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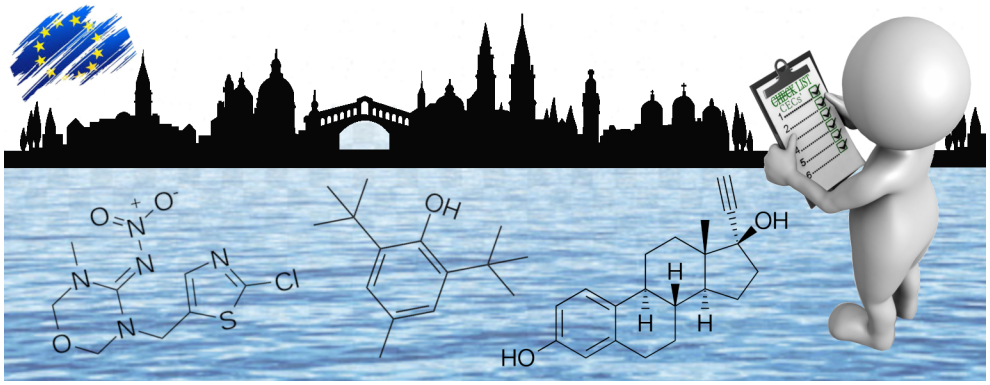

CONTAMINANTS OF EMERGING CONCERN IN WATER AND SEDIMENT OF THE VENICE LAGOON, ITALY

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Abstract

This study investigates for the first time the contamination of water and sediment of the Venice Lagoon by twenty Contaminants of Emerging Concern (CECs): three hormones, six pharmaceutical compounds (diclofenac and five antibiotics, three of which are macrolides), nine pesticides (methiocarb, oxadiazon, metaflumizone, triallate, and five neonicotinoids), one antioxidant (BHT), and one UV filter (EHMC). Water and sediment samples were collected in seven sites in four seasons, with the aim of investigating the occurrence, distribution, and possible emission sources of the selected CECs in the studied transitional environment. The most frequently detected contaminants in water were neonicotinoid insecticides (with a frequency of quantification of single contaminants ranging from 73% to 92%), and EHMC (detected in the 77% of samples), followed by BHT (42%), diclofenac (39%), and clarithromycin (35%). In sediment the highest quantification frequencies were those of BHT (54%), estrogens (ranging from 35% to 65%), and azithromycin (46%). Although this baseline study does not highlight seasonal or spatial trends, results suggested that two of the major emission sources of CECs in the Venice Lagoon could be tributary rivers from its drainage basin and treated wastewater, due to the limited removal rates of some CECs in WWTPs. These preliminary results call for further investigations to better map priority emission sources and improve the understanding of CECs environmental behavior, with the final aim of drawing up a site-specific Watch List of CECs for the Venice Lagoon and support the design of more comprehensive monitoring plans in the future.

Keywords

Emerging contaminants; Pharmaceuticals; Neonicotinoid insecticides; Plant Protection Products (PPPs); Industrial chemicals; Watch List.

Abbreviations

BHT: 2,6-Di-*tert*-butyl-4-methylphenol; EHMC: 2-Ethylhexyl-4-methoxycinnamate; WWTP: Waste Water Treatment Plants.

1. Introduction

The Lagoon of Venice is a complex and vulnerable transitional environment where human activities and natural dynamics have always been interconnected. Chemical pollution has been recognized as one of the major threats to this environment, posing risks to human health and local ecosystems (Micheletti *et al.*, 2011). Pollutants may reach lagoon waters both directly from civil, agricultural, and industrial discharges, or through the hydrographic network of its drainage basin.

Because of its peculiarity, the occurrence of target and "conventional" pollutants in water, sediment, and biota of the Venice Lagoon has been quite extensively studied, focusing particularly on heavy metals and certain categories of persistent organic substances (Corami *et al.*, 2020; Losso and Volpi Ghirardini, 2010; Manodori *et al.*, 2006; Morabito *et al.*, 2018; Pizzini *et al.*, 2021). The occurrence of priority substances in the Venice Lagoon is routinely controlled by dedicated periodic monitoring, according to the requirements of the EU Water Framework Directive (WFD; Directive 2000/60/EC; European Commission, 2000), other related directives, and the corresponding national regulations. Conversely, pollutants that are not on the list of priority substances, such as many Contaminants of Emerging Concern (CECs), have been only marginally investigated (Feltracco *et al.*, 2022; Vecchiato *et al.*, 2016), and their potential for adverse effects on human health and local ecosystems is still largely unknown.

CECs are defined as "any synthetic or naturally occurring chemicals that are not already regulated and not commonly monitored, though having the potential to enter soil and aquatic ecosystems and cause adverse effects in humans, wildlife, and the environment" (Barbosa *et al.*, 2016; US EPA, 2008). CECs include synthesized and commercialized compounds that have just entered the environment as well as a range of chemicals that have been produced and released for long, for which new concerns on their occurrence, fate, adverse effects on human health and the environment, have recently been raised. CECs encompass different classes of substances like Pharmaceuticals and Personal Care Products (PPCPs), pesticides, industrial and household products. The hazard of these substances is mainly linked to their ability to generate long-term toxic effects (Carvalho *et al.*, 2015; Loos *et al.*, 2018), individually and in mixture. Furthermore, locally their impact on the environmental quality of water bodies could be even higher than that of other well-known priority pollutants (Hernando *et al.*, 2006; Kümmerer, 2009; Sposito *et al.*, 2018).

Although over the past recent years there has been an increase in publications dealing with CECs in the environment (*e.g.*, Ramírez-Malule *et al.*, 2020; Sousa *et al.*, 2018), available studies do not

84 homogenously cover different classes of CECs or complex environmental media, such as brackish
85 water or sediment. Most of the available studies investigated the occurrence of CECs in surface
86 freshwater, mainly in rivers and lakes, rather than transitional environments, and often including
87 sampling points downstream to Waste Water Treatment Plants (WWTPs). Moreover, information
88 about the presence of CECs in the sediment compartment is relatively scarce, and this limitation can
89 hamper the understanding of partitioning and transformation dynamics of different classes of CECs
90 in water systems. Indeed, hydrophobic CECs, easily bound to sediment, can be mobilized if changes
91 in site-specific hydrodynamic conditions (flow rate, tidal currents, Eh and pH values, etc.; Eggleton
92 and Thomas, 2004; Fitri *et al.*, 2019) and/or sediment resuspension occur, enhancing their
93 bioavailability and ability to enter the food chain (Pignotti and Dinelli, 2018). Therefore, to better
94 understand the behavior and impacts of CECs within aquatic ecosystems and better target
95 environmental monitoring efforts, it is important to include sediment as target medium of chemical
96 characterization.

