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Predicted concentrations of anticancer drugs in the aquatic environment: What should we monitor and where should we treat?

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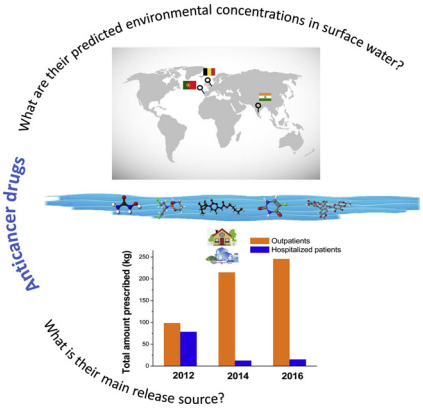
GRAPHICAL ABSTRACT



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ABSTRACT

Anticancer drugs have been detected in the aquatic environment, they have a potent mechanism of action and their consumption is expected to drastically increase in the future. Consequently, it is crucial to routinely monitor the occurrence of anticancer drugs and to develop effective treatment options to avoid their release into the environment.

Prior to implementing a monitoring program, it is important to define which anticancer drugs are more prone to be found in the surface waters. In this study the consumption of anticancer drugs in the Lisbon region (Portugal), Belgium and Haryana state (India) were used to estimate the concentrations that can be expected in surface waters.

Moreover, one important aspect is to define the major entry route of anticancer drugs in the aquatic environment: is it hospital or household effluents? The results disclosed in this study showed that in Belgium and Lisbon, 94 % of the total amount of anticancer drugs were delivered to outpatients, indicating that household

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effluents are the primary input source of these drugs and thus, upgrading the treatment in the domestic wastewater facilities should be the focus.

1. Introduction

During the last years, there has been a growing worldwide concern about the presence of pharmaceuticals in the aquatic environment (Ebele et al., 2017). Indeed, many pharmaceutical groups have already been detected in surface waters (Tiwari et al., 2017; Kümmerer, 2001; Rowney et al., 2009). Even though anticancer drugs have received less attention in terms of occurrence studies compared to other pharmaceuticals classes, these drugs have a highly potent mechanism of action. They are designed to kill rapidly growing cells such as those found in cancer tumours. However, since many of these drugs present lack of selectivity (Chari, 2008), they attack both tumour and healthy cells, causing cytotoxic, genotoxic, mutagenic, teratogenic as well as endocrine disruptor effects in any eukaryotic living organism (Kümmerer et al., 2000; Johnson et al., 2008).

According to the World Health Organization (WHO), cancer is the second leading cause of death globally, right after cardiovascular diseases. In 2012, there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in the world (Ferlay et al., 2013). By 2032, the annual new cancer cases are expected to rise to 22 million, which means that the consumption of anticancer drugs will drastically increase (Ferlay et al., 2013).

Anticancer drugs are classified by the WHO as antineoplastic and immunomodulating agents class, which can be further divided in four groups: antineoplastic agents, endocrine therapy, immunostimulants and immunosupressants. Moreover, some drugs belonging to the sex hormones and modulators of the genital system and corticosteroids classes are also widely administered in cancer treatments and thus, they are often included in the consumption list of anticancer drugs.

Similarly to other pharmaceuticals, some anticancer drugs are incompletely assimilated and metabolized by the human body and are thus, excreted via urine or faeces and released to wastewater treatment plants (WWTPs). However, since most anticancer drugs have limited biological degradability, their removal in conventional WWTPs is expected to be low and, as a result, these drugs may be continuously discharged into the aquatic environment (Kosjek and Heath, 2011).

Indeed, a growing number of studies have reported the occurrence of anticancer drugs in hospital effluents, wastewater effluents as well as in river water samples at concentrations up to hundreds of $\mu g\,L^{-1}$. For example, Mahnik et al. (2007) detected the presence of 5-fluorouracil in a concentration level ranging from 8.6 to 124 $\mu g\,L^{-1}$ in an hospital wastewater. Negreira et al. (2014) investigated the occurrence of 13 anticancer drugs in the effluent of several wastewater treatment plants located in Spain and detected the presence of 5 drugs (capecitabine, tamoxifen, cyclophosphamide, ifosfamide, irinotecan) in concentrations ranging from 2.2 $ng\,L^{-1}$ to 147 $ng\,L^{-1}$, which corroborates the fact that these drugs may be incompletely removed by conventional WWTPs. With regard to the presence of these compounds in surface waters, ifosfamide was detected in Guadarrama river at concentration levels up to 41 $ng\,L^{-1}$ (Valcárcel et al., 2011) and tamoxifen was present in Tyne river at concentrations up to 212 $ng\,L^{-1}$ (Roberts and Thomas, 2006).

Consequently, it is crucial to routinely monitor the occurrence of anticancer drugs in the aquatic environment so that, when needed, effective treatment options can be applied to avoid the release of these drugs into the surface waters.

However, it is not conceivable to evaluate the concentration of all anticancer drugs that may enter the environment due to the high number and diversity of anticancer molecules dispensed to patients, high costs and time required for the analysis. Hence, prior to the implementation of a monitoring program, it is extremely important to develop a methodology that allows to prioritize which anticancer drugs are more prone to be found in the aquatic environment.

The European Medicine Agency developed a model to determine the predicted environmental concentration (PEC) values of pharmaceuticals in surface waters and suggests that if a certain pharmaceutical has a PEC value higher than 10 $ng\,L^{-1}$ then its presence, environmental fate and toxicity effects should be further evaluated. Although this model has been extensively used for different therapeutic groups (e.g., antibiotics, analgesics, anti-inflamatories) (e.g., Besse and Garric (2008), Fick et al. (2010), Lindim et al. (2016)) there are still some drawbacks. For example, for most of the pharmaceuticals there is a discrepancy between the amount that is being sold and the amount that is indeed being consumed by the patients, leading to an overestimation of the PEC values. Nevertheless, in the case of anticancer drugs, all the prescribed amounts are consumed by the patients, and consequently, the PEC model is a very suitable approach to prioritize the drugs that should be monitored. Indeed, some studies have already reported the predicted environmental concentration of anticancer drugs in different areas such as France, United Kingdom, Spain, Catalonia and Portugal (Besse et al., 2012; Booker et al., 2014; Franquet-Griell et al., 2017, 2015; Santos et al., 2017).

A second point of attention is the need to define what is the major entry route of anticancer drugs into the environment: is it hospital or household effluents?

During the last years, there was a common idea that hospitals were the major input source of anticancer drugs into the aquatic environment since most of these drugs were widely administered at hospitals and, after their administration, they were excreted into hospital effluents, which were usually discharged into the WWTPs without any preliminary treatment. Nonetheless, due to the development of new drugs and improvement in the comfort of people under treatment, a great number of patients are nowadays taking anticancer drugs at home, indicating that household discharges may be a major route of entrance of these drugs into the environment. Furthermore, most of the people that are under the so called “daily chemotherapy” at hospitals, go home after treatment and consequently, a great part of these anticancer drugs are excreted at home. To the best of our knowledge, few studies have performed a detailed discussion about the consumption of anticancer drugs by outpatients and hospitalized patients. Besse et al. (2012) found out that around 86 % of the total amount of anticancer drugs delivered in France would enter the WWTPs via household effluents. However, this author stated that this assumption should be verified with other data sources.

