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Deposited in *Repositório ISCTE-IUL*:
2018-04-17

Deposited version:
Post-print

Peer-review status of attached file:
Peer-reviewed

Citation for published item:
Lacorte, S., Luís, S., Gómez-Canela, C., Sala-Comorera, T., Courtier, A., Roig, B....Calas-Blanchard, C. (2018). Pharmaceuticals released from senior residences: occurrence and risk evaluation. Environmental Science and Pollution Research. 25 (7), 6095-6106

Further information on publisher's website:
10.1007/s11356-017-9755-1

Publisher's copyright statement:
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Environmental Science and Pollution Research

Pharmaceuticals released from senior residences: occurrence and risk evaluation

--Manuscript Draft--

Manuscript Number:	ESPR-D-17-02015
Full Title:	Pharmaceuticals released from senior residences: occurrence and risk evaluation
Article Type:	Research Article
Keywords:	senior residences; pharmaceuticals; predicted environmental concentrations; risk management; 10 µg/L.
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Funding Information:	
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, for the first time, senior residences from south European countries as an important source of pharmaceuticals in the environment. We have estimated that compounds released from effluents of senior residences at a concentration of only 10 µg/L can reach river waters at a concentration higher than 0.01 µg/L, which is the European Medicines Agency threshold for risk evaluation of pharmaceuticals in surface waters. This study has been based on 5 establishments for the elder in Portugal, Spain and France, hosting from 52 to 139 patients. We have compiled the pharmaceuticals dispensed on a daily base and calculated the consumption rates. Up to 636 g of pharmaceuticals are consumed daily, being analgesics, antiepileptic, antibiotic, anticonvulsant, antidiabetic

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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, for the first time, senior residences from south European countries as an important source of pharmaceuticals in the environment. We have estimated that compounds released from effluents of senior residences at a concentration of only 10 µg/L can reach river waters at a concentration higher than 0.01 µg/L, which is the European Medicines Agency threshold for risk evaluation of pharmaceuticals in surface waters. This study has been based on 5 establishments for the elder in Portugal, Spain and France, hosting from 52 to 139 patients. We have compiled the pharmaceuticals dispensed on a daily base

and calculated the consumption rates. Up to 636 g of pharmaceuticals are consumed daily, being analgesics, antiepileptic, antibiotic, anticonvulsant, antidiabetic and laxatives the main drugs families administered. According to excretion rates, dilution in the sewage grid and elimination in wastewater treatment plants and reported toxicity, amoxilin, glucosamide, ibuprofen, metformin, paracetamol and megestrol were the compounds bearing the higher environmental hazards. Finally, we discuss the risk management actions related to the discharge of pharmaceuticals from senior residences to surface waters.

Keywords: senior residences; pharmaceuticals; predicted environmental concentrations; risk management; 10 µg/L.

Introduction

Water pollution today represents a major challenge both at the economic and social level. Quality of water must be preserved both for human protection and to safeguard the environment from compounds capable to exert an effect at low levels of concentration. Although the Water Framework Directive requires European countries to control certain compounds classified as "priority pollutants", monitoring programs have identified a diffuse and persistent pollution in water due to other compounds. These compounds are the so-called emerging pollutants and are refractory to traditional wastewater treatment. Among others, pharmaceuticals are of concern given their high incidence and global distribution 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 &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), but to date, no attention has been paid to senior residences.

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. Countries with aging populations have to increase their resources according to the demands of elderly people being necessary to ensure environmental sustainability and

public health. The homes for elderly people are infrastructures that articulate diverse services in response to biopsychosocial needs and have become popular in most European countries. Senior residences have a configuration of typically 50-150 individuals and provide lodging, meal services and health and social assistance. With an estimated consumption of 5-10 pills/patient, the total consumption of pharmaceuticals is of hundreds of milligrams. These compounds are excreted through urine of faeces and are released to the main urban grid without any type of treatment. There, waters are transported to the WWTP, which unable to eliminate the total load of pharmaceuticals, contribute to their release to receiving waters, posing the environment at risk (Figure 1). This problem is magnified all around the world due to the aging effect and the increased population established in senior residences. Thus, senior residences can represent a point source pollution of pharmaceuticals to the environment.

The European Medicines Agency (EMEA) 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 (EMEA) 2006). Among other activities, they monitor the safety of medicines across their life cycle. In 2006, EMEA 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 pharmacological 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 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 &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) and Poland (Oldenkamp et al. 2013). Consumption or prescription data have demonstrated to be very valuable to determine the

occurrence of pharmaceuticals in the environment (Ortiz de García et al. 2013, van Nuijs et al. 2015). According to PEC values and toxicological information, it is then possible to determine the potential risk of pharmaceuticals in the environment (van Leeuwen &Vermeire 2007).

Our hypothesis is that senior residences represent an important source, yet unexplored, of pharmaceuticals to the environment. In this study we propose an innovative scheme for the prioritization and risk management of pharmaceuticals discharged from senior residences based on consumption data, excretion, dilution and toxicity. We have followed EMEA guidelines for risk evaluation and we provide a list of pharmaceuticals consumed in high quantities in senior residences for which actions have to be implemented to reduce the environmental impact.

Methodology

Nursing homes studied

Home for the elderly 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 5 residences, 1 in France, 2 in Spain and 2 in Portugal. For comparability purposes among the three countries, the residences selected were all mixed model residences that had a high number of beds (>50), and that were located in urban areas. We considered as mixed model residences those that were either i) oriented to housing (i.e, for independent individuals that do not require help or assistance) and oriented to general impairment (for individuals with general loss of activities of daily function), or ii) oriented to housing, or general impairment, or specific types of diseases, and, in addition, provide services to other elderly people, such as day care center. The specific description of each residence (number of beds, type of facility and the annual water consumption) is indicated in Table 1.

In each residence, 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 define the typology of the residence and treatments performed. Then, each residence provided 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 (g per day) in each residence. To compare the consumption rates in the 5 residences, consumption data was normalized per patient so that data is given also in mg/d/inhab. Data correspond to consumptions in 2015, except for F1 and S1 which correspond to 2016.

Estimation of the Predicted Environmental Concentrations

PECs calculation were adapted from EMEA guidelines to determine the predicted concentrations in effluents from senior residences (PECres) and in rivers waters (PECriv). The former permitted to determine pharmaceuticals released to sewage waters according to high consumption and high excretion. On the other hand, PECriv considered the dilution in the sewage grid, the elimination in WWTP and the final dilution to receiving waters. PEC values are always given in µg/L.

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:

$$PECres = \frac{consumption\ x\ Fexc\ x\ Fdiap}{water\ consumption\ x\ inhab} \qquad \textit{(eq. 1)}$$

where,

- *Consumption* (g/day) is the quantity of each pharmaceutical delivered in each senior residence.
- *Fexc* is the excreted fraction of the unchanged drug, considering both urine and feces. When different values were reported in the bibliography, the highest one was used to consider the worst case scenario. Selected values ranged from negligible to >90%, depending on the compound. For those drugs whose values could not be found, no value was assigned.

