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Pharmaceuticals released from senior residences: occurrence and risk evaluation

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Abstract One of the main pursuits, yet most difficult, in monitoring studies is to identify the sources of environmental pollution. In this study, we have identified health-care facilities from south European countries as an important source of pharmaceuticals in the environment. We have estimated that compounds consumed in by the elderly and released from effluents of senior residences can reach river waters at a concentration higher than 0.01 μg/L, which is the European Medicines Agency (EMA) threshold for risk evaluation of pharmaceuticals in surface waters. This study has been based on five health institutions in Portugal, Spain, and France, with 52 to 130 beds. We have compiled the pharmaceuticals dispensed on a daily base and calculated the consumption rates. From 54.9 to 1801 g of pharmaceuticals are consumed daily, with laxatives, analgesics, antiepileptics, antibiotics, and antidiabetic agents being the main drug families administered. According to excretion rates, dilution in the sewerage system, and elimination in wastewater treatment plants, macrogol, metformin, paracetamol, acetylcysteine, amoxicillin, and gabapentin, among others, are expected to reach river waters. Finally, we discuss the risk management actions related to the discharge of pharmaceuticals from senior residences to surface waters.

Keywords Health care institutions · Pharmaceuticals · Predicted environmental concentrations · Risk management

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Introduction

Water pollution today represents a major challenge both at the economic and social level. The quality of water must be preserved both for human protection and to safeguard the environment from compounds capable of exerting an effect at low levels of concentration. Among others, pharmaceuticals are of concern because they are consumed in high quantities; many are refractory to traditional wastewater treatment and thus become widely distributed in river waters (Banjac et al. 2015; Zhang et al. 2013). Their presence in the environment has been attributed to the discharge of hospital effluents (Gómez-Canela et al. 2014, Langford and Thomas 2009; Santos et al. 2013; Verlicchi et al. 2010), domestic water (Rabiet et al. 2006), and effluents from wastewater treatment plants (WWTP) (Gómez-Canela et al. 2012; Santos et al. 2013; Verlicchi et al. 2012). This study explores senior residences and sociosanitary centers as a source of pharmaceuticals to environmental waters.

In Europe and over the world, the phenomenon of aging and over-aging has led to societies where 15–20% of the population is over 65 years. Part of this population reside in homes for the elderly or in sociosanitary centers if the level of impairment is high. The homes for elderly or health care institutions are infrastructures that emerge in response to biopsychosocial needs and have become popular in most European countries. On the other hand, sociosanitary centers provide integral attention to people that require special care because of the low health status, either physic, psychic, or intellectual. These establishments have a configuration of typically 50–150 beds and provide lodging, meal services, and health and social assistance. With an estimated consumption of 5–10 pills/patient, much higher than the healthy population, the total consumption of pharmaceuticals is of hundreds of milligrams. These compounds are excreted through urine or feces and are released to the main urban sewerage system without any type of treatment. Then, waters are transported to the WWTP and a fraction is eliminated during primary and secondary treatment, but depending on the configuration of the WWTP, pharmaceuticals can also be discharged to receiving waters. Due to the aging effect and the increased population established in homes for the elderly or health care institutions, senior residences. Thus, senior residences these establishments can represent a point source pollution of pharmaceuticals to the environment.

The European Medicines Agency (EMA) is an agency of the European Union (EU), responsible for the scientific evaluation, supervision, and safety monitoring of medicines developed by pharmaceutical companies for use in the EU (European Medicines Agency (EMA) 2006). Among other activities, they monitor the safety of medicines across their life cycle. In 2006, EMA proposed the calculation of predicted environmental concentrations (PEC) to estimate the presence of pharmaceuticals in environmental waters and recommended to evaluate their risk when PEC values in surface water were equal or above the threshold value of 0.01 μg/L. This model takes into account the consumption of a specific drug, the excretion rates, and the dilution factor in a particular region and permits to prioritize specific drugs with potential to cause toxic effects at specific water concentrations (Fick et al. 2010). The efficiency and applicability of the approach to determine the theoretical presence of pharmaceuticals in surface waters and wastewaters and to prioritize compounds for further monitoring has been demonstrated by the increasing number of research papers that use this methodology, as in Italy (Riva et al. 2015), Germany (Kümmerer and Al-Ahmad 2010), NW England (Booker et al. 2014), France (Besse et al. 2008), Catalonia (Franquet-Griell et al. 2015), the Netherlands (Oosterhuis et al. 2013), Spain (Ortiz de García et al. 2013) and Poland (Oldenkamp et al. 2013). van Nuijs et al. 2015). According to prescription data (van Nuijs et al. 2015), PEC values and toxicological information, it is then possible to determine the potential risk of pharmaceuticals in the environment (van Leeuwen and Vermeire 2007).

Our hypothesis is that senior residences represent an important source of pharmaceuticals to the environment. In this study, we propose an innovative scheme for assessing the loads and discharge of pharmaceuticals from four senior residences and one sociosanitary center from France, Portugal, and Spain. We have followed EMA guidelines for PEC calculation and risk evaluation based on consumption data, excretion, dilution, and toxicity. We finally provide a list of pharmaceuticals consumed in high quantities in senior establishments and discuss their environmental impact.

Methodology

Health Institutions studied

Health Institutions can be classified in different categories, each with its own specialization, particularity, and functioning, as they host people with different types of illnesses. In this study, we have selected five establishments, one in France, two in Spain, and two in Portugal. For comparability purposes among the three countries, the establishments selected had a high number of beds (>50) and were located in urban areas. Selected establishments were (i) residences oriented to housing or day care for independent individuals that do not require help or assistance and also general impairment (for individuals with general loss of activities of daily function) and (ii) a sociosanitary center which has a high level of impairment. The detailed description of each residence (number of beds, type of facility, and the annual water consumption) is indicated in Table 1.