97 If we look at recent studies in Italy, there are still significant knowledge gaps about CEC occurrence
98 and dynamics, especially for certain environmental compartments. Most of the literature studies
99 focused on freshwater (Calamari *et al.*, 2003; Castiglioni *et al.*, 2018a; Mascolo *et al.*, 2019; Pignotti
100 and Dinelli, 2018; Riva *et al.*, 2018; Verlicchi *et al.*, 2014), on WWTPs to attest their removal
101 efficiency (Andreozzi *et al.*, 2004, 2003; Castiglioni *et al.*, 2005; Spataro *et al.*, 2019; Zuccato *et al.*,
102 2010), and just a few studies included groundwater (Castiglioni *et al.*, 2018b; Riva *et al.*, 2018).
103 Knowledge about CEC contamination of transitional environments in Italy is still scarce and studies
104 mostly targeted estrogenic compounds (Casatta *et al.*, 2015; Feo *et al.*, 2020; Pojana *et al.*, 2007).
105 With regard to the Venice Lagoon, data on CEC concentration in water and sediment are almost
106 absent and this area is not covered by the national monitoring network of Watch List contaminants
107 (ISPRA, 2017). The only exception is represented by two studies (Pojana *et al.*, 2007, 2004)
108 investigating the occurrence of some estrogenic compounds.

109 This work reports and discusses, for the first time, data on the environmental occurrence in the
110 Venice Lagoon of the twenty CECs listed in the EU Watch Lists issued in 2015 and 2018 (Decisions
111 2015/495/EU and 2018/840/EU; European Commission, 2018, 2015), investigated through the
112 analysis of water and sediment samples across four seasons. This study is meant to act as a baseline
113 for further investigations, with the final aim of drawing up a site-specific Watch List for the Venice
114 Lagoon (based on additional investigations on CEC exposure and hazard) and providing
115 recommendations for CEC monitoring in the area. Although a specific case study is described, the

presented results could have widespread implications also at a global scale, providing useful data to better address existing knowledge gaps on the occurrence, sources, transport, and fate of CECs in aquatic ecosystems.

2. Materials and methods

2.1 Analytes

The analytes considered in this work are the twenty CECs listed in the first and the second EU Watch Lists (Table S1), due to the absence of systematic monitoring activities in Italy to investigate their presence in transitional waters.

17β-Estradiol (E2) and estrone (E1) are the main human estrogens, natural feminine sexual hormones, commonly used in the menopausal hormone therapy, whereas 17α-Ethynylestradiol (EE2) is a synthetically produced hormone, metabolite of mestranol, the estrogen used in contraceptives. All of them are known to act as Endocrine Disrupting Chemicals (EDCs) on aquatic organisms (Nikolaou *et al.*, 2007; Sumpter and Johnson, 2008), and EE2 has proven to be more persistent than natural estrogens in WWTPs (Miège *et al.*, 2009). Diclofenac is one of the most frequently and abundantly detected Non-Steroidal Anti-Inflammatory Drug (NSAID; Bonnefille *et al.*, 2018; Gusmaroli *et al.*, 2019), due to its widespread usage in human and veterinary medical care to treat pain and inflammatory diseases, and to the low removal rates recorded in WWTPs (Al Aukidy *et al.*, 2012; Castiglioni *et al.*, 2018b; Miège *et al.*, 2009). Antibiotics are unstable and biologically active substances that could undergo environmental degradation in the time scale of days. Amoxicillin, which is a broad-spectrum aminopenicillin antibiotic, shows fast degradation in water, with a half-life time that ranges from 1 to 8 days (Andreozzi *et al.*, 2004), due to the chemical instability of the β-lactam ring that readily undergoes hydrolysis, shortly after excretion. Conversely, the fluoroquinolone antibiotic ciprofloxacin shows high resistance towards abiotic degradation reactions such as hydrolysis (Girardi *et al.*, 2011). The three macrolide antibiotics erythromycin, clarithromycin, and azithromycin are commonly employed to treat severe bacterial infections in humans, animals, and in aquaculture, and there is evidence in literature studies of their incomplete removal by WWTPs, in particular for clarithromycin and azithromycin (Al Aukidy *et al.*, 2012; Miège *et al.*, 2009; Verlicchi *et al.*, 2014). Their widespread use has been recognized as one of the major causes of the spread of antibiotic resistance genes and antibiotic resistant bacteria in the environment (Grenni *et al.*, 2018).

Neonicotinoids (*i.e.* imidacloprid, clothianidin, thiacloprid, thiamethoxam, and acetamiprid) represent the most widely used insecticide class worldwide, which find several applications, from the protection of plants (crops, vegetables, fruit) to the use as veterinary products and as biocides to invertebrate pest control in fish farming. Their high persistence, water solubility, and mobility, combined with an extensive use, have led to a widespread environmental contamination (ISPRA, 2020). As for the others Plant Protection Products (PPPs) included in the EU Watch Lists, methiocarb is a carbamate pesticide used as insecticide, acaricides, molluscicide, and bird repellent; oxadiazon is a oxadiazole herbicide used for control of a wide variety of annual broadleaf and grassy weeds; metaflumizone is a broad-spectrum semicarbazone insecticide used to prevent lepidopterous pests and indicated also for the veterinary treatment of fleas and ticks; triallate is a thiocarbamate herbicide widely used to control annual and perennial grasses in wheat, barley, legumes, and a number of other crops. These PPPs are characterized by scarce literature data, both about their occurrence in different environmental matrices, their effects and fate, and about their removal by WWTPs (Pietrzak *et al.*, 2019).

2,6-Di-*tert*-butyl-4-methylphenol (BHT) is an antioxidant commonly used to preserve and stabilize the freshness, nutritive value, flavor, and color of food and animal feed products. It is also used to improve the stability of pharmaceuticals and cosmetics and increase the durability of rubber and plastics (Barbosa *et al.*, 2016). 2-Ethylhexyl-4-methoxycinnamate (EHMC) is an organic UV filter used in many PCPs that could enter in the environment by wash off from skin, through wastewater or swimming pool water and, finally, reach the sediment and the biota (Barbosa *et al.*, 2016).

All the chemicals and reagents employed in this study are detailed in the Supplementary data.

