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Predicted concentrations of antineoplastic drugs in the aquatic environment: The case of Ría de Vigo (NW, Spain)

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ABSTRACT

The European Medicines Agency (EMA) mandates Environmental Risk Assessments (ERAs) since 2006 to determine potential risks of new marketed medicines. Drugs with a Predicted Environmental Concentration (PEC) in inland surface waters exceeding 0.01 μg L^{-1} require further environmental risk assessment. PEC may be refined based on prevalence data and/or based on the treatment regimen. In this study, based on EMA regulations, refined PEC of 108 antineoplastic drugs in coastal waters were determined based on the consumption in a coastal health area during 2021, identifying six drugs with potential environmental risk in surface waters (hydroxyurea, capecitabine, abiraterone, ibrutinib, imatinib and 5-fluorouracil) and two in marine ecosystem (hydroxyurea and capecitabine). Comparison of these refined PECs with data from marketing laboratories revealed significant disparities, suggesting the need for regular updates, especially with changes in drug indications or financing. Notably, the identified drugs are not yet on the main reference lists of emerging contaminants.

1. Introduction

In the last decades, due to the progressive improvement of analytical techniques, numerous pharmaceuticals have been detected in various compartments of the water cycle, including drinking water (World Health Organization, 2012). Many of these compounds can have toxic effects on aquatic organisms at very low concentrations (Küster and Adler, 2014; Gunnarsson et al., 2008; Hutchinson et al., 2014) and even present synergistic toxic effects when several of these compounds are combined (Elersek et al., 2016). In addition, many medicines have not yet been fully assessed in terms of their ecotoxicological risk due to the lack of large and standardized studies, because many drugs have only been evaluated in a limited number of organisms (Corcoran et al., 2010; Gunnarsson et al., 2019). Abiotic factors, such as temperature, can affect the bioaccumulation of these substances (Cerveny et al., 2021), making the assessment of the effects of pharmaceuticals on the environment even more complex. Potentially chronic exposure to these substances, in combination with variability in wastewater management and policies in different countries, show that the impact of medicines as emerging pollutants is underestimated (Ebele et al., 2017; Nassour et al., 2020).

Life expectancy is increasing and consequently, the future will be characterized by an aging society with more chronic diseases. In the case of the European Union (EU-27), the number of people aged 65 and over is projected to increase from 90.5 million in 2019 (20.03 % of the population) to 129.8 million in 2050 (29.4 % of the total population) (EUROSTAT, 2020). As a result, the consumption of medicines is constantly increasing and is expected to reach a 2023–2027 spending growth of ~30 % and ~45 % in the Western and Eastern European markets, respectively (IQVIA, 2023). Antineoplastic drugs represent a good example of this situation, as it has been estimated that the number of cancer patients will reach around 30 million worldwide by 2040 (Bray et al., 2018). Due to the development of new molecular and genetic targets, the oncology field is expected to add numerous treatments in the very near term (Jaffee et al., 2017), with global spending of more than $370 billion by 2027 (IQVIA, 2023). This situation opens the door to potential new ecotoxicological mechanisms that go further than endocrine disruption or the creation of antimicrobial resistance (Heath et al., 2016). In the case of antineoplastics, the concentrations detected may

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cause chronic toxicity in aquatic organisms by impacting their genetic material, which may have a significant environmental impact (Jureczko and Kalka, 2020; Negreira et al., 2014).

In 2004, a US federal agency, the National Institute for Occupational Safety and Health (NIOSH), considered drugs to be "hazardous" when they induce carcinogenic, teratogenic, reproductive or genotoxic effects on organisms. Most antineoplastics drugs are part of groups 1 and 2 of the list compiled by NIOSH, providing recommendations for the transport, cleaning of surfaces, and disposal of waste related to these types of drugs (NIOSH, 2016). This has made it necessary to develop special protective measures for their handling and administration (Valero-García et al., 2021).

Due to the potential impact of pharmaceuticals and their metabolites on the environment, health regulatory agencies in developed countries have been incorporating environmental risk assessment (ERA) regulations that the pharmaceutical industry must carry out as a prerequisite for the marketing and use of medicines. However, there is no uniformity in the recommendations and limits established in the different territories (Lee and Choi, 2019). In the UE, the ERA obligation for human and veterinary medicinal products was adopted with EC Directives 2004/27/EC and 2004/28/EC. Since 2006, the European Medicines Agency (EMA) has set the guidelines for the implementation of an ERA, which is mandatory for all medicinal products for human use except amino acids, peptides and proteins, although the outcome of this assessment does not condition the approval or refusal of authorisation for use in clinical practice. An ERA refers to the acute toxic risk occurring in the aquatic environment. This risk is calculated as the ratio of the predicted environmental concentration (PEC) to the highest predicted no-effect concentration (PNEC). In the first step, the PEC is estimated based on the fraction of the overall market penetration of the drug based on the number of candidate patients. For drugs with a PEC higher than 0.01 μg L^{-1} or high lipophilicity (logKow $\geq$4.5), studies on potential effects on aquatic organisms must be carried out. The results are published through European Public Assessment Reports (EPARs), but the reported estimates vary depending on the drug and the pharmaceutical laboratory conducting the study (Oelkers, 2020).

Nassour et al. (2020) conducted a systematic review of 75 studies that demonstrated the presence of anticancer drugs in different water resources that failed to be eliminated by conventional wastewater treatment plants. The study concluded that the most abundant anticancer drugs were cyclophosphamide, tamoxifen, ifosfamide and methotrexate, with concentrations above 0.01 ng/L. However, the significant heterogeneity within methodologies made it difficult to compare results and draw conclusions. In a similar way, Domingo-Echaburu et al. (2022) analyzed the published evidence on the presence in the environment of the hazardous drugs (NIOSH group 1) and their possible environmental impact. Of the 90 drugs considered, there was evidence of presence in the environment for 19. Drugs with more studies reporting positive detections were: the antibiotic chloramphenicol, the alkylating agents cyclophosphamide and ifosfamide, and the estrogen receptor modulator tamoxifen.