In each establishment, we interviewed the manager and the head health professional to obtain information on the type of patients, sickness, and level of impairment. All this information was key to defining the typology of the residence and treatments performed. Then, each establishment provided complete data on the consumption of pharmaceuticals, as the number of pills, injections or other presentations of a specific drug, and their concentration. This information was compiled to identify the main pharmaceutical families administered and to calculate the total amount consumed (milligrams per day) in each establishment (Table 2). To compare the consumption rates in the five establishments, consumption data was normalized per patient so that data is given also in milligrams per day per patient. Data correspond to consumptions in 2015, except for F1 and S1 which correspond to 2016.

Estimation of the predicted environmental concentrations

PEC calculations were adapted from EMA guidelines to determine the predicted concentrations in effluents from senior

Table 1 Number of pharmaceuticals administered in five establishments for the elderly according to consumption data in 2015 and 2016

Residence	Size		Facility type	Water consumption (m^3/year)	Pharmaceuticals administered
	Beds	Day center			
F1	75	6	Housing and general impairment	4560	133
S1	100	30	Sociosanitary center, general impairment, and psychiatric unit	6679	164
S2	130	0	Housing, general impairment	7100	134
P1	52	0	Housing, general impairment	5230	116
P2	61	0	Housing, general impairment	4859	146

residences (PECres), the predicted concentration in the sewerage system (PECgrid), and the predicted concentrations in river (PECriv). The former permitted to determine pharmaceuticals released from health-care establishments according to high consumption and high excretion. On the other hand, PECgrid considered the dilution of the effluent from the health-care facilities to the urban sewerage system. Finally, PECriv considered the elimination in WWTP and the final dilution in receiving waters. PEC values are always given in micrograms per liter.

When calculating PECres, one of the main particularities that might affect the discharge of pharmaceuticals is the people wearing diapers. This implies that an inferior amount of pharmaceuticals than the one that was actually consumed will be discharged. This factor is included in the PECres formula:

$$\mathrm{PECres} = \frac{\mathrm{DRUG}_{\mathrm{consumption}} \times F_{\mathrm{Excretion}} \times (1-F_{\mathrm{Pads}})}{\mathrm{WATER}_{\mathrm{consumption}}} \times 10^6 \quad (1)$$

where

- $\mathrm{DRUG}_{\mathrm{consumption}}$ (g/day) is the quantity of each pharmaceutical delivered in each senior residence.
- $F_{\mathrm{Excretion}}$ is the excreted fraction of the unchanged drug, considering both urine and feces. Excretion data was obtained from Theriaque database (Amiel and Husson, 1994). Selected values ranged from negligible to 100%, depending on the compound.
- F_{Pads} is the percentage of patients using incontinence pads. In this study, we used the value of 50% as it represents the mean percentage of patients using incontinence pads in the establishments studied.
- $\mathrm{WATER}_{\mathrm{consumption}}$ (L/day) is the water consumed in each residence per patient per year (Table 1).
- 10^6 is a conversion factor so that *PECres* are expressed in micrograms per liter.

To evaluate the amount of pharmaceuticals discharged to the river waters, PECriv (in μg/L) were estimated using the formulas:

$$\mathrm{PECgrid} = \frac{\mathrm{PECres}}{\mathrm{DF}_{\mathrm{GRID}}} \quad (2)$$

$$\mathrm{PECriv} = \mathrm{PECgrid}\frac{(1-F_{\mathrm{WWTP}})}{\mathrm{DF}_{\mathrm{RIVER}}} \quad (3)$$

where

- $\mathrm{DF}_{\mathrm{Grid}}$ is an expected dilution factor from senior residences to the general sewage grid. To calculate this factor, we determined the percentage of water from senior establishment to the general volume of water in the sewerage system. In Barcelona and Lisbon, the dilution factor is more than 2500, and in Nimes of 1300 times, based on the volume of sewage water in each sewerage system collected in each treatment plant (27,000 m^3/day in Nimes, 450,000 m^3/day in Barcelona, 350,000 m^3/day in Lisbon). We used an agreement value of 100 times for all three sites considering that the total sewage water is divided in 5-10 collectors in each city and the flow can vary substantially according to discharges, rains, etc..
- F_{WWTP} is the removal fraction in WWTP. Removal data was obtained from EPI Suite by Environmental Protection Agency (EPA) (EPA 2013). Here, when different data were obtained from the bibliography, the lowest value was applied. In the cases that no information was available, a default value of 0 was used indicating that a given compound is not eliminated.
- $\mathrm{DF}_{\mathrm{RIVER}}$ is the dilution factor from WWTP effluents to receiving water and was considered 75.73 for France, 25.92 for Spain, and 61.23 for Portugal, as suggested by Keller et al. (2014). This differential dilution factor is used to better estimate PEC values according to the differences in river flows and dynamics among countries.

For compounds with PECriv >0.01 μg/L, as proposed by EMA, the toxicity data was compiled according to ECOTOX (EPA), DrugBank, or toxicological data sheets of Sigma-Aldrich, ScienceLab, and Santa Cruz Biotechnology.

Table 2 Pharmaceuticals administered in each residence ordered by consumption data (>1000 mg/day, > 400 mg/day in France given the overall low consumptions), PECres, PECgrid, and PEC river