2.2 Study area

With an extension of about 550 km^2, the Lagoon of Venice is the largest transitional water system of the Mediterranean Sea (Madricardo *et al.*, 2019), characterized by a variety of valuable habitats and high biodiversity (Sfriso *et al.*, 2019). It is a shallow coastal lagoon (average depth of 1 m) featured by the presence of fens, salt marshes, and a complex network of tidal canals. Its drainage basin extends for about 2500 km^2 and a freshwater input of about 35.5 $m^3 s^{-1}$ is ensured by natural rivers and artificially-controlled canals that flows into the Lagoon (Zuliani *et al.*, 2005). The high population density (about 250 inhabitants per km^2) and the intense agricultural and industrial activities in the surroundings result in diverse anthropogenic pressures on the area, including

chemical contamination (Micheletti *et al.*, 2011). Since more than half of the drainage basin surface is devoted to agriculture (Veneto Region, 2020), different types of PPPs, such as herbicides and pesticides, are widely applied and can eventually reach lagoon waters due to run-off or leaching to surface and groundwater (Calgaro *et al.*, 2023). Moreover, the dense urbanization and highly-developed animal breeding activities (UNEP/MAP Plan Bleu, 2020) lead to the discharge of several components used in PPCPs, as well as hormones of natural origin, through the effluents from WWTPs and the improper disposal of unused and/or expired pharmaceuticals (Fernandes *et al.*, 2021).

The sampling sites (Figure 1) were chosen as representative either of potential CEC emission sources or of zones where the diffusion and mixing of pollutants are expected to occur, to obtain an overview of the three main Lagoon areas (Northern, Central, and Southern).

The sites associated to specific sources were the mouth of the Dese River (DE), St. Erasmo (SE), the Venice hospital (OS), and Rio Marin (RM). The first sampling site is in proximity to the mouth of the Dese River, which is a tributary of the Venice Lagoon drainage basin: with a main stream of about 50 km, it covers an area of more than 240 km^2, receiving the inputs from several pumping plants (Zonta *et al.*, 2005). St. Erasmo is an island of the Northern Lagoon historically devoted to agriculture (so much to be called “the vegetable garden of Venice”), and the related sampling site is close to a WWTP. The site close to the Venice hospital has been selected as possibly affected by the discharge of pharmaceutical products in its treated wastewater, while Rio Marin can provide information about inputs deriving from the activities of the Venice historical center, being one of the most important urban canals. According to the second sampling criterion, three sites were chosen: Palude Maggiore (PM), Sacca Sessola (SS), and Petta di Bò (PB), located in the Northern, Central, and Southern Lagoon, respectively.

2.3 Sample collection

The sampling campaigns were carried out considering weather and tidal conditions, to avoid the dilution effect due to heavy rain or tide entering the Lagoon from the Adriatic Sea. In particular, at the mouth of the Dese River, the sampling was always performed during the outgoing tide, in order to be sure to sample the actual contribution of the river. Four sampling campaigns were carried out during April-May 2019 (spring campaign), October-November 2019 (autumn campaign), July 2020 (summer campaign), and January-February 2021 (winter campaign). The sampling at Rio Marin was

206 only performed during the summer and winter campaigns. In Table S2 the sampling data for the
207 four campaigns are reported.

208 About 20 L of water were collected at each site by immersing solvent-rinsed steel bottles to a depth
209 of approximately 10-20 cm below the surface, in order to minimize any enrichment effect due to
210 the microlayer (Manodori *et al.*, 2006; Zaborska *et al.*, 2019). To avoid any contamination, the
211 immersion pump has not been used and the sampling was carried out with the boat in slight motion
212 and the engine stopped. The 0-10 cm sediment layer was sampled in three or more replicates by
213 using a SG-400 stainless steel Van Veen grab (Aquatic BioTechnology, Cádiz, Spain), with a sampling
214 area of roughly 400 cm^2. Immediately before sampling, water temperature, pH, and Eh were
215 measured at each site with a multiparametric probe (Table S2).

216 **2.4 Sample treatment**

217 On return to the laboratory the water samples were filtered by a Combisart® six-branch stainless
218 steel vacuum manifold (Sartorius Lab Instruments, Göttingen, Germany), using Whatman® glass
219 microfiber filters (Grade GF/F, 0.7 µm, 47 mm diameter; Sigma-Aldrich, Saint Louis, MO, USA)
220 previously decontaminated in a muffle furnace at 400°C for 4 h. The sediment samples were
221 homogenized and quartered in a glovebox, under a nitrogen flow, to minimize any eventual
222 interference with the chemical and redox equilibria. Filtered water and quartered sediment were
223 divided into different sub-samples, depending on the planned analytical methodology, in solvent-
224 rinsed glass bottles or aluminum containers, respectively, and stored at -20°C until processing and
225 analysis.

226 Each sample-preparation phase was performed inside an ISO class 7 cleanroom at the Ca' Foscari
227 University of Venice and all glassware and tools were previously pre-cleaned with dichloromethane
228 and methanol.

229 The analytical pretreatment procedure differed according to the investigated contaminant and the
230 individual adopted protocols are described in detail in the Supplementary data.

231 **2.5 Instrumental analysis**

232 Pharmaceutical, methiocarb, oxadiazon, and metaflumizone analyses were performed using a
233 Bruker Elute LC series UHPLC, coupled with a quadrupole-time of flight Bruker Compact™ LC-MS/MS
234 System, equipped with an ElectroSpray Ionization (ESI) source (Bruker Daltonik, Bremen, Germany),

operating both in positive and negative polarity. The chromatographic separation was obtained as detailed in Table S3. Data acquisition was obtained in bbCID (broad-band Collision Induced Dissociation) mode, alternating HRMS and stepping fragmentation between 24 and 36 eV.

Neonicotinoid insecticide analyses were performed using an Agilent 1100 Series HPLC Value System (Agilent Technologies, Santa Clara, CA, USA), coupled with a triple quadrupole API 4000™ LC-MS/MS System, equipped with an ESI Turbo V™ source (Applied Biosystems/MDS SCIEX, Toronto, ON, Canada), operating in positive polarity. The chromatographic separation was obtained as detailed in Table S4. Data acquisition was obtained in MRM (Multiple Reaction Monitoring) mode with a 50 ms dwell time/transition.

Triallate, BHT, and EHMC analyses were performed using a TRACE™ 1310 GC, coupled with a triple quadrupole TSQ™ 9000 GC-MS/MS System (Thermo Fisher Scientific, Waltham, MA, USA), operating in Electron Ionization (EI, 70 eV) mode. The chromatographic separation was obtained as detailed in Table S5. Data acquisition was obtained in MRM mode with a 30 ms dwell time/transition.

