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New insights on cytostatic drug risk assessment in aquatic environments based on measured concentrations in surface waters

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ABSTRACT

Cytostatic drugs are compounds used to treat cancer, one of the deadliest diseases worldwide with a rising yearly incidence. However, the occurrence and concentrations of a large number of cytostatics in waters and wastewaters are unknown. Thus, this study sought to analyze the concentrations of these compounds in different aquatic environments worldwide to assess the risk that these compounds pose to aquatic organisms. The top five most monitored cytostatics in aquatic environments are fluorouracil, methotrexate, tamoxifen, ifosfamide, and cyclophosphamide. Risk quotients (RQs) based on maximum reported measured concentrations revealed that mycophenolic acid and tamoxifen pose a high risk to aquatic organisms ($RQ_{max} \geq 1$) at concentrations observed in surface waters. Moreover, methotrexate and tegafur were categorized as moderate risk compounds, and bicalutamide was found to pose a low risk. Importantly, the available analytical methodologies for the quantification of some cytostatics (e.g., cisplatin, fluorouracil, daunorubicin, imatinib, and mycophenolic acid) in water could not rule out potential risk to aquatic biota, since estimated risks for these compounds using the lowest method detection limits reported in the literature (RQ MDL) were all ≥ 0.01 (i.e., low risk or higher). Moreover, risks based on predicted concentrations (RQ PEC) were consistently lower than those based on measured concentrations, highlighting the importance of risk assessment based on measured values. Thus, accurate and sensitive analytical methods are crucial to identify and quantify cytostatic exposure in aquatic ecosystems in order to preserve biodiversity and ensure a safer environment.

1. Introduction

Cancer is one of the deadliest diseases worldwide and its incidence has been increasing every year. The International Agency for Research on Cancer (IARC) estimates that 29.5 million new cancer cases will be diagnosed by 2040, with more than 16 million deaths expected worldwide (IARC, 2018a). This increase in cancer incidence will be consequently accompanied by an increase in cytostatic use to treat this disease. However, cytostatics (i.e., also known as antineoplastic or anticancer drugs), are not exclusively specific to cancerous cells and can also affect healthy tissues, representing a potential risk to virtually any living being (Escudero-Oñate et al., 2017; Olalla et al., 2017). Once administered, these compounds are excreted through the urine and feces either in their original chemical form or as metabolites, after which the resulting effluents from hospitals, homes, and pharmacies reach the sewage system (Giri and Pal, 2014; Tauxe-Wuersch et al., 2006). Importantly, given that the current treatment processes implemented in wastewater treatment facilities are not completely effective in degrading these hazardous compounds, they ultimately reach the surface waters and threaten the aquatic biota (Santos et al., 2017; Zenker et al., 2014).

Despite the potential risks of cytostatics, studies addressing their occurrence in different environments remain scarce, which may either be due to their generally low environmental concentrations (i.e., typically in the ng/L range or lower) and/or the lack of analytical methods for their accurate quantification (Booker et al., 2014; Martin et al., 2011; Pieczyńska et al., 2017; Santana-Viera et al., 2016). Therefore, the development of sensitive and robust analytical methods is critical for the identification and quantification of cytostatics in aquatic environments (Pieczyńska et al., 2017; Santos et al., 2017).

In our study, the environmental risk posed by pharmaceuticals was prioritized through the determination of risk quotients (RQs) according to the guidelines for environmental risk assessment of pharmaceuticals proposed by the European Medicines Agency (EMEA, 2006). To our knowledge, the risks associated to cytostatic exposure in aquatic organisms have so far only been estimated based on their predicted

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concentrations in surface waters (Bueno et al., 2014; Franquet-Griell et al., 2017b; Heijnsbergen and Schmitt, 2008; Johnson et al., 2013; Lenz et al., 2007; Moermond et al., 2018; Santos et al., 2017; Zounkova et al., 2010; Zounková et al., 2007). Furthermore, most studies to date have reported that cytostatics are generally safe to aquatic biota, with only a few exceptions. For instance, a moderate to high risk has been attributed for doxorubicin, cyclophosphamide, mycophenolic acid, mycophenolate mofetil, vinorelbine, fluorouracil, and tamoxifen (Bueno et al., 2014; Franquet-Griell et al., 2017a; Franquet-Griell et al., 2017b; Moermond et al., 2018; Santos et al., 2017), while the occurrence of cisplatin, methotrexate, cytarabine, gemcitabine, doxorubicin, bicalutamide, ifosfamide, and epirubicin in surface waters has been found to pose a low environmental risk (Bueno et al., 2014; Franquet-Griell et al., 2017a; Moermond et al., 2018; Santos et al., 2017). However, recent evidence suggests that predicted environmental concentrations underestimate the true concentrations of cytostatics in water bodies (Franquet-Griell et al., 2017a; Franquet-Griell et al., 2016) and, in turn, their associated risks. Therefore, performing risk assessment based on measured cytostatic concentrations in environmental waters is of the utmost importance.

For the first time, our study has compiled a comprehensive dataset of measured cytostatic concentrations reported by several authors in different water bodies; this dataset was then used to estimate risk quotients for each cytostatic compound accordingly. The specific objectives of this work were (1) to review the occurrence of cytostatics in hospital effluents, influents and effluents of urban wastewater treatment plants (WWTPs), and surface waters; (2) to review the toxicity values of cytostatics for different aquatic organisms; (3) to estimate cytostatic-associated risks to aquatic biota, comparing the risk quotients obtained from measured versus predicted concentrations.

2. Materials and methods

2.1. Data sources

An extensive literature search was performed to identify studies focused on the measurement of cytostatics in environmental waters. Published studies were obtained from three search engines (i.e., PubMed, Scopus, and ScienceDirect) using the following keywords: "*cytostatics*" (i.e., along with its synonyms), *"measured/predicted environmental concentrations," "analytical methods,"* and *"risk assessment."* These keywords were systematically combined resulting in 12 key phrases, which were then searched in the three aforementioned databases. A total of 103 published studies were found after removing duplicates. Then, additional criteria were applied to exclude (1) non-original research articles (i.e., reviews), (2) publications that are not considered full reports (i.e., letters to the editor and gray literature), (3) documents not written in English, and (4) studies published after December 31st, 2018. A total of 81 studies remained after applying said criteria.