- *Fdiap* is the percentage of patients using diapers. In this study, we used the value of 50% as it represents the mean percentage of patients in senior residences using diapers.
- *Water consumption* (L/d) is the water consumed in each residence per patient per day in 2015 (Table 1).
- *Inhab* is the number of patients in each residence (Table 1).

To evaluate the amount of pharmaceuticals discharged to the river waters, PECriv were estimated using the formula:

$$PECriv = \frac{consumption\ x\ Fexc\ x\ Fdiap\ x\ Fgrid\ x\ (1 - F_{WWTP})}{water\ consumption\ x\ inhab\ x\ DF} \qquad (eq.\ 2)$$

where:

- *Fgrid* is an expected 10% dilution of effluent waters from senior residences to the general sewage grid.
- *Fwwtp* is the removal fraction in WWTP. Removal data was obtained from EPI Suite by Environmental Protection Agency (EPA) (EPA 2013). In the cases that no information was available a default value of 0 was used.
- *DF* 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 (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 EMEA, the environmental hazards were calculated. Environmental risks to aquatic animals were estimated from the hazard quotient index (HQ) depicted in eq 3, using the estimated PECs and PNECs. The latter parameters was obtained from eq 4 using reported ecotoxicological information from Ecotox (EPA), Drugbank or toxicological data sheets of Sigma-Aldrich, Sciencelab and Santa Cruz Biotechnology. As limited information for aquatic species ecotoxicity was found for most selected pharmaceuticals, PNEC was estimated using the lowest chronic LOEC or acute LC50s considering application factors (FA) of 100 and

1000, respectively. For those substances having only mammalian toxicological LD50 information an additional factor of 10 was used (i.e. FA=10000).

$$HQ = \frac{PEC_i}{PNEC_i} \qquad (eq.3)$$

$$PNECi = \frac{ENPOINTi}{FA} \qquad (eq.4)$$

where PECi and PNEC are the estimated PEC and PNEC of contaminant i.

Total hazard quotients HQTotal considering all selected pharmaceuticals were determined using the independent action concept (eq. 5) assuming that compounds act independently and that their effects were uncorrelated.

$$HQ_{Total} = 1 - \prod_{i=1}^{n} [1 - HQ_i] \qquad (eq.5)$$

where HQi is the hazard quotient of compound i.

Prioritization and risk evaluation

As highlighted by Donnachie et al. (2016), 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. Figure 2 exemplifies the workflow used, which is based on:

(i) listing of pharmaceuticals according to the consumed data in each senior residence.

(ii) calculation of the predicted concentration in the effluents of the senior residence (PECres) for all compounds and all residences.

(iii) preselection of compounds with PECres > 10 µg/L to study their transport through the sewage grid and elimination in the WWTP. This concentration was tentatively selected to obtain the EMEA threshold level of 0.01 µg/L.

(iv) calculation of PEC in river waters and ranking of compounds with PECriv higher than the 0.01 µg/L threshold level proposed by EMEA.

(v) toxicity evaluation using *Daphnia magna* or other species EC_{50} or LC_{50} values, depending on available data.

(vi) selection of toxic compounds for which risk assessment is needed.

All this information has been compiled in a database that allows the prioritization of those substances that may produce an environmental effect.

Results

Consumption of pharmaceuticals

Figure 3 shows the consumption of pharmaceuticals in the 5 senior residences located in France, Spain and Portugal. The net total amount of pharmaceuticals ranged between 7.9 and 636 g/d, being the residences in Spain the ones with the highest consumption. According to the size of each residence, this corresponds to an average consumption per day per patient ranged from 48.3 mg in F1 to 4889 mg in S2, although the levels were quite similar in S2 and P1 and P2 (between 365 to 563 mg/inhab/d). 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 sewage grid can become a real problem. For instance, there are >8000 senior residences in France, 5339 in Spain and 4787 in Portugal, which suggest that the estimated total consumption of pharmaceuticals from senior residences should not be disregarded in terms of contribution of pharmaceuticals load to the sewage grid and indirectly, to the environment. If we consider an average discharge of 100 g/day in a median residence of 100 patients, that would mean than on a country base, from 478 to 800 kg of pharmaceuticals are discharged daily from senior residences in south-west Europe. These waters enter the sewage system in most countries, but eventually could be discharged without any treatment. Thus, the incurred risk is high.

The number of pharmaceuticals consumed in each senior residence ranged between 133 and 164 (Table 1). Main pharmaceuticals consumed (> 1 g/d) in each of the five studied residence are also indicated in Table 1. These highly consumed drugs are similar to those detected in Iraq where paracetamol, amoxicillin and metformin has an annual consumption exceeding 1000 tonnes

per year (Al-Khazrajy &Boxall 2016). 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 5 senior residences studied, which belong to 90 therapeutic classes. Table SI1 shows all pharmaceuticals consumed in the 5 senior residences studied, indicating their Anatomical Therapeutic Chemical classification code (ATC) (WHO 2017). On the other hand, the main therapeutic classes consumed are indicated in Figure 3 and include antidiabetic, analgesic, antibiotics, and antiepileptics as the main treatments for the elderly. Figure 3 also reflects the high variability of each therapeutic group consumed in the 3 countries, suggesting specific pharmacological protocols per country 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 diapers. 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.

The PECres varied from negligible to mg/L level (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 initially set a threshold value of 10 µg/L for further risk evaluation. Such threshold was chosen because once these pharmaceuticals are discharged to the sewage grid, they are diluted, biodegraded in the WWTP to be finally diluted in receiving surface waters (Figure 1). This process of dilution and elimination of pharmaceuticals in WWTP would presumably lead to a concentration in river waters close to the EMEA value of 0.01 µg/L.

Among the total 397 pharmaceuticals administered in each residence, only 23 had PECres > 10 µg/L, being 5 for F1, 18 for S1, 7 for S2, 9 for P1 and 10 for P2. Table 2 indicates the compounds with PECres > 10 µg/L for which PECriv was further studied.

The PECriv are also indicated in Table 2 and ranged between 0.002 and 1.15 µg/L, with the highest levels found in Spain due to the lower dilution factor. Comparing the PECres and PECriv, the concentrations estimated in river waters represent between 0.12-0.38% of the initially discharged by the effluents of the senior residence. This decrease in concentration is basically due to dilution in the sewage grid 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 4 shows, using a double axis, this difference. For the studied compounds, there was very little variability on the percentage of pharmaceuticals detected in river in comparison to the effluents of the residences, indicating a similar behavior of all pharmaceuticals once discharged to the sewage grid.

In France, 5 compounds with concentrations higher than 10 µg/L in PECres had PECriv between 0.002 to 0.203 µg/L, which represent 0.13±0.0002% of the concentration initially discharged, except for dabigatran which was highly biodegradable in WWTP and whose PEcriv was of 0.0023 µg/L. Therefore, 4 compounds having PECriv > 0.01 µg/L included metformin, paracetamol, levetiracetam and amoxicillin.