Pharmaceutical	ATC code	Category	Consumption (mg/day)	Excretion (%)	PECres (μg/L), 50% of diapers	PECgrid (μg/L), 100% DF	PEC river (μg/L)
Residence F1 (81 beds)							
Paracetamol	N02BE01	Analgesic	27233	5	54.5	0.545	0.007
Metformin	A10BA02	Antidiabetic	4355	77	134	1.342	0.017
Levetiracetam	N03AX14	Antiepileptic	2043	66	54.0	0.540	0.007
Amiodarone	C01BD01	Antiarrhytmic	815	0.5	0.16	0.002	0.000
Irbesartan	C09CA04	Antihypertensive	735	31	9.13	0.091	0.001
Furosemide	C03CA01	Diuretic	595	0.5	11.9	0.119	0.002
Acebutolol	C07AB04	β-blokers	594	50	7.14	0.071	0.001
Amoxicillin	J01CA04	Antibiotic	547	30	16.2	0.162	0.002
Dabigatran etexilate	B01AE07	Anticoagulant	463	74	16.7	0.167	<0.001
Tramadol	N02AX02	Analgesic	405	90	4.86	0.048	<0.001
Sociosanitary center S1 (130 beds)							
Macrogol	A06AD15	Laxative	581336	100	15885	158	6.015
Paracetamol	N02BE01	Analgesic	166329	5	227	2.272	0.086
Metamizole	N02BB02	Analgesic	24486	0.5	3.35	0.033	0.001
Metformin	A10BA02	Antidiabetic	17466	77	367	3.675	0.139
Acetylcysteine	R05CB01	Mucolytic	13151	50	180	1.797	0.069
Amoxicillin	J01CA04	Antibiotic	9897	70	189	1.893	0.072
Valproic acid	N03AG01	Antiepileptic	8603	3.2	7.52	0.075	0.003
Gabapentin	N03AX12	Antiepileptic	7781	100	213	2.126	0.081
Ibuprofen	M01AE01	NSAID*	5753	10	15.7	0.157	0.004
Acetylsalicylic acid	N02BA01	Analgesic	5562	10	15.2	0.152	0.006
Quetiapine	N05AH04	Antipsychotic	4422	5	6.04	0.060	0.002
Clomethiazole	N05CM0	Hypnotic	3314	5	4.53	0.045	0.002
Cyanocobalamine	V09XX01	Vitamin	2795	90	68.7	0.687	0.027
Pyridoxine (vit B6)	A11HA02	Vitamin	2795	0.5	009	0.004	0.000
Levetiracetam	N03AX14	Antiepileptic	2466	66.3	44.7	0.447	0.017
Trazodone	N06AX05	Antidepressant	2466	0.13	0.09	0.001	<0.001
Sulfamethoxazole	J01EC01	Antibiotic	2301	20	12.6	0.126	0.005
Ascorbic acid	A11GA	Vitamin	2178	2.6	1.55	0.015	0.001
Oxerutin	C05CA02	Vasoprotector	1973	24.2	13.0	0.130	0.005
Furosemide	C03CA01	Diuretic	1779	50	24.3	0.243	0.009
Levofloxacin	J01MA12	Antibiotic	1644	85	38.2	0.382	0.014
Omeprazole	A02BC01	Antiulcer	1617	20	8.84	0.088	0.003
Oxcarbazepine	N03AF02	Antiepileptic	1315	1	0.36	0.004	0.000
Mupirocin	D06AX09	Antibiotic	1216	4.6	1.53	0.015	0.001
Carbamazepine	N03AF01	Antiepileptic	1096	1	0.30	0.003	<0.001
Megestrol	G03DB02	Sex hormone	1056	86	24.8	0.248	0.007
Spironolactone	C03DA01	Antihypertensive	1045	0.5	0.14	0.001	<0.001
Residence S2 (130 beds)							
Insulin	A10AB	Insulins	396279	1	83.3	0.833	0.032
Lactitol	A06AD12	Laxative	150874	1.4	44.4	0.444	0.017
Macrogol	A06AD15	Laxative	57729	100	1213	12.13	0.459
Paracetamol	N02BE01	Analgesic	16912	5	17.7	0.178	0.007
Metformin	A10BA02	Antidiabetic	8269	77	134	1.338	0.051
Valproic acid	N03AG01	Antiepileptic	5768	3.2	3.88	0.039	0.001
Trazodone	N06AX05	Antidepressant	4742	0.13	0.13	0.001	<0.001

Table 2 (continued)

Pharmaceutical	ATC code	Category	Consumption (mg/day)	Excretion (%)	PECres (μg/L), 50% of diapers	PECgrid (μg/L), 100% DF	PEC river (μg/L)
Carvedilol	C07AG02	β-blokers	3146	2	1.32	0.013	0.001
Levodopa	N04BA01	Antiparkinsonian	2928	10.5	6.46	0.065	0.002
Levetiracetam	N03AX14	Antiepileptic	2625	66.3	36.6	0.366	0.014
Quetiapine	N05AH04	Antipsychotic	2506	5	2.63	0.026	0.001
Acetylsalicylic acid	N02BA01	Analgesic	2021	10	4.25	0.042	0.002
Furosemide	C03CA01	Diuretic	1344	50	14.1	0.141	0.005
Gabapentin	N03AX12	Antiepileptic	1200	100	25.2	0.252	0.010
Pentoxifylline	C04AD03	Vasodilator	1200	1	0.25	0.003	<0.001
Phenytoin	N03AB02	Antiepileptic	1050	1	0.22	0.002	<0.001
Troxerutin	C05CA04	Vasoprotector	1033	65	14.1	0.141	0.005
Residence P1 (52 beds)							
Metformin	A10BA02	Analgesic	12025	77	323	3.231	0.052
Paracetamol	N02BE01	Antiparkinsonian	8975	5	15.6	0.157	0.003
Levodopa	N04BA01	Analgesic	3900	10.5	14.3	0.143	0.002
Acetylsalicylic acid	N02BA01	Analgesic	3771	10	13.2	0.132	0.002
Glucosamine	M01AX05	Antiulcer	3000	21.3	22.3	0.223	0.004
Sucralfate	A02BX02	Antiepileptic	3000	0.5	0.52	0.005	<0.001
Valproic acid	N03AG01	Antiepileptic	2750	0.5	0.48	0.005	<0.001
Tiotropium bromide	R03BB04	vasculoprotector	2000	74	51.6	0.516	0.008
Diosmin	C05CA03	Antidepressant	1800	7	4.40	0.044	0.001
Sertraline	N06AB06	Antidepressant	1200	0.2	0.08	0.001	<0.001
Ibuprofen	M01AE01	NSAID*	1200	10	4.19	0.042	0.001
Levodopa	N04BA01	Antiparkinsonian	1025	30	10.7	0.107	0.002
Levetiracetam	N03AX14	Antiepileptic	1000	66.3	23.1	0.231	0.004
Residence P2 (61 beds)							
Macrogol	A06AD15	Laxative	13125	100	492	4.930	0.079
Paracetamol	N02BE01	Analgesic	17600	5	33.1	0.331	0.005
Metformin	A10BA02	Antidiabetic	5425	77	156	1.569	0.026
Glucosamine	M01AX05	Analgesic	4500	21.3	36.0	0.360	0.006
Diosmin	C05CA03	vasculoprotector	4500	7	11.8	0.118	0.002
Metamizole	N02BB02	Analgesic	4025	0.5	0.76	0.008	<0.001
Piracetam	N06BX03	Psychostimulant	3600	100	135	1.352	0.022
Pentoxifylline	C04AD03	Vasodilator	2000	1	0.75	0.008	<0.001
Acetylsalicylic acid	N02BA01	Analgesic	1850	10	6.95	0.069	0.001
Levetiracetam	N03AX14	Antiepileptic	1600	66.3	39.8	0.398	0.007
Valproic acid	N03AG01	Antiepileptic	1600	3.2	3.12	0.031	0.001
Allopurinol	M04AA01	Hypo-uricemic	1450	8	4.36	0.044	0.001
Trazodone	N06AX05	Antidepressant	1275	0.13	0.06	0.001	<0.001
Sulfasalazine	A07EC01	Antiinflammatory	1000	5	1.88	0.019	<0.001