Moreover, toxicity data for aquatic organisms from different trophic levels were obtained from data sheets, scientific papers, and safety data sheets provided by pharmaceutical companies. In the absence of experimental data, theoretical values obtained from the Ecological Structure Activity Relationships (ECOSAR) predictive model were used.

2.2. Risk quotients

Risk quotients (RQs) are defined as the ratio between the exposure and the effects, and were calculated from measured (MECs) or predicted (PECs) environmental concentrations through Eq. (1) or Eq. (2), respectively:

$$RQ = \frac{MECs}{PNECs} \quad (1)$$

$$RQ_{PEC} = \frac{PECs}{PNECs} \quad (2)$$

PECs were all obtained from the Iberian Peninsula (Franquet-Griell et al., 2017a; Santos et al., 2017) and their calculation was based on Eq. (3), as indicated below.

$$PEC = \frac{Consumption \times F_{exc} \times (1 - F_{WWTP})}{WWinhab \times inhab \times DF} \quad (3)$$

where *Consumption* (ng yr^{-1}) is the quantity of the active pharmaceutical ingredient (i.e., cytostatic) consumed over one year in a given region, WW_{inhab} is the water consumption (i.e., in liters) per person (i.e., "inhabitant") per year, *inhab* is the number of inhabitants of a defined zone, *DF* is the dilution factor from WWTP effluents to surface waters, F_{exc} is the fraction of parent compound that is excreted without chemical alteration, and F_{WWTP} is the fraction removed in WWTPs.

The predicted no-effect concentrations (PNECs) were defined as the lowest values obtained from the quotient between the toxicity values found for each cytostatic and an assessment factor (AF). Depending on the toxicological dose descriptor (e.g., EC50, LC50, NOEC, and LOEC), the nature of the toxicity value (i.e., acute or chronic toxicity), and the number of known trophic toxicological levels, the following AF values were assumed: AF = 1000, when at least one short-term toxicological value was available for each trophic level; AF = 100, when at least one long-term result was available for one trophic level; AF = 50, when two long-term results from species representing two trophic levels were available; AF = 10, when long-term results from at least three species representing three trophic levels existed.

Whenever available, long-term toxicity values were used instead of short-term values, even though short-term values may result in lower PNECs. In the absence of experimental toxicity data, ECOSAR models were used for PNEC calculations. Afterward, a widely-acknowledged criterion for risk quotient interpretation was applied (EC, 1996; Sánchez-Bayo et al., 2002), whereby $RQ \geq 1$ indicates high risk, $0.1 \leq RQ < 1$ indicates moderate risk, and $0.01 \leq RQ < 0.1$ indicates low risk.

3. Results and discussion

3.1. Occurrence of cytostatics in water and wastewater

Eighty-one original research articles reporting measurements of cytostatics in wastewater and surface waters were found, with 2009 being the year with the highest number of published studies (i.e., nine publications; Fig. 1a). The first studies appeared in the 1980s and a rising number of publications on this topic was observed until 2009 when they reached a maximum, after which continuously fewer articles were published, likely due to a decrease in cytostatic use in favor of targeted cancer therapies between 2005 and 2015 (IMS, 2016). Interestingly, most of the publications correspond to European studies, which may suggest that European scientists have been more active in researching cytostatics environmental contamination than their worldwide peers.

The top five most studied cytostatics in aquatic environments are cyclophosphamide, ifosfamide, tamoxifen, methotrexate, and fluorouracil (Fig. 1b), and were featured in nearly half of the total studies found. This may be due to (1) their higher consumption rate, (2) their higher toxicity to aquatic organisms and/or humans, or (3) the existence of analytical methods for their accurate measurement in water environments (Ferrando-Climent et al., 2014; Isidori et al., 2016; Kosjek and Heath, 2011; Negreira et al., 2013). Although cytostatic use is highly region-dependent (Buerge et al., 2006; Franquet-Griell et al., 2017b; Kümmerer et al., 2016; Santos et al., 2017), fluorouracil is by far one of the most consumed in Europe (Besse et al., 2012; Hamon et al., 2018; Kovalova, 2009; Mahnik et al., 2007; Martin et al., 2011; Mugada et al., 2016; Santos et al., 2018). Ifosfamide, cyclophosphamide,

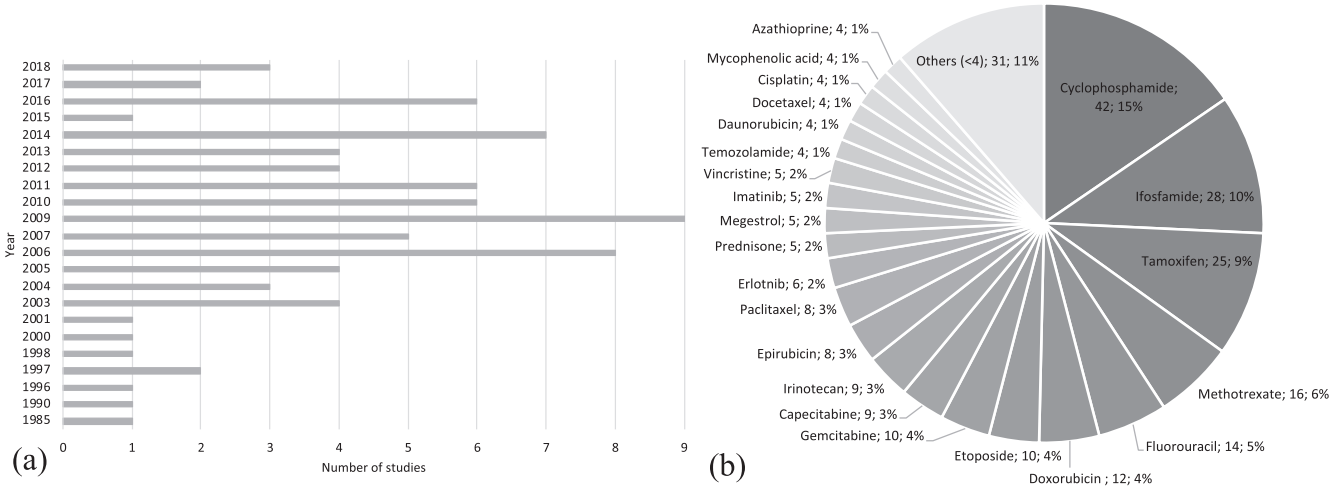

Fig. 1. Monitoring of cytostatics in surface and wastewaters between 1985 and 2018: (a) Number of scientific studies per year; (b) Number of scientific studies per cytostatic (cytostatic; number of studies, percentage).

capecitabine, gemcitabine, cytarabine, paclitaxel, mycophenolic acid, hydroxycarbamide, and platinum cytotoxics are also highly prescribed worldwide, albeit at relatively lesser amounts (Besse et al., 2012; Franquet-Griell et al., 2017a, 2017b; Kovalova, 2009; Kumar et al., 2018; Mahnik et al., 2007; Martin et al., 2011; Mugada et al., 2016; Santos et al., 2018; Santos et al., 2017). Also, it is worth noting that cyclophosphamide and tamoxifen are classified as Group 1 agents (i.e., carcinogenic to humans) by the International Agency for Research on Cancer (IARC, 2018b).

