1 **Psychoactive pharmaceuticals and illicit drugs in coastal waters of North-** 2 **Western Spain: environmental exposure and risk assessment.**

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26 **Abstract:** The knowledge on the presence of pharmaceutical compounds, and possible risks, in
27 coastal and marine systems is still limited. This study represents the first attempt at monitoring
28 psychoactive pharmaceuticals (PaPs) (benzodiazepines and anxiolytics) and illicit drugs (IDs) in
29 the Rías Baixas coastal area of Northwestern Spain, an area of economic and ecological
30 relevance, leader in shellfish production. Fourteen PaPs and 9 IDs were detected in the water
31 samples with venlafaxine (59%), benzoylecgonine (40%), EDDP (40%), and citalopram (36%)
32 showing the highest detection frequencies. The highest concentrations were measured for
33 venlafaxine (291 ng L⁻¹), benzoylecgonine (142 ng L⁻¹), lorazepam (95.9 ng L⁻¹), and citalopram
34 (92.5 ng L⁻¹). Risk assessment, based on hazard quotients suggested that venlafaxine, citalopram,
35 sertraline, and EDDP were present in concentrations potentially able to cause chronic effects in
36 exposed organisms. Based on the results obtained further monitoring of venlafaxine, citalopram,
37 and EDDP in coastal waters is recommended.

39 **Keywords:** Psychoactive drugs, occurrence, seawater, hazard quotients, emerging contaminants

1 Introduction

The use of pharmaceutically active compounds (PhACs) is in an increasing trend, both in terms of expenditure and consumption (OECD, 2011). The growth in the use of psychoactive pharmaceuticals (PaPs), in particular, anxiolytics and antidepressants, has been especially noteworthy. Psychoactive substances commonly used worldwide also include illicit drugs (IDs). Therefore, it is perhaps not-surprising that psychoactive substances (both PaPs and IDs) are among the many PhACs that are frequently detected in surface waters (Brieudes et al., 2017; Fick et al., 2017; Marsik et al., 2017).

Historically, coastal areas have preferentially attracted human settlement. The impact of this human presence, and associated activities, in the surrounding coastal environments is, thus, worth investigating. In this context, a growing number of studies have assessed the presence of PhACs in marine and coastal waters (Alygizakis et al., 2016; Arpin-Pont et al., 2016; Borecka et al., 2015; Gaw et al., 2014; Nödler et al., 2014). However, only a few works focused on psychoactive substances (Jiang et al., 2014; Klosterhaus et al., 2013; Nödler et al., 2016; Nödler et al., 2014; Pereira et al., 2016).

Despite their presence, the risk posed by psychoactive substances in aquatic systems has proven hard to determine, in part due to limited availability of data on their effects in aquatic organisms, communities, and ecosystems (Arnold et al., 2014). Most studies examining the effects of psychoactive compounds in aquatic organisms have focused on freshwater organisms (De Solla et al., 2016; Grabicova et al., 2017; Valdés et al., 2016; Xie et al., 2017). Exposure to PaPs like oxazepam and fluoxetine has been linked to behavioral alterations in fish, e.g., increased activity and feeding rates, and reduced survival and delayed escape time (Brodin et al., 2013; Huerta et

al., 2016; Pelli and Connaughton, 2015). Fluoxetine also produced behavioral alterations in other aquatic organisms, like cephalopods and freshwater crustaceans: alteration of memory processing and learning (Di Poi et al., 2013) and a decrease of feeding rates (De Castro-Català et al., 2017). But exposure to PaPs has been shown to induce more direct effects than behavioral. Potential genotoxic effects of fluoxetine and venlafaxine in fish have been observed at 10 and 50 $\mu\text{g L}^{-1}$, respectively (Thomas et al., 2011). Varied reproductive effects from exposure to fluvoxamine and fluoxetine have been reported in mussels, e.g., increased spawning (Fong, 1998; Fong and Ford, 2014); reduction in larval viability and alteration of steroidal metabolism (Bringolf et al., 2010; Lazzara et al., 2012). Antidepressants (e.g. venlafaxine, citalopram, fluoxetine, sertraline) effects in mussels have been extensively reviewed by Fong and Ford (2014).

In the case of IDs, effects in aquatic organisms have been also reported. Kirla et al. (2016) showed the ability of cocaine to reduce activity and locomotion of zebrafish. Cocaine and its main metabolite (benzoylecgonine) were found reported to be genotoxic and cytotoxic to mussels (Binelli et al., 2012; Maranhão et al., 2017; Parolini et al., 2013).

The seafood industry is of high economic importance to Spain, which ranks as the largest producer of mollusks in Europe and the fifth worldwide (FAO, 2016). Most of the production occurs in the region of Galicia (North-Western Spain) due to the nutrient-rich waters associated with East-Atlantic upwelling areas (Costas-Rodríguez et al., 2010; Doval et al., 2016; Fernández et al., 2016; Figueiras et al., 2002; Lopez-Lopez et al., 2017; Prego et al., 1999) The area selected for this study, the Rías Baixas area (Galicia) is one of the main centers of the fishing, seafood, and associated processing industries in Spain (Bello Bugallo et al., 2013). While of great economic and environmental importance, the environmental pressure in the Rías Baixas is

extremely high. Much of the waste generated by cities, towns, fish farms and seafood processing facilities in the area ends up, with or without treatment, in the *rías* (Rodríguez-Germade et al., 2014; Rubio et al., 2000; Vega et al., 2008), where fish and seafood are growing.

In this context, the main objectives of this study were: 1) performing a preliminary assessment of the presence of PaPs and IDs in coastal waters from the Rías Baixas area in North-Western Spain; 2) assessing the potential risk posed by the presence of these compounds to this coastal zone; and 3) comparing the results obtained to previously published data for other coastal/marine regions around the world.

2 Materials and methods

2.1. Study area

The selected sampling sites for this study were located along the coastline of the Rías Baixas area which includes three different *rías*, namely, Ría de Muros e Noia, Ría de Arousa, and Ría de Pontevedra (Fig. 1). The geographical feature known as a *ría* is occasionally considered as a type of estuary; however, due to their geomorphology and geological origin - they are incised valleys, more similar to fjords, it is generally considered that typical estuarine processes are of limited influence in these systems (Evans and Prego, 2003). As such, the water bodies enclosed within the *ría* can be considered more as coastal waters than as estuaries. In this way, the samples collected in this study have been classified as coastal and compared to other coastal water samples.

The Rías Baixas extend over the Spanish provinces of A Coruña (to the North) and Pontevedra (to the South). The three studied *rías* are home to a combined population of 368,000 inhabitants

(IGE, 2015) and are served by 16 wastewater treatment plants (WWTPs) (Xunta de Galicia, 2017). All of these are equipped with secondary and tertiary treatment technologies, including nutrient removal, disinfection and, in one case, microfiltration (WWTP of Muros). The effluents of these WWTPs are released *via* marine outfalls directly into the *rías* or into the Atlantic coast. As indicated, numerous seafood harvesting and farming activities also take place in the study area with special predominance of mussel farming in culture rafts. The density of these rafts is especially high in the Ría de Arousa (Xunta de Galicia, 2017).

Figure 1: Map of the study area and location of sampling sites

2.2. *Sampling*

Figure 1 shows the locations of the selected sampling sites. A total of 22 grab samples of coastal water and a single sample from a WWTP outflow were collected during the second and third week of July 2015. At least one of the following characteristics was taken into consideration when selecting the sampling points: distance from, and ease of access to, the discharge zone for a WWTP, and distance from densely populated municipalities. All water samples, except Noia sampling point (Ría de Muros e Noia), were collected in the vicinity of the WWTP outfalls, and thus, in the mixing zone. These sampling locations were located either within meters from the coastline or 1-2 Km offshore (in tourist areas). In the case of the Noia sampling point, the sample was taken from the treatment plant outflow (before dilution in seawater) as it proved impossible to obtain a sample of seawater in the mixing zone. In each sampling point, 0.5 liters of water were collected in opaque PET bottles previously washed with distilled water. All samples were stored refrigerated and, once fieldwork was completed, they were frozen at -20 °C and maintained at this temperature in the dark until analysis. Table 1 shows the samples collected, the sampling locations and some basic water chemistry parameters.

Table 1. Summary of the coastal water samples collected, location of sampling sites and basic water chemistry parameters.