For all the analytes, quantification was performed using internal standards and the isotopic dilution technique. Results were corrected using the instrumental response factors and subtracting the procedural blanks. All sediment concentrations were calculated on a dry weight (dw) basis. Instrumental operating conditions and target ion masses are presented in detail in Table S6.

2.6 Quality control

The concentration ranges in which the linearity of the instrumental response was checked, as well as the related coefficients of determination (R^2), are reported in detail in Table S7 for each analyte under investigation. The Instrumental Detection Limits (IDLs) were obtained by setting a Signal-to-Noise ratio (S/N) ≥ 3, whereas Instrumental Quantification Limits (IQLs) by setting a S/N ≥ 10 (Table S7). Since there was no available Standard Reference Materials (SRMs) for the analytes of interest in water and sediment, the quality control of the entire analytical procedure, in terms of repeatability (expressed as relative standard deviation), trueness (expressed as relative error), and percentage of recovery, was performed on five replicates of fortified artificial/real environmental matrices (Table S7). Thus, for the validation of the analytical method for the determination of neonicotinoid insecticides in brackish water and sediment, a known amount of surrogate and isotope-labeled internal standards was spiked to filtered lagoon water and to sediment collected in Venice Lagoon at a depth of 10 m, dated back to Pleistocene age (Teatini *et al.*, 2017), and for this

reason judged free from modern contaminants. For the validation of the analytical methods for the determination of the other compounds, a known amount of surrogate and isotope-labeled internal standards was spiked to artificial lagoon water and sediment, following the procedure described in the Joint Research Centre (JRC) Technical Report on the first Watch List (Carvalho *et al.*, 2015). Both the matrices without the addition of surrogate spikes were considered as blanks. Method Detection Limits (MDLs) and Method Quantification Limits (MQLs) were estimated using the concentrations equivalent to three (MDLs) or ten (MQLs) times the standard deviation of five replicate measurements of spiked blanks (Table S7). The MDLs achieved were lower than the maximum acceptable ones required by the two EU Decisions (Table S1).

3. Results and discussion

The concentration range and quantification frequency of the studied compounds are shown in Figure 2, while all the concentration values for water and sediment samples are reported in Table S8, Table S9, and Table S10. The occurrence, seasonality, and concentration range of the investigated CECs in the Venice Lagoon are described and discussed in the following paragraphs according to the classes of chemicals to which they belong.

3.1 Pharmaceuticals

3.1.1 Estrogenic compounds

At all seven sites and in all sampling campaigns, EE2 and E2 were always undetectable in water samples, while E1 was occasionally quantified in samples collected at SS, OS, DE, SE, and RM sites (range between 0.9-4.2 ng L^{-1}), except for the winter sampling.

In sediment samples, all estrogenic compounds were detected with a similar range of concentration (about 10^2-10^4 ng kg^{-1} dw). In particular, E1 was detected during all the sampling campaigns with the highest overall quantification frequency (65%), while EE2 was found only in summer and winter at all the sampling sites except for OS and SE. The highest concentrations were found at PM, RM, and DE sites for EE2, E2, and E1, respectively.

Estrogenic compounds were measured in the Venice Lagoon in 2000s, when the concern about EDCs was growing worldwide (Pojana *et al.*, 2007, 2004). A comparison with these previous data is not straightforward, since these studies included several sampling sites and seasonal samplings and, consequently, the results showed a significant spatial and temporal variability. In general, it can be

observed that in the studies carried out by Pojana and colleagues, estrogens showed higher concentrations in water compared to the present study, especially EE2 and E2, detected at concentrations from < 1 ng L^{-1} up to more than 100 ng L^{-1}. Conversely, in sediment samples only EE2 was detected, at concentrations in the range < 2000-41000 ng kg^{-1} dw (Pojana *et al.*, 2004).

Our data on water samples are in accordance with those found in literature related to coastal and riverine water (Barreca *et al.*, 2019; Castiglioni *et al.*, 2020; Feo *et al.*, 2020; Solaun *et al.*, 2021). In particular, literature data on EE2 and E2 were often under the quantification limits (EE2: 0.035-3.51 ng L^{-1}; E2: 0.1-1.0 ng L^{-1}) while E1 values ranged from the quantification limits (0.07-0.13 ng L^{-1}) to 488 ng L^{-1} (Augusta Bay, Southern Italy; Feo *et al.*, 2020).

A comparison for sediment samples is feasible with quite recent data from Augusta Bay (Feo *et al.*, 2020), and Emilia Romagna Region (Northern Italy; Pignotti and Dinelli, 2018), where estrogen concentrations in sediment were often under the quantification limits (EE2: 2780 ng kg^{-1} dw; E2: 2490 ng kg^{-1} dw; E1: 1600 ng kg^{-1} dw), or with data from another coastal lagoon (Sacca di Goro, Northern Italy; Casatta *et al.*, 2015), where estrogens in sediment were always undetectable (EE2 < 670 ng kg^{-1} dw; E2 < 330 ng kg^{-1} dw; E1 < 50 ng kg^{-1} dw). In our study, estrogen concentrations in sediment, when above the MQLs, are significantly higher than those found in cited literature.

The concentrations of estrogens measured in our study suggest that their occurrence in the Venice Lagoon is largely driven by the discharge of wastewater (SE and RM sites) and of the tributary rivers of the Lagoon drainage basin (DE site), confirming the indications of the Italian Institute for Environmental Protection and Research (Calgaro *et al.*, 2023; ISPRA, 2017). Moreover, the data indicates evidence of accumulation of these compounds in the sediment compartment. It is well-known that sediment is one of the major sinks for EDCs due to their high hydrophobicity (Gong *et al.*, 2012): rather high values of log K_{ow} (between 3.40 and 4.31, Table S1) indicate a significant potential for their sorption onto sediment.

3.1.2 Diclofenac

Diclofenac was quantified in 39% of water samples in all the sampling campaigns, with the highest concentrations at the SE site (181-371 ng L^{-1}) while the levels detected at the DE and RM sites were about an order of magnitude lower. This might suggest that, similarly to estrogenic compounds, its occurrence in the Venice Lagoon can be due mainly to wastewater discharge and riverine inputs.

323 Furthermore, despite the direct discharge of hospital wastewater into the Lagoon close to the OS
324 site, diclofenac was detected there only once, during the fourth sampling campaign (4.9 ng L^{-1}).