Lesser monitored cytostatics in aquatic environments (represented as "others" in Fig. 1b) are bicalutamide (i.e., featured in three studies); chlorambucil, melphalan, fludarabine, cytarabine, vinorelbine, mitomycin, carboplatin, oxaliplatin, procarbazine, leuprorelin, goserelin, and cyproterone (i.e., featured in two studies each); and tegafur, vinblastine, bleomycin, and hydroxycarbamide (i.e., featured in one study each). Although hydroxycarbamide and mycophenolic acid are among the most prescribed cytostatics, the lack of accurate and sensitive analytical methodologies for their quantification in water may have contributed to their relative obscurity in published literature. To our knowledge, there is only one analytical method with a high detection limit for hydroxycarbamide quantification in waters (Usawanuwat et al., 2014) and the analytical methods to identify and quantify mycophenolic acid in surface and wastewaters were made available only recently (Franquet-Griell et al., 2017d, 2016; Giebułtowicz and Nałęcz-Jawecki, 2016; Santos et al., 2018; Usawanuwat et al., 2014). Concerning other cytostatics, the lack of monitoring studies may be associated both to the lack of analytical methodologies and their low stability in water (Chang et al., 1978; Franquet-Griell et al., 2017a; Negreira et al., 2013).

3.1.1. Cytostatic occurrence in hospital effluents

The occurrence of the most studied cytostatics in hospital effluents is depicted in Fig. 2a, and more detailed information can be found in Table SI1. The concentrations of cytostatics in hospital effluents range from non-detectable to 687,000 n gL^{-1}, which was the maximum value observed for cyclophosphamide (Hamon et al., 2018). Moreover, two exceptionally high values (i.e., outliers) were reported for ifosfamide (6,820,000 ng L^{-1}) and fluorouracil (1,280,000 ng L^{-1}) in hospital effluents taken directly from the sink, shower, and toilet of an oncological ward of a French Hospital (Hamon et al., 2018). As demonstrated in Fig. 2a, the reported cyclophosphamide and fluorouracil concentrations exhibit a broader interquartile range than those for other cytostatics, which indicates high data variability. A high variability outside the upper quartile is also noticeable for all cytostatics except for tamoxifen.

The less studied cytostatics aggregated into two groups, those for which at least one concentration reported was > 100 ng L^{-1}, and those for which the maximum measured concentration was < 100 ng L^{-1}. The first group is integrated by doxorubicin, etoposide, capecitabine, prednisone, megestrol, azathioprine, goserelin, irinotecan, cisplatin, and epirubicin. Cisplatin exhibited the highest concentration in hospital effluents (1700–266,000 ng L^{-1}) and is categorized as a Group 2A (i.e., probably carcinogenic to humans) agent (IARC, 2018b). The cytostatics from this group, along with the top five most studied cytostatics, are among the drugs found at higher concentrations in hospital effluents. Gemcitabine, vincristine, erlotinib, paclitaxel, docetaxel, and bicalutamide were found at concentrations of up to 100 ng L^{-1}. Furthermore, our study encountered cytostatics that were considered in the monitoring plan but were not detected in hospital effluents, such as chlorambucil, melphalan, temozolomide, fludarabine, vinblastine, daunorubicin, cyproterone, leuprorelin, imatinib, procarbazine, oxaliplatin, and carboplatin. Low method sensitivities, low excretion rates, and low consumption trends may be the main causes for the non-detection of these compounds in hospital effluents (Gómez-Canela et al., 2014; Isidori et al., 2016; Mahnik et al., 2007, 2006; Negreira et al., 2014; Yin et al., 2010a).

Among the 26 studies with measurements of cytostatics in hospital effluents, only three mentioned the use of an onsite wastewater pretreatment procedure (Hamon et al., 2018; Mahnik et al., 2007; Yin et al., 2010a). These treatment processes consisted of disinfection with chlorine (Yin et al., 2010a), coupled with membrane bioreactors and activated sludge (Hamon et al., 2018; Mahnik et al., 2007). However, Yin et al. demonstrated that chlorine treatment was ineffective at degrading cytostatics in wastewaters, as some drugs (e.g., methotrexate, azathioprine, cyclophosphamide, ifosfamide, and etoposide) were detected at relatively high concentrations (i.e., up to 10,647 ng L^{-1}) even after said treatment (Yin et al., 2010a). Moreover, membrane bioreactors and activated sludge have been reportedly very effective in the degradation of fluorouracil and doxorubicin (i.e., ≥90% elimination), but relatively ineffective at removing other cytostatics (e.g., 49% elimination for ifosfamide and 59% for cyclophosphamide) (Hamon et al., 2018; Mahnik et al., 2007).