In both Spanish residences, 17 out of 18 compounds exceeded the EMEA threshold value (0.01 µg/L). PECriv ranged from 0.03 to 1.07 µg/L, except for macrogol which had PECriv from 4.59 to 46.2 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 (57-580 g/d in the 2 Spanish residences or from 0.5 to 5 g/inhab/d) and is rapidly excreted and poorly degraded in WWTP. This compound has never been monitored in surface waters. The relatively high PECriv levels are mainly attributed to the low biodegradability in the WWTP. Three compounds, namely alcaphor (urinary alkalinizer), megestrol (a steroidal progestin) and ibuprofen

(an anti-inflamatory) were highly degradable. Specifically, PECriv for alcaphor was of 0.0068 µg/L due to 94% elimination in the WWTP, suggesting that there would be no risk. In contrast, WWTP were only partially efficient in eliminating ibuprofen (29%) and megestrol (30%) but given the high PECres, 0.03 and 0.05 µg/L, they would be expected to be found in river waters. Overall, in Spanish residences, compounds with the highest PECriv were macrogol, metformin, paracetamol, gabapentin and amoxicillin. The low dilution factor is mainly responsible for the high PECriv of these compounds, which exceeded the value of 0.5 µg/L.

Finally, in Portugal 9 compounds in P1 and 10 in P2 had PECres > 10 µg/L (Table 2) and PECriv higher than the EMEA 0.01 µg/L, 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 waters contamination. In Portugal, the compounds with the highest PECriv were macrogol, metformin, and piracetam.

When estimating the PECriv for compounds with PECres < 10 µg/L, we observed that dilution in the sewage grid, elimination in the WWTP and dilution in river waters was not enough to eliminate those pharmaceuticals. We have then identified that compounds present in effluents from senior residences at concentrations lower than 10 µg/L would be presumably detected in river waters at levels of 0.01-0.02 µg/L. The following compounds should be considered as suspect compounds as they could be present in river waters at concentrations > 0.01 µg/L: sulfamethoxazole, rifaximine, pentosane polysulfate sodique, omeprazole, valproic acid, trimethoprim, ketoconazole, carbidopa, donezepil, valsartan, sitaglipin, tramadol, ranitidine and acetylsalicylic acid.

Considering the 3 countries, the most consumed drugs and for which the PECriv is higher than 0.01 µg/L proposed by EMEA are listed in Table 2. Altogether, 23 compounds of the 397 commonly administered in senior residences had PECres > 10 µg/L and PECriv > 0.01 µg/L. Of the 23 prioritized compounds, only 3 compounds were common in all countries: paracetamol, levetiracem and metformin. Compounds used both in Spain and Portugal are acetylsalicylic acid, gabapentin, pregabalin, carbidopa, furosemide and macrogol. The rest of the compounds are specific of a given country or even

residence, 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).

Prioritization of pharmaceuticals for further treatment and risk assessment

Table 3 gives the physico-chemical characteristics of the prioritized pharmaceuticals according to PECriv. 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, make 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, 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 so that remediation technologies can be implemented. These tools can be extrapolated to other areas with similar problems (e.g. kindergartens, hospitals, etc.).

For the 23 prioritized compounds, we determined the aquatic toxicity using different organisms according to available data from the open bibliography (Table 4). Using this data and the maximum PECriv, the risk quotients were calculated. Table 4 includes aquatic and mammalian toxicological information and estimated PNECs and environmental hazards of the pharmaceutical most used in the SUDOE regions. From the 23 selected substances eight did not have toxicological information. From the remaining 16 environmental hazards ranged from 5 x 10^{-5} of gentamicin to 0.1 of paracetamol. The combined hazards of these 16 substances was 0.22, which is rather close to 1, the

benchmark for severe risk. From the 16 studied substances 6 of them amoxilin, glucosamide, ibuprofen, metformin, paracetamol and megestrol accounted for 98% of risks. Note, however, that environmental hazards for glucosamide and megestrol were estimated from toxicity data reported on mammalian species, whose dosage was administered quite different (oral or injected) than that of aquatic organisms, thus for these two compounds there is more uncertainty than for the rest.

When evaluating the environmental risks of pharmaceuticals consumed in Sweden, it was concluded there the risk for acute toxic effects with the current active pharmaceuticals was unlikely but highlight the lack of chronic ecotoxicity data for a correct evaluation of risk (Carlsson et al. 2006).

Main risk compounds were analgesic and antipyretic drugs such as paracetamol, ibuprofen, metamizole and acetylcysteine, antibiotics such as amoxicillin and sulfamethoxazole, gabapentin and valproic acid for the treatment of epilepsy and neuropathic pain, sedative and hypnotic compounds such as clomethiazole and pharmaceuticals for the treatment of diabetes (metformin). However, it has been pointed out that there is a very little known information about long term effects of pharmaceuticals to aquatic organisms, in particular with respect to biological targets (Fent et al. 2006).

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 prevent pollution of water by cities and to ensure the quality of water for urban use.

In this study we have identified senior residences as a point source pollution of pharmaceuticals to the environment. The number of homes for elderly people is currently high and is expected to increase in the future. This is alarming 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 pose a higher risk. This is clearly the case for the homes for elderly people, where people consume a high number of pharmaceuticals. Therefore, regulations regarding the direct discharge in surface water and the indirect discharge in a municipal wastewater treatment plant, should consider possible onsite treatment, and water reuse. Onsite treatment could be an effective strategy to manage the risk of pharmaceuticals in the environment at this moment. Prioritization according to PECs would help in the implementation of focused monitoring and remediation technologies that consider only the most toxic compounds, which would ensure the effectiveness in the control and risk assessment of pharmaceuticals. A future avenue for this area would be to conduct cost-benefit analysis and economic and sociological studies to know the viability of this strategy.

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. It must be ensured that environmental, social and economic objectives for risk management are clear and established early in the process, and that these are achieved. To facilitate this process, risk assessment and risk management should be integrated activities and should share a common requirement that is effective risk communication (Naidu et al. 2016).

A challenging issue in communicating the risks associated with pharmaceutical residues in wastewater is the unfamiliar nature of the concept, and that presents particular challenges to the risk communication strategy. The pharmaceutical residues in water can be considered emerging pollutants and, as could be expected, so can be the risks posed by these. These risks can be described as emerging risks, due to the fact that the evidence of the negative effects of the pharmacological pollution of water is relatively recent, sometimes controversial, and in part unknown (García-Santiago et al. 2016, Touraud et al. 2011). It is thus predictable that the familiarity with these risks should be particularly low.