325 In sediment, diclofenac was detected only at the RM site during the winter campaign (253 ng kg^{-1}
326 dw), confirming its low affinity to organic matter and adsorption onto sediment (Buser *et al.*, 1998;
327 ISPRA, 2017). Furthermore, it has been shown that diclofenac is not very persistent in brackish
328 environments where it is rapidly degraded, most likely *via* direct photolysis (Buser *et al.*, 1998; Tixier
329 *et al.*, 2003), and the same process can be expected in other water bodies such as streams and rivers
330 (Radke *et al.*, 2010).

331 To our knowledge, no previous data on diclofenac within the Venice Lagoon and its drainage basin
332 are available, since this pharmaceutical has been mostly analyzed in influents/effluents of WWTPs
333 (Al Aukidy *et al.*, 2012; Andreozzi *et al.*, 2003; Verlicchi *et al.*, 2014) and in riverine water (Castiglioni
334 *et al.*, 2018b; da Silva *et al.*, 2011; Feo *et al.*, 2020; Mandaric *et al.*, 2017; Mascolo *et al.*, 2019; Riva
335 *et al.*, 2019).

336 The concentrations found in the water of the Venice Lagoon are in accordance with those detected
337 in the coast of the Basque Country (Spain; Solaun *et al.*, 2021) , in the Ebro River (Northern Spain;
338 da Silva *et al.*, 2011), and in the Como Lake in Northern Italy (Castiglioni *et al.*, 2020), and are on
339 average lower than those detected in other Northern Italy rivers (*e.g.*, Lambro River basin) and
340 WWTP influents and effluents (Castiglioni *et al.*, 2020; Mandaric *et al.*, 2017; Riva *et al.*, 2019).

341 Only a few studies examined diclofenac occurrence in sediment. Concentrations found in the Venice
342 Lagoon are in accordance with those measured in the Augusta Bay (< 560-1100 ng kg^{-1} dw; Feo *et*
343 *al.*, 2020), in the salt marsh area of the Bay of Cádiz in Southern Spain (100-1500 ng kg^{-1} dw;
344 Maranho *et al.*, 2015), and in the sediment of the Ebro River (< 90-3360 ng kg^{-1} dw; da Silva *et al.*,
345 2011).

346 3.1.3 Antibiotics

347 Amoxicillin was not quantified in any of the investigated water and sediment samples. In literature,
348 except for the investigations related to WWTP inflow and outflow (Feo *et al.*, 2020; Spataro *et al.*,
349 2019), only few studies report concentrations of amoxicillin in surface water: 1.5-25.2 ng L^{-1} were
350 detected in the Lambro River basin (Riva *et al.*, 2019), < 100 ng L^{-1} in the Jarama River sub-basin in
351 Central Spain (de Santiago-Martín *et al.*, 2020), < 6 ng L^{-1} in the Po and Lambro Rivers in Northern
352 Italy (Calamari *et al.*, 2003), but limited data are available for marine water and sediment (Bonnefille

353 *et al.*, 2018; Sathishkumar *et al.*, 2020). This is also in accordance with literature information on the
354 fast degradation of this antibiotic in both the water and sediment compartments (half-life time of
355 about 9 and 25 hours, respectively; Andreozzi *et al.*, 2004).

356 Ciprofloxacin was quantified in water samples only during the spring and autumn campaigns, with
357 concentration values ranging from 7 (OS 2 sample) to 678 ng L^{-1} (SE 1 sample). The absence of
358 detectable concentrations in all sediment samples could be attributed to the low affinity of this
359 substance to organic matter (log K_{ow} of 0.28, Table S1). According to the available literature,
360 ciprofloxacin was frequently detected in surface water: in the range 1.67-236 ng L^{-1} in the coast of
361 the Basque Country (Solaun *et al.*, 2021), 4.9-60.1 ng L^{-1} in the Lambro River basin (Riva *et al.*, 2019),
362 < 0.27 to 26.15 ng L^{-1} in surface water of the Po and Lambro Rivers (Calamari *et al.*, 2003), < 100 ng
363 L^{-1} in the Jarama River sub-basin (de Santiago-Martín *et al.*, 2020), while Castiglioni and coworkers
364 (2018b) reported concentration values ranging between 6 and 70 ng L^{-1} in surface water of the Po
365 River. To the best of our knowledge, the majority of studies in literature focused on WWTPs and
366 very few reported ciprofloxacin analysis in marine water and sediment (Feo *et al.*, 2020; Verlicchi *et*
367 *al.*, 2014; Zuccato *et al.*, 2010).

368 As for macrolide antibiotics, among 2792 surface water samples considered by Loos and coworkers
369 (2018) from different European countries, erythromycin was detected with a frequency of 8.4%
370 (range of mean detected values: 5-26 ng L^{-1}), clarithromycin with a frequency of 58.8% (range of
371 mean detected values: 16-34 ng L^{-1}), and azithromycin with a frequency of 17.1% (range of mean
372 detected values: 22-23 ng L^{-1}).

373 In our study, erythromycin was quantified in four water samples of the autumn campaign (mean of
374 quantified values: 7 ng L^{-1}) and in two of the summer campaign (5-54 ng L^{-1}). It was also detected in
375 most of the sediment samples collected during the spring and autumn campaigns (mean of
376 quantified values: 3524 ng kg^{-1} dw). This can be associated with the half-life time of erythromycin in
377 seawater (about 38 days; Kwon, 2016), relatively longer than that in freshwater (3-10 days; Batchu
378 *et al.*, 2014). Moreover, the hydrophobic behavior of the substance (log K_{ow} of 3.06, Table S1) could
379 lead to higher concentrations in the sediment compartment. Erythromycin also showed significant
380 differences in its partitioning between water and sediment among the sampling campaigns: in water
381 it had higher concentrations in autumn than in spring, while in sediment it showed an opposite
382 tendency. In literature, most of the studies investigating erythromycin occurrence focused on
383 aqueous matrices and reported concentration values often lower than the detection/quantification

limits, both in studies in surface freshwater (Castiglioni *et al.*, 2020; da Silva *et al.*, 2011; Mandaric *et al.*, 2017; Riva *et al.*, 2019), and in WWTP influents and effluents (Castiglioni *et al.*, 2018a; Feo *et al.*, 2020; Spataro *et al.*, 2019). Erythromycin presence in solid environmental matrices has been less studied, and in general it showed concentrations ranging from values lower than the detection/quantification limits to hundreds of ng g^{-1} dw (Kafaei *et al.*, 2018; Li *et al.*, 2020; Senta *et al.*, 2021; Yang *et al.*, 2010; Zhao *et al.*, 2016).

