	0.0009
			Crustacean	*D. magna*	EC_{50} 48 h	Mortality	(S. Aldrich, 2016a)	9.2	0.01	0.0114
				D. magna	LC_{50} (96 h)	Mortality	(Iannacone and Alvariño, 2009)	62.3	0.06	0.0019
				D. magna	NOEC	Reproduction	(E.P.A. (EPA), 2018)	5.7	0.57*	0.00020
			Fish	*P. promelas*	EC_{50} (96 h)	Mortality	(S. Aldrich, 2016a)	814	0.81	0.00014
				O. latipes	LC_{50} (96 h)	Mortality	(S. Aldrich, 2016a)	160	0.16	0.00071
				D. rerio	EC_{50} (168 h)	Mortality	(Osorio et al., 2016)	0.01	0.00001	11.43
A10BA02	Metformin	0.026	Aquatic plant	*Lemmna*	EC_{50} (7d)	Growth	(Cleuvers, 2003)	110	0.11	0.241
			Crustacean	*D. magna*	LC_{50} (48 h)	Mortality	Present study	16.9	0.02	1.325
				D. magna	LC_{50} (48 h)	Mortality	(Cleuvers, 2003)	64	0.06	0.442
			Fish	*Fathead minnows*	LOEC	Endocrine disruption	(Niemuth et al., 2015)	0.4	0.04*	0.663
				Pimephales promelas	LOEC	Reproduction	(Niemuth and Klaper, 2015)	0.04	0.004*	6.625
J01CA04	Amoxicillin	0.021	Algae	*M. aeruginosa*	EC_{50}	Mortality	(Lützhøft et al., 1999)	0.0037	0.000004	5325
				R. salina	EC_{50}	Mortality	(Lützhøft et al., 1999)	3.108	0.003	7.1
				S. capricornutum	EC_{50}	Mortality	(Lützhøft et al., 1999)	250	0.25	0.0852
			Fish	*D. rerio*	EC_{50} (48 h)	Mortality	(Oliveira et al., 2013)	132.4	0.13	0.164
				O. latipes	LC_{50} (48 h)	Mortality	(Park and Choi, 2008)	>1000	1	0.0213
			Crustacean	*D. magna*	LC_{50} (96 h)	Mortality	(Iannacone and Alvariño, 2009)	6950	6.95	0.0031
N02BB02	Metamizole	0.0085	Fish	*Rhamdia quelen*	LOEC	DNA damage	(Pamplona et al., 2011)	0.0005	0.00005*	170
M01AE01	Ibuprofen	5.8e−4	Algae	*Not indicated*	*Not indicated*	Mortality	(Osorio et al., 2016)	4	0.004	0.1178
				D. subspicatus	EC_{50}*	Mortality	(Cleuvers, 2003)	342.2	0.34	0.0014
			Crustacean	*D. magna*	LC_{50} (96 h)	Mortality	(Iannacone and Alvariño, 2009)	175	0.18	0.0026
				D. magna	LC_{50} (48 h)	Mortality	(Cleuvers, 2003)	101.2	0.1	0.0047
			Fish	*D. rerio*	LC_{50} (96 h)	Mortality	(E.P.A. (EPA), 2018)	0.35	0.0004	1.18
				D. rerio	LC_{50} (7d)	Mortality	(E.P.A. (EPA), 2018)	0.001	0.0001*	4.71
B01AC06	Acetylsalicylic acid	4.7e−4	Algae	*D. subspicatus*	EC_{50} (72 h)	Growth	(Cleuvers, 2003)	106.7	0.11	0.0053
			Fish	*Cyprinus carpio*	LC_{50} (48 h)	Mortality	(S. Aldrich, 2016b)	1000	1	0.0006
			Crustacean	*D. magna*	EC_{50} (48 h)	Mortality	(Cleuvers, 2003)	88.1	0.09	0.0064
			Cnidiaria	*Hydra* sp	LOEC	Viability	(E.P.A. (EPA), 2018)	1	0.1*	0.0058
N03AX14	Levetiracetam	4.5e−3	Not data	*Not data*	–	–	–	–	–	–
N03AX14	Gabapentin	2.9e−3	Fish	*D. rerio*	LOEC	Malformation	(Li et al., 2018)	0.1	0.01*	0.29
C04AD03	Pentoxifylline	2.9e−3	Not data	*Not data*	–	–	–	–	–	–