3.1.2. Cytostatic occurrence in WWTP influents

Fig. 2b represents the measured concentrations of the top five most studied cytostatics (i.e., cyclophosphamide, ifosfamide, tamoxifen, methotrexate, and fluorouracil) in WWTP influents. Their concentrations vary from non-detectable to a maximum of 308 ng L^{-1} observed for methotrexate (Isidori et al., 2016). One exceptionally high

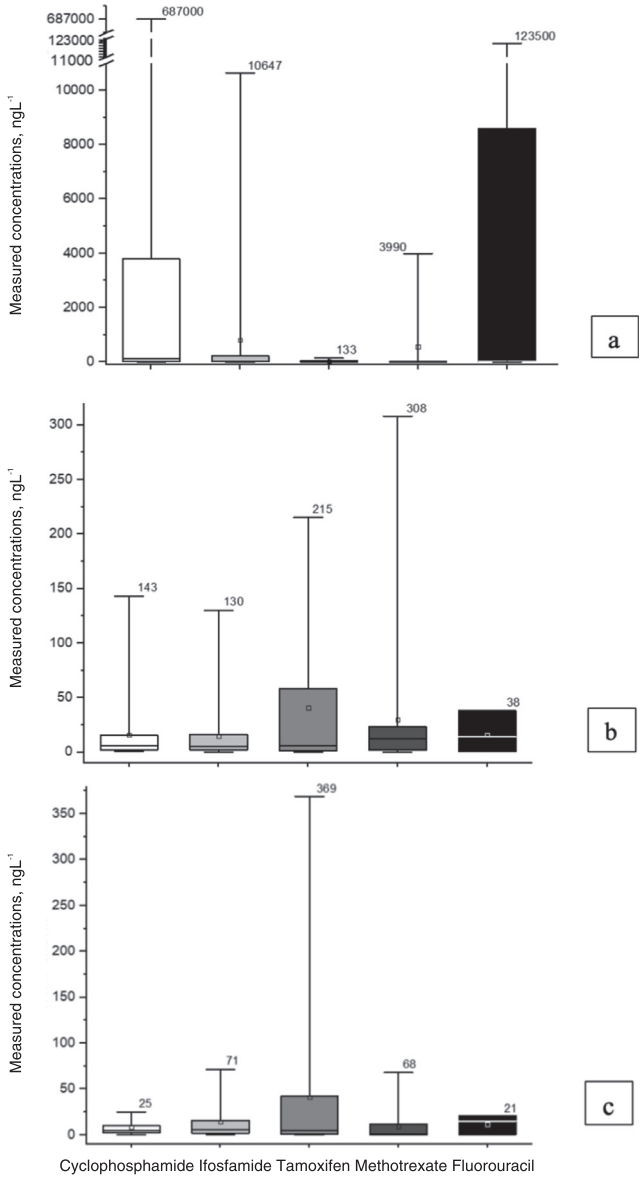

Fig. 2. Measured concentrations (ngL^{-1}) of the top five most monitored cytostatics (i.e., cyclophosphamide, ifosfamide, tamoxifen, methotrexate and fluorouracil) in wastewaters: (a) hospital effluents, (b) WWTP influents, and (c) WWTP effluents.

cyclophosphamide concentration (i.e., 13,100 ng L^{-1}) was reported in Spain (Gómez-Canela et al., 2012); however, we did not include this finding in Fig. 2b. This high concentration was likely due to abnormally high doses of cyclophosphamide being administered during the sampling week. Tamoxifen was the only cytostatic that exhibited higher concentrations in WWTP influents than in hospital effluents (Fig. 2a and b). This could be due to the administration of tamoxifen at home, which may be contributing to the contamination of WWTP influents via domestic sewages (Quirke, 2017; Tauxe-Wuersch et al., 2006).

Although detected less frequently, cisplatin and carboplatin exhibited the highest concentrations in WWTP influents (i.e., up to 1120 ng L^{-1} and 1600 ng L^{-1}, respectively), after cyclophosphamide (Ghafuri et al., 2017). Similarly, to the findings in hospital effluents, capecitabine and megestrol were detected at concentrations above 100 ng L^{-1} in WWTP influents. However, the concentrations of imatinib (54–180 ng L^{-1}), carboplatin (up to 1600 ng L^{-1}), oxaliplatin (up to 600 ng L^{-1}) and docetaxel (up to 219 ng L^{-1}) in WWTP influents were found to be much higher than in hospital effluents (Table SI1). As imatinib is orally administered at home, a higher concentration would be expected in WWTP influents than in hospital effluents (FDA, 2006). Moreover, the metabolism of docetaxel and oxaliplatin in the human body is very slow, being excreted only seven and five days after administration, respectively (Ferrando-Climent et al., 2014; Graham et al., 2000). Carboplatin is 58–72% excreted after 24 h, and the remaining is slowly excreted thereafter (Oguri et al., 1988). Fluorouracil, gemcitabine, vincristine, etoposide, paclitaxel, doxorubicin, erlotinib, irinotecan, azathioprine, and prednisone were all found at concentrations < 100 ng L^{-1}. Chlorambucil, melphalan, temozolomide, fludarabine, vinblastine, vinorelbine, daunorubicin, procarbazine, leuprorelin, and cyproterone remained undetected, possibly due to the previously explained methodological limitations. Goserelin, which was found at concentrations > 100 ng L^{-1} in hospital effluents, was not detected in WWTP influents. This indicates that goserelin may be more prone to degradation before reaching WWTPs (Gómez-Canela et al., 2014). Additionally, these compounds may be diluted when hospital effluents are mixed with domestic and industrial sewages, resulting in lower observed concentrations (Isidori et al., 2016). This may also explain the slight decrease in fluorouracil and prednisone concentrations, among other cytostatics (Table SI1).

3.1.3. Cytostatic occurrence in WWTP effluents

Fig. 2c presents the measured concentrations of the most monitored cytostatics in WWTP effluents. The measurements of all cytostatics reported in the literature until 2018 are detailed in Table SI1 of the supporting information. The concentrations of the most studied cytostatics in WWTP effluents varied from non-detectable to 369 ng L^{-1}, the latter being the maximum value observed for tamoxifen (Roberts and Thomas, 2006). An extraordinarily high ifosfamide concentration of 2900 ng L^{-1} was reported by Ternes et al. However, it was not presented in Fig. 2c. Moreover, the authors only detected this compound in 2 out of 16 WWTPs; thus, this occurrence of ifosfamide was considered an exception (Ternes, 1998). The comparison between the maximum measured concentrations depicted in Fig. 2b and c suggests that all top five cytostatics undergo degradation/removal at WWTPs, except for tamoxifen, which exhibited a 215 ng L^{-1} influent concentration and a 369 ng L^{-1} effluent concentration in WWTPs. However, based on median concentrations, the degradation/removal of all cytostatics except for methotrexate at WWTPs was not significant. Cyclophosphamide has been frequently reported as a notoriously difficult compound to degrade in WWTPs, withstanding primary, secondary (Steger-Hartmann et al., 1997; Yin et al., 2010b), and even tertiary treatments based on sand filtration (Buerge et al., 2006), ozonation (Azuma et al., 2015), UV radiation (Llewellyn et al., 2011; Rabii et al., 2014), chlorine disinfection (Azuma et al., 2015), and trickling filters (Llewellyn et al., 2011). Ifosfamide is another example of a pollutant resistant to physical, biological, and chemical processes (e.g., adsorption, biodegradation, and hydrolyzation) (Buerge et al., 2006; Busetti et al., 2009; Kümmerer et al., 1997; Yin et al., 2010b). Tamoxifen exhibited a poor removal fraction (i.e., approximately 0.2) in many WWTPs throughout the UK with activated sludge plants, trickling biofilters, membrane bioreactors, and oxidation ditches (Comber et al., 2018). Moreover, poor removal has also been reported for sand filtration and ticking filters (32–45% removal) (Zhou et al., 2009). Ozonation and UV radiation are relatively efficient for tamoxifen removal (Azuma et al., 2015; Roberts and Thomas, 2006); however, their implementation in WWTPs is still scarce. No sufficient data were available to evaluate fluorouracil degradation at WWTPs; the majority of the studies measuring its concentration both in WWTPs influents and effluents indicated concentrations below the detection limit (Yu et al., 2006). As previously reported, there is a lack of analytical methodologies able to identify and quantify fluorouracil in wastewaters, and matrix interferences are frequently reported (Santos et al., 2018). In contrast with the other top-five cytostatics, methotrexate median concentration decreased from approximately 13 ng L^{-1} to 1 ng L^{-1}, suggesting a