In the Venice Lagoon, clarithromycin was quantified in 35% of the water samples, mostly during the spring and autumn campaigns, at concentrations ranging from 1.6 up to 193 ng L^{-1}, with a mean of quantified values of 36 ng L^{-1}. The highest concentration was found at DE site, suggesting an important contribution of the Lagoon drainage basin to the clarithromycin contamination, while the concentration levels detected near the Hospital (OS site) and the St. Erasmo WWTP (SE site) were significantly lower. In sediment clarithromycin was quantified only at DE and RM sites, at concentration ranging from 664 to 5366 ng kg^{-1} dw. The concentrations found in the Venice Lagoon fall in the range of those measured in the marine water samples collected at the Augusta Bay (Feo *et al.*, 2020), except for the water sample collected during the first sampling campaign at DE site (193 ng L^{-1}), that is considerably higher.

Azithromycin was quantified in 46% of sediment samples, showing a similar range of concentrations (about 1600-6000 ng kg^{-1} dw) at PM, SS, OS, DE, and SE sites, while the concentrations detected within Venice historical center (RM site) were about one order of magnitude higher (48-102 µg kg^{-1} dw). Conversely, azithromycin was not quantified in any water sample, probably due to its high affinity to organic matter (log K_{ow} of 4.02, Table S1) and low water solubility (2.3 mg L^{-1}; PubChem, 2019). Azithromycin is among the less studied macrolide antibiotics (Loos *et al.*, 2018; Sousa *et al.*, 2018), even if have been show that its environmental concentration may reach levels of µg L^{-1} (*e.g.*, 16.633 µg L^{-1} along the El Albujón watercourse, in Southern Spain (Moreno-González *et al.*, 2014), reflecting the fact that it is one of the most widely consumed macrolide antibiotics (Robertson *et al.*, 2021). Similarly to other considered antibiotics, most of the available studies on this compound neglect transitional and marine environments, being mostly focused on WWTPs and riverine water analysis (Solaun *et al.*, 2021; Verlicchi *et al.*, 2014), and often report concentration values above the detection limits (Fick *et al.*, 2011; Gusmaroli *et al.*, 2019).

In our study, the macrolide antibiotics in water were more frequently detected at sites in proximity of anthropogenic sources, such as OS (near the Venice hospital), DE (near the mouth of Dese River),

SE (near St. Erasmo WWTP), and RM (within the Venice historical center), while in the sampling sites characterizing the rest of the Lagoon (*i.e.* PB, PM, and SS) only in the latter two a low concentration of erythromycin and clarithromycin was found. Among all the considered antibiotics, only erythromycin, clarithromycin, and azithromycin were quantified in sediment, and the highest concentrations were found at RM, SS, DE, and OS sites. As found also for other pharmaceutical compounds, an important emission source of antibiotics in the Venice Lagoon is the discharge of tributaries from its drainage basin, even if the emissions from the historical center and hospital should not be disregarded, especially in the case of azithromycin (101733 ng kg^{-1} dw detected at RM site during the winter campaign). Furthermore, while the highest concentrations of these compounds were found near the above-mentioned point sources, a lower diffuse contamination was detected also at the sampling sites further inside the Lagoon, such as PB and PM sites (Figure 1).

3.2 Plant Protection Products (PPPs)

3.2.1 Neonicotinoid insecticides

The concentration of neonicotinoid insecticides detected in water samples ranged between 0.03-40.4 ng L^{-1} for imidacloprid, 0.01-1.55 ng L^{-1} for clothianidin, 0.001-0.39 ng L^{-1} for thiacloprid, 0.02-1.97 ng L^{-1} for thiamethoxam, and 0.004-2.64 ng L^{-1} for acetamiprid. Neonicotinoid insecticides showed a widespread occurrence across all the sampling sites, with a quantification frequency ranging from 73% to 92% if considering the four sampling campaigns. It is not surprising that the highest concentrations of these systemic insecticides were detected at DE and SE sites, because the sampling at DE site intercepts contributions from the run-off water from the agricultural land located in the Lagoon drainage basin, while samples collected at SE site are affected by chemical releases related to agricultural activities on St. Erasmo Island. Furthermore, these compounds were detected in water samples mainly during spring, summer, and winter campaigns, which coincide with their main periods of application (*e.g.*, for the treatment of winter wheat, corn, soybeans, and rice; Morrissey *et al.*, 2015; van der Zee *et al.*, 2015; Zhang *et al.*, 2016). Based on sales data of neonicotinoid insecticides in the Veneto Region for the 2016-2020 period (Calgaro *et al.*, 2023), the concentration ranges detected in water mirrored the sold amount of each compound. Moreover, it is worth noting that, since only a limited amount of PPPs containing clothianidin were sold, part of its presence could be attributed to the degradation of its precursor thiamethoxam (Nauen *et al.*, 2003; Simon-Delso *et al.*, 2015).

A quite diffuse contamination by neonicotinoids was detected also in the sediment samples. However, they were quantified only in samples collected during the spring and summer campaigns, except for imidacloprid, whose concentration was always lower than the MQL at all the sampling sites. The detected concentration ranged between 2.44-60.3 ng kg^{-1} dw for clothianidin, 0.56-54.3 ng kg^{-1} dw for thiacloprid, 3.15-12.7 ng kg^{-1} dw for thiamethoxam, and 0.68-51.8 ng kg^{-1} dw for acetamiprid. The highest concentrations were found at DE and RM sites, which were the only sampling sites where clothianidin was quantified. Thiacloprid was detected at OS and DE sites (average value of 27.3 ng kg^{-1} dw), while acetamiprid at PM, DE, and SE sites, with an average value of 15.3 ng kg^{-1} dw. Finally, thiamethoxam highlighted a widespread diffusion within the Venice Lagoon, reaching also an usually less-polluted site such as PM (11.5 ng kg^{-1} dw detected during the spring campaign, Figure 2).

Generally, concentrations of neonicotinoids detected in the Venice Lagoon water samples are lower than those reported in the last national monitoring of pesticides (ISPRA, 2020). Most literature studies report the presence of neonicotinoids in riverine and surface water, only rarely groundwater and coastal water (De Liguoro *et al.*, 2014; Li *et al.*, 2019; Xie *et al.*, 2019). The reported concentration of each neonicotinoid insecticide ranges from values lower than the MQLs (0.01-25 ng L^{-1}) to hundreds of ng L^{-1}. Similarly to what has been observed in the Venice Lagoon, imidacloprid concentration is often higher than that of other analyzed neonicotinoids (Criquet *et al.*, 2017; Gusmaroli *et al.*, 2019; Loos *et al.*, 2018; Rubirola *et al.*, 2017; Solaun *et al.*, 2021; Sousa *et al.*, 2019; Xiong *et al.*, 2019; Zhang *et al.*, 2019).