*Nonsteroidal anti-inflammatory drugs

Prioritization and risk evaluation

It is not feasible to monitor all possible pharmaceuticals present in the environment, and it is necessary to prioritize those that can represent the greatest threat (Donnachie et al. 2016). The consumption data permitted to prioritize compounds with the highest potential impact in river waters from France, Spain, and Portugal. The workflow used is based on

1. Listing of pharmaceuticals according to the consumed data in each senior residence.

2. Calculation of the predicted concentration in the effluents of the senior residence (PECres) for all compounds and all residences.
3. Calculation of PEC in river waters and ranking of compounds with PECriv higher than the 0.01-μg/L threshold level proposed by EMA.
4. Toxicity evaluation using *Daphnia magna* or other species EC_{50} or LC_{50} values, depending on available data.
5. Selection of toxic compounds for which risk assessment is needed.

All this information has been compiled in a database that allows to identify those substances discharged from healthcare facilities that may produce an environmental effect.

Results

Consumption of pharmaceuticals

Figure 1 shows the consumption of pharmaceuticals in the five senior residences located in France, Spain, and Portugal. The net total amount of pharmaceuticals ranged between 54 and 1801 g/day, with the residences in Spain being the ones with the highest consumption. According to the size of each residence, this corresponds to an average consumption per day per person ranged from 677 mg in F1 to 13,856 and 9755 mg in S1 and S2, respectively, although the levels were quite similar in P1 and P2 (between 1279 and 1714 mg/person/day). Considering these quantities and taking into account that senior residences have become a living preference in many countries, the amounts of pharmaceuticals discharged to the sewerage system can become a real problem. For instance, there are >8000 public senior residences in France, 5339 in Spain, and 4787 in Portugal, besides the number of sociosanitary centers, which suggests that the estimated total consumption of pharmaceuticals from senior residences should not be disregarded in terms of contribution of pharmaceutical load to the sewerage system and indirectly, to the environment. A rough estimation average discharge considers a consumption of 100 g/day in a median residence of 100 patients, which would mean than on a country base, from 478 to 800 kg of pharmaceuticals are discharged daily from health institutions in south-west Europe. These figures are similar to those reported in Germany (Herrmann et al. 2015). Thus, the incurred impact on WWTP or rivers can be high. In comparison, the potential discharge of pharmaceuticals from the normal healthy population dwelling in an urban area is much lower as consumption is not in such high amounts and discharge is not concentrated in time or space.

The number of pharmaceuticals consumed in each senior residence ranged between 116 and 164 (Table 1). Main pharmaceuticals consumed (>1000 mg/day, 400 mg/day in F1) in each of the five studied residences are indicated in Table 2. Observed differences in main consumed drugs in French, Spanish, and Portuguese residences evidenced the different and specific treatments that patients can receive. A total of 397 common pharmaceuticals were consumed in the five senior residences studied, which belong to 90 therapeutic classes. Table SI1 shows all pharmaceuticals consumed in the five senior residences studied, indicating their Anatomical Therapeutic Chemical (ATC) classification code (WHO 2017). On the other hand, the main therapeutic classes consumed are indicated in Fig. 2 and include antidiabetic agents, analgesics, antibiotics, and antiepileptics as the main treatments for the elderly. Figures 1 and 2 also show the high variability of each therapeutic group consumed in the three countries, reflecting specific treatments according to the different health problems in each establishment or either specific medication according to impairment intrinsic of each patient or typology of residence.

Flow of pharmaceuticals from senior residences to river waters

Of the total number of pharmaceuticals consumed, we determined the PEC values in the effluents of senior residences. These calculations took into account that approximately half of the people living in the residences wear incontinency pads. At a glance, this appears to minimize the problem of pharmaceuticals discharged into the wastewaters. However, it is important to note that this is adding up to another problem. If diapers are not properly disposed as biohazard waste in the senior residences, a similar amount of residues is polluting other places, e.g., landfills.