For these reasons, related knowledge, attitudes and social representations have yet to be established. Social sciences approaches to risk perception of emerging risks suggests that, given such constraints, stakeholder's responses on these topics are not pre-established, but will be constructed (Pidgeon et al. 2011). This elaboration process starts in the inquiries about the topic, when the persons are for the first time confronted with these risks and they have to create an interpretation to deal with them (Lichtenstein &Slovic 2006) and are also influenced by the cultural and social dispositions people (Kahan 2009). For this reason, the key aspects of risk communication that are important to develop and maintain trust and "active transparency" in the case of risk and benefits of pharmaceuticals (namely openness through frequent dialogues, decisions based on the best available science, transparency, timeliness and responsiveness, should be taken into consideration about this topic (Bouder 2011). Furthermore, campaigns to increase risk awareness should be initiated before any alarm episode (Barnett &Breakwell 2003) or crisis (Gaspar et al. 2015). Otherwise, such episodes will dramatically influence the way society, in general, and stakeholders, in particular, deem about this topic.

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 EMEA threshold for risk analysis. 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 > 10 µg/L. Because these effluents are discharged to sewage grids 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.

Acknowledgements

This study has been financed by the SUDOE program with the project Innovec'Eau (2016-2019) / Project SOE1/P1/F0173 Interreg SUDOE funded by FEDER: 1.177.875,64 €; http://innovec-eau.univ-perp.fr. We would like to acknowledge the associated partners of project: Syndicat National des Établissements et Résidences Privés pour Personnes Âgées (SYNERPA), Sant Joan de Deu (SJD), Llars d'Avis de Catalunya (L'Onada), and Santa Casa da Misericórdia de Lisboa (SCML), in particular Filomena Gerardo and Sónia Pereira da Silva. We would also like to thank the personnel from the elderly homes from the elderly are acknowledged for their assistance and guidance and for providing consumption data of pharmaceuticals. Silvia Sachetti and Emanuella Scudellaro, Erasmus students from the University Federico II in Naples are gratefully thanked for their advice on the toxicity of pharmaceuticals.

Table 1. Number of pharmaceuticals administered in 2015.

Residence	Size		Mixed facility type	Water consumption (m^3/year)	Pharmaceuticals administered	Compounds consumed at doses > 1000 mg/d
	Beds	Day center				
F1	75	6	Housing and general impairment	4560	133	Metformin
S1	100	30	Housing, general impairment psychiatric unit	6679	164	Macrogol Metformin Paracetamol Gabapentin Amoxicillin Cyanocobalamine (vitB12) Levetiracetam Alcaphor Levofloxacine
S2	130	0	Housing, general impairment	7100	134	Macrogol Metformine Levetiracetam Gabapentin
P1	52	0	Housing, general impairment	5230	116	Metformin Tiotropium bromide
P2	61	0	Housing, general impairment	4859	146	Macrogol Metformin Piracetam Levetiracetam

Table 2. Compounds prioritized in each residence according to consumption data, PECres > 10 µg/L and PECriv > 0.01 µg/L.

Pharmaceutical	Consumption (mg/day)	PEC res (µg/L), 50% of diapers	PEC res (µg/L), with 10% DF	PEC river (µg/L)
Residence		**F1**		
Metformin	1569	157	16	0.203
Paracetamol	545	55	5.4	0.071
Levetiracetam	540	54	5.4	0.076
Dabigatran etexilate	167	17	1.7	0.002
Amoxicillin	162	16	1.6	0.021
Residence		**S1**		
Macrogol	581336	12213	1221	46.20
Metformin	13449	283	28	1.070
Paracetamol	8316	175	17	0.662
Gabapentin	7781	163	16	0.619
Amoxicillin	6928	146	15	0.551
Cyanocobalamine	2515	52.8	5.3	0.204
Levetiracetam	1635	34.3	3.4	0.130
Alcaphor	1414	29.7	3.0	0.007
Levofloxacine	1397	29.4	2.9	0.111
Megestrol	909	19.1	1.9	0.052
Furosemide	890	18.7	1.9	0.070
Gentamycine	699	14.7	1.5	0.056
Ceftriaxone	592	12.4	1.2	0.047
Ibuprofen	575	12.1	1.2	0.033
Acetylsalicylique	556	11.7	1.2	0.044
Pregabalin	490	10.3	1.0	0.039
Ciprofloxacine	477	10.0	1.0	0.038
Troxerutin	477	10.0	1.0	0.038
Residence		**S2**		
Macrogol	57729	1213	121	4.590
Metformine	6367	134	13.4	0.506
Levetiracetam	1740	36.6	3.7	0.138
Gabapentin	1200	25.2	2.5	0.095
Paracetamol	846	17.8	1.8	0.067
Furosemide	672	14.1	1.4	0.053
Troxerutin	671	14.1	1.4	0.053
Residence		**P1**		
Metformin	10823	378	37.8	0.610
Tiotropium bromide	1480	51.6	5.2	0.083
Levetiracetam	663	23.1	2.3	0.037
Glucosamine	639	22.3	2.2	0.036
Paracetamol	449	15.7	1.6	0.025
Levodopa	410	14.3	1.4	0.023
Acetylsalicylic acid	377	13.2	1.3	0.021
Carbidopa	308	10.7	1.1	0.017
Gabapentin	300	10.5	1.0	0.017
Residence		**P2**		
Macrogol	13125	164	16.4	0.26
Metformin	4177	157	15.7	0.25
Piracetam	3600	135	13.5	0.22
Levetiracetam	1061	39.8	4.0	0.064
Glucosamine	959	36.0	3.6	0.058
Paracetamol	880	33.1	3.3	0.053
Gabapentin	500	18.8	1.9	0.030
Pregabalin	417	15.6	1.6	0.025
Diosmin	315	11.8	1.2	0.019
Furosemide	280	10.5	1.1	0.017

Table 3. Physico-chemical properties of prioritized pharmaceuticals according to PEC data.