Most of these studies focused on detecting a specific drug in the environment, following the trends of previous studies or under the assumption that the selected drug is, in fact, one of the most consumed drugs. However, studies focused on the detection based on actual drug consumption are scarce. Kümmerer et al. (2016) published an article that includes 102 cytostatics, which were consumed in 2012 throughout Germany, and computed their PEC. More recently, Dominguez-García et al. (2022) computed the PEC of 132 cytostatic drugs in Catalonia (Spain), based on the consumption during the period 2013–2017.

This study presents an evaluation, from an environmental perspective, of the set of antineoplastic drugs administered in a densely populated coastal area (Ría de Vigo, NW Spain). With this objective, based on consumption during a complete year (2021), the predicted environmental concentration based on real consumption (PECc) was calculated, which allows comparison with the PEC previously published by industry as a prerequisite to market the product (PECt). In this study, the refinement process took into account the fact that wastewater in this region has the marine environment as its final receiver, serving as an example for future studies on cytostatic consumption in coastal areas. The results are discussed within the environmental regulatory framework for both surface inland and marine waters. The results shown in this study may be helpful for the reclassification of pharmaceuticals on priority lists of substances to be monitored in the environment, and thus help to shape environmental policies and future environmental monitoring programmes.

2. Material and methods

2.1. Study area

This study compiles the consumption of anticancer drugs prescribed and administered during 2021 in the Vigo Health Area, with a reference population of 565,764 inhabitants. Although the population of the sanitary area is mainly concentrated in the city of Vigo, population settlements are dispersed on both sides of an estuary (Ría de Vigo, NW Spain) (Fig. 1).

The "rías" define a coastal typology characterized by an ancient fluvial valley flooded by seawater. In the case of the Ría de Vigo, the Verdugo and Oitavén rivers are the main tributaries in the inner part of the estuary. As we move away from the mouth of the rivers, the estuary widens and deepens, until it reaches the outermost part separated from the adjacent ocean by an archipelago of small islands that constitute the natural area Atlantic Island National Park. From an oceanographic point of view, the ría is a highly productive ecosystem, allowing the development of an important fishing and shellfishing activity, as well as intense mussel aquaculture. This high biomass production capacity is related to its geographical location at the northern limit of the Canarian upwelling ecosystem (Arístegui et al., 2009; Barton, 1998). During prevailing upwelling events (northerly winds), cooler subsurface water (150–200 m) invades the continental shelf and can penetrate the estuary, promoting rapid water renewal (Álvarez-Salgado et al., 2000; Barton et al., 2015). This phenomenon leads to nutrient fertilisation causing the appearance of important phytoplankton blooms, the basis of the food web and the maintenance of important ecosystem resources (Fig. 1).

2.2. PEC calculation

The list of drugs included are those for hospital use or dispensation of the Anatomical Therapeutic Chemical (ATC) Group L "Antineoplastic and immunomodulating agents" ("L01: Antineoplastic Agents, L02: Endocrine Therapy and L04: Immunosuppressants") (World Health Organization, 2022). Monoclonal antibodies such as pembrolizumab and trastuzumab were excluded because they are metabolized and eliminated at the level of the endothelial reticulum system. Therefore, and following the 2018 update of the environmental risk regulations, these molecules are exempted from carrying out environmental risk assessments (EMA, 2018).

For each of the drugs, a bibliographic search was performed on the PEC declared by the industry, which we refer to in this study as the theoretical PEC (PECt). The calculation of this PECt is based on the formula used by the European Medicines Agency (2006) for the estimation of exposure in surface waters:

$$\mathrm{PECt} = (\mathrm{DOSEai}^{*}\ \mathrm{Fpen})/(\mathrm{WASTEWinhab}^{*}\ \mathrm{DF})$$

where *DOSEai* is the maximum daily dose consumed per inhabitant, *Fpen* is the fraction of market penetration, *WASTEWinhab* is the amount of wastewater per inhabitant per day (default value of 200 L day^{-1}) and *DF* is the dilution factor which in inland surface waters defaults to 10 (European Chemicals Bureau, 2003). In this formula, the estimated market penetration relies on the number of inhabitants (population) of