Additionally, during the last years the idea of the treatment of source separated urine has gained an increasing attention due to the fact that although urine contributes less than 1% for the total flow of domestic wastewater, it contains a large portion of micropollutants (e.g., pharmaceuticals) as well as nutrients (e.g., 50 % of phosphorous and 80 % of nitrogen) (Zhang et al., 2014) and thus, the separation and treatment of human urine could minimize the release of these compounds into the WWTPs. Consequently, the comparison of renal and faecal excretion is an important step to define whether source separation urine is a good approach to minimize the release of these drugs.

The aim of this study was to select the priority anticancer molecules that can be present in the surface waters of the Lisbon region in Portugal, Belgium and Haryana state in India by means of calculating the predicted environmental concentrations using the consumption data dispensed for the three study areas. Moreover, in terms of an effluent treatment perspective a comparison of renal and faecal excretion of each anticancer drug, as well as an evaluation of the amount of

anticancer drugs consumed by hospitalized and outpatients, was performed. To the best of our knowledge this is the first time that consumption trends and predicted environmental concentrations have been represented for Belgium and India. Even though in Portugal a study was already conducted to estimate the predicted environmental concentration of anticancer drugs in the different regions of the country (Santos et al., 2017), this study did not discuss the difference in the consumption pattern by outpatients and hospitalized patients.

2. Materials and methods

2.1. Consumption data of anticancer drugs in Lisbon, Belgium and India

In the present study, the consumption pattern of anticancer drugs was analyzed for three different areas: Lisbon (Portugal), Belgium and the Haryana State (India). These study areas were targeted due to a transnational cooperation developed through the Inno-Indigo program, in the thematic area "Clean Water and Health".

- Portugal

Regarding Portugal, the study was focused only on the Lisbon region. Consumption data was provided by the Portuguese Oncology Institute of Lisbon Francisco Gentil for the years 2012, 2014 and 2016. The Portuguese Oncology Institute of Lisbon is a state-run cancer hospital and is the main oncology hospital of the Lisbon region. A total of 123 anticancer drugs were dispensed during these years, orally or intravenously.

- Belgium

Belgium national consumption data was given by the National Institute for Health and Disability Insurance for the years 2012-2015. The consumption data dispensed contemplates only the anticancer drugs belonging to the antineoplastic agent group. No information about the endocrine therapy, immunostimulant and immunosupressant classes was available for Belgium. A total of 99 antineoplastic agents were administered in Belgium during these years, orally or intravenously.

- India

In the case of India, the study was focused on the consumption data provided by Sarvodaya Multispeciality & Cancer Hospital. The Sarvodaya Cancer hospital is an oncology hospital located in Hisar (Haryana) that provides specialized medical treatment to patients from Haryana, Punjab and Rajasthan states. According to the data provided by the Sarvodaya Hospital, a total of 40 anticancer drugs were administered in 2016, orally and intravenously.

For the three countries, the consumption data was given in the form of number of pills, capsules or any other formulation of each specific anticancer drug. The concentration of the active pharmaceutical ingredient was multiplied by the number of units used for each drug during a year. Moreover, since some anticancer drugs are available in the form of different formulations, the total amount of each formulation were summed in order to obtain the annual total consumption of each anticancer drug in kg. year^{-1}. The amount of anticancer drugs prescribed per year in the Portuguese Oncology Institute of Lisbon, Belgium and Sarvodaya Cancer Hospital are represented in Table AI, Table AII and Table AIII, respectively, of the Supporting Information (Section A).

Furthermore, in the case of the Portuguese Oncology Institute of Lisbon and Belgium, the usage data was provided in the form of two lists, one corresponding to the consumption of anticancer drugs by outpatients and other to the consumption by hospitalized patients (Supporting Information section B). Hospitalized patients refer to patients under complete hospitalization whereas outpatients refer to patients taking all treatment at home as well as the patients that go to the hospital, are subject to daily chemotherapy and then return home. Analysing these data separately is very important since it allows to define whether the treatment of effluents should be done: in hospitals or domestic wastewater treatment utilities.

2.2. Predicted environmental concentration

According to the European Medicine Agency guidelines, the predicted environmental concentration of each anticancer drug in the surface waters was calculated using Eq. 1:

$$PEC = \frac{Consumption \times F_{exc} \times (1 - F_{WWTP})}{WW_{inhab} \times inhab \times DF \times 365} \quad (1)$$

where,

- *Consumption* is the total amount of each anticancer drug consumed during a year in the Portuguese Oncology Institute of Lisbon, Belgium and Sarvadoya Cancer Hospital (kg. year^{-1});
- F_{exc} is the excreted fraction of the parent drug via both urine and faeces. Compounds excreted as glucuronides-conjugates were also considered since these compounds may be subsequently hydrolyzed and reconverted into the parent compound in the WWTPs (Ternes, 1998).
- The excretion of pharmaceuticals depends on several parameters (e.g., patient age, weight, health and co-medication) so, whenever different values were found in the literature, the highest value was assumed since it represents the worst-case scenario. Moreover, if no excretion data was found, a default value of 0.5 was assumed. Table CI of Supporting Information (Section C) represents the excretion values assumed for each anticancer drug;
- F_{WWTP} is the fraction of parent drug removed in the WWTPs. There are few literature studies that reported experimental data for the removal of anticancer drugs in WWTPs, therefore, for most cases, a theoretical model was used (EPISuite 4.11) (U.S. EPA, 2013). This model uses the structure of the chemical compounds to estimate their biodegradation or sorption to sludge and assumes a conventional WWTP that uses activated sludge as secondary treatment. If no data was found, a default value of 0.5 was assumed. The assumed F_{WWTP} values are represented in the Supporting Information (Section D);
- WW_{inhab} is the volume of wastewater (L) produced per inhabitant per day. The values assumed for the three different studied areas are represented in the Supporting Information (Section D);
- *Inhab* is the number of inhabitants of each study area. The Portuguese Oncology Institute of Lisbon is the main oncology hospital of Lisbon and thus, it was assumed that it is a good representation of the consumption pattern of anticancer drugs in the Lisbon region. Although Sarvodoya Cancer hospital is located in Haryana state, it also receives patients from Punjab and Rajasthan state, therefore, the number of inhabitants of the three states was considered. Moreover, in the case of Belgium the population of the all country was considered. The number of inhabitants assumed for each studied area are represented in the Supporting Information (Section A);
- *DF* is the dilution factor from the WWTP effluents to the surface waters. A default value of 10 was assumed as suggested by European Medicine Agency guidelines.

3. Results and discussion

3.1. Total consumption of anticancer drugs

The annual consumption of anticancer drugs in the Portuguese Oncology Institute of Lisbon, Belgium and Sarvodaya Cancer Hospital

are listed in Table AI, Table AII and Table AIII of the Supporting Information (Section A), respectively.

According to the data provided by the Portuguese Oncology Institute of Lisbon Francisco Gentil, a total of 123 anticancer drugs were dispensed during the last years, with a total consumption varying from 177.2 kg in 2012 to 260.9 kg in 2016 (Table AI).

Among the 123 anticancer drugs, 101 belong to the antineoplastic agent group, 9 to the endocrine therapy group, 1 to the immunostimulant group, 9 to the immunosuppressant group and 1 to the sex hormones and modulators of the genital system group. In 2016, the antineoplastic agent was the group with the highest consumption, with a total amount of 221.2 kg. Within this group, antimetabolite was the most relevant subgroup, with a total consumption of 106.3 kg (around 41 % of the total amount of anticancer drugs consumed in 2016).