Pharmaceutical	CAS num.	Molecular Formula	Mw	Water solubility (mg/L)	LogP	Pv (mmHg, 25°C)	Half-life
Acetylsalicylic acid	50-78-2	$C_9H_8O_4$	180.2	5295	1.19	6.6e-05	31 min
Amoxicillin	26787-78-0	$C_{16}H_{19}N_3O_5S$	365.4	3433	0.87	4.7e-17	61.3 min
Carbidopa	28860-95-9	$C_{10}H_{14}N_2O_4$	226.2	3.9E+5	-0.13	2e-09	1-2 h
Ceftriaxone	73384-59-5	$C_{18}H_{18}N_8O_7S_3$	554.6	786.7	-1.99	5E-24	5.8-8.7 h
Ciprofloxacin	85721-33-1	$C_{17}H_{18}FN_3O_3$	331.3	1.2E+4	0.28	3E-13	4 h
Cyanocobalamin	68-19-9	$C_{63}H_{88}CoN_{14}O_{14}P$	1355.4	1.3E+4	1.87	NA	6 d
Diosmin	520-27-4	$C_{28}H_{32}O_{15}$	608.5	407.8	0.14	6E-27	NA
Furosemide	54-31-9	$C_{12}H_{11}ClN_2O_5S$	330.7	149.3	2.03	3.1E-11	2 h
Gabapentin	60142-96-3	$C_9H_{17}NO_2$	171.2	4491	-1.1	3E-10	4–7 h
Gentamicin	1403-66-3	$C_{21}H_{43}N_5O_7$	477.6	2E+5	-1.48	3.5E-18	3-3½ h
Glucosamine	3416-24-8	$C_6H_{13}NO_5$	179.2	1E+6	-2.2	2E-08	NA
Ibuprofen	15687-27-1	$C_{13}H_{18}O_2$	206.3	41.05	3.97	1.9E-04	2-4 h
Levetiracetam	102767-28-2	$C_8H_{14}N_2O_2$	170.2	7910	-0.49	3.5E-06	6-8 h
Levodopa	59-92-7	$C_9H_{11}NO_4$	197.2	3E+5	-2.39	2.6E-10	1.5 h
Levofloxacin	100986-85-4	$C_{18}H_{20}FN_3O_4$	361.4	3E+4	-0.39	9.8E-13	6-8 h
Macrogol	25322-68-3	$H–(OCH_2CH_2)n–OH$	NA	1E+5	NA	NA	NA
Megestrol	3562-63-8	$C_{22}H_{30}O_3$	342.5	27.02	3.41	3.5E-10	34 h
Metformin	657-24-9	$C_4H_{11}N_5$	129.2	1E+6	-2.64	7.6E-05	6.2 h
Paracetamol	103-90-2	$C_8H_9NO_2$	151.2	3E+4	0.46	2E-06	1-4 h
Piracetam	7491-74-9	$C_6H_{10}N_2O_2$	142.2	8E+4	-1.54	6.4E-06	NA
Pregabalin	148553-50-8	$C_8H_{17}NO_2$	159.2	2E+4	-1.78	2E-09	6.3 h
Tiotropium bromide	136310-93-5	$C_{19}H_{22}BrNO_4S_2$	472.4	3E+4	-1.76	1.9E-18	5-6 d
Troxerutin	7085-55-4	$C_{33}H_{42}O_{19}$	742.7	2E+4	-2.86	2.3E-34	NA

Table 4. Reported aquatic (Aquatox µg/L) and mammalian(mg/kg) toxicological information for the 23 selected compunds, estimated Predicted No environmental concentration (PNEC, µg/L), hazard quotiont (HQ), % contribution to the total hazard of each compound (%). FA, application factor. PEC max, maximal predicted environmenta concentration (µg/L). NA, no data.

Compound	Aquatic	Organisms	Mammalian Tox	FA	PNEC	PEC	HQ	%
Acetylsalicylic acid	360314	D. pulex; LC50	Oral, rat: LD50 = 200	1000	360.314	0.04	0.0001	0.05
Amoxicillin	10000	D. magna LC50	NA	1000	10	0.55	0.055	22.58
Carbidopa	35300	D. magna LC50	Oral mice (LD50): 1750	1000	35.3	0.023	0.0007	0.27
Ceftriaxone	NA		Intravenous rat LD50=2000	10000	280	0.047	0.0002	0.07
Ciprofloxacin	1000000	Dugesia japonica ; LC50; 48h	intramuscular LD50 (mouse) 258	1000	1000	0.038	<0.0001	0.02
Cyanocobalamin	NA		NA		NA	0.204	NA	NA
Diosmin	NA		NA		NA	0.018	NA	NA
Furosemide	10000	Hydra vulgaris ;NOEC; 7d	oral Rabit (LD50): 800	100	100	0.07	0.0007	0.28
Gabapentin	NA		NA		NA	0.618	NA	NA
Gentamicin	9599679.6	Danio rerio; LC50; 24h	Intravenous, rat: LD50: 96	1000	9599.68	0.055	<0.0001	0
Glucosamine	NA		Oral mice: LD50=300	10000	3	0.057	0.019	7.8
Ibuprofen	1600	D. magna, LC50	Oral mice: LD50=1255	1000	1.6	0.033	0.0206	8.46
Levetiracetam	341000	D. magna, LC50	Intravenous DL50 (rat):1038	1000	341	0.138	0.0004	0.16
Levodopa	1780000		Oral, rat: LD50 = 1780	10000	178	0.023	0.0001	0.05
Levofloxacin	10000	D. magna; NOEC;48h	DL50 Oral rat; 1478	100	100	0.111	0.0011	0.46
Macrogol	>1000000	Oryzias latipes ; LC50; 24h	NA	1000	NA	1840	NA	NA
Megestrol	NA		Intravenous (mouse) LD50: 56	10000	5.6	0.051	0.0091	3.74
Metformin	3300	D. magna, EC50,	oral Rabbit: LD50 = 350	100	33	1.069	0.0324	13.3
Paracetamol	6400	D. magna, LC50	Oral rat: LD50 = 1944	1000	6.4	0.66	0.1031	42.33
Piracetam	NA		DL50 Oral mice, 2000	10000	200	0.216	0.0011	0.44
Pregabalin	> 1000000	D. magna, LC50	NA		NA	0.038	NA	NA
Tiotropium bromide	NA		NA		NA	0.082	NA	NA
Troxerutin	NA		NA		NA	0.053	NA	NA

Figure 1. Cycle of pharmaceuticals from their release in seniors' residences to the river, with all the process that play a role in their transport and fate.