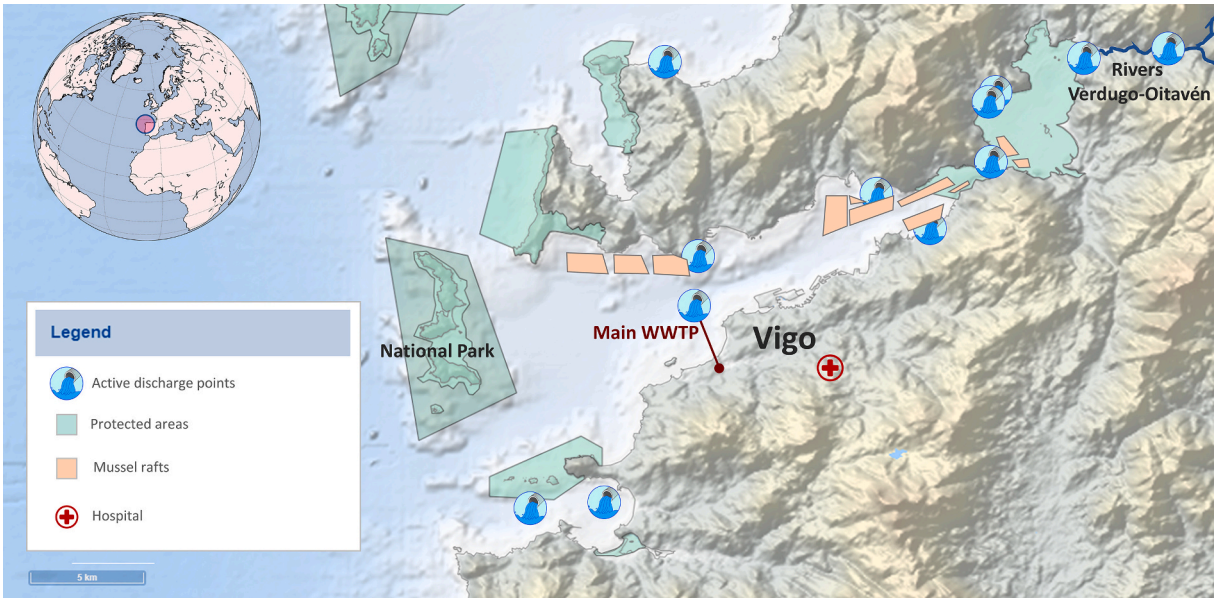

Fig. 1. Aquaculture polygons and environmentally protected areas (National Park and Red Natura 2000) in the Ría de Vigo (Northwest Iberian Peninsula; Spain). Discharge points from active WWTPs are also shown. Adapted from the EMODnet Human Activities portal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the country or geographic area where the product is going to be marketed. The resulting concentration is expressed in μg L^{-1}. If the PECt is below 0.01 μg L^{-1}, and no other environmental concerns are apparent, it is assumed that the medicinal product is unlikely to represent a risk to the environment following its prescribed usage in patients (European Medicines Agency, 2006). Under this estimation, there are many assumptions: the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry of the drug substance into the surface water, there is no biodegradation or retention of the drug in the wastewater treatment plant (WWTP), and metabolism in the patient is not considered.

2.3. Model refinement

The previous estimation includes all release sources in a large area. However, a local estimation can be performed in the vicinity of a representative source of the release to the environment. This implies a more accurate knowledge of the relationship between the local release routes and the subsequent distribution processes. With this in mind, the previous formula was adapted to account for the real consumption data in the Vigo Health Area (Fig. 1). In the Vigo estuary, the sewage network means that a large part of the wastewater goes directly to the WWTPs and from there is discharged into the marine environment. However, since most studies take into account the discharge into surface inland waters, we have also decided to include a similar estimate so that it can be compared with other studies. Therefore, different degrees of refinement were applied to facilitate this comparison. Thus, in addition to the standard water consumption, a daily water consumption per inhabitant of 130 L in the region (Galicia) was also used, according to the report on national statistics (Instituto Nacional de Estadística, 2022). Moreover, a dilution factor of 25.92 was employed to account for mean riverine regimes in Spain (Keller et al., 2014), which facilitates the comparison with other published studies in this country (e.g., Dominguez-García et al., 2022; Franquet-Griell et al., 2016).

As mentioned above, wastewater is released, after WWTP processing, into the Ría de Vigo through a network of submarine pipes. For this reason, a standard dilution factor in the marine environment of 100 was also considered (European Chemicals Agency, 2016). To account for a more refined estimation, WWTP influx rates were obtained from Augas de Galicia (https://augasdegalicia.xunta.gal/), and several oceanographic scenarios were considered (see discussion for further details).

Antineoplastic drugs are primarily excreted via urine and feces. Whereas a fraction of the drug is excreted unmetabolized (Fexc), other fractions are excreted in the form of inactive metabolites with no physiological effects and therefore of no environmental concern. Fexc varies in a wide range among substances depending on several factors, like patient age, health and co-medication. The excretion data correspond to published data in the EPAR. For those compounds whose values were not found, a default value of 0.5 was applied. No removal from WWTPs were considered in this study.

2.4. Risk Quotient (RQ) and Predicted No Effect Concentration (PNEC).

The Risk Quotient (RQ) expresses the risk of a chemical to the environment or organisms. It is calculated using our result of the predicted effect concentration (PECc) and the predicted no effect concentration (PNEC). The RQ has been determined according to the equation (Dominguez-García et al., 2022):

$$RQ = PECc/PNEC = PECc/(EC50 \text{ or } LC50/f)$$

The PNEC is estimated from the toxicological EC50 or LC50 values and a safety factor (f), which is used to adapt the formula to chronic toxicity (PNEC only refers to acute toxicity). These EC50 and LC50 values can be derived through computer modelling. In this study, Ecological Structure Activity Relationships software (ECOSAR) v2.2 was utilized for this purpose. The ECOSAR tool is freely accessible on the website: https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model (accessed 3.1.24).

3. Results and discussion

3.1. Results

During 2021, patients in the Vigo Healthcare Area consumed 108 different anticancer drugs included in ATC Groups L01, L02 and L04. Most of these drugs are classified in the NIOSH Group 1 and 2 list as “hazardous drugs” (NIOSH, 2016). ~236 kg of anticancer substances

with annual consumption ranging from 80,364 g of hydroxyurea to 0.022 g of trabectedin. Only 57 of these drugs have the PECt published in their corresponding Public Assessment Report, with 27 of them having a PECt >0.01 μg L^{-1} (Table 1).

Fig. 2 shows the comparison between PECt and PECc with different levels of refinement for the most consumed drugs; in the case of 5-fluorouracil there was no PECt at the time of market release. The first level of refinement was obtained by considering standard values for water consumption and for the dilution factor in inland surface water (EMA, 2006). Using these criteria, 6 drugs exceed the threshold value of 0.01 μg L^{-1}: hydroxyurea, capecitabine, abiraterone, ibrutinib, imatinib and 5-fluorouracil. When using the average water consumption in the region (130 L day^{-1} $inhabitant^{-1}$), alectinib and olaparib were added to this list. Abiraterone and imatinib had a PECt much higher than our local estimate (Abiraterone PECt 5 μg L^{-1}, PECc 0.03 μg L^{-1}; Imatinib PECt 4.2 μg L^{-1}, PECc 0.027 μg L^{-1}).

A higher degree of refinement is possible if the dilution factor is calculated according to the average river regime in Spain (25.92) (Keller et al., 2014). By doing so, alectinib and olaparib left the list of drugs for which further environmental risk assessment would be necessary. For the previous set of drugs, the excreted unchanged fraction of the active substance (Table 1) ranged from the low metabolization of alectinib (Fexc: 0.84) to the high metabolization of ibrutinib (Fexc: 0.01). When these values were taken into account in the estimation of the PECc, only hydroxyurea and abiraterone exceeded the threshold value (Fig. 2).