Ria	Samples		Location (decimal degrees)		pH	Conductivity (mS/cm)
	Code	Name	Latitude	Longitude		
Muros e Noia	N1	Noia (WWTP Effluent)	42.791624	-8.90426	8.06	3.41
Muros e Noia	N2	Esteiro	42.780889	-8.975481	8.06	51.71
Muros e Noia	N3	Muros	42.780514	-9.049539	8.14	52.91
Muros e Noia	N4	Carnota	42.726786	-9.082357	8.13	52.50
Muros e Noia	N5	Porto do Son	42.733104	-9.008448	8.23	12.22
Arousa	AR1	Rianxo	42.637179	-8.822977	8.17	39.44
Arousa	AR2	Boiro	42.624773	-8.898591	8.15	52.63
Arousa	AR3	La Puebla	42.605311	-8.925303	8.15	51.59
Arousa	AR4	Ribeira	42.557275	-8.979453	8.13	52.00
Arousa	AR5	Salvora	42.479966	-9.000078	7.94	51.53
Arousa	AR6	O Grove	42.50833	-8.879009	8.13	53.38
Arousa	AR7	Meloxo	42.500024	-8.89653	8.19	50.29
Arousa	AR8	Dena	42.46207	-8.830783	8.25	51.91
Arousa	AR9	Ribadumia	42.520352	-8.846725	7.95	19.65
Arousa	AR10	Cambados	42.514623	-8.830583	8.14	53.07
Arousa	AR11	A Illa	42.523366	-8.880433	8.03	52.56
Arousa	AR12	Canal	42.588041	-8.83186	8.14	53.45
Arousa	AR13	Villagarcia	42.606066	-8.784769	8.13	53.09
Pontevedra	PO1	Placeres	42.406386	-8.702766	8.04	28.00
Pontevedra	PO2	Tambo	42.413307	-8.705033	8.20	53.10
Pontevedra	PO3	Marin	42.402519	-8.713282	8.17	36.86
Pontevedra	PO4	Sanxenxo	42.389957	-8.809515	8.12	52.30
Pontevedra	PO5	Bueu	42.339566	-8.786919	8.15	48.43

2.3. *Analysis*

In this study, we monitored a total of 16 PaPs belonging to the groups of benzodiazepines and anxiolytics, as well as 19 IDs, including cocaine, amphetamine-type stimulants, cannabinoids, opioids, and lysergic compounds. The full list of compounds is provided in Table 2.

For analysis, target drugs were preconcentrated onto disposable PLRP-s cartridges using a sample processor Symbiosis Pico (Spark Holland, Emmen, The Netherlands) and determined by means of liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a 4000QTRAP hybrid quadrupole-linear ion trap system (Applied Biosystems-Sciex, Foster City, CA). Both instruments were connected in series allowing the fully automated analysis of the samples. Manual pre-treatment of the samples, performed upon their reception in the laboratory, just required fortification of the samples with a mixture of isotopically labeled compounds used as surrogate standards in the quantification process, and subsequent vacuum filtration (1 μ m glass fiber over 0.45 μ m nylon membrane filters).

Five-mL of the water samples were passed through the cartridges previously conditioned with 1 mL of acetonitrile followed by 1 mL of LC-grade water. The cartridges were then washed with 5 mL of LC-grade water to remove salt excess before analyte elution and avoid its precipitation in the instrument. Analytes retained were eluted with the chromatographic mobile phase that consisted of LC-grade water containing 20 mM ammonium formate and acetonitrile. Chromatographic separation was carried out with a column Purospher Star RP-18, 125 mm x 2 mm i.d., 5 μ m particle size (Merck, Darmstadt, Germany). Detection was performed under positive electrospray ionization mode, by acquiring two selected reaction monitoring transitions per target compound. Analytical standards used were of high-purity (>96%) (Cerilliant, Round

Rock, TX). All solvents used and formic acid were purchased from Merck, and ammonium formate was acquired from Sigma-Aldrich (Steinheim, Germany).

Quantification was performed by the isotope dilution method based on the response ratio of the analyte and its corresponding surrogate standard found in calibration solutions (LC-grade water fortified with the analytes within the range 0.1-500 ng/L, and a fix concentration of surrogate standards). Calibration curves, constructed within the studied range using a linear least square model, presented coefficients of determination above 0.99.

The method, which is based on a methodology previously developed for analysis of psychoactive drugs in wastewater (where washing of the cartridges is performed with 1 mL instead of 5 mL of LC-grade water) (López-García et al. 2018), was shown to be accurate (with relative recoveries between 85 and 116%, except for heroin (72%)) and precise (with relative standard deviations below 9 %, except in the case of THC-COOH (18%)), thanks to the use of surrogate standards (available for all compounds except methoxetamine). Analyte relative recoveries and relative standard deviations obtained after online SPE-LC-MS/MS analysis of a coastal water sample fortified at a concentration of 50 ng/L (n=5) are shown in Table 2.

The method exhibited also satisfactory sensitivity, with limits of detection (LODs) and quantification (LOQs), calculated considering a signal-to-noise ratio of 3 and 10, respectively, below 2.6 ng/L and 9.5 ng/L, respectively. The only exception in this respect was THC-COOH, which under the selected conditions (positive ionization mode) exhibited a LOD of 10 ng/L and a LOQ of 42 ng/L. These limits are listed in Table 2.

181 **Table 2.** Method performance in terms of analyte recovery (R), repeatability (RSD), and limits
182 of detection and quantification, and frequency of detection (Freq. and Positive Samples) of each
183 investigated analyte in the samples investigated.

Name	Code	R* (%)	RSD* (%)	LOD (ng L ⁻¹)	LOQ (ng L ⁻¹)	Freq.† (%)	Positive samples†
<i>Benzodiazepines</i>							
Alprazolam	ALP	109	3.6	0.19	0.63	18.2	4 / 22
α-Hydroxyalprazolam	OH-ALP	102	4.6	0.30	1.25	9.1	2 / 22
Diazepam	DIAZ	96	5.3	0.16	0.56	9.1	2 / 22
Lorazepam	LORZ	100	4.5	2.55	9.49	13.6	3 / 22
Midazolam	MIDZ	102	1.7	0.18	0.62	0	0 / 22
α -Hydroxymidazolam	OH-IMI	104	6.1	0.51	1.87	4.6	1 / 22
Lormetazepam	LORM	102	4.3	0.21	0.71	13.6	3 / 22
Temazepam	TEMZ	106	3.4	1.55	3.84	9.1	2 / 22
Oxazepam	OXAZ	92	6.5	0.70	2.31	13.6	3 / 22
<i>Antidepressants</i>							
Citalopram	CTLP	99	2.68	0.27	0.45	36.4	8 / 22
Fluoxetine	FLU	92	7.7	0.18	0.62	22.7	5 / 22
Hydroxyzine	HDXZ	100	3.9	0.14	0.31	4.6	1 / 22
Sertraline	SERT	97	7.8	0.35	1.70	13.6	3 / 22
Chlorpromazine	CHLR	99	4.8	0.11	0.33	0	0 / 22
Venlafaxine	VEN	102	3.8	0.19	0.65	59.1	13 / 22
Zolpidem	ZOLP	85	2.9	0.10	0.55	9.1	2 / 22
<i>Cocainics</i>							
Cocaine	COC	103	5.6	0.11	0.58	18.2	4 / 22
Benzoyllecgonine	BE	116	7.4	0.43	1.44	40.9	9 / 22
Cocaethylene	CE	102	2.4	0.60	2.01	4.6	1 / 22
<i>Amphetamine-type stimulants</i>							
Ephedrine	EPH	102	4.1	0.86	2.71	13.6	3 / 22
Amphetamine	AM	110	4.6	1.05	3.51	0	0 / 22
Methamphetamine	MA	94	9.1	0.11	0.23	0	0 / 22
3,4-methylenedioxymethamphetamine	MDMA	101	3.8	0.42	1.32	13.6	3 / 22
Mephedrone	MEPH	98	6.3	0.14	0.37	0	0 / 22
3,4-Methylene-dioxypyrovalerone	MDPV	96	3.8	0.28	0.93	0	0 / 22
Methoxetamine	MTHX	94	3.6	0.11	0.36	0	0 / 22
Ketamine	KET	107	4.8	0.23	0.79	0	0 / 22
<i>Opioids/opiates</i>							
Morphine	MOR	103	5.2	0.92	3.06	18.2	4 / 22
6-acetylmorphine	6ACM	111	2.9	0.73	2.46	0	0 / 22
AH7921	AH7921	97	5.3	0.38	1.26	0	0 / 22
Heroin	HER	72	5.0	0.80	2.71	0	0 / 22
Methadone	METH	103	3.9	0.07	0.15	31.8	7 / 22
2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium	EDDP	105	4.8	0.03	0.09	40.9	9 / 22
<i>Cannabinoids</i>							
11-nor-9-carboxy-Δ ⁹ THC	THC-COOH	96	17.7	10.00	42.00	0	0 / 22
<i>Lysergic compounds</i>							
Lysergic acid diethylamide	LSD	93	5.9	0.10	0.33	0	0 / 22

184 *Replicate analysis of n=5 samples fortified at a level of 50 ng/L

185 †WWTP effluent sample (N1_Noia) not considered

2.4. *Exposure characterization*

The distribution of concentrations observed for each compound, for all samples collected in this study – including censored data below the LOD or interval data between the LOD and the LOQ–, was examined following the methodologies described in Rodriguez-Gil et al. (2018). Briefly, empirical environmental exposure distributions (EEDs) were generated from the collected exposure data by fitting the data to a gamma distribution via maximum likelihood estimation (MLE) with the `fitdistr` function in the R package `fitdistrplus` (Delignette-Muller et al., 2010; R Development Core Team, 2008). The fit to other distributions (Logistic, Weibull, Gompertz, Bur, and Pareto) was also tested and the best fit was chosen via comparison of the Akaike information criterion (AIC). The gamma distribution provided the best fit in all cases. EEDs were only generated for compounds that showed at least a 10% detection frequency.