In the case of Belgium, consumption data was provided regarding only the antineoplastic agent group. As described in Table AII, a total of 99 anticancer drugs were dispensed within this group, with a total consumption ranging from 2897.4 kg in 2012 to 3004.2 kg in 2015. Among this group, antimetabolite was also the subgroup with the highest consumption, with a total amount of 1072.5 kg (36 % of the total amount of antineoplastic agents dispensed in 2015).

Similar to other studies, the local (Portuguese Oncology Institute of Lisbon) and national (Belgium) consumption data present in this study both indicate a significant increase in the consumption of anticancer drugs during the last years. This consumption trend is expected to endure in the future since the number of cancer cases are expected to drastically rise and thus, it is extremely important to keep surveying the presence of these drugs in WWTP effluents and the aquatic environment.

Regarding India, consumption data was only available for 2016. A total of 40 anticancer drugs were dispensed in Sarvodaya Multispeciality & Cancer Hospital, with 33 drugs belonging to the antineoplastic group, 5 to the endocrine therapy group and 2 to the immunosuppressant group.

Fig. 1 depicts the 10 most relevant anticancer drugs consumed in Portuguese Oncology Institute of Lisbon (123 anticancer analyzed in 2016), Belgium (99 antineoplastic agents analyzed in 2015) and Sarvodaya Multispeciality & Cancer Hospital (40 anticancer drugs delivered in 2016).

Of the ten most consumed anticancer drugs, four (capecitabine, imatinib, fluorouracil and cyclophosphamide) were found to be highly consumed in the three different regions and three other drugs (hydroxycarbamide, tamoxifen and bicalutamide) in two of the three studied areas.

As represented in Fig. 1a, capecitabine was the most prescribed anticancer drug in the Portuguese Oncology Institute of Lisbon, with a consumption equivalent to 82.6 kg in 2016. Capecitabine, an orally administered prodrug of 5-fluorouracil, is used in the treatment of metastic breast cancer, which according to the International Agency for Research on Cancer is the type of cancer with the highest incidence in Portugal (International Agency for Research on Cancer). Likewise, tamoxifen and megestrol are mainly used for breast cancer treatment and as described in Fig. 1a are also among the most relevant anticancer drugs, with concentrations up to 11.4 kg.

Capecitabine may also be used for the treatment of colorectum and gastric cancer, which are also among the most common types of cancer in Portugal. Furthermore, it is interesting to note that in 2012 the annual consumption of fluorouracil and capecitabine was similar. However, in the following years, the administration of capecitabine drastically increased, being 84 % higher than the fluorouracil use in 2016 (Fig. 1) and almost four times higher in 2016 when compared to the consumption data from 2012 (Table AI of Supporting Information). The shift in the consumption pattern of these two anticancer drugs can be explained by the fact that unlike fluorouracil, capecitabine is orally administered, which allows to increase the patient comfort as well as to decrease the risk of thrombosis and infection that is associated with

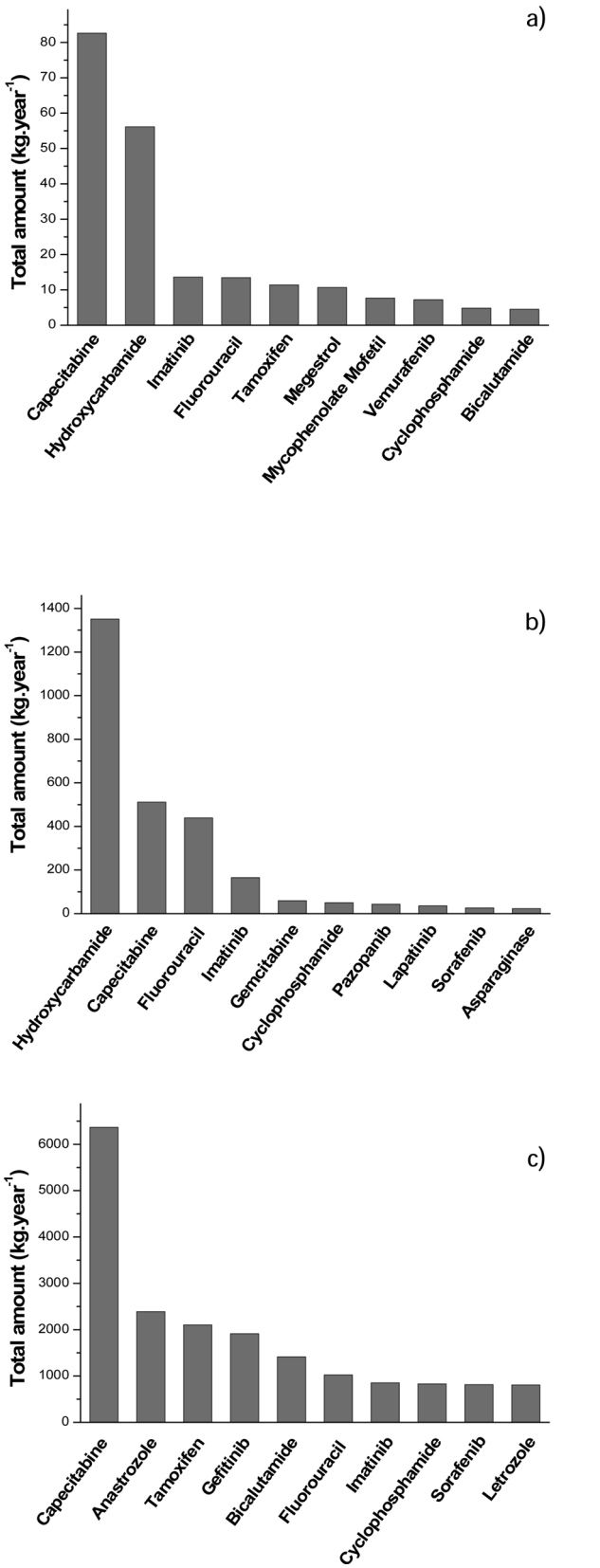

Fig. 1. List of the most consumed anticancer drugs in (a) Portuguese Oncology Institute of Lisbon (Portugal); (b) Belgium; (c) Sarvodaya Multispeciality & Cancer hospital (India).

intravenous chemotherapy. Furthermore, the use of capecitabine is associated with a higher tumor-targeting specificity, consequently decreasing the non-tumor cytotoxicity (Aguado et al., 2014).

Hydroxycarbamide was the second most consumed anticancer drug, with a substantial increase between 2012 and 2016 (from 41.1 to 56.1 kg). Following hydroxycarbamide, the most consumed anticancer drugs were imatinib, fluorouracil, tamoxifen, megestrol, mycophenolate mofetil, vemurafenib, cyclophosphamide and bicalutamide, with no significant variation within the annual consumption amounts.

In 2015, hydroxycarbamide was the most consumed antineoplastic agent in Belgium, with a total consumption of 1350.9 kg. Hydroxycarbamide is an oral administered drug used in the treatment of several types of cancer, including different sorts of leukemia and malignant melanomas, which are among the most common types of cancer in Belgium (International Agency for Research on Cancer). In the case of the treatment of leukemia, hydroxycarbamide is frequently replaced by imatinib that was also among the most consumed anticancer drugs, with a total consumption of 165.4 kg.