Finally, after considering the standard dilution factor to the marine environment (100), the list of antineoplastics with PECc >0.01 μg L^{-1} was reduced to hydroxyurea and capecitabine. With the annual intakes of these substances, a dilution factor higher than 300 and 264 respectively is necessary for these drugs not to be considered for subsequent environmental risk studies. The dilution factors were reduced to 264 and 8 respectively if the fractions excreted after metabolization were considered.

These PECc data can be complemented with values obtained from the QSAR model and the calculation of the Risk Quotient (RQ). In the supplementary material (Table S1) these values are available for the eight drugs with the highest PECc.

3.2. Discussion

3.2.1. PECc in inland surface waters

The most common way of estimating the PEC considers discharge to inland waters, with a standard dilution factor and water consumption, as well as the absence of metabolization and retention by WWTP. Under these criteria, our results show 6 cytostatics exceeding the threshold value: hydroxyurea, capecitabine, abiraterone, imatinib, ibrutinib, and 5-fluorouracil. However, water consumption per capita in the region is lower than this standard value, leading to a higher expected environmental concentration of alectinib and olaparib. The most important factor that may vary this classification is the degree of metabolization of the excreted drug. Capecitabine is an example of a highly metabolized and highly excreted drug, which means that it does not exceed the threshold for further environmental risk assessment.

Many drugs, once metabolized in the human body, produce metabolites that also exhibit physiological activity. Consequently, when released into the environment, these metabolites may pose potential environmental risks. For instance, among the most consumed drugs in this study, it is known that capecitabine, imatinib, or alectinib have metabolites with equal or even greater activity than the original compound (CIMA, AEMPS, n.d.). However, due to uncertainties regarding the exact proportion of active metabolites generated and excreted in the human body for many of these drugs, as well as the possibility of formation of these metabolites in the environment through biodegradation or chemical degradation processes, this factor has not been taken into account in this study. Instead, only the original drug consumed has been considered, which represents a limitation in interpreting the final PECs results.

Moreover, this research did not consider the degradation and retention of drugs in WWTPs. Given the variable metabolic stability of drugs, some compounds may be more susceptible to biodegradation than others. The lack of information on all metabolites formed in WWTPs raises concerns about the potential formation of toxic subproducts, which would present risks to the marine environment. The current lack of information highlights the need for further studies to make the determination of the first stage of ERA more accurate.

Despite the above-mentioned limitations, the calculation of PECc in surface water allows comparison with similar studies in other regions. This is the case of the analysis based on consumption data for the period 2013–2017 in Catalonia (Dominguez-García et al., 2022). These authors observed that hydroxyurea, capecitabine, imatinib, imatinib, abiraterone, pazopanib, paclitaxel, nilotinib, rituximab, trastuzumab, pemetrexed, mercaptopurine and ifosfamide are the antineoplastics that exceed the threshold of 0.01 μg L^{-1} in wastewater and rivers. Our study matches four of them (hydroxyurea, capecitabine, imatinib and abiraterone) and shows that ibrutinib, alectinib and olaparib are substances with potential environmental risk (Fig. 2). The latter three drugs were more recently marketed and with increasing consumption given their indications in hematological malignancies, and lung and ovarian cancer.

An 8-year study in Portugal were conducted (Santos et al., 2017) focusing on cytostatic drug consumption, where they identified 11 drugs exceeding established limits for PEC, potentially posing environmental risks (mycophenolate mofetil, mycophenolic acid, hydroxyurea, capecitabine, bicalutamide, megestrol, cyproterone, cyclophosphamide, flutamide, ifosfamide, and imatinib). Three of them, hydroxyurea, capecitabine and imatinib, were also among the drugs with the highest risk in our study.

Our results show capecitabine as one of the cytostatics with the highest consumption and predicted environmental concentration. The presence of this drug in wastewater and surface water has already been detected almost a decade ago in Spain (Ferrando-Climent et al., 2014; Negreira et al., 2014). Other cytostatics such as cyclophosphamide and methotrexate detected in these studies do not have a high consumption in our region, at least not to the extent that their PECc exceeds the threshold value. The inter-annual variation in the pattern of consumption and the scarcity of water monitoring studies make it difficult to draw conclusions about the presence of these substances in the aquatic environment.

In 2017, Franquet-Griell et al. (2017) conducted a study assessing the concentration of 19 antineoplastic drugs in a Catalan river (Spain). Among the drugs examined, 7 compounds were detected at concentrations ranging from 0.0005 μg L^{-1} to 0.656 μg L^{-1}: mycophenolic acid, tamoxifen, ifosfamide, cyclophosphamide, megestrol, chlorambucil, and erlotinib. None of these drugs are classified among those posing the highest risk in our study.

Regarding studies conducted on other continents, Azuma et al. (2015) conducted a study in 2015 in Japan aiming to detect 6 antineoplastic drugs (bicalutamide, capecitabine, cyclophosphamide, doxifluridine, tamoxifen and tegafur) in rivers and effluents from WWTPs. Concerning the two drugs also included in this study, capecitabine was found in 88 % of measurements in the main stream of rivers and in 100 % of WWTP effluents, with average concentrations of 0.003 μg L^{-1} and 0.006 μg L^{-1}, respectively. Meanwhile, although cyclophosphamide does not represent one of the drugs with the highest environmental risk in this study, it was detected in 63 % of measurements in rivers and in 90 % of WWTP effluents, with average concentrations of 0.003 μg L^{-1} and 0.011 μg L^{-1}, respectively.

Some of the drugs reported in the previous studies were not included in our analysis because they are not commonly used or dispensed in a hospital setting.