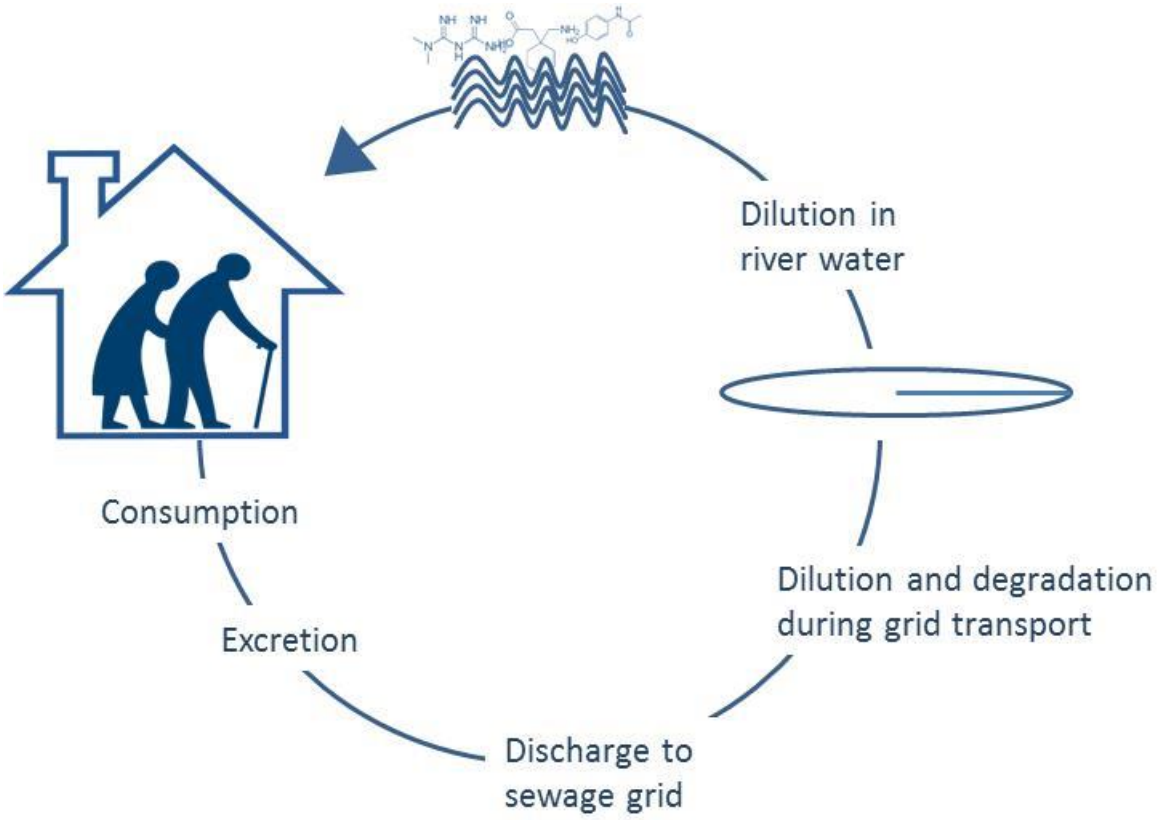


Figure 2. Workflow designed to prioritize pharmaceutical of environmental concern for which risk assessment and remediation actions.

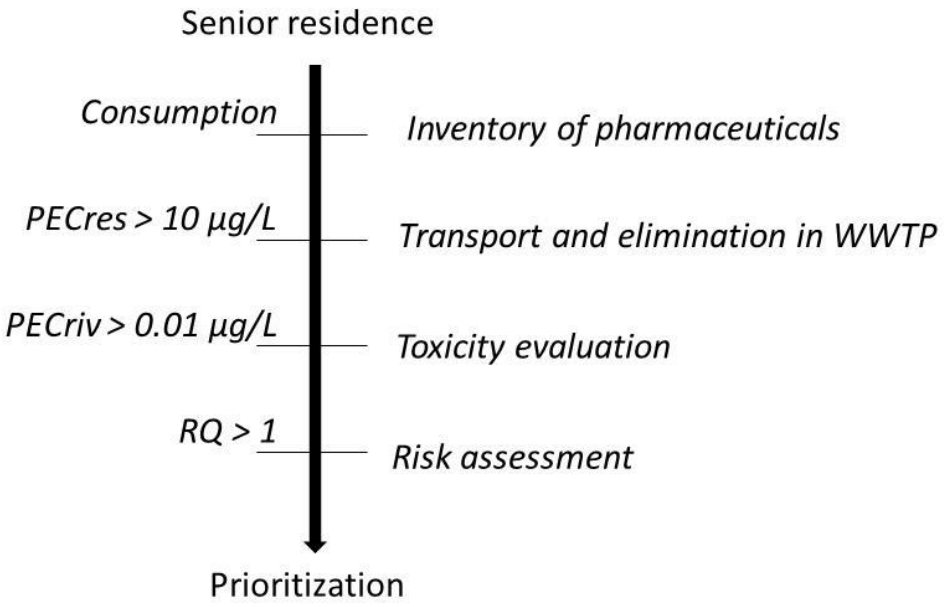


Figure 3. Total daily consumption of pharmaceuticals in each residence, indicating the number of residents (N) and the families consumed in each establishemnt (pie diagrams).

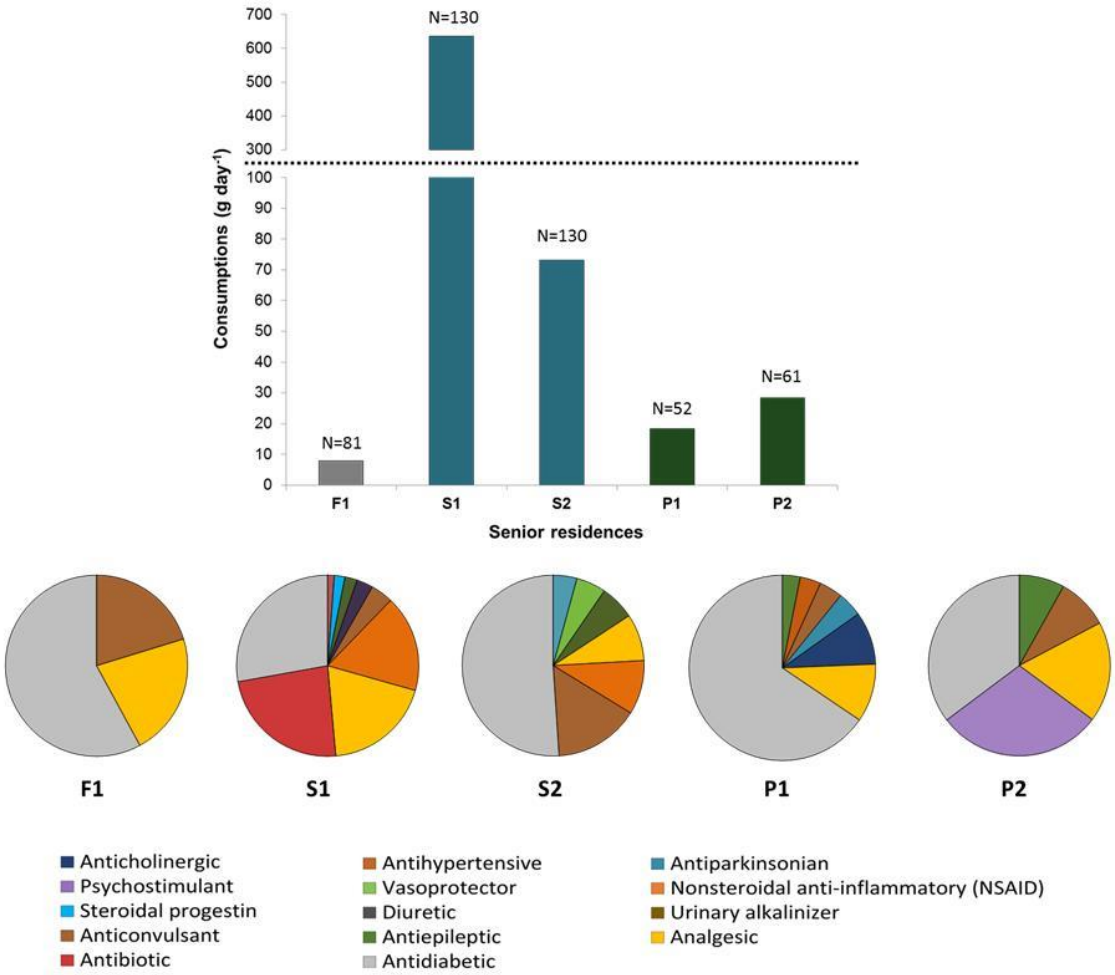


Figure 4. Families of pharmaceuticals (in percentage) most widely consumed in residences from southwest Europe (France, Spain and Portugal). N indicates the number of pharmaceuticals dispensed for each family. Macrogol (laxative) is not represented as its consumption ranges from 13 to 580 g/d which would represent 86% of the total pharmaceuticals consumed.