Following hydroxycarbamide, capecitabine was the most dispensed antineoplastic agent, with a total consumption of 511.8 kg. As in Portugal, breast is the sort of cancer with the highest incidence (International Agency for Research on Cancer), which explains the great amount of capecitabine dispensed in 2015 as well as the high consumption of gemcitabine and lapatinib.

Based on the data provided by Sarvodaya Multispeciality & Cancer Hospital, capecitabine, anastrozole and tamoxifen were the most prescribed anticancer drugs in 2016, with a total consumption of 6364 kg, 2388 kg and 2103 kg, respectively. These drugs are often dispensed for the treatment of breast cancer, which according to the International Agency of Cancer Research is the main form of cancer in India. Following up these drugs, gefitinib and bicalutamide were highly used in the treatment of lung and prostate cancer, respectively, which are also among the most relevant types of cancer in India (International Agency for Research on Cancer).

3.2. Comparison of anticancer drugs consumption trends in Portugal, Belgium and India with different European countries

With the aim of comparing the consumption trends of the three studied areas as well as with other European countries, usage data was normalized to $\mu g\,hab^{-1}\,day^{-1}$. Table AI, AII and AIII of the Supporting Information (Section A) display the consumption rate of each anticancer drug taking into account the consumption data provided by the Portuguese Oncology Institute of Lisbon, National Institute for Health and Disability Insurance (Belgium) and Sarvodaya Multispeciality & Cancer Hospital, respectively.

Within this study, it was assumed that the consumption data provided by the Portuguese Oncology Institute of Lisbon, represents the consumption trend of anticancer drugs in the Lisbon region since it is the main oncology hospital of this area. However, it is well known that nowadays some anticancer drugs are also prescribed in other hospitals and acquired in town pharmacies, and thus, the daily usage amounts may be larger than reported. Moreover, the use of chemotherapeutic drugs in nonmalignant diseases (e.g., rheumatoid arthritis, Crohn's disease, organ transplantation, sickle cell anemia and psoriasis) is widely increasing (Brunton et al., 2011).

Indeed, Santos et al. (2017) conducted a study about the consumption trends of anticancer drugs in the different regions of Portugal. This study focused on data provided by National Authority of Medicines and Health Products, I.P (INFARMED, I.P) and considered the total amount of anticancer drugs delivered to patients in pharmacies and hospitals during 2007–2015.

In general, for most of the molecules, the consumption patterns were quite similar with the ones reported in Santos et al. (2017), in particular for the drugs that are intravenously administered. As an example, Santos et al. (2017) reported for ifosfamide a daily consumption rate of $6\,\mu g\,hab^{-1}\,day^{-1}$, which is quite similar to the $3\,\mu g\,hab^{-1}\,day^{-1}$ calculated in our study. Also, it is possible to conclude that monoclonal antibodies have very similar consumption rates between the two studies, indicating that the prescription of this antineoplastic agent subgroup was mainly restricted to the Portuguese Oncology Institute of Lisbon.

Nevertheless, in the case of some anticancer drugs there was a substantial difference in the daily consumption rates. For example, according to Santos et al. (2017), mycophenolate mofetil was the most consumed anticancer drug in 2015, with a total consumption of $882\,\mu g\,hab^{-1}\,day^{-1}$ in the Lisbon region but the amount of mycophenolate mofetil delivered in the Portuguese Oncology Institute of Lisbon was drastically lower (up to $8\,\mu g\,hab^{-1}\,day^{-1}$). This significant difference can be explained by the fact that mycophenolate mofetil (a prodrug of mycophenolic acid) is an immunosuppressant drug mainly used to prevent rejection in organ transplantation and thus, it can be administered in several hospitals, including non-specialized cancer hospitals.

The other major differences were noticed for capecitabine and hydroxycarbamide, which was already expected since these drugs are widely delivered in town pharmacies. Consequently, the amounts reported by Santos et al. (2017) for the Lisbon region were much higher, with consumption rates of $368\,\mu g\,hab^{-1}\,day^{-1}$ for hydroxycarbamide and $329\,\mu g\,hab^{-1}\,day^{-1}$ for capecitabine whereas in our study the usage rates for these two drugs were $55\,\mu g\,hab^{-1}\,day^{-1}$ and $80\,\mu g\,hab^{-1}\,day^{-1}$, respectively. Furthermore, with regard to hydroxycarbamide, it can also be used for the treatment of nonmalignant diseases such as sick cell anemia and psoriasis, which may also contribute to this considerable difference (Navarra and Preziosi, 1999).

As represented in Table AII, most of the drugs prescribed in Belgium are in the range of what was reported for other European Countries and regions (e.g., France, Portugal, UK, Catalonia and Spain). Hydroxycarbamide was the antineoplastic agent with the highest daily usage, $309\,\mu g\,hab^{-1}\,day^{-1}$, which is similar to the values described for France, Catalonia, Spain and Portugal (284, 221, 237 and $301\,\mu g\,hab^{-1}\,day^{-1}$, respectively) (Besse et al., 2012; Franquet-Griell et al., 2017, 2015; Santos et al., 2017). Although capecitabine was the second most consumed antineoplastic agent in Belgium, it had a consumption rate of $131\,\mu g\,hab^{-1}\,day^{-1}$, which is substantial lower when compared with France ($213\,\mu g\,hab^{-1}\,day^{-1}$), Catalonia ($280\,\mu g\,hab^{-1}\,day^{-1}$), Spain ($236\,\mu g\,hab^{-1}\,day^{-1}$) and Portugal ($249\,\mu g\,hab^{-1}\,day^{-1}$). On the other hand, the consumption rate of fluorouracil ($110\,\mu g\,hab^{-1}\,day^{-1}$) was higher than the range values that have been reported for the other European countries and regions, $0.04-73\,\mu g\,hab^{-1}\,day^{-1}$.

Regarding imatinib, the consumption rate was of $41\,\mu g\,hab^{-1}\,day^{-1}$, which is quite similar with the values reported for Portugal ($42\,\mu g\,hab^{-1}\,day^{-1}$) (Santos et al., 2017), France ($36.3\,\mu g\,hab^{-1}\,day^{-1}$) (Besse et al., 2012) and Catalonia ($33.6\,\mu g\,hab^{-1}\,day^{-1}$) (Franquet-Griell et al., 2015). In the same way, gemcitabine and cyclophosphamide presented consumption rates really similar to the ones already reported in the literature.

Finally, with regard to Sarvodaya Multispeciality & Cancer Hospital data, although this hospital is located in the Haryana state, it also provides medical care to inhabitants from Punjab and Rajasthan state. Therefore, the total of inhabitants from these three states were used to estimate the daily use rate. As described in Table AIII, capecitabine and anastrozole were the anticancer drugs with the highest daily usage rates, 132 and $50\,\mu g\,hab^{-1}\,day^{-1}$. Then, tamoxifen and gefitinib presented similar usage values, 44 and $40\,\mu g\,hab^{-1}\,day^{-1}$, respectively.

The daily consumption of anticancer drugs was also estimated considering only the number of inhabitants of the Haryana state since the mentioned hospital is located in this state. In this case, as represented in Table AIII, the values of daily consumption would be much higher. For example for capecitabine and the anastrozole, the daily usage values would be 632 and $237\,\mu g\,hab^{-1}\,day^{-1}$, respectively.