These results also demonstrate that those newer drugs such as imatinib and ibrutinib, both tyrosine kinase inhibitors, are gaining market share over older drugs such as epirubicin, etoposide, gemcitabine,

Table 1
Consumed Anatomical Therapeutic Chemical (ATC) Group L medicines in 2021. Predicted Environmental Concentrations (PEC) in different situations. LogKow: logarithm of the octanol–water partition coefficient. PECt: PEC published by the pharmaceutical company. DF: Dilution factor. (10: Standard value for inland surface water; 25.92: Value for inland surface water adapted to the environment of Vigo; 100: Standard value for marine water). WW: water consumption in L day-1 per inhabitant (200 L day^{-1} $inhabitant^{-1}$: Standard value in European regulations; 130 L day^{-1} $inhabitant^{-1}$: Daily water consumption per inhabitant in the region).

Drug	logKow	PECt ($\mu g\ L^{-1}$)	Drug use (g)	PEC VIGO DF 10 WW 200	PEC VIGO DF 10 WW 130	PEC VIGO DF 25.92 WW 130	PEC VIGO DF 100 WW 130
Hydroxyurea	1.27	0.21	80,364	0.1946	0.2994	0.1155	0.0299
Capecitabine	0.56	0.081	71,103.15	0.1722	0.2649	0.1022	0.0265
Abiraterone	5.12	5	14,060	0.0340	0.0524	0.0202	0.0052
Ibrutinib	4	0.012	11,478.46	0.0278	0.0428	0.0165	0.0043
Imatinib	2.24	4.2	11,218.7	0.0272	0.0418	0.0161	0.0042
Fluorouracil	−0.89	no data	7830	0.0190	0.0292	0.0113	0.0029
Alectinib	3.8	0.00025	3659.55	0.0089	0.0136	0.0053	0.0014
Olaparib	1.55	0.0014	2686.6	0.0065	0.0100	0.0039	0.0010
Nilotinib	5.01	0.028	2609.2	0.0063	0.0097	0.0037	0.0010
Nintedanib	3.3	2.5	2488.45	0.0060	0.0093	0.0036	0.0009
Sorafenib	3.7	0.0376	2412.4	0.0058	0.0090	0.0035	0.0009
Abemaciclib	3.6	2	2309.65	0.0056	0.0086	0.0033	0.0009
Mitotane	6	no data	2134.5	0.0052	0.0080	0.0031	0.0008
Pazopanib	3.2	0.4	1967	0.0048	0.0073	0.0028	0.0007
Ribociclib	0.6	3	1758.6	0.0043	0.0066	0.0025	0.0007
Cyclophosphamide	0.8	no data	1575.6	0.0038	0.0059	0.0023	0.0006
Gemcitabine	−1.4	no data	1550	0.0038	0.0058	0.0022	0.0006
Venetoclax	5.91	2	1484.01	0.0036	0.0055	0.0021	0.0006
Enzalutamide	3	0.08	1327.36	0.0032	0.0049	0.0019	0.0005
Dasatinib	3.56	1.8	751.45	0.0018	0.0028	0.0011	0.0003
Cytarabine	−2.8	no data	732.1	0.0018	0.0027	0.0011	0.0003
Osimertinib	2.69	0.0033	688.48	0.0017	0.0026	0.0010	0.0003
Ifosfamide	0.86	no data	651	0.0016	0.0024	0.0009	0.0002
Lapatinib	5.29	no data	642.5	0.0016	0.0024	0.0009	0.0002
Palbociclib	1.1	>0.1	589.62	0.0014	0.0022	0.0008	0.0002
Dabrafenib	3.3	1.5	487.47	0.0012	0.0018	0.0007	0.0002
Carboplatin	0.14	no data	437.85	0.0011	0.0016	0.0006	0.0002
Paclitaxel	3	0.0015	433.2	0.0010	0.0016	0.0006	0.0002
Crizotinib	3.88	no data	407.5	0.0010	0.0015	0.0006	0.0002
Vemurafenib	4.74	3.61	394.56	0.0010	0.0015	0.0006	0.0001
Pemetrexed	−1.5	no data	352.5	0.0009	0.0013	0.0005	0.0001
Bosutinib	3.56	1.8	351.3	0.0009	0.0013	0.0005	0.0001
Temozolomide	1.32	no data	322.14	0.0008	0.0012	0.0005	0.0001
Niraparib	no data	no data	301.4	0.0007	0.0011	0.0004	0.0001
Methotrexate	−1.85	<0.01	288.9	0.0007	0.0011	0.0004	0.0001
Lenalidomide	0.4	0.007	271.85	0.0007	0.0010	0.0004	0.0001
Irinotecan	3.2	0.00064	252	0.0006	0.0009	0.0004	0.0001
Ruxolitinib	1.47	0.008	250.82	0.0006	0.0009	0.0004	0.0001
Erlotinib	3.57	0.003	245.05	0.0006	0.0009	0.0004	0.0001
Bexarotene	7.99	no data	226.95	0.0005	0.0008	0.0003	0.0001
Rucaparib	0.71	0.013	219	0.0005	0.0008	0.0003	0.0001
Etoposide	0.6	no data	212.5	0.0005	0.0008	0.0003	0.0001
Oxaliplatin	−0.47	no data	192.2	0.0005	0.0007	0.0003	0.0001
Dacarbazine	−0.24	no data	170	0.0004	0.0006	0.0002	0.0001
Azacitidine	−3.5	0.00035	157	0.0004	0.0006	0.0002	0.0001
Vismodegib	2.7	no data	138.6	0.0003	0.0005	0.0002	0.0001
Cabozantinib	5.15	0.3	119.24	0.0003	0.0004	0.0002	< 0.0001
Apalutamide	2.9	1.2	118.32	0.0003	0.0004	0.0002	< 0.0001
Tucatinib	3.94	0.74	110	0.0003	0.0004	0.0002	< 0.0001
Trifluridine	no data	no data	108.01	0.0003	0.0004	0.0002	< 0.0001
Capmatinib	no data	no data	96	0.0002	0.0004	0.0001	< 0.0001
Mercaptopurine	0.71	0.00116	93.75	0.0002	0.0003	0.0001	< 0.0001
Cisplatin	−2.19	no data	92.6	0.0002	0.0003	0.0001	< 0.0001
Doxorubicin	1.27	no data	91.08	0.0002	0.0003	0.0001	< 0.0001
Regorafenib	3.9	0.6	85.64	0.0002	0.0003	0.0001	< 0.0001
Everolimus	4	no data	83.3	0.0002	0.0003	0.0001	< 0.0001
Gefitinib	no data	no data	75	0.0002	0.0003	0.0001	< 0.0001
Lorlatinib	2.45	0.005	65.25	0.0002	0.0002	0.0001	< 0.0001
Brigatinib	1.62	0.0036	57.6	0.0001	0.0002	0.0001	< 0.0001
Afatinib	3.8	0.25	54.99	0.0001	0.0002	0.0001	< 0.0001
Ripretinib	no data	0.0098	54	0.0001	0.0002	0.0001	< 0.0001
Sunitinib	5.2	no data	52.49	0.0001	0.0002	0.0001	< 0.0001
Procarbazine	0.06	no data	49.85	0.0001	0.0002	0.0001	< 0.0001
Docetaxel	2.4	44.2E-05	43.6	0.0001	0.0002	0.0001	< 0.0001
Vinorelbine	4	no data	35.84	0.0001	0.0001	0.0001	< 0.0001
Encorafenib	2.6	0.016	33.6	0.0001	0.0001	< 0.0001	< 0.0001
Lenvatinib	3.3	0.0012	31.22	0.0001	0.0001	< 0.0001	< 0.0001
Tretinoin	no data	no data	29.28	0.0001	0.0001	< 0.0001	< 0.0001
Bendamustine	1.8	no data	27.67	0.0001	0.0001	< 0.0001	< 0.0001
Selumetinib	no data	no data	21.6	0.0001	0.0001	< 0.0001	< 0.0001