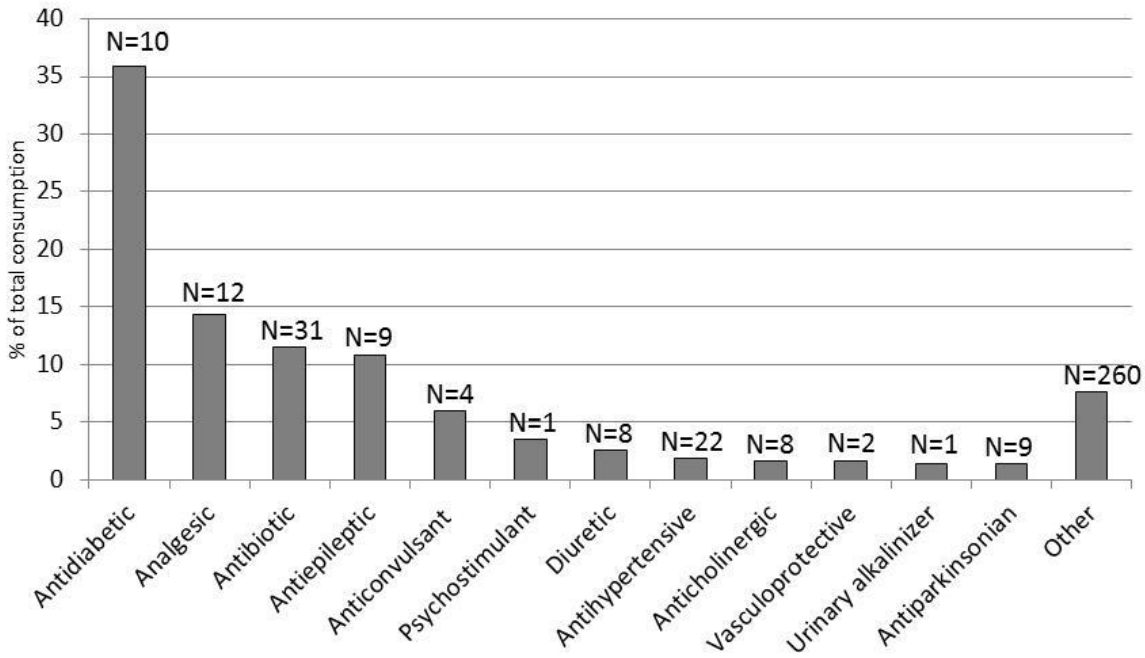
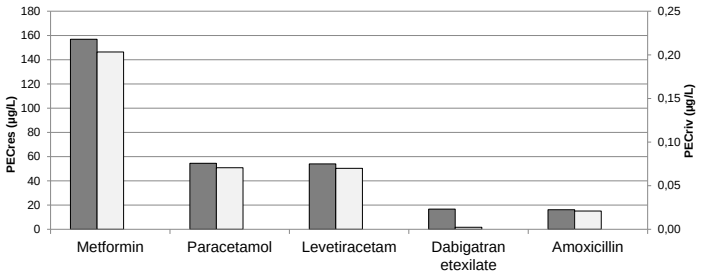
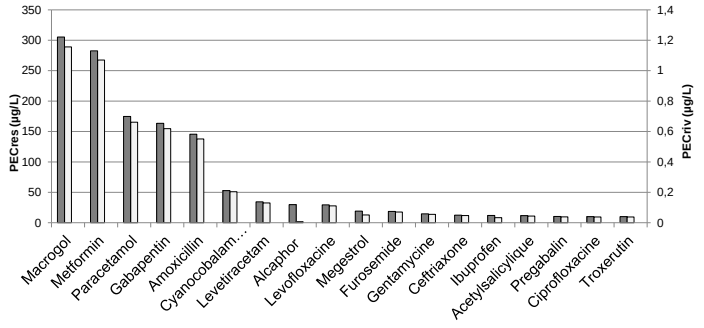


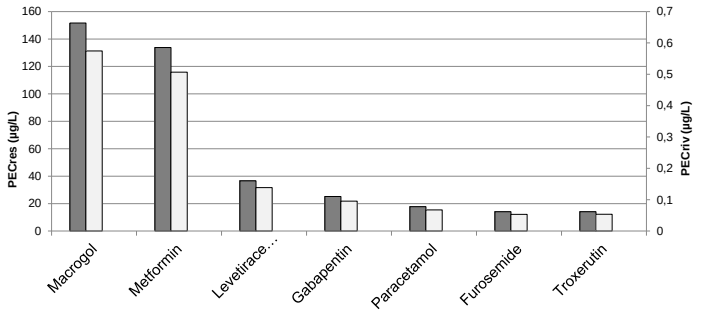
Figure 5. PECres (grey, left axis) and PECriv (light grey, right axis) in each country (F1=France, S1 and S2, Spain and P1 and P2, Portugal). This represents a decrease in % of more than 99%.



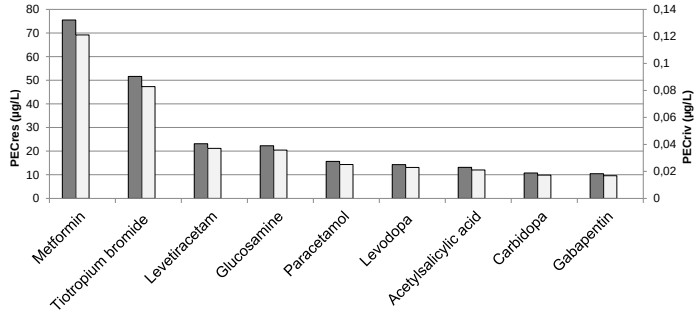
F1



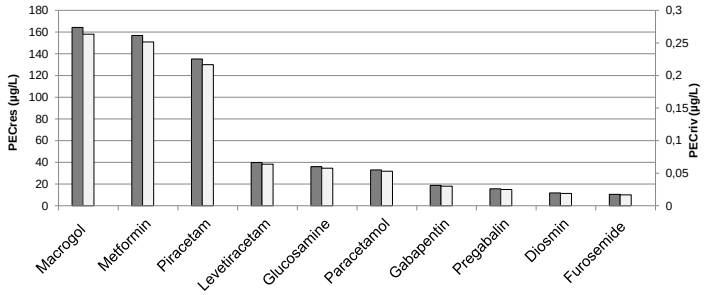
S1



S2



P1



P2

References

Al-Khazrajy OSA, Boxall ABA (2016) Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. Environ. Sci. Pollut. Res. 23: 15712-15726

Banjac Z, Ginebreda A, Kuzmanovic M, Marcé R, Nadal M, Riera JM, Barceló D (2015) Emission factor estimation of ca. 160 emerging organic microcontaminants by inverse modeling in a Mediterranean river basin (Llobregat, NE Spain). Sci. Total Environ. 520: 241-252

Barnett J, Breakwell GM (2003) The social amplification of risk and the hazard sequence: The October 1995 oral contraceptive pill scare. Health, risk & society 5: 301-313

Besse JP, Kausch-Barreto C, Garric J (2008) Exposure assessment of pharmaceuticals and their metabolites in the aquatic environment: Application to the French situation and preliminary prioritization. Human and Ecological Risk Assessment 14: 665-695

Booker V, Halsall C, Llewellyn N, Johnson A, Williams R (2014) Prioritising anticancer drugs for environmental monitoring and risk assessment purposes. Sci. Total Environ. 473-474: 159-170

Bouder F (2011) Benefit/Risk Communication by the European Medicines Agency: a Study of influential Stakeholders' Expectations and Attitudes.