2.5. *Risk characterization*

The hazard quotient (HQ) method [also known as risk quotients (RQ), or risk characterization ratios (RCRs)] was used in order to carry out a screening-level, deterministic assessment of the risk posed by the presence of the studied compounds in the area of study. The HQ is defined by the United States Environmental Protection Agency (US EPA) as the ratio between potential exposure to a substance and the concentration thereof below which no adverse effects are expected (US EPA, 1997). This is usually calculated as the ratio between two values: the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) (ECHA, 2012).

Given the continuous release of the assessed compounds into the studied area, and following European Union's recommendations (EMEA, 2006; Ferrari et al., 2004), chronic exposure was

considered as the most appropriate exposure scenario for this assessment. The PNEC for each of the studied compounds, shown in Table 3, was determined on the basis of a benchmark concentration selected as the lowest reliable toxicity value from the available experimental effects data in aquatic organisms. In order to collect any available laboratory toxicity data, a search was carried out in the US EPA ECOTOX database (US EPA, 2017) as well as in other literature sources not contained in the ECOTOX database via searches in the PubMed database. All the chosen endpoints were directly related to the fitness of the organism, and impairment of any of them would result in alterations in survival, growth or reproduction, all of which could have a direct impact at the population level. Toxicity data for those compounds for which empirical laboratory toxicity data were not available were obtained via Quantitative Structure-Activity Relationship (QSAR) models. The Ecological Structure Activity Relationships (ECOSAR) model of the US EPA (U.S. Environmental Protection Agency, 2012) was used for this purpose. The lowest chronic toxicity value for the most sensitive organisms amongst the collected data was used as the benchmark concentration for the derivation of a PNEC to ensure that a worst-case scenario was being considered. An appropriate assessment factor (AF), selected according to ECHA (2008), was applied to this benchmark concentration on the basis of the nature/quantity of the dataset from which it was selected. An attempt was made to compile and use toxicity data for marine and coastal species. The full list of toxicological data used to calculate the HQs for each compound, as well as the different AFs employed is provided in Table 3.

Table 3. Summary of the lowest toxicological data for algae, crustaceans and fish available in the literature for the compounds detected. The selected value, the applied assessment factor (AF), and the calculated PNEC are also presented (all data in mg L⁻¹).

Compound	Algae			Crustaceans			Fish			Selected value	AF	PNEC
	Value	Type	Source	Value	Type	Source	Value	Type	Source			
<i>Cocainics</i>												
COC	1.47E+00	ChV	ECOSAR	4.59E-01	ChV	ECOSAR	2.34E+00	ChV	ECOSAR	4.59E-01	1000	4.59E-04
BE	2.63E+03	ChV	ECOSAR	3.84E+02	ChV	ECOSAR	1.00E+00	NOEC	(García-Camero et al., 2015)	1.00E+00	100	1.00E-02
CE	7.18E-01	ChV	ECOSAR	2.56E-01	ChV	ECOSAR	1.03E+00	ChV		ECOSAR	2.56E-01	1000
<i>Amphetamine-type stimulants</i>												
EPH	3.13E+00	NOEC	(ECHA, 2016)	5.61E+01	EC50	(ECHA, 2016)	4.60E+02	LC50	(ECHA, 2016)	3.13E+00	100	3.13E-02
MDMA	7.83E-01	ChV	ECOSAR	2.23E-01	ChV	ECOSAR	8.60E-01	ChV	ECOSAR	2.23E-01	1000	2.23E-04
<i>Opioids</i>												
MOR	2.38E+00	ChV	ECOSAR	8.50E-02	ChV	ECOSAR	5.05E-01	ChV	ECOSAR	8.50E-02	1000	8.50E-05
METH	6.90E-02	ChV	ECOSAR	3.60E-02	ChV	ECOSAR	6.10E-02	ChV	ECOSAR	3.60E-02	1000	3.60E-05
EDDP	1.90E-02	ChV	ECOSAR	1.20E-02	ChV	ECOSAR	1.30E-02	ChV	ECOSAR	1.20E-02	1000	1.20E-05
<i>Cannabinoids</i>												
THC-COOH	7.40E-02	ChV	ECOSAR	9.00E-03	ChV	ECOSAR	5.00E-03	ChV	ECOSAR	5.00E-03	1000	5.00E-06

(*) (Q)SAR data for salt water species
 ChV, the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC);
 IC50, half maximal inhibitory concentration; EC50 lowest median effective concentration value; LC50, lowest median lethal concentration value.

Compound	Algae			Crustaceans			Fish			Selected value	AF	PNEC
	Value	Type	Source	Value	Type	Source	Value	Type	Source			
Benzodiazepines												
ALP	1.00E+00	EC50	ECOSAR	1.41E-01	Chv	ECOSAR	1.8E-02	ChV	ECOSAR	1.8E-02	1000	1.80E-05
OH - ALP	6.17E+00	ChV	ECOSAR	1.19E+00	ChV	ECOSAR	1.42E-01	ChV	ECOSAR	1.42E-01	1000	1.42E-04
DIAZ	1.65E+01	IC50	(Nunes et al., 2005)	4.64E+00	EC50	(Lilius et al., 1994)	2.91E-01	NOEC	(Oggier et al., 2010)	2.91E-01	100	2.91E-03
LORZ	1.88E+00	ChV	ECOSAR	3.28E+00	ChV	ECOSAR	1.07E-01	ChV	ECOSAR	1.07E-01	1000	1.07E-04
OH - IMI	2.46E-01	ChV	ECOSAR	5.10E-02	ChV	ECOSAR	5.10E-02	ChV	ECOSAR	5.10E-02	1000	5.10E-05
LORM	2.33E+00	ChV	ECOSAR	4.40E+00	ChV	ECOSAR	1.34E-01	ChV	ECOSAR	1.34E-01	1000	1.34E-04
TEMZ	2.28E+00	ChV	ECOSAR	4.47E+00	ChV	ECOSAR	1.32E-01	ChV	ECOSAR	1.32E-01	1000	1.32E-04
OXAZ	1.83E+00	ChV	ECOSAR	3.32E+00	ChV	ECOSAR	1.05E-01	ChV	ECOSAR	1.05E-01	1000	1.05E-04
Antidepressants												
CTLP	1.38E-01	ChV	ECOSAR	8.00E-01	NOE C	(Henry et al., 2004)	1.00E-03	NOEC	(Olsén et al., 2014)	1.00E-03	50	2.00E-05
FLU	1.70E-01	EC50	(DeLorenzo and Fleming, 2008)	3.60E-02	NOE C	(Flaherty and Dodson, 2005)	5.40E-04	NOEC	(Mennigen et al., 2010)	5.40E-04	50	1.08E-05
HDXZ	1.35E+00	ChV	ECOSAR	4.43E-01	ChV	ECOSAR	2.13E+00	ChV	ECOSAR	4.43E-01	1000	4.43E-04
SERT	1.21E-02	IC50	(Johnson et al., 2007)	3.20E-02	NOE C	(Minagh et al., 2009)	1.43E-01	LC50	(Johnson, 2004)	1.21E-02	100	1.21E-04
VEN	2.41E-01	ChV	ECOSAR	1.01E-01	ChV	ECOSAR	2.28E-04	NOEC	(Galus et al., 2013)	2.28E-04	100	2.28E-06
ZOLP	1.13E-01	ChV	ECOSAR	1.90E-02	ChV	ECOSAR	1.70E-02	ChV	ECOSAR	1.70E-02	1000	1.70E-05

238 (*) (Q)SAR data for salt water species

239 ChV, the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC);

240 IC50, half maximal inhibitory concentration; EC50 lowest median effective concentration value; LC50, lowest median lethal
 241 concentration value.