(*continued on next page*)

Table 1 (*continued*)

Drug	logKow	PECt (μg L^{-1})	Drug use (g)	PEC VIGO DF 10 WW 200	PEC VIGO DF 10 WW 130	PEC VIGO DF 25.92 WW 130	PEC VIGO DF 100 WW 130
Carfilzomib	4.6	0.0049	19.56	< 0.0001	0.0001	< 0.0001	< 0.0001
Melphalan	−0.52	>0.01	16.38	< 0.0001	0.0001	< 0.0001	< 0.0001
Busulfan	−0.52	1.20E-06	16.23	< 0.0001	0.0001	< 0.0001	< 0.0001
Decitabine	−0.32	5.80E-05	15.2	< 0.0001	0.0001	< 0.0001	< 0.0001
Selpercatinib	3.45	0.0099	14.4	< 0.0001	0.0001	< 0.0001	< 0.0001
Thioguanine	0.07	no data	12.96	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Mitomycin	−0.4	no data	12.04	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Pomalidomide	0.58	0.0003	10.57	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Axitinib	2	0.1	9.72	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Thiotepa	0.53	<0.01	9.2	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Estramustine	5.7	no data	8.4	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Carmustine	1.53	0.0057	8.1	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Lomustine	2.84	no data	7.32	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Fludarabine	−2.8	no data	6.37	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Epirubicin	no data	no data	5.2	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Nelarabine	−1	no data	5	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Ponatinib	4.5	0.0045	4.5	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Trametinib	4.04	0.0024	3.81	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Bortezomib	2	5.20E-06	3.49	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Arsenic trioxide	1.07	0.00225	2.27	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Bleomycin	−0.41	no data	1.86	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Daunorubicin	1.83	no data	1.86	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Chlorambucil	no data	no data	1.66	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Erdafitinib	no data	no data	1.62	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Cabazitaxel	3.69	no data	1.56	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Vinblastine	3.7	no data	1.54	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Vincristine	2.82	no data	1.12	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Cobimetinib	4.5	0.3	0.84	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Idarubicin	0.2	no data	0.79	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Clofarabine	0	no data	0.28	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Eribulin	2.25	9.7E-05	0.24	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Fotemustine	1.23	no data	0.21	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Mitoxantrone	−3.1	no data	0.16	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Topotecan	0.8	no data	0.06	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Raltitrexed	−1.2	no data	0.048	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Dactinomycin	1.6	no data	0.043	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Vindesine	2.9	no data	0.03	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Trabectedin	2.04	0.0003	0.022	< 0.0001	< 0.0001	< 0.0001	< 0.0001

ifosfamide, irinotecan and others. In the case of imatinib, the PECc (0.016 μg L^{-1} using WW = 130 L and DF = 25.92) is considerably lower than its PECt (4.5 μg L^{-1}), but the first studies on its presence and ecotoxicity have already been published (Secrétan et al., 2019). On the other hand, ibrutinib, approved by the EMA in 2014, for which there is no evidence of ecotoxicity, but consumption is expected to gradually increase in the coming years. Among the medicines that started to be marketed before the 2006 obligation to estimate the PEC, only 5-fluorouracil has a PECc for surface water higher than the limit value of 0.01 μg L^{-1}. It is therefore necessary to be attentive to changes in market and therapeutic preference when considering priority substances in environmental monitoring systems.

3.2.2. *Potential impact in coastal waters: the case of Ría de Vigo*

In our study area the discharge of wastewater is mostly into the marine environment after treatment at the WWTP (Fig. 1). The marine environment includes many distinct regions, including transition zones, estuaries, and the open ocean, each of them with its circulation and physico-chemical characteristics that affect the degradation and dispersion of pollutants. Due to the complexity, a dilution factor of 100 is used as standard in the marine environment. Taking this value into account, only hydroxyurea and capecitabine would require further environmental risk assessment, with hydroxyurea being limited to the unchanged excretion fraction. However, in the case of the Vigo estuary, the dilution factor can be approximated by taking into account the volume of wastewater discharged, the volume of the estuary and the residence time of the water in the estuary. There are several limitations to this estimation. First, the information about the load is rarely provided by the companies responsible for the WWTPs. Second, the residence time in an estuary is dependent on tides and meteo-ocean conditions. In the particular case of the Ría de Vigo, upwelling (northerly) winds, spring tides, and high river discharge conditions favor the interchange of waters between the ria and the open ocean, reducing the residence time. On the contrary, downwelling (southerly) winds, neap tides, and low river discharge conditions may favor higher renewal times. Third, circulation within the estuary varies both along-shore and across-shore, so the dispersion of released water will depend on the point of discharge. This means that some areas may have greater persistence of a pollutant than others.