Among the total 397 pharmaceuticals administered in all residences, Table 2 indicates those with amounts administered in quantities higher than 1000 mg/day (400 mg/day in France). PECres varied from negligible to hundreds of micrograms per liter (Table 2). Given the large number of pharmaceuticals administered, it is obvious that the ones consumed at the highest concentration and showing high excretion rates will have higher chances to reach surface waters. We observed that compounds consumed in amounts >1000 mg can be discharged to the sewerage system, and even they are diluted and biodegraded in the WWTP, and they can reach receiving surface waters at the nanogram per liter level. This process of dilution and elimination of pharmaceuticals in WWTP would presumably lead to a concentration in river waters close to the EMA value of 0.01 μg/L. Only 20 had PECriv >0.01 μg/L, with 1 being for F1, 9 for S1, 6 for S2, 1 for P1, and 3 for P2. Table 2 indicates these compounds.

PECriv are also indicated in Table 2 and ranged between 0.001 and 6.15 μg/L, with the highest levels found in Spain due to the lower dilution factor. Comparing PECres and PECriv, the concentrations estimated in river waters represent

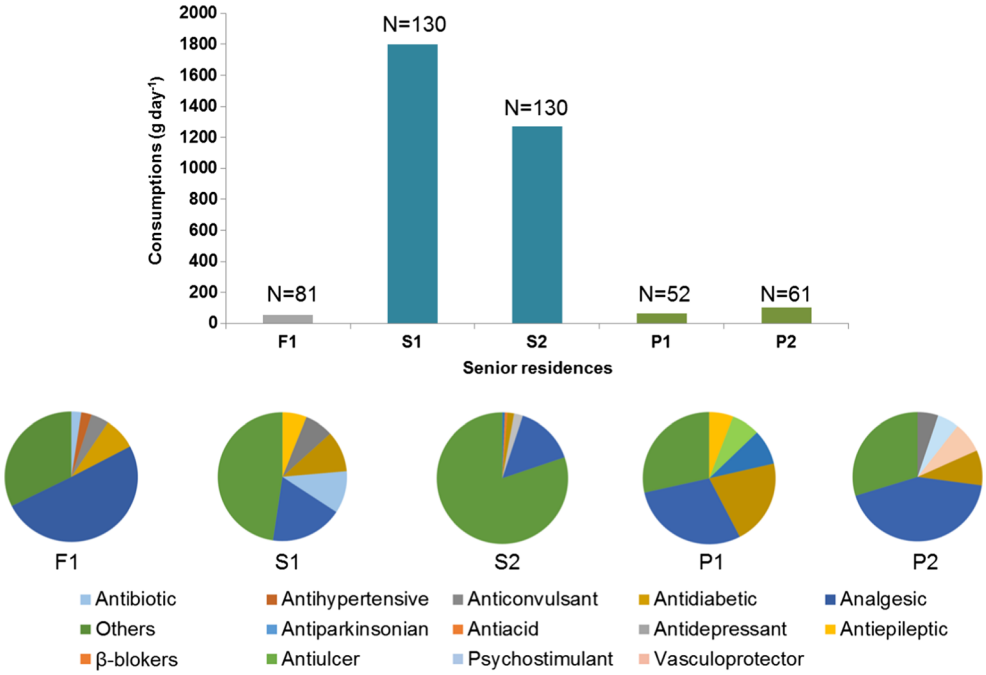

Fig. 1 Total daily consumption of pharmaceuticals in each residence, indicating the number of residents (*N*) and the families consumed in each establishment (pie diagrams)

on average 0.01% or less of the initially discharged by the effluents of the health-care establishments. This decrease in concentration is basically due to 100× dilution in the sewerage system and dilution in river. The WWTP degradability for most of the compounds was very low, and thus, a high proportion of pharmaceuticals will be potentially discharged by the WWTP effluents to receiving waters. Figure 3 shows, using a double axis, this difference. For the studied compounds, the percentage of pharmaceuticals detected in river is low in comparison to the effluents of the residences, indicating that dilution is the main process for the removal of pharmaceuticals once discharged to the sewerage system.

In France, only one compound, metformin, had PECres of 134 μg/L and PECriv of 0.017 μg/L, which represents 0.013% of the concentration initially discharged given a high excretion rate. Paracetamol had high PECres but was highly eliminated in WWTPs and thus had low PECriv. Dabigatran and amoxicillin were highly biodegradable in WWTP, and the rest of the compounds are expected to be found in the effluents of the WWTP, but once diluted to the river their concentration is expected to be at the low nanogram per liter level.

In both Spanish residences, 15 compounds exceeded the EMA threshold value (0.01 μg/L). PECriv ranged from 0.01 to 0.086 μg/L, except for macrogol which had PECriv from 0.459 to 6.015 μg/L. Macrogol is the international nonproprietary name for polyethylene glycol used primarily as laxative or also as excipient in many pharmaceutical products. It is consumed in high amounts in Spain (57–581 g/day in the two Spanish residences or from 0.5 to 5 g/inhab/day) and is rapidly excreted and poorly biodegraded in WWTP. WWTP were only

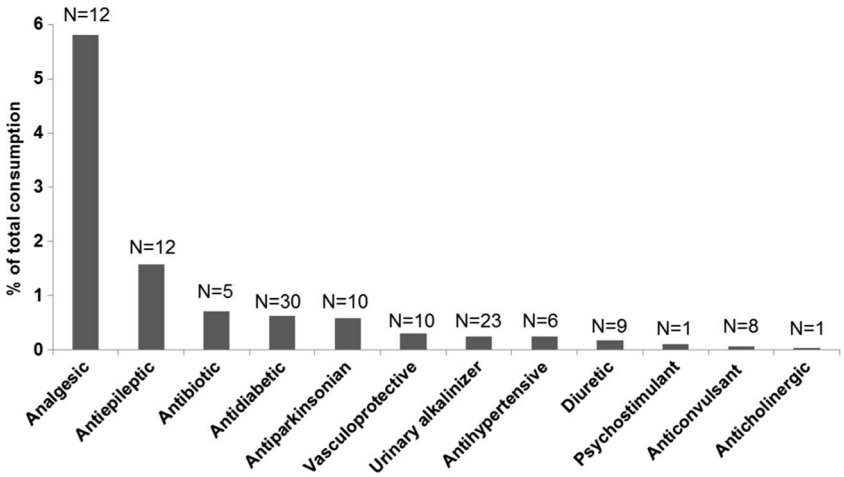

Fig. 2 Families of pharmaceuticals (in percentage) most widely consumed in health institutions from southwest Europe (France, Spain, and Portugal). *N* indicates the number of pharmaceuticals dispensed for each family. Macrogol (laxative) is not represented as its consumption ranges from 13 to 580 g/day which would represent 86% of the total pharmaceuticals consumed