3.3. Hospital versus outpatients consumption — what is the main release source?

The type of cancer treatment (complete hospitalization and outpatient treatment) influences the input routes of anticancer drugs in the sewage system and consequently, in the aquatic environment. With regard to the hospitalized patients, anticancer drugs are completely excreted in the hospital effluents which, in most countries, are directly discharged in WWTP without any preliminary treatment and are therefore co-treated with domestic wastewaters. On the other hand, in the case of the outpatients, some of these patients receive treatment at hospitals, however, after their daily treatment, go home, evacuating most of these drugs into the household effluents while the rest of the outpatients perform all the treatment at home, excreting 100 % of the drugs outside the hospital. Consequently, it is extremely important to compare the hospital and household emissions of anticancer drugs in order to define whether the implementation of a hospital effluent treatment on-site is a good solution to reduce the environmental contamination by these drugs or if it is wiser to act on the domestic wastewater treatment facilities. Table BI and BII of the Supporting Information (Section B) display the amount of anticancer drugs consumed by outpatients and hospitalized patients in the Portuguese Oncology Institute of Lisbon and Belgium, respectively.

Fig. 2 represents the local consumption data from the Portuguese Oncology Institute of Lisbon as well as the Belgium national consumption data depending on the type of treatment for a specific year.

Overall, based on the local consumption data (Lisbon) as well as on national consumption data (Belgium), the data present in Fig. 2 indicates that the consumption of anticancer drugs is much higher by outpatients than hospitalized patients. With regard to the Portuguese Oncology Institute of Lisbon, it is interesting to note that in 2012, although the consumption of anticancer drugs by outpatients was slightly higher than hospitalized patients, the difference between both scenarios was not considerable when compared to the subsequent years. The observed shift in recent years is related to the fact that nowadays the trend of cancer treatment is towards the non-hospitalization of patients and to the development of more home treatments that will improve the patients wellbeing.

According to Besse et al. (2012), 86.2 % of the total amount of anticancer drugs delivered in France during 2008 entered the WWTPs from the household effluents whereas 13.8 % came from hospital effluents. However, this author enhanced the fact that other studies should be performed in order to confirm these findings. Indeed, in our study, considering both countries and observing the scenario corresponding to the last year when data was available (2016 for Portuguese Oncology Institute of Lisbon and 2015 for Belgium), it is worth noting that in both cases, 94 % of the total amount of anticancer drugs were delivered to patients in the ambulatory regime, which corroborates the findings of the study previously mentioned.

As represented in Table BI and Table BII of the Supporting Information (Section B), it is possible to conclude that this consumption trend towards the non-hospitalization of patients is general to most of the anticancer drugs, which indicates that household effluents are the main input source of these drugs into the environment. Indeed, looking at the local consumption data provided by the Portuguese Oncology Institute of Lisbon, it is possible to see that out of 116 drugs delivered in 2016, 100 of them presented consumptions higher than 90 % by the outpatients. Furthermore, out of the 90 antineoplastic agents delivered in Belgium in 2015, 60 of them presented consumptions higher than 80 % by the outpatients.

With regard to the top 10 most consumed anticancer drugs, Fig. 3 describes the consumption of each of these drugs separated in terms of outpatients and hospitalized patients in the Portuguese Oncology Institute of Lisbon and Belgium.

For most of the drugs represented in Fig. 3 it can be seen the discrepancy between the consumption by the outpatients and hospitalized patients, which is in alignment with what has been discussed. Indeed, among the top 10 drugs consumed in the Portuguese Oncology Institute of Lisbon (Fig. 3a), only mycophenolate mofetil presented quite similar usage patterns between the two regimes of treatment, 56.4 % administered to outpatients and 43.4 % to hospitalized patients.

Nevertheless, it should be pointed out that there are still some molecules that are more restricted to hospitals and almost completely delivered to hospitalized patients (ifosfamide, streptozotocin, treosulfan, azathioprine, daunorubicin, carmustine, nelarabine, decitabine, clofarabine, dinutuximab, tasonermin, blinatumomab and thiotepa in Portugal; cytarabine, ifosfamide, aminolevulinic acid, melphalan, daunorubicin, busulfan, idarubicin, amsacrine, clofarabine, thiotepa and dactinomycin in Belgium; Tables BI and BII from the supporting information section). Consequently, for these particular drugs hospitals effluents remain a specific entry route of them into the environment.

From Tables BI and BII, it can be observed that the drugs capecitabine, ifosfamide, fluorouracil, cyclophosphamide, hydroxycarbamide, cytarabine, methotrexate, gemcitabine and etoposide are among the most used by hospitalized patients.

3.4. Is source separated urine a solution?

Although hospital effluents are not the main input source of anticancer drugs in the WWTPs, the possibility of treating this effluent should also not be discarded because it would mean treating a lower volume highly concentrated and also because some anticancer drugs are still more restricted to hospital.

With this in mind, the treatment of source separated urine in hospitals, and eventually also at home, may be a good approach since a large proportion of pharmaceuticals are excreted via urine.

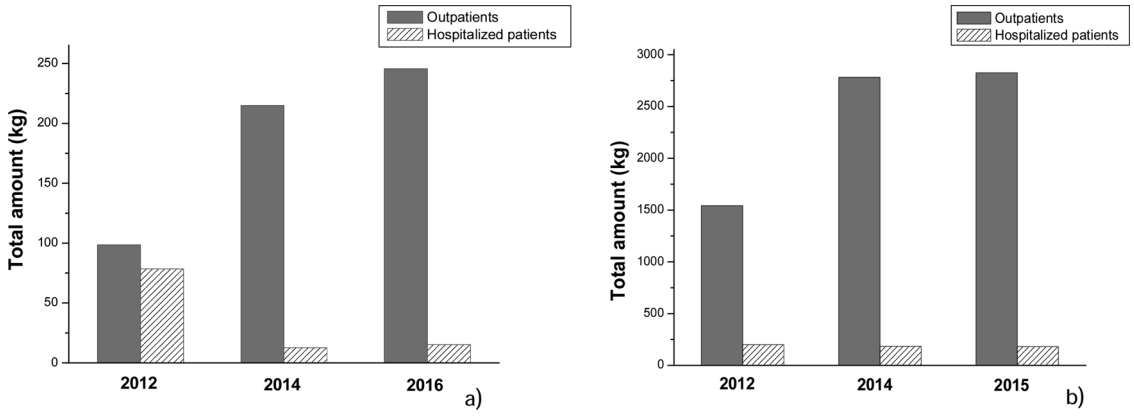

Fig. 2. Consumption of anticancer drugs by outpatients versus hospitalized patients in the Portuguese Oncology Institute of Lisbon (a) and Belgium (b).