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243

244 The exposure value used in this study was the measured environmental concentration (MEC) in
245 each sampling location. For samples with a measured concentration below the LOD, a value of
246 LOD/2 was used as the MEC. For samples between LOD and LOQ, the midpoint between these
247 two values was used as the MEC. Substances that were below the LOD in all sampling points
248 were excluded from the risk characterization (EFSA, 2010).

249 The final HQ was calculated as $HQ = MEC / PNEC$, where the $PNEC = \text{Benchmark}$
250 $\text{concentration} / AF$. If the value of HQ is less than 0.1, no adverse effects are expected; if the
251 value is between 0.1 and 1, possible adverse effects should be taken into consideration; if the
252 value obtained is between 1 and 10, it is probable that adverse effects may occur; finally, if HQ
253 is greater than 10, adverse effects are likely (US EPA, 1997).

254 In order to provide a way of comparing the risk observed in the different sampling sites, Toxic
255 Units (TUs) were generated for each site as the sum of all HQs calculated for that particular site.

256

257 **3 Results and discussion**

258 *3.1. Psychoactive substances in the study area*

259 Table 2 summarises the detection frequency of the different compounds for the whole dataset
260 compiled in this study. The full list of measured concentrations for those sites where at least one
261 compound was detected is presented in Tables 4 and 5.

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263

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Table 4. Concentration (ng L⁻¹) of the psychoactive pharmaceuticals in the investigated samples and total amount found for each compound /ría. Only sampling sites for which at least one compound was measured about the LOD are shown.

Sample	ALP	OH-ALP	DIAZ	LORZ	OH-IMI	LORM	TEMZ	OXAZ	CTLP	FLU	HDXZ	SERT	VEN	ZOLP	Site sum
<i>Ría de Muros e Noia</i>															
N1_Noia (WWTP eff.)	5.85	5.49	3.47	69.00	<0.51	23.70	<1.15	34.60	66.40	22.70	3.09	5.67	205.00	<0.10	444.97
N4_Carnota	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	<0.27	<0.18	<0.14	<0.35	2.01	<0.10	2.01
N5_Porto do Son	10.80	12.90	5.22	95.90	5.05	42.80	23.60	47.70	92.50	10.60	0.57	11.50	291.00	1.17	651.31
Compound Ría sum*	10.80	12.90	5.22	95.90	5.05	42.80	23.60	47.70	92.50	10.60	0.57	11.50	293.01	1.17	653.32*
<i>Ría de Arousa</i>															
AR1_Rianxo	7.97	10.70	3.12	63.30	<0.51	21.90	16.70	59.00	45.10	9.27	<0.14	15.30	180.00	1.46	433.82
AR2_Boiro	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	<0.27	<0.18	<0.14	2.48	0.69	<0.10	3.17
AR3_La Puebla	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	2.16	<0.18	<0.14	<0.35	11.30	<0.10	13.46
AR7_Meloxo	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	7.58	1.27	<0.14	<0.35	32.70	<0.10	41.55
AR8_Dena	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	<0.27	<0.18	<0.14	<0.35	2.41	<0.10	2.41
AR9_Ribadumia	1.16	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	9.79	<0.18	<0.14	<0.35	39.60	<0.10	39.6
AR11_A Illa	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	4.06	0.60	<0.14	<0.35	16.50	<0.10	16.5
Compound Ría sum	9.13	10.70	3.12	63.30	-	21.90	16.70	59.00	68.69	11.14	-	17.78	283.20	1.46	550.51
<i>Ría de Pontevedra</i>															
PO1_Placeres	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	0.36†	<0.18	<0.14	<0.35	1.45	<0.10	1.81
PO2_Tambo	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	<0.27	<0.18	<0.14	<0.35	0.42†	<0.10	0.42
PO3_Marin	<0.19	<0.30	<0.16	<2.55	<0.51	<0.21	<1.15	<0.70	<0.27	<0.18	<0.14	<0.35	0.42†	<0.10	0.42
PO5_Bueu	1.22	<0.30	<0.16	6.02†	<0.51	3.66	<1.15	6.24	10.80	2.14	<0.14	<0.35	36.60	<0.10	66.68
Compound Ría sum	1.22	-	-	6.02	-	3.66	-	6.24	10.80	2.14	-	-	38.89	-	69.33

*WWTP effluent sample (N1_Noia) not considered in the sum

† Samples between LOD and LOQ levels, numeric value calculated as LOD + ((LOQ-LOD)/2).

Table 5. Concentration (ng L⁻¹) of the illicit drugs and metabolites in the investigated samples and total amount found for each compound /ría. Only sampling sites for which at least one compound was measured about the LOD are shown.

Sample	COC	BE	CE	EPH	MDM A	MOR	METH	EDDP	THC- COOH	Site sum
<i>Ría de Muros e Noia</i>										
N1_ Noia (WWTP eff.)	295.00	972.00	<0.60	495.00	7.81	136.00	41.20	83.80	256.00	2286.81
N2_Esteiro	<0.11	<0.43 0.94	<0.60	<0.86	10.00	<0.92	<0.07	<0.03	<10.00	10.00
N4_Carnota	<0.11	(**)	<0.60	<0.86	<0.42	<0.92	<0.07	1.02	<10.00	1.96
N5_Porto do Son	<0.11	11.20	<0.60	57.80	<0.42	15.70	22.40	71.70	<10.00	178.80
Compound Ría sum*	-	12.14	-	57.80	10.00	15.70	22.40	72.72	-	190.76*
<i>Ría de Arousa</i>										
AR1_Rianxo	<0.11	18.70	<0.60	18.00	2.60	<0.92	22.70	67.60	<10.00	129.60
AR2_Boiro	<0.11	<0.43	<0.60	<0.86	<0.42	<0.92	0.11†	0.46	<10.00	0.57
AR3_La Puebla	<0.11	7.13	<0.60	<0.86	<0.42	3.33	2.69	6.71	<10.00	19.86
AR7_Meloxo	<0.11	<0.43	<0.60	<0.86	<0.42	<0.92	2.45	8.26	<10.00	10.71
AR9_Ribadumia	<0.11	1.50	<0.60	<0.86	<0.42	<0.92	<0.07	0.06†	<10.00	1.56
AR11_A Illa	42.30	142.00	5.20	<0.86	2.28	8.82	0.11†	1.12	<10.00	201.83
Compound Ría sum	42.30	169.33	5.20	18.00	4.88	12.15	28.06	84.21	-	364.13
<i>Ría de Pontevedra</i>										
PO1_Placeres	5.51	4.16	<0.60	<0.86	<0.42	<0.92	<0.07	<0.03	<10.00	9.67
PO3_Marin	20.60	6.78	<0.60	<0.86	<0.42	<0.92	<0.07	<0.03	<10.00	27.38
PO5_Bueu	7.52	46.00	<0.60	8.48	<0.42	3.22	3.09	11.40	<10.00	79.71
Compound Ría sum	33.63	56.94	-	8.48	-	3.22	3.09	11.40	-	116.76

* WWTP effluent sample (N1_Noia) not considered in the sum

†Samples between LOD and LOQ levels, numeric value calculated as LOD + ((LOQ-LOD)/2)

3.1.1. *Psychoactive pharmaceuticals*

Fourteen out of the 16 analyzed PaPs were detected in at least one of the collected samples. Venlafaxine was the most frequently detected compound among all collected coastal water samples, being detected in 59 % of the samples (Noia WWTP effluent excluded). Citalopram was the second most ubiquitous PaP with a detection frequency of 36 %, followed by fluoxetine (23 %) and alprazolam (18 %). Table 6 summarizes the upper centiles of the EEDs generated for those compounds with > 10% detection frequency. Venlafaxine appears as the compound with the highest measured concentration (291 ng L⁻¹), as well as the highest estimated 99th centile (384 ng L⁻¹). It is interesting to notice how for all compounds, with the exception of venlafaxine, the estimated 50th centile of the distribution falls below the compound's LOD. While this is consistent with the general trends observed in detection frequencies, this approach actually provides a numerical value that is directly comparable with the LOD. The distribution of measured concentrations for each compound with > 10% detection frequency is presented in Figure 2. This figure also compares these measured data with the 50th and 99th centile of the distribution as well as the LOD and PNEC for each compound.