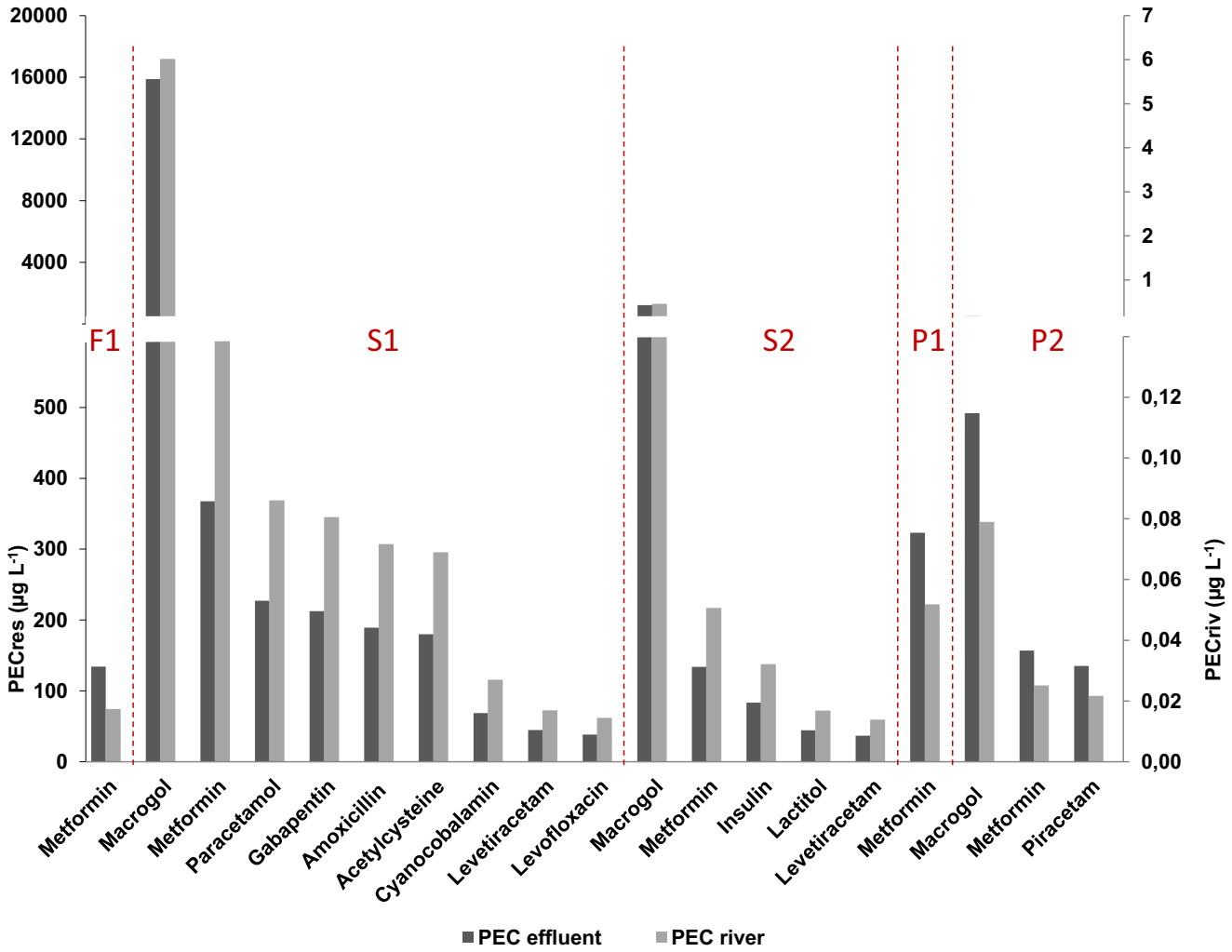

Fig. 3 PECres (*gray*, *left axis*) and PECriv (*light gray*, *right axis*) in each country (F1 = France, S1 and S2, Spain and P1 and P2, Portugal). Only compounds with PECriv >0.01 μg/L according to EMA threshold are represented. This represents a decrease in percentage of more than 99%

partially efficient in eliminating ibuprofen (29%) and megestrol (30%), but despite the high PECres, they would not be expected to be found in river waters if originating only from health-care facilities. However these compounds are widely used by the overall population and frequently detected in river waters (van Nuijs et al. 2015). Overall, in Spanish residences, compounds with the highest PECriv were macrogol, paracetamol, metformin, acetylcysteine, amoxicillin gabapentin, cyanocobalamin, levetiracetam, levofloxacin, and megestrol. The low dilution factor is mainly responsible for the high PECriv of these compounds.

Finally, in Portugal one compounds in P1 and 3 in P2 were consumed in amounts which produced PECriv higher than the EMA 0.01 μg/L threshold value (Table 2), indicating that despite the high dilution factor compared to Spain (61.23 vs 25.92), the pharmaceuticals consumed in senior residences might contribute to river water contamination. In Portugal, the compounds with the highest PECriv were macrogol, metformin, and piracetam.

When estimating PECriv for compounds with consumption of 1000 mg/day, we observed that dilution in the sewerage system, elimination in the WWTP, and dilution in river waters may not be enough to eliminate all pharmaceuticals. We have then identified that some compounds present in effluents would be presumably detected in river waters at levels of 0.01–6.15 μg/L. The compounds that should be considered as suspect compounds as they could be present in river waters at concentrations >0.01 μg/L are indicated in Table 2 for each establishment.