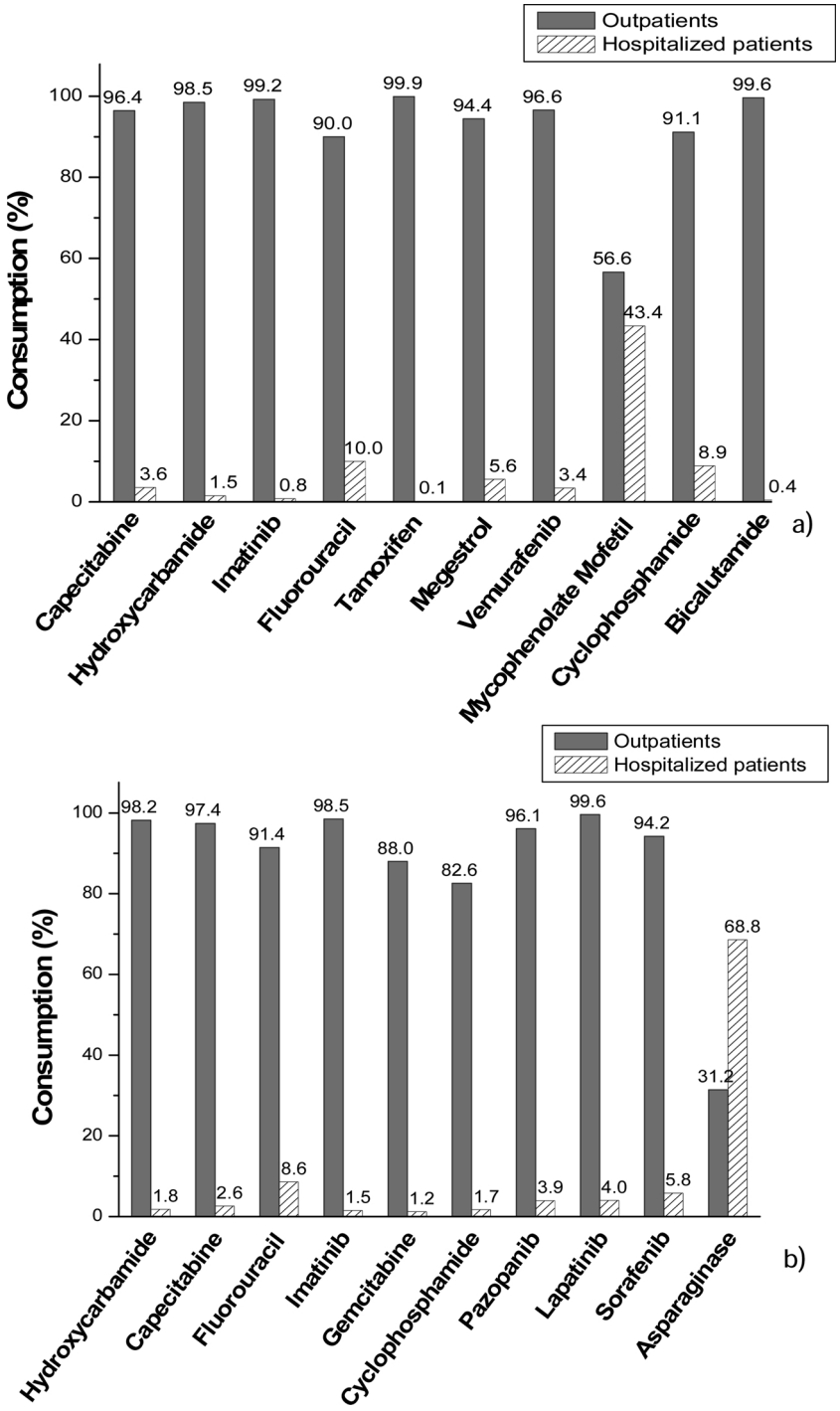

Fig. 3. Consumption of the top 10 anticancer drugs by outpatients versus hospitalized patients in the Portuguese Oncology Institute of Lisbon (a) and Belgium (b).

Consequently, a comparison of renal and faecal excretion of the target pharmaceuticals is an important step to define whether source separated urine is a good solution. Even though some anticancer drugs have low excretion fractions of the unchanged form, the excretion of their metabolites should also be considered since they can also exert negative effects in the aquatic organisms. The excretion fractions of anticancer drugs together with their metabolites in urine and faeces are presented in Table CI of Supporting Information (Section C).

First of all, it is important to note that 19.3 % of the target anticancer drugs do not present any data about their excretion fractions mainly because some of them were recently introduced to the market, which is the case of the monoclonal antibodies subgroup.

Considering the remaining anticancer drugs, it is possible to observe that similar percentages are found, 39.3 % of the drugs represented in Table CI have faecal excretions higher than urine excretions while 41.5 % of the drugs are excreted principally in the urine.

Fig. 4 represents the urine and faecal excretion fractions (considering both unchanged drug and metabolites) of the most consumed anticancer drugs by the hospitalized patients and by the outpatients in the Portuguese Oncology Institute of Lisbon and Belgium.

With regard to the most consumed anticancer drugs by hospitalized patients, it can be seen that 14 of the drugs have urine as major excretion route whereas 5 of the drugs have faeces as the main excretion route. While for the most consumed anticancer drugs by outpatients, it

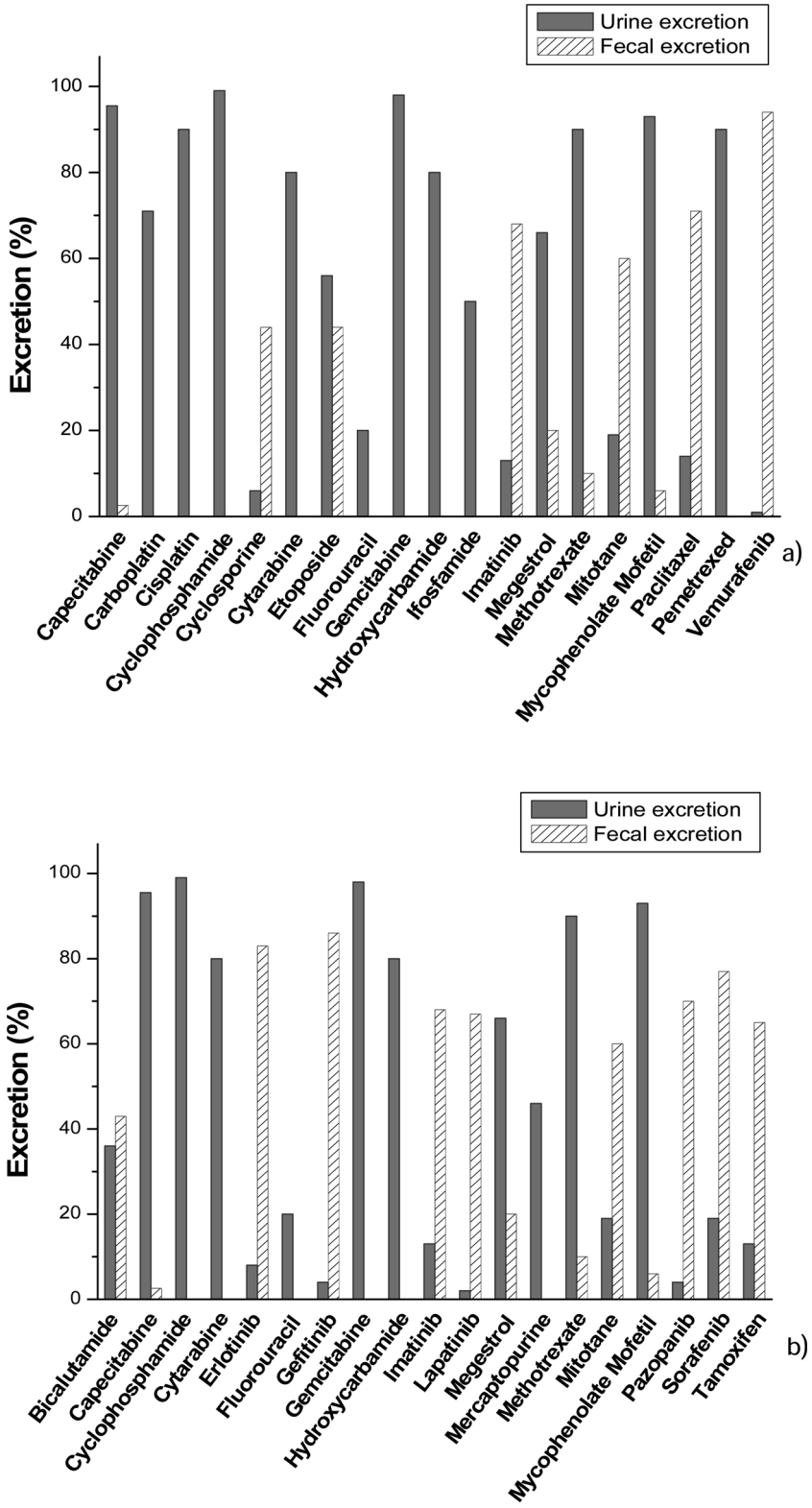

Fig. 4. Total urine versus fecal excretion considering both unchanged drug and metabolites for the most consumed anticancer drugs by the hospitalized patients (a) and outpatients (b).

can be observed that 10 of the drugs have urine as the main excretion route whereas 9 drugs are more excreted in faeces.