Table 1
Lowest MDLs and maximum measured concentration (MEC_{max}) for each cytostatic in surface waters reported in the literature.

Name	MDL (ngL^{-1})	Reference	MEC_{max} (ngL^{-1})	Reference
Azathioprine	1.2	Ferrando-Climent et al. (2014)	–	Ferrando-Climent et al. (2014)
Bicalutamide	0.1	Azuma et al. (2015)	254	Azuma et al. (2015)
Bleomycin	5.0	Aherne et al. (1990)	17	Aherne et al. (1990)
Capecitabine	0.2	Azuma et al. (2015)	20	Azuma et al. (2015)
Carboplatin	13.0	Ghafuri et al. (2017)	–	Ghafuri et al. (2017)
Chlorambucil	1.0	Franquet-Griell et al. (2017a)	4.8	Franquet-Griell et al. (2017a)
Cisplatin	17	Ghafuri et al. (2017)	–	Ghafuri et al. (2017)
Cyclophosphamide	0.0074	Calamari et al. (2003)	65/1907*	Moldovan (2006)/Usawanuwat et al. (2014)
Cyproterone	1.8	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Cytarabine	1.4	Martin et al. (2011)	13	Martin et al. (2011)
Daunorubicin	26.0	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Docetaxel	3.8	Ferrando-Climent et al. (2014)	–	Ferrando-Climent et al. (2014)
Doxorubicin	1.1	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Epirubicin	2.1	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Erlotinib	2.5	Franquet-Griell et al. (2017a)	3.9	Franquet-Griell et al. (2017a)
Etoposide	2.2	Martin et al. (2011)	–	Martin et al. (2011)
Fludarabine	11.0	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Fluorouracil	0.16	Kosjek et al. (2013)	–/578*	Kosjek and Heath (2011)/Usawanuwat et al. (2014)
Gemcitabine	1.0	Martin et al. (2011)	2.4	Martin et al. (2011)
Goserelin	41.0	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Hydroxycarbamide	50.0	Usawanuwat et al. (2014)	–/788*	Usawanuwat et al. (2014)
Ifosfamide	0.02	Buerge et al. (2006)	41	Valcarcel et al. (2011)
Imatinib	35.0	Santos et al. (2018)	–	Santos et al. (2018)
Irinotecan	0.9	Martin et al. (2011)	–	Martin et al. (2011)
Leuprorelin	2.4	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Megestrol	0.03	Chang et al. (2009)	34	Chang et al. (2009)
Melphalan	1.9	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Methotrexate	0.044	Zuccato et al. (2005)	5	Franquet-Griell et al. (2017a)
Mitomycin	2.2	Martin et al. (2011)	–	Martin et al. (2011)
Mycophenolic acid	0.077	Giebułtowicz and Nałęcz-Jawecki (2016)	656	Franquet-Griell et al. (2017a)
Oxaliplatin	9.0	Ghafuri et al. (2017)	–	Ghafuri et al. (2017)
Paclitaxel	0.3	Martin et al. (2011)	–	Martin et al. (2011)
Prednisone	1.8	Franquet-Griell et al. (2017a)	–	Franquet-Griell et al. (2017a)
Tamoxifen	0.003	Zhang and Zhou (2007)	212	Roberts and Thomas (2006)
Tegafur	0.2	Azuma et al. (2015)	56	Azuma et al. (2015)
Vincristine	6.4	Ferrando-Climent et al. (2014)	–	Ferrando-Climent et al. (2014)
Vinorelbine	4.0	Martin et al. (2011)	–	Martin et al. (2011)

* Values considered exceptions; MDL: minimum method detection limit reported in the monitoring studies; MEC_{max}: maximum measured concentration in surface waters.

degradation/removal mechanism at WWTPs (Fig. 2b and c). Although methotrexate is resistant to UV disinfection (Rabii et al., 2014), it was found that a 98% removal rate could be achieved via biodegradation after seven days (Kiffmeyer et al., 1998; Rabii et al., 2014).