Considering the three countries, the most consumed drugs and for which PECriv is higher than 0.01 μg/L proposed by EMA are listed in Table 2. Altogether, 12 compounds of the 397 commonly administered in health institutions had PECriv >0.01 μg/L. Of these, only metformin was common in all countries. The rest of the compounds are specific of a given country or even health institution, indicating that there is a wide variability on the pharmaceuticals administered to patients, even though most belong to the same family. Many of

these compounds have been previously identified as most commonly detected in the environment. For instance, metformin has been previously identified as one of the main pharmaceuticals in wastewaters in the Netherlands (Oosterhuis et al. 2013). Similarly, Van Nuijs et al. detected metformin, valsartan, and tramadol in sewage water with good correlation with prescribed values (van Nuijs et al. 2015). In Iraq, paracetamol, amoxicillin, and metformin had an annual consumption exceeding 1000 t per year and were expected to produce a risk (Al-Khazrajy and Boxall 2016).

Prioritization of pharmaceuticals for further treatment and risk assessment

Table 3 gives the physico-chemical characteristics of the prioritized pharmaceuticals according to PECriv >0.01 μg/L EMA threshold and includes also common phramaceuticals in the 3 countries with levels >0.001 μg/L. Most of them have high solubility and low logP, indicating that preferentially they will remain in water. Even though pharmaceuticals can be degraded in water (Carlsson et al. 2006), their continuous discharge, even at low concentrations, makes these drugs recalcitrant and environmentally hazardous compounds. Because of the lack of a legislation that controls the levels of drug residues in discharges and in surface waters, it is important to prioritize actions that minimize the impact of these pollutants on the environment. Thus, the theoretical evaluation of presence and risk can provide a new and simple to use tool to predict their presence in the environment. These tools can be extrapolated to other areas with similar problems (e.g., kindergartens, hospitals).

For the 12 compounds likely to be consumed in amounts that can reach river waters, we determined the aquatic toxicity using different organisms according to available data from the open bibliography (Table 3). The toxicity in general is low. However, it has been pointed out that there is scarce information about long-term effects of pharmaceuticals to aquatic organisms, in particular with respect to biological targets (Fent et al. 2006). In the environment, acute toxic effects of pharmaceuticals are unlikely but chronic ecotoxicity data is needed for a correct evaluation of risk (Carlsson et al. 2006).

Main compounds to be released from health-care institutions were laxatives such as macrogol and lactitol; analgesic and antipyretic drugs such as paracetamol and piracetam; antibiotics such as amoxicillin and levofloxacin, gabapentin, and levetiracetam for the treatment of epilepsy and neuropathic pain; and pharmaceuticals for the treatment of diabetes (metformin and insulin). Prioritization according to PECs helps in the implementation of focused monitoring programs that consider only the most abundant and toxic compounds, in an attempt to control and mitigate the release of pharmaceuticals consumed in health care institutions.

Risk management

The new "Urban Water Agenda 2030," addressed at the Leeuwarden Conference (02.2016), incorporates concerns about wastewater treatment by focusing on emerging contaminants to contribute to the achievement of the good chemical status of water bodies. The main objective is to ensure the quality of water for urban use.

In this study, we have identified health institutions as a point source pollution of pharmaceuticals to the environment, with similar conclusions as those obtained in Germany (Herrmann et al. 2015). The number of homes for elderly people is currently high and is expected to increase in the future. This is worrying because these establishments are a considerable source of emerging pollutants and, hitherto, there are no guidelines or information about the risk management of effluents, which are typically classified as domestic. Nonetheless, the World Health Organization (Chartier 2014) alerts that although a large part of the wastewater from health-care facilities can be considered domestic (because they pose the same risks as domestic wastewater), depending on the service and tasks of the facility, these wastewaters might contribute to the contamination of rivers. This is clearly the case for the sociosanitary centers, where the consumption of pharmaceuticals is high.

Consequently, as for classical hospitals, risk assessments have to be envisaged for elderly residences. Several possibilities can be imagined. One of them could be the application of the recent French guideline for good management of waste produced by health-care establishments (edited by the French Ministry of Health) that propose initiatives to organize the management of liquid waste (http://social-sante.gouv.fr/IMG/pdf/pour_une_bonne_gestion_des_dechets_produits_par_les_etablissements_de_sante_et_medico-sociaux.pdf).

Onsite treatment could be another effective strategy to manage the release of pharmaceuticals to the environment. A future avenue for this area would be to conduct a cost-benefit analysis and sociological studies to know the viability of this strategy.

Daily practices could be also a good but challenging procedure to mitigate the release of pharmaceuticals, and this can be done specifically for incontinency pads.

Overall risk management is a complex issue because it involves many and different types of stakeholders, such as environmental and health authorities, the pharmaceutical sector, water and waste industries, health practitioners, researchers, and elderly home managers and clients, as well as the general public. Environmental, social, and economic objectives have to be considered for identifying the problem and determining the risk clearly and early in the process, so that mitigation actions can be achieved. To facilitate this process, risk assessment and risk management should be integrated activities and should share a

Table 3 Physico-chemical properties of prioritized pharmaceuticals according to PEC data with values higher than 0.001 μg/L and reported aquatic toxicity (Aquatox μg/L)