When examining the geographic distribution of the samples, all the analyzed PaPs, with the exception of midazolam and chlorpromazine, were detected in at least one sample collected from the Ría de Muros e Noia. However, two of the 5 sampling locations within this *ría* (N2_Esteiro and N3_Muros) showed no detectable concentrations of any of the analyzed PaPs. The highest concentrations in this *ría* were registered for venlafaxine (291 ng L⁻¹), followed by lorazepam (96 ng L⁻¹), and citalopram (93 ng L⁻¹), all measured in the same location (N5_Porto do Son), which showed the highest total load of PaPs with a total concentration of 651 ng PaPs L⁻¹. A

sample of undiluted effluent of the Noia WWTP was also collected in this *ría*. Consistent with what was observed in the coastal (diluted) water samples, venlafaxine was the PaP that presented the highest concentration measured in this sample (205 ng L⁻¹).

Table 6. Summary of upper centiles of the Environmental Exposure Distributions (EEDs) generated from the concentrations (including wastewater effluent) observed in the Rías Baixas area. The maximum concentration measured for each compound and the location where this sample was collected are also presented. EEDs were only calculated for compounds showing >10 % detection. All values are in ng L⁻¹.

Comp.	50 th centile	75 th centile	99 th centile	Max conc.	Site of max conc.
<i>Psychoactive pharmaceuticals</i>					
VEN	7.09E-01 (1.13E-02 - 5.82)	1.60E+01 (1.73 - 4.62E+01)	3.84E+02 (63.09 - 775.35)	291	N5
LORZ	2.30E-06 (0 - 1.31)	7.2E-02 (0 - 4.64)	1.80E+02 (3.40 - 3.52E+02)	95.9	N5
CTLP	1.95E-02 (0 - 7.14E-01)	2.06 (2.95E-2 - 9.90)	1.33E+02 (2.04E+01 - 2.81E+02)	92.5	N5
OXAZ	1.34E-08 (0 - 6.2E-03)	8E-03 (0 - 1.60)	1.32E+02 (8.33 - 2.43E+02)	59.0	AR1
LORM	2.00E-10 (0 - 9E-04)	1E-03 (0 - 5.72E-01)	8.31E+1 (4.74 - 1.71E+02)	42.8	N5
SERT	1.30E-07 (0 - 7.7E-03)	8E-03 (0 - 6.95E-01)	3.26E+01 (3.32 - 5.87E+01)	15.3	AR1
FLU	2.763E-04 (0 - 7.33E-02)	1.28E-01 (0 - 1.32)	2.12E+01 (1.97 - 3.83E+01)	10.6	N5
ALP	1.21E-05 (0 - 3.45E-02)	3.8E-02 (0 - 1.00)	2.10E+01 (1.64 - 4.12E+01)	10.8	N5
<i>Illicit drugs</i>					
BE	9.67E-02 (0 - 1.66)	4.40 (0.24 - 16.23)	166.41 (23.52 - 393.81)	142	AR11
EDDP	3.62E-03 (0 - 2.68E-1)	1.12 (3.3E-3 - 7.52)	143.48 (17.13 - 301.48)	71.7	N5
EPH	1.51E-07 (0 - 4.03E-2)	1.7E-2 (0 - 2.81)	95.26 (11.30 - 202.33)	57.8	N5
COC	5.75E-08 (0 - 1.07E-2)	1.1E-2 (0 - 1.37)	86.49 (16.67 - 171.43)	42.3	AR11
METH	7.38E-04 (0 - 9.85E-2)	0.30 (2E-04 - 2.38)	46.71 (4.74 - 92.12)	22.7	AR1
MOR	2.41E-03 (0 - 3.33E-1)	3.33E-1 (0 - 2.55)	25.61 (4.40 - 46.33)	15.7	N5

Figure 2: Summary of measured concentrations for compounds showing >10% detection frequency. Additionally, the 99th (red diamonds) and 50th (blue diamonds) centiles of the calculated environmental exposure distribution (EED) for each compound are presented. The red-shaded area represents concentrations above the predicted no-effect concentration (PNEC) for each compound, while the grey-shaded area represents concentrations below the limit of detection (LOD) for each compound. The numbers of the framed boxes indicate the number of samples below the LOD (remaining samples represented by symbols in the figure).

Twelve of the 16 analyzed PaPs were detected, at least once, in 7 out of the 13 sites sampled in the Ría de Arousa (AR1_Rianxo, AR2_Boiro, AR3_La Puebla, AR7_Meloxo, AR8_Dena, AR9_Ribadumia, and AR11_A Illa). The highest concentrations of PaPs were measured in AR1_Rianxo (total (sum) concentration of PaPs of 434 ng L⁻¹), with venlafaxine (180 ng L⁻¹), lorazepam (63 ng L⁻¹) and oxazepam (59 ng L⁻¹) as the most abundant compounds.

Seven out of the 16 analyzed PaPs were detected, at least once, in 4 out of the 5 sites sampled in the Ría de Pontevedra (all compounds were below the LOD in the sample from N4_Sanxenxo).

The highest measured concentrations were for venlafaxine (37 ng L⁻¹), followed by citalopram

(11 ng L⁻¹) and oxazepam (6.2 ng L⁻¹), all of them measured in PO5_Bueu. The total sum of PaPs for this point was 61 ng L⁻¹.

3.1.2. *Illicit drugs*

As summarised in Table 2, nine out of the 19 IDs analyzed in this study were detected in at least one sample.

Benzoylecgonine (metabolite of cocaine) and EDDP (metabolite of methadone) were the most commonly detected IDs, both with a 41 % frequency of detection (excluding the Noia WWTP sample), followed by methadone (32 %). Table 6 summarizes the upper centiles of the EEDs generated for those compounds with > 10% detection frequency. Benzoylecgonine appears as the compound with the highest measured concentration (142 ng L⁻¹), as well as the highest estimated 99th centile (166 ng L⁻¹). Similarly to what was observed for the PaPs, the estimated 50th centile of the distribution, for all IDs, falls below each compound's LOD. The distribution of measured concentrations for each compound with > 10% detection frequency is presented in Figure 2.

When exploring the geographic distribution of these compounds in the Rías Baixas area, 6 out of the 19 analyzed compounds (benzoylecgonine, ephedrine, MDMA, morphine, methadone, and EDDP) were detected in at least one sample from 3 sites in the Ría de Muros e Noia (excluding the WWTP effluent sample). EDDP showed the highest concentration in this *ría* (72 ng L⁻¹) followed by ephedrine (58 ng L⁻¹), both measured at N5_Porto do Son. This sampling point (N5_Porto do Son) showed the highest loads of IDs in this *ría* with a total sum of 179 ng L⁻¹. The WWTP effluent sample collected in this *ría* (N1_Noia WWTP) contained the same 6 compounds detected in the coastal water samples, plus cocaine and THC-COOH. The differences observed between this effluent sample and the coastal water samples were much larger for the

IDs than for the PaPs. Benzoylecgonine concentrations in this sample reached 972 ng L⁻¹ followed by ephedrine (495 ng L⁻¹), cocaine (295 ng L⁻¹), and THC-COOH (256 ng L⁻¹). Interestingly, neither cocaine nor THC-COOH was detected elsewhere in this *ría*. In fact, THC-COOH was not detected in any other sample in this study.

The Ría de Arousa showed the largest number of detected IDs with 8 (cocaine, benzoylecgonine, cocaethylene, ephedrine, MDMA, morphine, methadone, and EDDP) out of the 19 measured compounds being detected in at least one of 6 sites within this *ría*. The most abundant ID was benzoylecgonine (142 ng L⁻¹), followed by EDDP (68 ng L⁻¹) and cocaine (42 ng L⁻¹). AR11_A Illa was the site presenting the highest loads of IDs in this *ría*, with a total sum of 202 ng L⁻¹. From an epidemiological point of view, this *ría* shows very interesting results. While AR11_A Illa shows high concentrations of cocaine and its metabolites and very low levels of methadone and EDDP, Rianxo presents a completely opposite pattern, with almost no presence of cocaine and its metabolites, and noticeably presence of methadone and its metabolite.

Only 6 IDs were detected in 3 sites within the Ría de Pontevedra (cocaine, benzoylecgonine, ephedrine, morphine, methadone, and EDDP). The highest concentrations were measured for cocaine (21 ng L⁻¹ at PO3_Marín) and benzoylecgonine (46 ng L⁻¹ at PO5_Bueu). PO5_Bueu showed the highest total loads of IDs in this *ría* with a sum of 80 ng L⁻¹. In general, ID concentrations were lower in this *ría* than in the other two.

It is also interesting that in the case of PO1_Placeres and PO3_Marin cocaine was at a higher concentration than its metabolite benzoylecgonine, when according to excretion rates their relative abundance should be opposite.

3.2. Risk characterization

A summary of the considered toxicity values, assessment factors and final PNECs used for HQ calculation is presented in Table 3. The calculated HQs are presented in Table 7 for the PaPs and Table 8 for the IDs. Additionally, Figure 2 provides a visual representation of the relationship between the measured concentrations (MEC), the PNECs and the HQ for the different compounds that showed a detection frequency > 10%.