Gross estimations based on a complete renewal of the water in the estuaries that conform the Rías Baixas, with residence time from 4 to 17 days (e.g., Gómez-Gesteira et al., 2003; Pardo et al., 2001; Prego and Fraga, 1992), imply large outflows which would lead to large dilution factors, in the order of thousands. Despite the high dilution, we can expect the treated waters to affect the vicinity areas of the submarine pipes. Values from a simple stationary box model for the calculation of residual flow in the ria, estimated outflows from 211 to 1624 $m^3 s^{-1}$ in the area where it is currently located the outflow of the main WWTP (Box 4 in Prego and Fraga, 1992); these estimates are used considering that in recent decades there have been no substantial changes in estuarine dynamics, given that no significant statistical trends in upwelling-favorable winds have been observed in the 1987–2020 period (Otero et al., 2023). If we consider that all the consumed water by the population is released to the ría in this section (~0.8 $m^3 s^{-1}$), we obtain with previous values a dilution factor that ranges from 263 to 2030. In contrast, larger outflows (~2500–4000 $m^3 s^{-1}$) were also estimated in a similar box (Gilcoto et al., 2007) which would lead to higher dilution factors. As stated in our results, dilution factors below 300 are sufficient

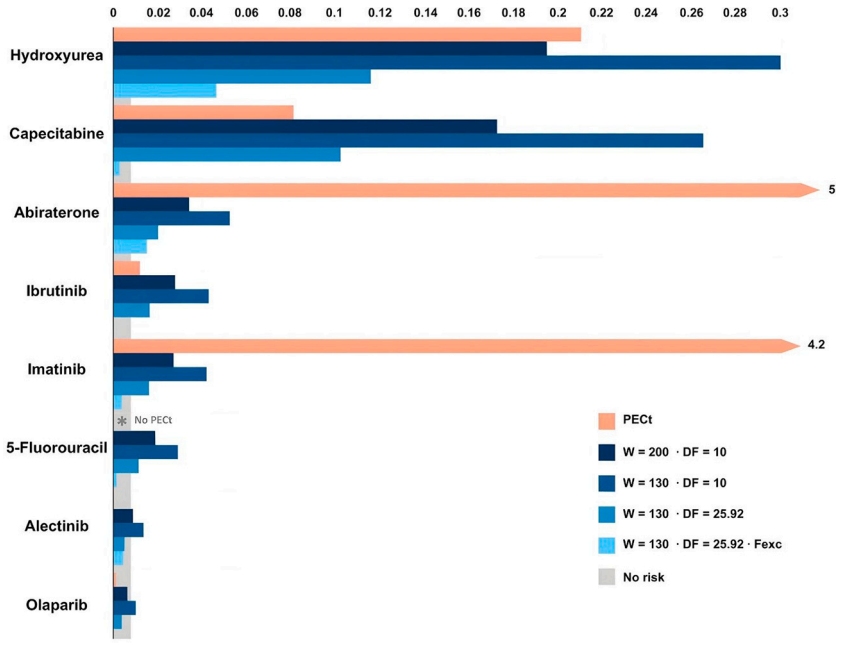

Fig. 2. Comparison of the Predicted Environmental Concentration (PEC) of the most consumed antineoplastic drugs in the Vigo Health Area during 2021. The estimation done by the industry prior to marketing the product (PECt) is compared to the estimation based on real consumption (PECc). Drugs are sorted by consumption. An increasing degree of refinement is shown (from darker to lighter blue): a) W = 200 and DF = 10. b) W = 130 and DF = 10. c) W = 130 and DF = 25.92 (Spain) and d) W = 130 and DF = 25.92 (Spain) with excretion factor considered. W is the water consumption in L day^{-1} per inhabitant, and DF is the Dilution Factor. The unmetabolized excretion factor (Fexc) is also taken into account. The threshold 0.01 μg L^{-1} above which there is a potential environmental risk is indicated by a grey zone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for hydroxyurea to have a potential environmental impact. Thus, during low estuarine outflows and according to this estimation, the excreted hydroxyurea would remain with PECc over the 0.01 threshold in this particular area. It is important to note that our estimate is based on total water consumption and not on the capacity of the treatment plants. Currently, in the Vigo estuary, there is a treatment plant with an average daily flow of 4 m^3 s^{-1} and a peak design flow of 8 m^3 s^{-1}, values higher than the previously estimated water consumption.

Other studies, like the one by Sousa et al. (2021), have focused on the emission of microplastics from the outfall network of the Ría de Vigo. Microplastics with very long degradation times can be used as tracers of the circulation in the estuary and thus help to understand the mixing and dispersion at the outlet of the outfalls. This study, based on the analysis of a Lagrangian model, concluded that 5 days after emission, only 3.70 % of microplastics left the head of the estuary in neap tide (flood) situations, as opposed to the strong export, during spring tide ebb conditions, in which 45.38 % left the estuary. Since this study considered only the percentage of particles and not concentrations, it is not possible to establish a dilution factor. However, it does highlight the strong concentration of particles around the underwater outfalls and how particles reach the Cies Islands National Park, as well as nearby shellfish farming areas (Fig. 1). This last aspect is of vital importance, as the shellfish beds extend over 24.6 km^2 while the mussel beds produce 37,000 t $year^{-1}$ of mussels (Surís-Regueiro et al., 2014). Mussels are great filter feeders, being able to filter between 4 and 5 L h^{-1} and as sessile organisms they are considered sentinel organisms of pollution, without entering into the important consideration of public health as they are a product for human consumption. Substances that have not been retained in WWTPs therefore have the potential to affect the ecosystem resources of the estuary.