Although for some therapeutic groups of pharmaceuticals the effective separation and treatment of urine has been considered a promising approach to lower their load into the wastewater treatment facilities (Escher et al., 2006), in the case of anticancer drugs it can be observed that faecal excretion can also have a significant contribution and should not be neglected, therefore, the treatment of both should be considered.

3.5. What are the predicted environmental concentrations of anticancer drugs in the surface waters?

Prior to the implementation of a monitoring program, it is crucial to define what are the anticancer drugs that are more prone to be found in the aquatic environment as well as their predicted environmental concentrations. For this purpose, the consumption data of the Portuguese Oncology Institute of Lisbon, National Institute for Health and Disability Insurance and Sarvodaya cancer hospital were used to predict the environmental concentrations of anticancer drugs in the surface waters of each studied area.

For the determination of the predicted environmental concentration values, two important parameters were taken into account: the excretion fraction and the fraction of parent compound removed in the WWTP. Regarding the excretion fraction, many factors may influence this parameter and thus, different values can be found in the literature, which can lead to an inaccurate comparison of the PEC values determined by the different authors. In the same way, different removal fractions of anticancer drugs in conventional WWTP can be found in the literature. Table DI, DII and DIII of the Supporting Information display the PEC values determined for each anticancer drug for the three study areas as well as the excretion fractions as unchanged drug and the wastewater removal fractions assumed.

Fig. 5 represents the anticancer drugs with PEC values higher than 1 ng L^{-1} estimated based on the Portuguese Oncology Institute of Lisbon (a), Belgium (b) and Sarvodaya Multispeciality & Cancer Hospital (c) consumption data.

Considering the PEC values obtained using the Portuguese Oncology Institute of Lisbon consumption data, only hydroxycarbamide presents a value (16 ng L^{-1}) higher than the threshold value proposed by the European Medicine Agency (10 ng L^{-1}). Even though capecitabine, tamoxifen, mycophenolic acid, bicalutamide and imatinib present a PEC value lower than the threshold value, their PECs are above 1 ng L^{-1} that for most of the authors is a trigger concentration to perform risk analysis assessment studies.

Comparing these values with the ones reported by Santos et al. (2017), it can be observed that for some of the drugs the PEC values are highly underestimated if using only the consumption data of Portuguese Oncology Institute of Lisbon. According to Santos et al. (2017), mycophenolate mofetil is the anticancer drug that is more prone to be found in the environment, with an estimated concentration of 149 ng L^{-1}. However after its administration, this drug is rapidly and completely converted into mycophenolic acid, which is the active metabolite (Roche monograph database). Mycophenolic acid is then metabolized to the phenolic glucuronide of mycophenolic acid, which is the main form eliminated in urine (Roche monograph database). For this reason and also since the compounds excreted as glucuronides-conjugates may be deconjugated in the WWTPs, mycophenolic acid is the compound that is expected to be found in the aquatic environment.

The second and the third highest PEC in the Lisbon region reported by Santos et al. (2017) belongs to hydroxycarbamide and capecitabine, 92 ng L^{-1} and 16 ng L^{-1}, respectively. Moreover, the anti-androgen bicalutamide was expected to be at a concentration of 12 ng L^{-1}, which is also higher than the threshold value.

Overall in Belgium, among the 90 antineoplastic agents used in 2015, 19 drugs had a PEC value higher than 1 ng L^{-1} but only hydroxycarbamide and fluorouracil are expected to be above the threshold value. As represented in Table DII of the Supporting Information (Section D), the PEC value estimated for hydroxycarbamide (136 ng L^{-1}) is slightly higher than the values already reported for other European countries. For example, in Catalonia region (Spain) the PEC value determined was 32 ng L^{-1} (Franquet-Griell et al., 2015). This difference can partially be attributed to the use of quite different values for the parameter WWinhab as well as to the use of 25.92 as the dilution factor instead of the default value proposed by the European Medicine Agency. A major difference was noticed for the PEC value reported for UK, 0.5 ng L^{-1}, which can be explained by the fact that the authors used a removal of rate (95 %) much higher than the value used in our study (2%) (Booker et al., 2014).

As for fluorouracil (18 ng L^{-1}), in our study, it was assumed a WWTP removal rate of 2% instead of the 90 % obtained from a batch experiment with activated sludge and thus, this is the main reason that explains the differences with the PEC values reported for Portugal (0.6 ng L^{-1}) (Santos et al., 2017), France (0.8 ng L^{-1}) (Besse et al., 2012b) and UK (0.9 ng L^{-1}) (Booker et al., 2014). Also, as discussed in chapter 3.2 the consumption of fluorouracil was slightly higher in Belgium when compared to the other European countries.