Regarding PaPs, venlafaxine was the compound that was most often present in concentrations above the PNEC ($HQ > 1$), exceeding this limit in 8 of the 22 sampled sites (excluding the WWTP effluent). In 6 out of these 8 points, the HQ was higher than 10, indicating a high likelihood of effects. Furthermore, the concentration of venlafaxine at N5_Porto do Son (Ría de Muros e Noia) resulted in an HQ of 127.9, indicating that the environmental concentration of venlafaxine in the water at this site was over 100 times higher than the chosen PNEC of 2.28 ng L⁻¹, which is based on experimental NOEC data for zebrafish (Galus et al., 2013). In addition to venlafaxine, citalopram (at N5_Porto do Son and AR1_Rianxo) and sertraline (at AR1_Rianxo) were also present at concentrations resulting in $HQ > 1$.

In an attempt to perform a preliminary assessment of the potential cumulative effects of the exposure to all the detected PaPs, Toxic Units (TUs) were calculated for each site as the sum of the HQs for each compound in that site. While this method is better suited for the joint assessment of compounds with a similar mode of action, we consider its application here as a good preliminary approximation to the potential hazard of the mixture, especially given the modeled nature (i.e. QSAR) of most of the available toxicity data, more indicative of basal narcotic effects, common among the studied compounds. In this way, N5_Porto do Son was the

sampling site that showed the highest cumulative risk (TU value of 136.3), followed by AR1_Rianxo (84.4). In general, the cumulative hazard was driven by the HQ of venlafaxine. Only three points (N4_Carnota, AR2_Boiro, and PO1_Placeres) presented TU values below 1, indicating no expected effects.

Regarding IDs, the measured concentrations of EDDP resulted in the highest HQ values exceeding 1 in two sites (5.98 in N5_Porto do Son and 5.63 in AR1_Rianxo). No other detected compound resulted in $HQ > 1$. THC-COOH, however, presented an interesting case. THC-COOH was not detected in any of the coastal water samples (it was only detected in the WWTP effluent sample). Whenever methods able to make use of censored data (such as the ones employed here for compounds showing $> 10\%$ detection) are not applicable, it is common to consider an arbitrary number, such as $\frac{1}{2}$ the LOD as the expected concentration in the environment. Given the relatively high LOD for THC-COOH in our method (10 ng L^{-1}) and its relatively low PNEC (5 ng L^{-1}), the resulting HQ was found to be $HQ = 1$ for all our samples. In a very precautionary way, this would indicate that the hazard posed by THC-COOH in the area of the study cannot be discarded, and a more sensitive method for the analysis of this compound should be applied.

TU were calculated for each point to assess the cumulative risk of the analyzed IDs. The TU results match closely what was seen for the individual HQs with N5_Porto do Son and AR1_Rianxo showing TU values above 6 (driven, in the most part, by the risk posed by EDDP). When considering all compounds together another site, PO5_Bueu, exceeded the threshold with a TU value of 1.1, also mainly driven by an EDDP HQ of 0.95.

Many times it is hard to obtain valuable information from HQs. Most studies present the final HQ value on its own. However, an $HQ > 1$ can result from two very different scenarios: a) a compound that is present at a very high concentration, b) a compound that is highly toxic (with a very low PNEC) or c) a combination of both. For risk managers, addressing a situation in which an $HQ > 1$ results from scenario a, or b, or a combination of both, would require very different solutions. While engineering solutions (e.g. improvement of tertiary treatment) could reduce the risk posed by a compound being found at very high concentrations, other approaches (e.g. substitution) might be needed for compounds where a high HQ is driven by a very low PNEC. Figure 2 attempts to present the risk information in a more visual way by displaying the MECs for each compound (for those with a detection frequency $> 10\%$) together with information about their PNEC and LOD. Additionally, the 50th and 99th centiles of their calculated EED are also presented in an attempt to indicate the range of observed concentrations. As described in the paragraphs above, venlafaxine was the compound that showed the highest number of HQ values above 1. From the figure, it can be determined that this is due to a combination of the previously mentioned scenarios a and b. Venlafaxine showed some of the highest measured concentrations, but its PNEC is also the lowest. Both factors together contributed to the high HQ. While the measured concentrations of IDs were, in general, similar to those of the PaPs, Figure 2 clearly shows that the general lack of risk (with the exception of EDDP), is due to their low toxicity (high PNEC values), especially for the most commonly detected compounds, such as BE.

Table 7: Summary of hazard quotients (HQ) resulting from the concentrations of psychoactive pharmaceuticals measured in this study.

Location	ALP	OH-ALP	DIAZ	LORZ	OH-IMI	LORM	TEMZ	OXAZ	CTLP	FLU	HDXZ	SERT	VEN	ZOLP	TU
<i>Ría de Muros e Noia</i>															
N1_Noia (WWTP effl.	0.33	0.04	0.00	0.64	0.01	0.18	0.00	0.33	3.32	2.10	0.01	0.05	90.11	0.00	97.12
N4_Carnota	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00	0.88	0.00	<i>0.93</i>
N5_Porto do Son	0.60	0.09	0.00	0.90	0.10	0.32	0.18	0.45	4.63	0.98	0.00	0.10	127.91	0.07	136.33
<i>Ría de Arousa</i>															
AR1_Rianxo	0.44	0.08	0.00	0.59	0.01	0.16	0.13	0.56	2.26	0.86	0.00	0.13	79.12	0.09	84.43
AR2_Boiro	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.02	0.30	0.00	<i>0.37</i>
AR3_La Puebla	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.11	0.01	0.00	0.00	4.97	0.00	5.12
AR7_Meloxo	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.38	0.12	0.00	0.00	14.37	0.00	14.90
AR8_Dena	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00	1.06	0.00	1.11
AR9_Ribadumia	0.06	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.49	0.01	0.00	0.00	17.41	0.00	17.99
AR11_A Illa	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.20	0.06	0.00	0.00	7.25	0.00	7.54
<i>Ría de Pontevedra</i>															
PO1_Placeres	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.02	0.01	0.00	0.00	0.64	0.00	<i>0.70</i>
PO5_Bueu	0.07	0.00	0.00	0.06	0.01	0.03	0.00	0.06	0.54	0.20	0.00	0.00	16.09	0.00	17.06
Average HQ	0.13	0.02	0.00	0.19	0.02	0.06	0.03	0.12	1.00	0.37	0.00	0.03	30.01	0.01	31.97

435 **Table 8:** Summary of hazard quotients (HQ) resulting from the concentrations of illicit drugs measured in this study

Location	COC	BE	CE	EPH	MDMA	MOR	METH	EDDP	THC-COOH (*)	TU (**)
<i>Ría de Muros e Noia</i>										
N1_Noia (WWTP eff.)	0.64	0.10	0.00	0.02	0.04	1.60	1.14	6.98	51.20	10.5
N2_Esteiro	0.00	0.00	0.00	0.00	0.04	0.01	0.00	0.00	1.00	0.05
N4_Carnota	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.09	1.00	0.10
N5_Porto do Son	0.00	0.00	0.00	0.00	0.00	0.18	0.62	5.98	1.00	6.78
<i>Ría de Arousa</i>										
AR1_Rianxo	0.00	0.00	0.00	0.00	0.01	0.01	0.63	5.63	1.00	6.28
AR2_Boiro	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.04	1.00	0.05
AR3_La Puebla	0.00	0.00	0.00	0.00	0.00	0.04	0.07	0.56	1.00	0.67
AR7_Meloxo	0.00	0.00	0.00	0.00	0.00	0.01	0.07	0.69	1.00	0.77
AR9_Ribadumia	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	1.00	0.02
AR11_A Illa	0.09	0.01	0.02	0.00	0.01	0.10	0.00	0.09	1.00	0.32
<i>Ría de Pontevedra</i>										
PO1_Placeres	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	1.00	0.02
PO3_Marin	0.04	0.00	0.00	0.00	0.00	0.01	0.00	0.00	1.00	0.05
PO5_Bueu	0.02	0.00	0.00	0.00	0.00	0.04	0.09	0.95	1.00	1.10
Average HQ	0.06	0.01	0.00	0.00	0.01	0.16	0.20	1.62	4.86	2.05

436 (*) None of the samples contained detectable concentrations of THC-COOH. The MEC used for the HQ calculation was ½ LOD.

437 (**)HQs for THC-COOH were not considered in TU calculations

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441 3.3. *Global perspective*

442 The number of studies currently available in the literature that have assessed the presence of
443 PaPs and/or IDs in marine and coastal waters is very limited. Tables 9 and 10, summarise, to the
444 best of our knowledge, the data currently available.