Estimated risks reported in Table 4 showed the same high variability within and among species and chemicals than PNEC. Thus to properly prioritize environmental risks of the studied compounds we excluded out the extreme values for ibuprofen (RQ = 4.71), paracetamol (RQ = 11.43), metformin (RQ = 6.22) and amoxicillin (RQ = 5325). Except for metamizole and gabapentin, whose high risk quotients (170 and 0.29, respectively) were based on a single study, the compound having the greatest risks to aquatic biota was amoxicillin (average ± SE, RQ = 1.47 ± 1.40) followed by decreasing order by metformin (0.66 ± 0.21), ibuprofen (0.26 ± 0.23), acetylsalicylic acid (0.004 ± 0.001) and paracetamol (0.002 ± 0.002). For amoxicillin, metformin and ibuprofen predicted risks exceeded for some species. Therefore, environmental risk assessment data depicted in Table 4 allowed identifying key features among the prioritized 5 pharmaceuticals with at least three RQ. Amoxicillin is expected to pose adverse effects for cyanobacteria, and metformin and ibuprofen pose a small potential for adverse effects to invertebrates and fish, and fish, respectively. Alternatively, paracetamol and acetylsalicylic acid posed no risk to aquatic biota.

As a final remark it is important to take into account that in this study we based our prioritization on PECs and not on toxicity. For example, among the 43 compounds depicted in Table 2 disulfiram followed by fluoxetine, lithium and diclofenac were quite toxic having EC_{50} for zebrafish embryonic development or *D. magna* immobilization of (Mean ± SE): 0.027 ± 0.013 mg L^{-1} for disulfiram, 0.399 ± 0.104 mg L^{-1} for fluoxetine, 3.340 ± 1.274 mg L^{-1} for lithium and 4.752 ± 1.248 mg L^{-1} for diclofenac (data obtained from E.P.A. (EPA), ECOTOX Knowledgebase). These values are quite low when compared with those reported in Table 4, which means that the above reported compound can also be considered potential toxic to aquatic biota. Future research, thus, should assess if there is a need to prioritize compounds by their toxicity rather than by their PECs.

4. Conclusions

This study reveals the importance of consumption data and temporal patterns for estimating the occurrence and risk of pharmaceuticals consumed by elderly people in surface waters. An extensive data compilation on pharmaceuticals consumption in Catalonia was performed. The mean total consumption of these pharmaceuticals in the period studied (2013–2016) was 623 ± 3 t per year. ATC groups N (nervous system), A (alimentary tract and metabolism) and M (musculo-skeletal system) showed the highest consumptions, being paracetamol, metformin and ibuprofen the top consumed. However, metformin, amoxicillin, metamizole, were the pharmaceuticals with highest PEC values (>0.01 μg L^{-1}). In addition, recalculation of PECs according to specific river dilution factors permits to refine the levels likely to be detected at river basin scale. It is clear from this study that PEC calculation permits to better prioritize compounds, which have high probability to be detected in the environment. Finally, predicted environmental levels together with acute and chronic toxicological data allowed estimating the risks of these compounds. Amoxicillin is expected to pose adverse effects for cyanobacteria, and metformin and ibuprofen pose a small potential for adverse effects to invertebrates and fish, and fish, respectively. Alternatively, paracetamol and acetylsalicylic acid posed no risk to aquatic biota.

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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.2019.02.078.

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