Among the least studied cytostatics, platinum drugs (i.e., cisplatin and carboplatin) remained among the cytostatics with the highest concentrations in WWTP effluents (i.e., up to 430 $ng\,L^{-1}$ and 1200 $ng\,L^{-1}$, respectively), although 52% and 59% removals of these compounds have been reported in WWTPs with secondary activated sludge treatment (Ghafuri et al., 2017). Mycophenolic acid was also found in high concentrations (i.e., 395–874 $ng\,L^{-1}$) after a WWTP treatment with UV-light, which may have improved its removal since it was recently proved that mycophenolic acid is partially degraded by UV light (Franquet-Griell et al., 2017c; Santos et al., 2018). The remaining cytostatics with WWTP effluent concentrations above 50 $ng\,L^{-1}$ were cytarabine, vinorelbine, epirubicin, gemcitabine, and bicalutamide, with epirubicin exhibiting the highest concentration (24,800 $ng\,L^{-1}$). Importantly, the authors indicated that high doses of epirubicin were administered during the week of sampling, which may justify such a high concentration value (Gómez-Canela et al., 2012). Cytostatics with concentrations below 50 $ng\,L^{-1}$ were tegafur, capecitabine, etoposide, paclitaxel, doxorubicin, bleomycin, oxaliplatin, erlotinib, irinotecan, megestrol, and prednisone. All these compounds exhibited a non-significant concentrations decrease at WWTPs, except imatinib and docetaxel. Imatinib was detected in WWTP influents in one instance at a concentration below the quantification limit (54–180 $ng\,L^{-1}$) and was thereafter undetectable in WWTP effluents (method detection limit (MDL) = 36 $ng\,L^{-1}$). Moreover, docetaxel was measured at concentrations above 100 $ng\,L^{-1}$ in WWTP influents and was not detected in WWTP effluents (Table SI1), which suggests that these compounds were degraded at the treatment plants. As observed in WWTP influents, chlorambucil, melphalan, temozolomide, fludarabine, vinblastine, daunorubicin, mitomycin, procarbazine, leuprorelin, and cyproterone were monitored, but not detected in any effluent.

3.1.4. Cytostatic occurrence in surface waters

Many factors may influence the pollutant degradation/removal performance of WWTPs. For instance, the physicochemical properties of the compounds, sewage composition, weather conditions, treatment process design, contaminant load, pollutant concentration of the influent, operation and maintenance, and the implementation (or lack thereof) of tertiary treatments (Al Qarni et al., 2016; Johnson and Sumpter, 2002; Le-Minh et al., 2010; Zorita et al., 2009). Current WWTP treatment procedures are generally ineffective at removing cytostatics; thus, these compounds are ultimately discharged into the environment. A total of 36 studies reported the occurrence of cytostatics in surface waters (Table SI1). The maximum concentrations and the lowest method detection limits (MDLs) reported by these studies are summarized in Table 1. Usawanuwat et al. detected 1907, 788, and 578 $ng\,L^{-1}$ of cyclophosphamide, hydroxycarbamide, and fluorouracil in the Chao Phraya river (Thailand), respectively; however, these values were considered exceptionally high (Usawanuwat et al., 2014). Additionally, said study focused primarily on analytical method development, and only one replicate of the measured concentrations was sampled (Usawanuwat et al., 2014).

Although a decrease in cytostatics concentration from WWTP

Table 2
PNECs for all cytostatics monitored in surface waters.

Cytostatics	Organism	Test*	AF	PNEC, ng L^{-1}	Reference
Azathioprine	Fish	NOEC	10	$1.68 \times 10^{+5}$	ECOSAR estimation
Bicalutamide	*D. magna*	Length, 21 days, NOEC	100	$5.60 \times 10^{+3}$	Santa-Cruz-Biotechnology (2010)
Bleomycin	Fish	NOEC	10	$2.26 \times 10^{+10}$	ECOSAR estimation
Capecitabine	*C. dubia*	Reproduction, 7 days, NOEC	50	$1.2 \times 10^{+4}$	Parrella et al. (2014)
Chlorambucil	Mysid	NOEC	10	$7.94 \times 10^{+4}$	ECOSAR estimation
Cisplatin	*D. magna*	Reproduction, 21 days, NOEC	50	$2.0 \times 10^{+1}$	Parrella et al. (2014)
Cyclophosphamide	*D. magna*	Reproduction, 21 days, NOEC	50	$1.12 \times 10^{+6}$	SFT (2006)
Cyproterone	*D. magna*	48 h, EC50	1000	$2.40 \times 10^{+3}$	Franquet-Griell et al. (2015)
Cytarabine	*D. magna*	Reproduction, 21 days, LOEC	10	$3.7 \times 10^{+5}$	Zounkova et al. (2010)
Daunorubicin	Fish	NOEC	10	$2.50 \times 10^{+3}$	ECOSAR estimation
Docetaxel	Fish	NOEC	10	$5.50 \times 10^{+3}$	ECOSAR estimation
Doxorubicin	*B. calyciflorus*	Growth inhibition, 48 h, NOEC	100	$5.00 \times 10^{+4}$	Parrella et al. (2014)
Epirubicin	Fish	NOEC	10	$3.20 \times 10^{+3}$	ECOSAR estimation
Erlotinib	*D. rerio*	Early-life stage, 30 days, NOEC	50	$1.12 \times 10^{+4}$	Roche (2015)
Etoposide	*C. dubia*	Reproduction, 7 days, NOEC	50	$1.95 \times 10^{+3}$	Parrella et al. (2014)
Fludarabine	Daphnid	NOEC	10	$1.75 \times 10^{+4}$	ECOSAR estimation
Fluorouracil	*D. magna*	Reproduction, 672 h, NOEC	10	6.00×10^{-1}	Załęska-Radziwiłł et al. (2011)
Gemcitabine	*D. magna*	Reproduction, 21 days, LOEC	10	$1.00 \times 10^{+5}$	Zounkova et al. (2010)
Goserelin	Green algae	NOEC	10	$2.43 \times 10^{+5}$	ECOSAR estimation
Hydroxycarbamide	*D. rerio*	Growth (length), NOEC	100	$5.70 \times 10^{+7}$	PHARMAS (2014)
Ifosfamide	*C. dubia*	Reproduction, 7 days, NOEC	50	$3.17 \times 10^{+5}$	Russo et al. (2018)
Imatinib	*C. dubia*	Reproduction, 7 days, NOEC	50	$5.40 \times 10^{+0}$	Parrella et al. (2014)
Irinotecan	Mysid	NOEC	10	$4.30 \times 10^{+2}$	ECOSAR estimation
Leuprorelin	Fish	NOEC	10	$4.61 \times 10^{+4}$	ECOSAR estimation
Megestrol	*D. magna*	Mortality, 48 h, LC50	1000	$5.00 \times 10^{+3}$	FDA (1996)
Melphalan	Daphnid	NOEC	10	$1.01 \times 10^{+7}$	ECOSAR estimation
Methotrexate	*X. laevis*	Growth inhibition, 96 h, EC50	1000	$1.50 \times 10^{+1}$	Besse et al. (2012)
Mitomycin	Green Algae	NOEC	10	$4.40 \times 10^{+3}$	ECOSAR estimation
Mycophenolic acid	*S. capricornutum*	Growth inhibition, 96 h, EC50	1000	$4.60 \times 10^{+0}$	Santa-Cruz-Biotechnology (2015)
Paclitaxel	*D. magna*	48 h, LC50	1000	$7.40 \times 10^{+2}$	FDA-CDER (1996)
Prednisone	Daphnid	NOEC	10	$2.48 \times 10^{+5}$	ECOSAR estimation
Tamoxifen	*D. pulex*	Size, reproduction, viability, 56 days, NOEC	10	$6.70 \times 10^{+1}$	Borgatta et al. (2016)
Tegafur	Green Algae	NOEC	10	$4.10 \times 10^{+2}$	ECOSAR estimation
Vincristine	Daphnid	NOEC	10	$2.60 \times 10^{+3}$	ECOSAR estimation
Vinorelbine	Daphnid	NOEC	10	$1.70 \times 10^{+3}$	ECOSAR estimation