445 3.3.1. *Data on psychoactive pharmaceuticals*

446 To the best of our knowledge, only 7 of the 16 PaPs analysed in this study, have ever been
447 detected in marine, coastal, or estuary waters (Table 9) (Alygizakis et al., 2016; Biel-Maeso et
448 al., 2018; Birch et al., 2015; Gros et al., 2012; Klosterhaus et al., 2013; Lara-Martín et al., 2014;
449 Minguez et al., 2016; Moreno-González et al., 2014, Moreno-González et al. 2015; Munaron et
450 al., 2012; Pait et al., 2006). Prior to our study, the most commonly detected PaPs in these
451 environments had been fluoxetine (6 studies), and diazepam (5 studies). The highest measured
452 concentrations of PaPs in these environments have been for lorazepam (117.1 ng L^{-1}) in the Mar
453 Menor lagoon (Spain) (Moreno-González et al., 2014), followed by fluoxetine (72.4 ng L^{-1}) in
454 Long Island Sound (USA) (Lara-Martín et al., 2014), and venlafaxine (52 ng L^{-1}) in the Gola de
455 Ter beach (Spain) (Gros et al., 2012).

456 The range of previously measured concentrations is consistent with the maximum concentrations
457 observed in our study (excluding the WWTP effluent sample from N1_Noia) for diazepam (5.22
458 ng L^{-1}) and fluoxetine (10.60 ng L^{-1}). This is also the case for lorazepam (95.90 ng L^{-1}) when
459 compared to samples collected in a coastal lagoon (Moreno-González et al., 2014, Moreno-

González et al., 2015). However, our results were much higher than values reported for open coastal and beach areas (Gros et al., 2012).

Our study reports the highest-ever measured values for venlafaxine (291 ng L⁻¹), alprazolam (10.8 ng L⁻¹), oxazepam (59.0 ng L⁻¹), citalopram (92.5 ng L⁻¹), and sertraline (15.3 ng L⁻¹) for this kind of environments. Additionally, to the best of our knowledge, our study is the first to report the presence of the benzodiazepines α -hydroxyalprazolam, α -hydroxymidazolam, lormetazepam, and temazepam, and the antidepressants hydroxyzine, sertraline, and zolpidem in coastal waters.

3.3.2. *Data on illicit drugs*

Only 4 of the 19 IDs analyzed in this study had ever been detected in coastal, marine or estuary waters (Table 10). From these, benzoylecgonine has been the most commonly studied and detected. It was found in 6 different studies from Brazil, Greece and Turkey, the USA, Italy and Spain (Klosterhaus et al., 2013; Nödler et al., 2014; Pereira et al., 2016). Cocaine, MDMA and EDDP complete the list of previously detected compounds (Alygizakis et al., 2016; Jiang et al., 2014; Klosterhaus et al., 2013; Pereira et al., 2015; Pereira et al., 2016;). The highest ID concentrations were reported for cocaine (537 ng L⁻¹), in Costa de Santos (Brazil) (Pereira et al., 2016), and benzoylecgonine (54 ng L⁻¹) in San Francisco Bay (USA) (Nödler et al., 2014).

To the authors' knowledge, the concentrations measured for benzoylecgonine (142 ng L⁻¹) and EDDP (71.7 ng L⁻¹) in our study represent the highest-ever measured levels for these two compounds in coastal waters. Our study is also the first to detect the presence of cocaethylene, ephedrine and the opioids morphine and methadone in this type of environments.

481 **Table 9:** Summary of available literature data reporting measured concentrations of psychoactive pharmaceuticals in marine, coastal
482 and estuarine waters. The location where the sample was collected, the range of concentrations and hazard quotient calculated for the
483 highest measured concentration are presented. HQ > 1 are flagged in bold.

Compound	Location	Environment	Range (ng L ⁻¹)	HQ*	Reference
<i>Benzodiazepines</i>					
Alprazolam	Rías Baixas (Spain)	Coastal water	n.d. – 10.80	0.60	Our study
	Mar Menor (Spain)	Coastal lagoon	n.d. – 7.4	0.41	(Moreno-González et al., 2014)
α -Hydroxyalprazolam	Rías Baixas (Spain)	Coastal water	n.d. – 12.90	0.09	Our study
Diazepam	Rías Baixas (Spain)	Coastal water	n.d. – 5.22	0.00	Our study
	Gulf of Lion (France)	Coastal lagoon	n.d. – 8	0.00	(Munaron et al., 2012)
	Gulf of Lion (France)	Coastal waters	n.d. – 5	0.00	(Munaron et al., 2012)
	San Francisco Bay (USA)	Estuary	n.d. – 0.5	0.00	(Klosterhaus et al., 2013)
	Gola de Ter beach (Spain)	Beach	>0.2 - <0.4	0.00	(Gros et al., 2012)
	Saronikos Gulf (Greece)	Seawater	n.d. – <4.0	0.00	(Alygizakis et al., 2016)
	Aegean Sea (Lesvos Island, Greece)	Coastal water	n.d.	0.00	(Nödler et al. 2016)
	Mar Menor (Spain)	Coastal lagoon	n.d. – 5	0.00	(Moreno-González et al., 2014)
	Rías Baixas (Spain)	Coastal water	n.d. – 95.90	0.90	Our study
Lorazepam	Gola de Ter beach (Spain)	Beach	>0.9 - <3.1	0.03	(Gros et al., 2012)
	Mar Menor lagoon (Spain)	Coastal lagoon	n.d. – 117.1	1.09	(Moreno-González et al., 2014)
	Mar Menor lagoon (Spain)	Coastal lagoon	n.d. – 41.8	0.39	(Moreno-González et al., 2015)
Midazolam	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
α -Hydroxymidazolam	Rías Baixas (Spain)	Coastal water	n.d. – 5.05	0.10	Our study
Lormetazepam	Rías Baixas (Spain)	Coastal water	n.d. – 42.80	0.32	Our study
Temazepam	Rías Baixas (Spain)	Coastal water	n.d. – 23.60	0.18	Our study
Oxazepam	Rías Baixas (Spain)	Coastal water	n.d. – 59.00	0.56	Our study
	Bay of Stockholm (Sweden)		10.4 -12.7	0.12	(Magnér et al., 2010)
<i>Antidepressants</i>					
Citalopram	Rías Baixas (Spain)	Coastal water	n.d. – 92.50	4.63	Our study
	Gola de Ter beach (Spain)	Beach	4	0.20	(Gros et al., 2012)

Fluoxetine	Saronikos Gulf (Greece)	Seawater	n.d. – 8.0	0.40	(Alygizakis et al., 2016)
	Aegean Sea (Lesvos Island, Greece)	Coastal water	n.d.	0.03	(Nödler et al., 2016)
	Mar Menor (Spain)	Coastal lagoon	n.d. – 22	1.10	(Moreno-González et al., 2014)
	Rías Baixas (Spain)	Coastal water	n.d. – 10.60	0.98	Our study
	Gulf of Lion (France)	Coastal lagoon	n.d - 1	0.09	(Munaron et al., 2012)
	Sydney estuary (Australia)	Estuary	<0.1 - 36.0	3.33	(Birch et al., 2015)
	Long Island Sound (USA)	Estuary	72.4 (Max)	6.70	(Lara-Martín et al., 2014)
	Gulf of Cadiz (Spain)	Coastal water	n.d. – 0.6	0.06	(Biel-Maeso et al., 2018)
	Gulf of Cadiz (Spain)	Seawater	n.d. – 1.6	0.15	(Biel-Maeso et al., 2018)
	Aegean Sea (Lesvos Island, Greece)	Coastal water	n.d.	0.25	(Nödler et al., 2016)
	Chesapeake Bay (USA)	Coastal water	3	0.28	(Pait et al., 2006)
Hydroxyzine	Rías Baixas (Spain)	Coastal water	n.d. – 0.57	0.00	Our study
Sertraline	Rías Baixas (Spain)	Coastal water	n.d. – 15.30	0.13	Our study
	Aegean Sea (Lesvos Island, Greece)	Coastal water	n.d.	0.02	(Nödler et al., 2016)
Chlorpromazine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
Venlafaxine	Rías Baixas (Spain)	Coastal water	n.d. – 291.00	127.91	Our study
	Gola de Ter beach (Spain)	Beach	52	22.86	(Gros et al., 2012)
	Sydney estuary (Australia)	Estuary	<0.1 - 31.6	13.89	(Birch et al., 2015)
Zolpidem /	Rías Baixas (Spain)	Coastal water	n.d. – 1.46	0.09	Our study

*MEC used for the HQ calculation was ½ LOD when the analyte was not detected in the investigated samples

487 **Table 10:** Summary of available literature data reporting measured concentrations of illicit drugs in marine, coastal and estuarine
488 waters. The location where the sample was collected, the range of concentrations and hazard quotient calculated for the highest
489 measured concentration are presented. HQ > 1 are flagged in bold.