It seems clear that further studies based mainly on hydrodynamic models are needed to estimate the dilution factors around outfalls from an Eulerian perspective. These studies should also take into account the different ocean-meteorological conditions that strongly impact the distribution processes. After initial mixing (dilution), other more complex processes such as adsorption on the suspended matter or chemical degradation must also be considered if these factors are to be adjusted to the specific behaviour of each molecule. In estuarine areas, with gradients in salinity, pH and alkalinity, it is even more complex to take degradation processes into account, so it is preferable to assume a conservative perspective.

The local PECc estimates shown here serve as an initial approximation for studies in other coastal areas. More than half of the world's population lives near the coast and the trend is increasing (Neumann et al., 2015), with an expected aggregation around coastal megacities. It is these same populations that will exploit the different ecosystem resources that provide them with nutritional and economic opportunities (Selig et al., 2019), as well as numerous intangible resources. This is coupled with an increase in the diagnosis and treatment of cancer in the world population (Bray et al., 2018; Ferrando-Climent et al., 2014), which will lead to increasing consumption of these drugs as long as there are no other therapeutic alternatives. Therefore, there is a need to adequately estimate the consumption of these drugs and their potential impact on the marine ecosystem. Even if this impact will not harm humans, there would still be an ethical argument for preserving biodiversity and ecosystem functions (Taylor et al., 2020).

3.2.3. *Regulatory framework*

None of the analyzed medicines require monitoring under the European water quality directives (Directive 2000/60/EC) as they are absent in the most recent revision of the monitoring lists (Commission Implementing Decision (EU) 2022/1307 of 22 July 2022). Despite this, the previous report (JRC, 2022) considers these substances in priority category 3 due to the lack of reliable PNECs, and considers them to be substances of concern. The NORMAN Substance Database - NORMAN SusDatcan includes those substances detected in the environment, but for which there is currently no monitoring obligation by routine monitoring programmes at European level, and for which the fate, behaviour and (eco)toxicological effects are not well known. Among the substances in Table 1, and in order of consumption, only cyclophosphamide, ifosfamide, doxorubicin, epirubicin, and daunorubicin are on the list. None

of these substances show PECt on release before 2006 and their PECc in surface waters do not reach the threshold of 0.01 μg L^{-1}. Also, none of the substances are found among those in the list of substances of possible concern by OSPAR, not even among those in Section A for which information is insufficient. However, in our study area, up to 8 antineoplastics have a potential environmental concentration risk in inland waters and even two of them, hydroxyurea and capecitabine, have a potential environmental risk in the marine environment.

Our study shows that of the >100 antineoplastics consumed in our healthcare area, only ~50 % have a prior estimate of environmental exposure published in the EPARs. As an example, 5-fluorouracil does not have a published PECt because it was marketed before the regulation came into application in 2006. However, based on local consumption, it has a PECc above the threshold for surface inland waters, and is one of the medicines with the most documented presence in the aquatic environment (Gouveia et al., 2019). This shows that health legislation on environmental risk assessment and risk characterisation is not uniform and is not monitored over time in terms of consumption. It also does not consider the use of off-label medicines and is focused on the short-term effects of acute exposure on a small number of organisms (Lee and Choi, 2019).

Although some drugs (e.g. macrolide antibiotics, amoxicillin, ciprofloxacin) have been timidly appearing since the second watch list (Decision (EU) 2018/8402) under the Water Framework Directive, no cytostatics have been included in subsequent reviews. This may be due to the fact that these lists are based on screening and environmental ecotoxicity studies whose search criteria do not include data on consumption in healthcare practice. Our results are in line with the study by Nassour et al. (2020), who recommend that the choice of inclusion in these lists should be based on actual consumption and take into account whether or not they are administered in the hospital. These authors also recommend renal excretion, type of elimination, removal efficiency in WWTP and stability in water as criteria to be considered.

4. Conclusions

Of the 108 antineoplastics consumed in the study area during 2021, 6 of them exceeded 0.01 μg L^{-1} in their PECc for inland surface water taking into account standard parameters of water consumption and dilution factor. However, with increasing refinement of the estimation, only hydroxyurea and abiraterone exceeded this threshold value (DF = 25.92 and Fexc considered). When wastewater discharge into the Vigo estuary was taken into account, only hydroxyurea presented a potential environmental risk due to its estimated concentration. However, it is expected that, due to mixing and dispersion, the area of influence is restricted to the vicinity of the submarine outfall. Even so, due to the amount of ecosystemic resources provided by the estuary, it is advisable to conduct studies to improve the estimation of local dilution factors, as well as to monitor cytostatic consumption in the face of changes in therapeutic preference and the emergence of new treatments.

Antineoplastics are essential drugs to improve survival and reduce mortality in cancer patients. Their potential environmental impact can not be reduced, as may be the case with other environmental pollutants, unless large financial investments are made in WWTPs, allowing them to have advanced depuration techniques. On the contrary, consumption is expected to increase in the coming years. But this reality does not exempt us from improving our knowledge of their potential ecotoxicity, helping to prevent environmental risks and achieve a more sustainable use. Environmental research on pharmaceuticals as potential emerging pollutants is necessary and should be coupled with local consumption data to optimise monitoring efforts, better understand ecotoxicity and improve wastewater treatment systems.

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CRediT authorship contribution statement

Moisés Couñago-Fernández: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Pablo Otero:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Marisol Samartín-Ucha:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Adolfo Paradela-Carreiro:** Writing – review & editing, Data curation, Conceptualization. **Soledad Muniategui-Lorenzo:** Writing – review & editing, Conceptualization. **Noemí Martínez-López de Castro:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing financial interests or other conflicts of interest.

Data availability

The authors do not have permission to share data.

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