The third highest PEC value was noticed for capecitabine (9 ng L^{-1}),

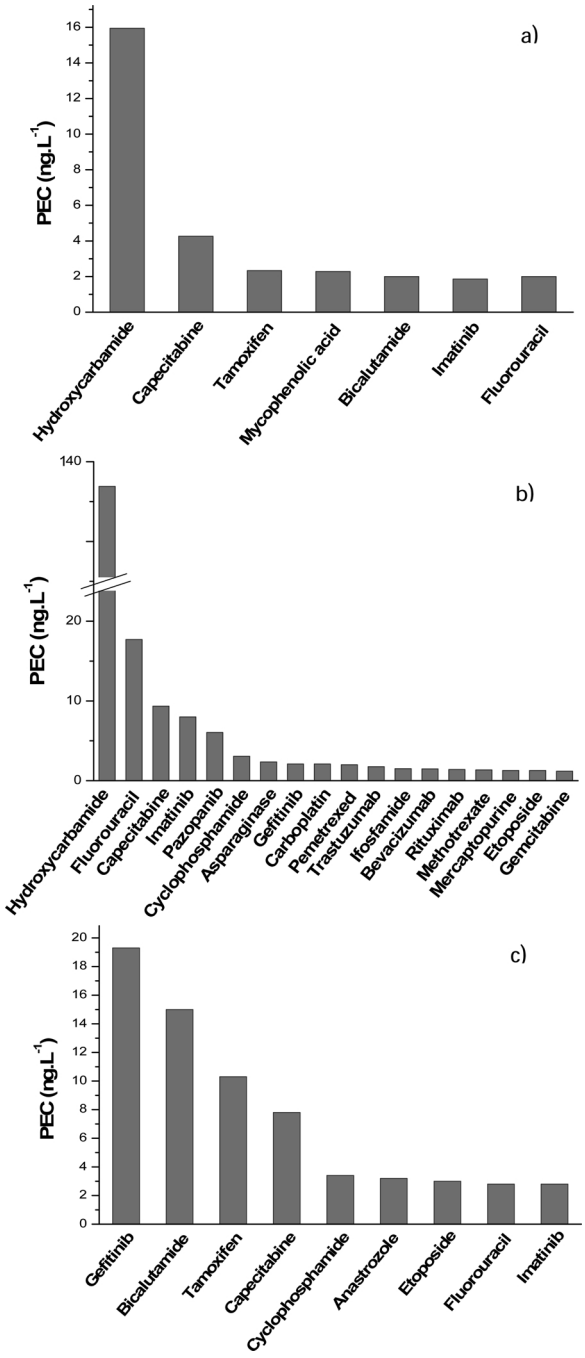

Fig. 5. Predicted environmental concentrations of the anticancer drugs with PEC values higher than 1 ng L^{-1} based on consumption data from the Portuguese Oncology Institute of Lisbon (a), Belgium (b) and Sarvodaya Multispeciality & Cancer Hospital (c).

which was highly close to the threshold value. This value was in the range of the values that have been reported for UK, France, Catalonia and Lisbon between 2 ng L^{-1} up to 16 ng L^{-1} (Booker et al., 2014; Franquet-Griell et al., 2015; Santos et al., 2017; Besse et al., 2012). The protein kinase inhibitor, imatinib, had a PEC value of 8 ng L^{-1}, which is in the same order of magnitude of the ones reported for Lisbon (6 ng L^{-1}) and France (5 ng L^{-1}). However, this value was slightly higher than the value estimated for UK (0.5 ng L^{-1}) since the latter considers only the consumption of anticancer drugs in hospitals. Pazopanib is also among the drugs with the highest PEC in Belgium (6 ng L^{-1}). This value is higher than in Catalonia (0.3 ng L^{-1}) and Lisbon (2 ng L^{-1}) due to its higher consumption rate in Belgium.

According to the Sarvodaya Cancer Hospital data, three anticancer drugs are expected to be in the environment at concentrations above the 10 ng L^{-1}. Gefitinib was found to be the anticancer with the highest PEC value (19 ng L^{-1}), followed by bicalutamide (15 ng L^{-1}) and tamoxifen (10 ng L^{-1}). Regarding gefitinib, much lower values have been reported in the literature (e.g. Lisbon and Catalonia regions) since the daily consumption is lower in those regions and also since in their study, it was considered only the excretion of gefitinib in urine (5%) whereas in our study, the excretion in faeces was also considered (85 %). Another noteworthy thing is that the predicted concentration of tamoxifen in other areas has been reported to be lower than 1 ng L^{-1} and this can be explained by the fact that in most studies a removal of 93 % has been assumed. This value was predicted by EPI suite (U.S. EPA, 2013), however, different studies have concluded that most of the tamoxifen remains unchanged through the WWTP (Ferrando-Climent et al., 2014). Following up, capecitabine, anastrozole, etoposide, cyclophosphamide, fluorouracil and imatinib were above 1 ng L^{-1}.

However, if these calculations are performed considering only the number of inhabitants of the Haryana state, much higher values of PEC are obtained as represented in Table DIII of the Supporting Information. In this scenario, 9 anticancer drugs (gefitinib, bicalutamide, tamoxifen, capecitabine, cyclophosphamide, anastrozole, etoposide, fluorouracil and imatinib) would have PEC values higher than the threshold value. For example, the PEC value of Gefitinib and Bicalutamide would be 92 and 72 ng L^{-1}, respectively.

Based on the predicted environmental concentrations estimated in this study as well as on the values reported for other areas of the world, it is extremely important to perform toxicity studies focusing not only on short term exposure but principally on long term exposures to these compounds. Furthermore, the exposure to mixtures of anticancer drugs should be evaluated since it is the reality of what we can find in the environment and can lead to synergy effects.

Furthermore, most anticancer drugs have limited biological degradability and thus, as represented in Section D of the Supporting Information, the conventional WWTPs are expected to be poorly effective on removing these drugs. Hence, the development of an effective treatment option as an alternative to these conventional methods is crucial to avoid the release of these drugs into the aquatic environment.

Different removal methods have been reported in the literature (e.g. activated carbon, ozonation, UVs and membrane filtration). One possible treatment approach could be the use of nanofiltration membranes, which have already been widely tested for the removal of a multitude of organic micropollutants from different matrices.

Yangali-Quintanilla et al. (2010) developed a QSAR model with the aim of predicting the rejection of organic compounds by a nanofiltration membrane. In this present study, membrane filtration rejections were predicted using this QSAR model for the anticancer drugs with the highest PEC values estimated and the results are disclosed in the Section E of the Supporting Information. Based on the predicted rejections, nanofiltration could be an alternative solution for the removal of anticancer drugs. The validity of these predictions were already proved at laboratory scale (Cristóvão et al., 2019) and should be evaluated in future pilot scale studies. However, if nanofiltration is used to treat these compounds, retentate treatment should be considered.

4. Conclusions

In our study, the consumption pattern of anticancer drugs in Lisbon (Portugal), Belgium and Haryana state (India) was evaluated.

Similar to other studies, the consumption data presented in this study shows that there was a significant increase of anticancer drugs consumption and release to the environment during the last years, which is expected to endure in the following years due to the expected drastically increase of cancer patients. Of the ten most consumed anticancer drugs, four (capecitabine, imatinib, fluorouracil and cyclophosphamide) were found to be highly consumed in the three different regions.

Anticancer drugs have a highly potent mechanism of action and consequently, it is extremely important to keep surveying their presence in the aquatic environment and to develop effective treatment options in order to avoid their release into the environment.

The predicted environmental concentrations determined will help prioritize the compounds that should be monitored in future occurrence studies in Portugal, Belgium and India. Although for some therapeutic groups of pharmaceuticals the effective separation and treatment of urine has been proposed, in the case of anticancer drugs, faecal excretion was also found to have a significant contribution and should therefore not be neglected.

According to the Lisbon and Belgium consumption data, 94 % of the total amount of anticancer drugs were delivered to patients in the ambulatory regime. Hence, based on these findings and discussing only the particular case of anticancer drugs, it can be concluded that hospital effluent treatment on-site may not be a sufficient solution since household effluents are the primary input source of these drugs into the aquatic system.

For this reason, upgrading the treatment in the WWTP is highly recommended due to the fact that most anticancer drugs have limited biological degradability and consequently, the conventional methods that are currently used in the WWTP are not enough for the removal of these drugs.

CRediT authorship contribution statement

M.B. Cristóvão: Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization. **R. Janssens:** Resources, Data curation, Writing - review & editing. **A. Yadav:** Resources, Data curation, Writing - review & editing. **S. Pandey:** Resources, Data curation, Writing - review & editing. **P. Luis:** Resources, Data curation, Writing - review & editing. **B. Van der Bruggen:** Resources, Data curation, Writing - review & editing. **K.K. Dubey:** Resources, Data curation, Writing - review & editing. **M.K. Mandal:** Resources, Data curation, Writing - review & editing. **J.G. Crespo:** Resources, Data curation, Writing - review & editing, Project administration. **V.J. Pereira:** Conceptualization, Resources, Data curation, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.122330.

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