* NOEC: No Observed Effect Concentration; EC50: median effective concentration; LC50: lethal concentration 50%; LOEC: lowest-observed-effect concentration.

effluents to surface waters would be expected due to the effect of dilution, this was not always verified in the studies examined herein. According to Fig. 2c and Table 1, the maximum concentrations of cyclophosphamide and fluorouracil were found to be slightly higher in surface waters than in WWTP effluents. Cyclophosphamide is also used to treat livestock in farms, which may justify its occurrence in surface waters (Ferrando-Climent et al., 2014). Similarly, tamoxifen is used for reproductive control or hormonal treatments in livestock, which is then excreted by animals (Ferrando-Climent et al., 2014) and likely incorporated into aquatic environments via surface runoff. Ifosfamide and methotrexate concentrations decreased in surface waters relative to their WWTP effluent concentrations; almost all values were below the detection limit.

Among the lesser-studied cytostatics, relatively high concentrations of mycophenolic acid in surface waters were reported by four different studies: 56.2 (Franquet-Griell et al., 2016), 168 (Giebułtowicz and Nałęcz-Jawecki, 2016), 541 (Santos et al., 2018) and 656 ng L^{-1} (Franquet-Griell et al., 2017a). Mycophenolic acid is produced by many *Penicillium* species and is present in silage in high quantities, therefore it reaches animals and surface waters very easily (Alsberg and Black, 1913; Ojo, 2012). High concentrations of bicalutamide and tegafur were also found in surface waters (254 ng L^{-1} and 56 ng L^{-1}, respectively), suggesting that the overall occurrence of these compounds in surface waters resulted from different scattered sources (Azuma et al., 2015). Vinorelbine was found at a concentration above 50 ng L^{-1} in WWTP effluents but was not detected in surface waters; as previously proposed, this is likely attributable to the dilution of the compound when it enters the aquatic environment (Isidori et al., 2016).

In summary, cyclophosphamide, ifosfamide, tegafur, tamoxifen, bicalutamide, mycophenolic acid, and megestrol occurred at least once at concentrations above 20 ng L^{-1} in surface waters. Erlotinib, bleomycin, capecitabine, gemcitabine, cytarabine, methotrexate, and chlorambucil were found in concentrations of up to 20 ng L^{-1}. Prednisone, cyproterone, azathioprine, goserelin, leuprorelin, irinotecan, epirubicin, etoposide, daunorubicin, doxorubicin, docetaxel, paclitaxel, vinorelbine, vincristine, fludarabine, melphalan, cisplatin, carboplatin, and oxaliplatin were undetectable or unquantifiable (Table 1).

It is worth noting that tamoxifen exhibited an extremely high concentration range (i.e., 9–223 ng L^{-1}) in groundwaters in Spain (López-Serna et al., 2013). Moreover, cisplatin, carboplatin, and oxaliplatin were detected in groundwaters, but could not be accurately quantified (i.e., their concentrations were < 56 ng L^{-1}, < 43 ng L^{-1} and < 36 ng L^{-1}, respectively). These findings clearly highlight the need for more comprehensive monitoring studies aimed at determining the occurrence of cytostatics in aquatic environments to more accurately estimate their risks. Moreover, our observations demonstrate that human exposure to hazardous concentrations of cytostatic compounds through drinking water is not unlikely.

3.2. Importance of MECs to estimate the risk of environmental exposure to cytostatics

As previously explained, based on the review of relevant literature and data extracted from 81 studies, a total of 14 cytostatics were detected in surface waters; namely, bicalutamide, bleomycin, capecitabine, chlorambucil, cyclophosphamide, cytarabine, erlotinib, gemcitabine, ifosfamide, megestrol, methotrexate, mycophenolic acid, tamoxifen, and tegafur. Then, a risk quotient was estimated for each of these cytostatics, including compounds that were undetected in surface

Table 3
Estimated risks to aquatic organisms associated with cytostatic exposure in surface waters worldwide.

Cytostatic	RQ PEC	RQ_{max}	RQ MDL
Azathioprine	<0.01		<0.01
Bicalutamide	<0.01	0.05	<0.01
Bleomycin	<0.01	<0.01	<0.01
Capecitabine	<0.01	<0.01	<0.01
Chlorambucil	<0.01	<0.01	<0.01
Cisplatin	0.01		0.85
Cyclophosphamide	<0.01	<0.01/ <0.01*	<0.01
Cyproterone	<0.01		<0.01
Cytarabine	<0.01	<0.01	<0.01
Daunorubicin	<0.01		0.01
Docetaxel	<0.01		<0.01
Doxorubicin	<0.01		<0.01
Epirubicin	<0.01		<0.01
Erlotinib	<0.01	<0.01	<0.01
Etoposide	<0.01		<0.01
Fludarabine	<0.01		<0.01
Fluorouracil	1.00	963.3*	0.27
Gemcitabine	<0.01	<0.01	<0.01
Goserelin	<0.01		<0.01
Hydroxycarbamide	<0.01	<0.01*	<0.01
Ifosfamide	<0.01	<0.01	<0.01
Imatinib	0.66		6.48
Irinotecan	<0.01		<0.01
Leuprorelin	<0.01		<0.01
Megestrol	<0.01	<0.01	<0.01
Melphalan	<0.01		<0.01
Methotrexate	<0.01	0.33	<0.01
Mitomycin	<0.01		<0.01
Mycophenolic acid	3.61	142.6	0.02
Paclitaxel	<0.01		<0.01
Prednisone	<0.01		<0.01
Tamoxifen	<0.01	3.16	<0.01
Tegafur	<0.01	0.14	<0.01
Vincristine	<0.01		<0.01
Vinorelbine	<0.01		<0.01

Note: PEC values were all obtained from Santos et al. (2017), with the exception of bleomycin, prednisone, and tegafur (Franquet-Griell et al. 2017a) and are compiled in Table SI2 of the Supplementary Information; *calculated based on exception values; Red – high risk; Orange – moderate risk; Yellow- low risk; Green – no risk.

waters but were included in the monitoring plans.