Only a few articles in literature deal with neonicotinoid concentrations in sediment, and mostly focus on riverine ecosystems, reporting values considerable higher than those found in our study (Chen *et al.*, 2015; Zhang *et al.*, 2019). However, it is worth noting that the cited studies investigated very polluted areas, with many sampling sites close to WWTP discharge points and areas with intensive agricultural activities, probably explaining the significant difference with respect to the concentrations found in the Venice Lagoon.

The results obtained also showed that neonicotinoid insecticides were detected much more frequently in the water than in the sediment compartment (average quantification frequency of 83% and 12%, respectively), and this could be attributed to their low affinity to organic matter (log K_{ow} values ranging between -0.10 and 2.06, Table S1) and their high water solubility (Bonmatin *et al.*, 2015; Zhang *et al.*, 2019).

3.2.2 Other pesticides

Methiocarb was quantified in the water samples only at the DE site during the spring campaign (1.27 ng L^{-1}), and this could be ascribed to the run-off or leaching of this compound from croplands located in the Venice Lagoon drainage basin. Indeed, the period of maximum utilization of methiocarb is spring, in particular for the treatment of vineyards and as bird repellent on corn (Arena *et al.*, 2018; Bailey and Smith, 1979; Rawn *et al.*, 2004). Not negligible concentrations of methiocarb were detected also in sediment samples collected at OS sites, within the historical center of Venice, during the summer and winter campaigns (about 20 ng kg^{-1} dw).

The main application period of oxadiazon is the spring and early summer season, before the target weeds (*i.e.* annual broad-leaved weeds and grasses in fruit trees, vines, rice, cotton, soybeans, onions, and flowers) have germinated or emerged (Pietrzak *et al.*, 2019). This oxadiazole herbicides was detected in water samples of the Venice Lagoon at low concentrations (1.20-2.83 ng L^{-1}) only during the summer campaign. In the sediment compartment, oxadiazon was found at concentrations in the range 26-49 ng kg^{-1} dw at PM, OS, and RM sites.

Metaflumizone was detected only in the sediment collected at DE sampling site (216 ng kg^{-1} dw), while its concentration in the water samples was always below its MQL (1.43 ng L^{-1}). Similarly, in all four sampling campaigns and at all the sampling sites investigated, triallate was always below the MQLs, both in water (4.9 ng L^{-1}) and in sediment (6434 ng kg^{-1} dw) samples.

In the recent Italian national monitoring of pesticides in water (ISPRA, 2020), metaflumizone and triallate were not detected at any monitoring point, methiocarb was present with a detection frequency of 2.1%, and oxadiazon with a detection frequency of 17.5%. As far as methiocarb and oxadiazon are concerned, literature data mainly focused on their occurrence in freshwater and often report values lower than their MQLs, that ranges from 0.3 to 10 ng L^{-1} for methiocarb (Gusmaroli *et al.*, 2019; Loos *et al.*, 2018; Masiá *et al.*, 2015; Rubirola *et al.*, 2017; Solaun *et al.*, 2021; Sousa *et al.*, 2019) and from 0.17 to 90 ng L^{-1} for oxadiazon (Gusmaroli *et al.*, 2019; Loos *et al.*, 2018; Solaun *et al.*, 2021; Sousa *et al.*, 2019). According to literature (Pietrzak *et al.*, 2019), metaflumizone was rarely analyzed (Loos *et al.*, 2018; Solaun *et al.*, 2021), while triallate has been more frequently studied, mainly in freshwater and WWTPs. As noticed for other PPPs, literature studies report that triallate concentration in freshwater is often lower than its MDL (0.035-17 ng L^{-1}) and MQL (0.17-52 ng L^{-1}; Gusmaroli *et al.*, 2019; Rubirola *et al.*, 2017; Solaun *et al.*, 2021; Sousa *et al.*, 2019; Wu *et al.*, 2017).

3.3 Industrial chemicals

BHT was detected in about half of the water and sediment samples (quantification frequency of 42% and 54%, respectively), especially during the summer and winter campaigns. In spring and autumn BHT was quantified in water samples only at SE site, with concentrations of 2.4 and 20 ng L^{-1}, respectively, while remaining below its MQL (1.7 ng L^{-1}) at the other sampling sites. Higher concentration levels were found during the summer and winter campaigns (17-104 ng L^{-1}), in which BHT was detected in almost all the sampling sites, except for DE. In sediment, BHT was found at all the sampling sites (except for PM), at concentrations ranging from 760 up to 17397 ng kg^{-1} dw, with the highest levels detected at DE and RM sites.

The diffuse accumulation of this preservative in sediment can be attributed both to its high affinity to organic matter (log K_{ow} of 6.20, Table S1), and persistence in the sediment (half-life time of 340 days; Liu and Mabury, 2020). BHT concentrations in water fall in a similar range to that found in natural surface freshwaters of Germany (Fries and Püttmann, 2004), Sweden (Bendz *et al.*, 2005), Spain (Gusmaroli *et al.*, 2019), and USA (Benotti *et al.*, 2009). On the other hand, BHT concentrations in sediment are substantially lower than those found in lacustrine sediment in the Nanjing area (China; 90-6390 µg kg^{-1} dw; Zhang *et al.*, 2018) and in surface sediment from the Bohai Sea and Yellow Sea (China; 76.7-2510 µg kg^{-1} dw; Wang *et al.*, 2018).

EHMC was detected in 77% of the water samples, at all the sampling sites, with a concentration range of 0.23-22.4 ng L^{-1}. The highest concentrations were found during the summer campaign, when an increased use of PCPs containing UV filters to protect from sunlight is expected. The SE site always turned out to be the most contaminated one in all the sampling campaigns, suggesting a key-influence of WWTP effluents to the load of this contaminant to the Venice Lagoon. A slight seasonal trend was detected also for the EHMC concentration in sediment. During the spring and summer campaigns it ranged between 470 and 4890 ng kg^{-1} dw, while in autumn and winter ones it remained below the MQL (469 ng kg^{-1} dw), except for the RM 4 sample (3316 ng kg^{-1} dw), confirming a general tendency to follow the usage period of this compound.