Compound	Location	Environment	Range (ng L ⁻¹)	HQ (*)	Reference
<i>Cocainics</i>					
Cocaine	Rías Baixas (Spain)	Coastal water	n.d. – 42.30	0.09	Our study
	Santos Coast (Brazil)	Seawater	12.6 - 537	1.17	(Pereira et al., 2016)
	San Francisco Bay (USA)	Estuary	n.d. - 2.4	0.01	(Klosterhaus et al., 2013)
Benzoylecgonine	Rías Baixas (Spain)	Coastal water	n.d. – 142.00	0.01	Our study
	Santos Coast (Brazil)	Seawater	4.6 - 20.8	0.00	(Pereira et al., 2016)
	Aegean Sea (Lesvos Island, Greece)	Coastal water	<2.3	0.00	(Nödler et al., 2016)
	San Francisco Bay (USA)	Estuary	2.8 – 7.2	0.00	(Klosterhaus et al., 2013)
	Aegean Sea & Dardanelles (Greece and Turkey)	Seawater	16 (Max)	0.00	(Nödler et al., 2014)
	Venice (Italy)	Seawater	13 (Max)	0.00	(Nödler et al., 2014)
	San Francisco Bay (USA)	Eastuary	54 (Max)	0.00	(Nödler et al., 2014)
	Balearic Sea (Spain)	Seawater	2.5 (Max)	0.00	(Nödler et al., 2014)
Cocaethylene	Rías Baixas (Spain)	Coastal water	n.d. – 5.20	0.02	Our study
<i>Amphetamine-type stimulants</i>					
Ephedrine	Rías Baixas (Spain)	Coastal water	n.d. – 57.80	0.00	Our study
Amphetamine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
Methamphetamine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
	Rías Baixas (Spain)	Coastal water	n.d. – 10.00	0.04	Our study
3,4-methylenedioxymethamphetamine	Southwestern coast of (Taiwan)	Coastal	n.d. – 4.82	0.02	(Jiang et al., 2014)
	Saronikos Gulf (Greece)	Seawater	n.d. - <0.3	0.00	(Alygizakis et al., 2016)
Mephedrone	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
3,4-Methylene-dioxypyrovalerone	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study

Methoxetamine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
Ketamine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
<i>Opioids</i>					
Morphine	Rías Baixas (Spain)	Coastal water	n.d. – 15.70	0.18	Our study
6-acetylmorphine	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
AH7921	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
Heroin	Rías Baixas (Spain)	Coastal water	n.d.	0.00	Our study
Methadone	Rías Baixas (Spain)	Coastal water	n.d. – 22.70	0.63	Our study
2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium	Rías Baixas (Spain)	Coastal water	n.d. – 71.70	5.98	Our study
	Saronikos Gulf (Greece)	Seawater	<0.02 -0.1	0.01	(Alygizakis et al., 2016)
<i>Cannabinoids</i>					
11-nor-9-carboxy- Δ^9 THC	Rías Baixas (Spain)	Coastal water	n.d.	1.00	Our study
<i>Lysergic compounds</i>					
Lysergic acid diethylamide	Rías Baixas (Spain)	Coastal water	n.d.	n/a	Our study

*MEC used for the HQ calculation was ½ LOD when the analyte was not detected in the investigated samples

3.3.3. *Previously observed risk levels*

Using the compiled list of PNECS (Table 3), hazard quotients (HQs) were calculated from the maximum measured concentration of each compound in the above-mentioned studies (Tables 9 and 10). In this way, the only locations where PaP concentrations resulted on $HQ > 1$ were the Mar Menor lagoon (Spain) (due to lorazepam, $HQ = 1.09$ and citalopram, $HQ = 1.10$) (Moreno-González et al., 2014), the Sydney estuary (Australia) and Long Island Sound (USA) (due to fluoxetine, $HQ = 3.3$ and 6.70 , respectively) (Birch et al., 2015; Lara-Martín et al., 2014), and the Sydney estuary (Australia) and Gola de Ter beach (Spain) (due to venlafaxine, $HQ = 22.86$ and 13.89 , respectively) (Birch et al., 2015; Gros et al., 2012). Concentrations of IDs resulting in $HQ > 1$, were only previously measured in Costa de Santos (Brazil) (cocaine, $HQ = 1.17$) (Pereira et al., 2016).

4 **Conclusions**

Fourteen out of the 16 PaPs and 9 out of the 19 IDs analyzed in this study were detected in at least one of the collected samples. Moreover, our study reports the highest-ever measured concentration of 5 PaPs (alprazolam, oxazepam, citalopram, sertraline, and venlafaxine) and 2 IDs (benzoylecgonine and EDDP) in coastal waters. Additionally, to the best of our knowledge, our study is the first to report the presence of 6 PaPs (α -hydroxyalprazolam, α -hydroxymidazolam, lormetazepam, temazepam, hydroxyzine, sertraline, and zolpidem) and 4 IDs (cocaethylene, ephedrine, morphine and methadone) in this type of environments.

When the measured concentrations were compared to PNECs for aquatic organisms, 3 of the measured PaPs and one ID (venlafaxine, citalopram, sertraline and EDDP) appeared in

concentrations resulting in $HQ > 1$, with venlafaxine reaching HQs as high as 127.9 indicating a high potential for negative effects in the environment near the sampling site (N5_Porto do Son).

Regarding the geographic distribution of the measured concentrations and estimated risks, N5_Porto do Son (Ría de Muros e Noia) was the sampling site that showed the highest cumulative risk for both PaPs and IDs (based on the calculation of TUs), followed by AR1_Rianxo (Ría de Arousa). In general, the cumulative hazard for the PaPs was driven by the HQ of venlafaxine, while EDDP drove the hazard observed for IDs. Only three points (N4_Carnota, AR2_Boiro, and PO1_Placeres) presented TU values below 1, indicating no expected effects. While a direct comparison between the water quality and potential risks among the different *rías* is hard, the measured concentrations and risk were generally higher in the Ría de Muros e Noia, followed by Arousa and finally by Pontevedra.

Our results point to the need to apply a higher sensitivity analytical method for THC-COOH. Compared to the other substances in this study, its relatively high limit of detection (10 ng L^{-1}), and low PNEC (5 ng L^{-1}) resulted in an $HQ = 1$, even when no THC-COOH was detected (considering a conservative value of $\frac{1}{2}$ LOD as the measured concentration).

The risks levels calculated in this study are, however, representative of a worst case scenario due to the nature of the collected samples (grab samples collected in the proximity of marine outflows from WWTPs) and the deterministic, screening-level, risks assessment approaches employed for their derivation. Further research is needed to characterize the real risk posed by these compounds in the Rías Baixas area, and marine and coastal areas around the world. These future assessments would greatly benefit from toxicity tests conducted with marine or salt-water species, which are currently greatly underrepresented (Marchand and Tissier, 2007).

Specific studies are recommended to assess the potential effects that the presence of these compounds in the Rías Baixas region might be having on the economically important seafood and mussels grown and harvested in these environments, as well as any potential implications to human health via their consumption.

Despite the interest of the scientific community, and a growing amount of data indicating the ubiquitous presence of contaminants of emerging concern (including PaPs and IDs) in coastal and marine environments, regulatory coverage in the area is low. In Europe, the Water Framework Directive (WFD) covers transition waters (e.g. estuaries and rías) (EC, 2000). In the 2013 amendment of the WFD (EC, 2013), the EU specifically flagged contamination of water and soil with pharmaceutical residues as an emerging environmental concern, and called for the need to study the risks of environmental effects from medicinal products and provide an analysis of the relevance and effectiveness of the current legislative framework in protecting the aquatic environment and human health. These amendments also called for the creation of a new mechanism to provide high-quality monitoring information on the concentrations of polluting substances in the aquatic environment across the EU in order to support the identification of priority substances for regulation under the WFD. In order to accomplish such a task, a dynamic watch list was created which included only 7 pharmaceuticals and personal care products (17-alpha-ethinylestradiol, 17-beta-estradiol, estrone, diclofenac, and the macrolide antibiotics erythromycin, clarithromycin, azithromycin) in its first iteration (Commission Implementing Decision (EU) 2015/495), while in the second list, diclofenac was removed and the antibiotics amoxicillin and ciprofloxacin were added (Commission Implementing Decision (EU) 2018/840). The results of this study will hopefully aid in the process of selection of future candidates (e.g. venlafaxine) for future revisions of the watch-list.

562

563 **Declarations of conflict of interest:**

564 None.

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