Carlsson C, Johansson AK, Alvan G, Bergman K, Kühler T (2006) Are pharmaceuticals potent environmental pollutants?. Part I: Environmental risk assessments of selected active pharmaceutical ingredients. Sci. Total Environ. 364: 67-87

Chartier Y (2014): Safe management of wastes from health-care activities. World Health Organization

Donnachie RL, Johnson AC, Sumpter JP (2016) A rational approach to selecting and ranking some pharmaceuticals of concern for the aquatic environment and their relative importance compared with other chemicals. Environ. Toxicol. Chem. 35: 1021-1027

EPA US (2013) Exposure Assessment Tools and Models. EPI Suite v4.1. 2013: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

European Medicines Agency (EMEA) (2006) EMEA/CHMP/SWP/4447/00 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf

Fent K, Weston AA, Caminada D (2006) Ecotoxicology of human pharmaceuticals. Aquat. Toxicol. 76: 122-159

Fick J, Lindberg RH, Tysklind M, Larsson DGJ (2010) Predicted critical environmental concentrations for 500 pharmaceuticals. Regul. Toxicol. Pharmacol. 58: 516-523

Franquet-Griell H, Gómez-Canela C, Ventura F, Lacorte S (2015) Predicting concentrations of cytostatic drugs in sewage effluents and surface waters of Catalonia (NE Spain). Environ. Res. 138: 161-172

García-Santiago X, Franco-Uría A, Omil F, Lema JM (2016) Risk assessment of persistent pharmaceuticals in biosolids: dealing with uncertainty. J. Hazard. Mater. 302: 72-81

Gaspar R, Barnett J, Seibt B (2015) Crisis as seen by the individual: the Norm Deviation Approach/La crisis vista por el individuo: el Enfoque de la Desviación de la Norma. Psyecology 6: 103-135

Gómez-Canela C, Cortés-Francisco N, Oliva X, Pujol C, Ventura F, Lacorte S, Caixach J (2012) Occurrence of cyclophosphamide and epirubicin in wastewaters by direct injection analysis-liquid chromatography-high-resolution mass spectrometry. Environ. Sci. Pollut. Res. 19: 3210-3218

Gómez-Canela C, Ventura F, Caixach J, Lacorte S (2014) Occurrence of cytostatic compounds in hospital effluents and wastewaters, determined by liquid chromatography coupled to high-resolution mass spectrometry. Anal. Bioanal. Chem. 406: 3801-3814

Kahan DM (2009) Nanotechnology and society: The evolution of risk perceptions. Nature Nanotechnology 4: 705-706

Keller VDJ, Williams RJ, Lofthouse C, Johnson AC (2014) Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. Environ. Toxicol. Chem. 33: 447-452

Kümmerer K, Al-Ahmad A (2010) Estimation of the cancer risk to humans resulting from the presence of cyclophosphamide and ifosfamide in surface water. Environ. Sci. Pollut. Res. 17: 486-496

Langford KH, Thomas KV (2009) Determination of pharmaceutical compounds in hospital effluents and their contribution to wastewater treatment works. Environ. Int. 35: 766-770

Lichtenstein S, Slovic P (2006): The construction of preference. Cambridge University Press

Naidu R, Espana VAA, Liu Y, Jit J (2016) Emerging contaminants in the environment: Risk-based analysis for better management. Chemosphere 154: 350-357

Oldenkamp R, Huijbregts MAJ, Hollander A, Versporten A, Goossens H, Ragas AMJ (2013) Spatially explicit prioritization of human antibiotics and antineoplastics in Europe. Environ. Int. 51: 13-26

Oosterhuis M, Sacher F, ter Laak TL (2013) Prediction of concentration levels of metformin and other high consumption pharmaceuticals in wastewater and regional surface water based on sales data. Sci. Total Environ. 442: 380-388

Ortiz de García S, Pinto Pinto G, García Encina P, Irusta Mata R (2013) Consumption and occurrence of pharmaceutical and personal care products in the aquatic environment in Spain. Sci. Total Environ. 444: 451-465

Pidgeon N, Harthorn B, Satterfield T (2011) Nanotechnology risk perceptions and communication: emerging technologies, emerging challenges. Risk Analysis 31: 1694-1700

Rabiet M, Togola A, Brissaud F, Seidel JL, Budzinski H, Elbaz-Poulichet F (2006) Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized mediterranean catchment. Environ. Sci. Technol. 40: 5282-5288

Riva F, Zuccato E, Castiglioni S (2015) Prioritization and analysis of pharmaceuticals for human use contaminating the aquatic ecosystem in Italy. J. Pharm. Biomed. Anal. 106: 71-78

Santos LHMLM, Gros M, Rodriguez-Mozaz S, Delerue-Matos C, Pena A, Barceló D, Montenegro MCBSM (2013) Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. Sci. Total Environ. 461-462: 302-316

Touraud E, Roig B, Sumpter JP, Coetsier C (2011) Drug residues and endocrine disruptors in drinking water: risk for humans? International journal of hygiene and environmental health 214: 437-441

van Leeuwen CJ, Vermeire TG (2007): Risk assessment of chemicals: an introduction. Springer Science & Business Media

van Nuijs ALN, Covaci A, Beyers H, Bervoets L, Blust R, Verpooten G, Neels H, Jorens PG (2015) Do concentrations of pharmaceuticals in sewage reflect prescription figures? Environ. Sci. Pollut. Res. 22: 9110-9118

Verlicchi P, Galletti A, Petrovic M, Barceló D (2010) Hospital effluents as a source of emerging pollutants: An overview of micropollutants and sustainable treatment options. J. Hydrol. 389: 416-428

Verlicchi P, Al Aukidy M, Zambello E (2012) Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment-A review. Sci. Total Environ. 429: 123-155

WHO WHO- (2017) ATC/DDD Index 2017. https://www.whocc.no/atc_ddd_index/

Zhang J, Chang VWC, Giannis A, Wang JY (2013) Removal of cytostatic drugs from aquatic environment: A review. Sci. Total Environ. 445-446: 281-298

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Supplementary Material
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