Pharmaceutical*	CAS num.	Molecular Formula	Mw	Water solubility (mg/L)	LogP	Pv (mmHg, 25°C)	Half-life	Aquatic toxicity (μg/L) and tested organism	
PECriv > 0.01 μg/L									
Metformin	657-24-9	$C_4H_{11}N_5$	129.2	1E+6	-2.64	7.6E-05	6.2 h	3300	*D. magna, EC50, reproduction*
Macrogol	25322-68-3	$H–(OCH_2CH_2)n–OH$	NA	1E+5	NA	NA	NA	>1000000	*Oryzias latipes LC50; 24h*
Paracetamol	103-90-2	$C_8H_9NO_2$	151.2	3E+4	0.46	2E-06	1-4 h	6400	*D. magna, LC50*
Gabapentin	60142-96-3	$C_9H_{17}NO_2$	171.2	4491	-1.1	3E-10	4–7 h	NA	
Amoxicillin	26787-78-0	$C_{16}H_{19}N_3O_5S$	365.4	3433	0.87	4.7e-17	1 h	10000	*D. magna LC50*
Acetylcysteine	616-91-1	$C_5H_9NO_3S$	163.2	5090	-0.03	1.09e-05	15 d	151000	*D. magna, EC50*
Cyanocobalamin	68-19-9	$C_{63}H_{88}CoN_{14}O_{14}P$	1355.4	1.3E+4	1.87	NA	6 d	20-100	*Poteriochromonas malhamensis EC50 72h*
Levetiracetam	102767-28-2	$C_8H_{14}N_2O_2$	170.2	7910	-0.49	3.5E-06	6-8 h	341000	*D. magna, LC50*
Levofloxacin	100986-85-4	$C_{18}H_{20}FN_3O_4$	361.4	3E+4	-0.39	9.8E-13	6-8 h	10000	*D. magna; NOEC;48h*
Lactitol	585-86-4	$C_{12}H_{24}O_{11}$	344.3	377000	-3.2	2.24E-17	2 d	NA	
Piracetam	7491-74-9	$C_6H_{10}N_2O_2$	142.2	8E+4	-1.54	6.4E-06	NA	NA	
PECriv > 0.001 <0.01 μg/L									
Acetylsalicylic acid	50-78-2	$C_9H_8O_4$	180.2	5295	1.19	6.6e-05	0.5 h	360314	*D. pulex; LC50*
Clomethiazole	533-45-9	C_6H_8ClNS	161.6	1041	2.83	0.0229	3.6-6 h	NA	
Diosmin	520-27-4	$C_{28}H_{32}O_{15}$	608.5	407.8	0.14	6E-27	NA	NA	
Furosemide	54-31-9	$C_{12}H_{11}ClN_2O_5S$	330.7	149.3	2.03	3.1E-11	2 h	10000	*Hydra vulgaris, NOEC 7d*
Glucosamine	3416-24-8	$C_6H_{13}NO_5$	179.2	1E+6	-2.2	2E-08	NA	NA	
Ibuprofen	15687-27-1	$C_{13}H_{18}O_2$	206.3	41.05	3.97	1.9E-04	2-4 h	1600	*D. magna, LC50*
Levodopa	59-92-7	$C_9H_{11}NO_4$	197.2	3E+5	-2.39	2.6E-10	1.5 h	1780000	*D. magna, LC50*
Megestrol	3562-63-8	$C_{22}H_{30}O_3$	342.5	27.02	3.41	3.5E-10	34 h	5	*D. magna, EC50*
Omeprazole	73590-58-6	$C_{17}H_{19}N_3O_3S$	345.4	359	2.23	1.16E-11	60 d	88	*D. magna, EC50*
Oxerutin**	96304-71-1	$C_{33}H_{42}O_{19}$	742.7	19300	-2.86	2.31E-34	15 d	NA	
Quetiapine	111974-69-7	$C_{21}H_{25}N_3O_2S$	383.5	40.3	2.8	2.74E-13	60 d	10-100	*D. magna, EC50*
Sulfamethoxazole	723-46-6	$C_{10}H_1N_3O_3S$	253.3	610	0.89	1.3E-07	37 d	3300	*D. magna, EC50*
Tiotropium bromide	136310-93-5	$C_{19}H_{22}BrNO_4S_2$	472.4	3E+4	-1.76	1.9E-18	5-6 d	69	*D. magna, EC50*
Troxerutin	7085-55-4	$C_{33}H_{42}O_{19}$	742.7	2E+4	-2.86	2.3E-34	NA	NA	
Valproic acid	99-66-1	$C_8H_{16}O_2$	144.2	1300	2.75	0.0847	15 d	NA	

*Insulin excluded as it is a peptide hormone; ** Plant constituents

common requirement which is effective risk communication (Naidu et al. 2016).

Knowledge on the risks associated with pharmaceutical residues in wastewater is very weak, sometimes controversial, and in part unknown (García-Santiago et al. 2016; Touraud et al. 2011). A perception study on elderly people's residences is currently in progress, and the first results show a real misunderstanding of the problem (data not shown). Related knowledge, attitudes, and social representations have yet to be established from a social science point of view (Pidgeon et al. 2011). This elaboration process starts in the inquiries about the topic (Lichtenstein and Slovic 2006) and the cultural and social dispositions of people (Kahan 2009). For this reason, the risk and benefits of pharmaceuticals, namely, openness through frequent dialogs, decisions based on the best available science, transparency, timeliness, and responsiveness, should be taken into consideration (Bouder 2011). Furthermore, campaigns to increase risk awareness should be initiated before any alarm episode (Barnett and Breakwell 2003) or crisis (Gaspar et al. 2015).

Conclusions

We have identified senior residences as a source of pharmaceuticals to surface waters at concentrations higher than 0.01 μg/L, which is the EMA threshold for risk assessment. Depending on the size of the elderly people's home, and taking into account the circumstances and medical treatments usually received, wastewaters contain pharmaceuticals in their effluents at concentrations of hundreds of micrograms per liter. Because these effluents are discharged to sewerage systems and WWTP are mostly inefficient to eliminate pharmaceuticals, residues are discharged to river waters, thus contributing to water pollution. This effect, amplified by the large number of residences in the south-west Europe, indicates the importance of controlling the discharges of pharmaceuticals form senior residences to minimize the impact on aquatic ecosystems. A protocol scheme and risk management actions foreseen should be used to implement focused monitoring and remediation technologies that consider the most toxic compounds to ensure effectiveness in the control and evaluation of the impact of pharmaceuticals released from health-care facilities.

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