For this purpose, the PNECs used for risk quotient estimation (Eqs. (1) and (2)) were obtained from toxicological studies or ECOSAR estimations whenever experimental data was not found for a particular cytostatic compound (e.g., azathioprine, bleomycin, chlorambucil, daunorubicin, docetaxel, epirubicin, fludarabine, goserelin, irinotecan, leuprorelin, melphalan, mitomycin, prednisone, vincristine, and vinorelbine). No toxicological information (experimental or theoretical) could be found for carboplatin and oxaliplatin. As recommended by risk assessment guidelines, chronic data was always preferred over acute toxicity, even though short-term values may lead to lower PNECs. Table 2 summarizes the PNECs observed for all cytostatics monitored in surface waters. These PNECs correspond to the lowest values obtained from the quotient between chronic or acute toxicity and the assessment factor.

To estimate the maximum cytostatic-associated risk to aquatic organisms, a maximum risk quotient (RQ_{max}; Table 3) was determined for each cytostatic based on its maximum measured concentration in surface waters (MEC_{max}; Table 1). In contrast, risk was also estimated based on the lowest MDL reported in the monitoring studies, since all cytostatics were not detected at least once in surface waters (RQ MDL; Table 3). PEC values and full information can be found in Table SI2.

According to the RQ_{max} values indicated in Table 3, mycophenolic acid and tamoxifen may pose a high risk to aquatic biota ($RQ_{max} \geq 1$). Methotrexate and tegafur are suspected to represent a moderate risk to aquatic organisms, as their RQ_{max} values fall within 0.1 and 1.0; bicalutamide was classified as a low-risk compound ($RQ_{max} = 0.05$). The abnormally high cyclophosphamide, fluorouracil, and hydroxycarbamide concentrations (1907, 578, and 788 ng L^{-1}, respectively) in the Chao Phraya river (Thailand) reported by Usawanuwat et al. were excluded from our risk analysis (Usawanuwat et al., 2014). However, when RQ_{max} is calculated for these extremely high concentrations, fluorouracil is associated with high risk, although cyclophosphamide and hydroxycarbamide continued to be classified as no-risk compounds.

Almost all risk quotients determined from the MDLs reported in the monitoring studies (RQ MDL) were below 0.01, indicating a low risk. However, cisplatin, daunorubicin, fluorouracil, imatinib, and mycophenolic acid were notable exceptions. In these cases, the available analytical methodologies for the quantification of said compounds in surface waters could not rule out their potential adverse effects on aquatic organisms (i.e., risk may exist even if it is not detected). Importantly, cisplatin and daunorubicin are classified by the IARC as Group 2B agents (i.e., possibly carcinogenic to humans) (IARC, 2018b). This clearly highlights the need for sensitive and accurate analytical methods for the identification and quantification of these compounds in water, in order to protect aquatic ecosystems and human health.

When RQs were calculated based on maximum predicted

environmental concentrations in the Iberian Peninsula (RQ PEC; Table 3), an interesting trend was observed. Cytostatics with RQ_{max} values in worldwide surface waters that were indicative of some degree of risk ($RQ_{max} \geq 0.01$) consistently exhibited lower RQ PEC values. No substantial risk was identified for bicalutamide, methotrexate, tamoxifen, and tegafur based on predicted environmental concentrations; however, low (bicalutamide), moderate (methotrexate and tegafur), and high risk (tamoxifen) compounds could be identified based on their measured environmental concentrations. We acknowledge that predicted environmental concentrations are highly region-dependent and that the Iberian Peninsula data considered herein may not be entirely representative of worldwide trends. However, our findings suggest that surface water contamination by cytostatics likely results from different sources, and PEC calculation only accounts for WWTP contamination (Eq. (3)), which may lead to discrepancies between the conclusions made based on predicted and measured concentrations. For instance, although calculations performed with both PECs and MECs identified mycophenolic acid as a potential threat to aquatic biota, the RQ was lower when determined via PECs (Table 3). This highlights the importance of calculating risks based on measured concentrations to validate the accuracy of predicted concentrations.

4. Conclusions

Our study established a precedent for risk assessment based on concentrations measured in surface waters worldwide. To the best of our knowledge, 81 original research articles have reported measured concentrations of cytostatics in different aquatic environments, including hospital effluents, WWTP influents and effluents, and surface waters. Relatively high concentrations of some cytostatics of concern (i.e., mycophenolic acid, bicalutamide, and tamoxifen) were reported in surface waters, which clearly highlights the need for more comprehensive monitoring studies to identify and quantify the occurrence of cytostatics in aquatic environment in order to estimate their risks.

The estimation of the risk posed by cytostatics to aquatic organisms resulted in the identification of priority drugs such as tamoxifen and mycophenolic acid, which may pose a high risk ($RQ \geq 1$); methotrexate and tegafur, with a moderate risk ($0.1 \leq RQ < 1$); and bicalutamide, with a low associated risk ($0.01 \leq RQ < 0.1$). Moreover, our study confirms that the currently available methodologies for the analysis of cisplatin, fluorouracil, daunorubicin, imatinib, and mycophenolic acid in surface waters do not allow for a proper assessment of whether said compounds represent a risk to aquatic organisms. Thus, developing more sensitive and robust analytical methodologies is critical.

Importantly, the RQs obtained from predicted concentrations were consistently lower than those obtained from measured concentrations. Although PECs are highly region-dependent and our study focused on data gathered from the Iberian Peninsula, our observations still suggest that risk assessments based on predicted concentrations may tend to underestimate true cytostatic exposure of aquatic organisms in the environment. PECs only account for WWTP effluents contamination; however, many other contamination sources are contributing to the spread of cytostatics into the environment. In summary, our study identified cytostatics of potential worldwide concern, as well as the need for more sensitive and accurate analytical methods for further monitoring studies. These enhancements will be critical to evaluate the current extent of hazardous compound exposure in aquatic organisms.

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