The concentrations of EHMC determined in the Venice Lagoon water fall among the lowest ranges characterizing various riverine and marine environments of Europe (Balmer *et al.*, 2005; Gusmaroli *et al.*, 2019; Negreira *et al.*, 2010; Picot-Groz *et al.*, 2018; Sousa *et al.*, 2019; Vila *et al.*, 2016), Australia (Allinson *et al.*, 2018), and Japan (Kameda *et al.*, 2011; Tashiro and Kameda, 2013), where the maximum concentrations detected exceed the µg L^{-1} level. Similarly, concentration levels

539 quantified in the sediment samples of the Venice Lagoon are lower than those found in the sediment
540 of other areas of the Adriatic Sea (900-10400 ng kg^{-1} dw; Combi *et al.*, 2016). Similar wide ranges of
541 values have also been detected in sediment along the coasts of Spain (Gago-Ferrero *et al.*, 2011;
542 Pintado-Herrera *et al.*, 2016), Lebanon (Amine *et al.*, 2012), and Brazilian rivers (Mizukawa *et al.*,
543 2017).

544 4. Conclusions

545 This study provides the first monitoring data on twenty CECs in water and sediment of seven
546 sampling sites in the Venice Lagoon, selected with the aim of intercepting possible sources of
547 contamination and characterizing the three macro-areas of the Lagoon.

548 While the characteristics of this baseline study prevent the identification of significant spatial and
549 temporal contamination trends, the outcomes suggests that two of the major emission sources of
550 CECs in the Venice Lagoon could be tributary rivers and treated wastewater, since the existing
551 WWTPs seems to be not entirely efficient in the removal of some CECs.

552 The information obtained can be considered a suitable starting point for planning further
553 investigations with a possibly higher spatial and temporal resolution within the Venice Lagoon, as
554 well as for other transitional environments subjects to anthropogenic pressures. In particular, the
555 identification of multiple CEC sources showed the need for more dedicated strategies for the
556 management of CEC emission within the agricultural, industrial, and PPCP sectors to avoid water
557 quality deterioration, especially within sensitive ecosystems such as the Venice Lagoon.

558 It is worth reporting that this baseline study is being complemented by the application of a fate and
559 transport multimedia model to simulate the environmental behavior of the target CECs, to
560 investigate the potential relevance of different emission sources and to better understand the
561 drivers of environmental partitioning in different media. The integration of experimental and
562 modeling efforts will support the development of a Watch List of CECs for the Venice Lagoon,
563 including contaminants to be included in future, and more comprehensive monitoring plans to
564 improve local environmental management.

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Declaration of competing interests

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

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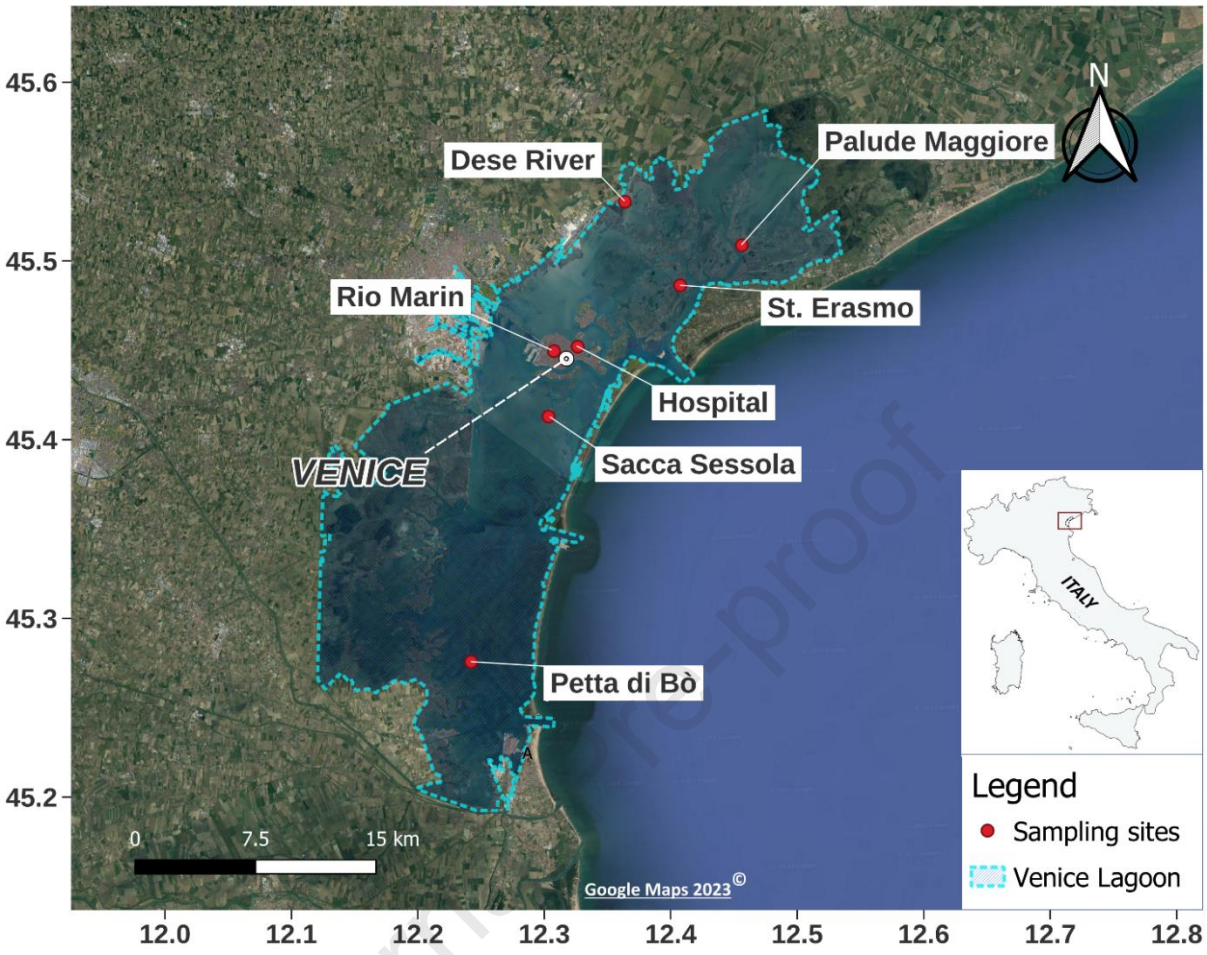
983 **Figures**



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985 **Figure 1.** Location of the seven sampling sites under investigation.

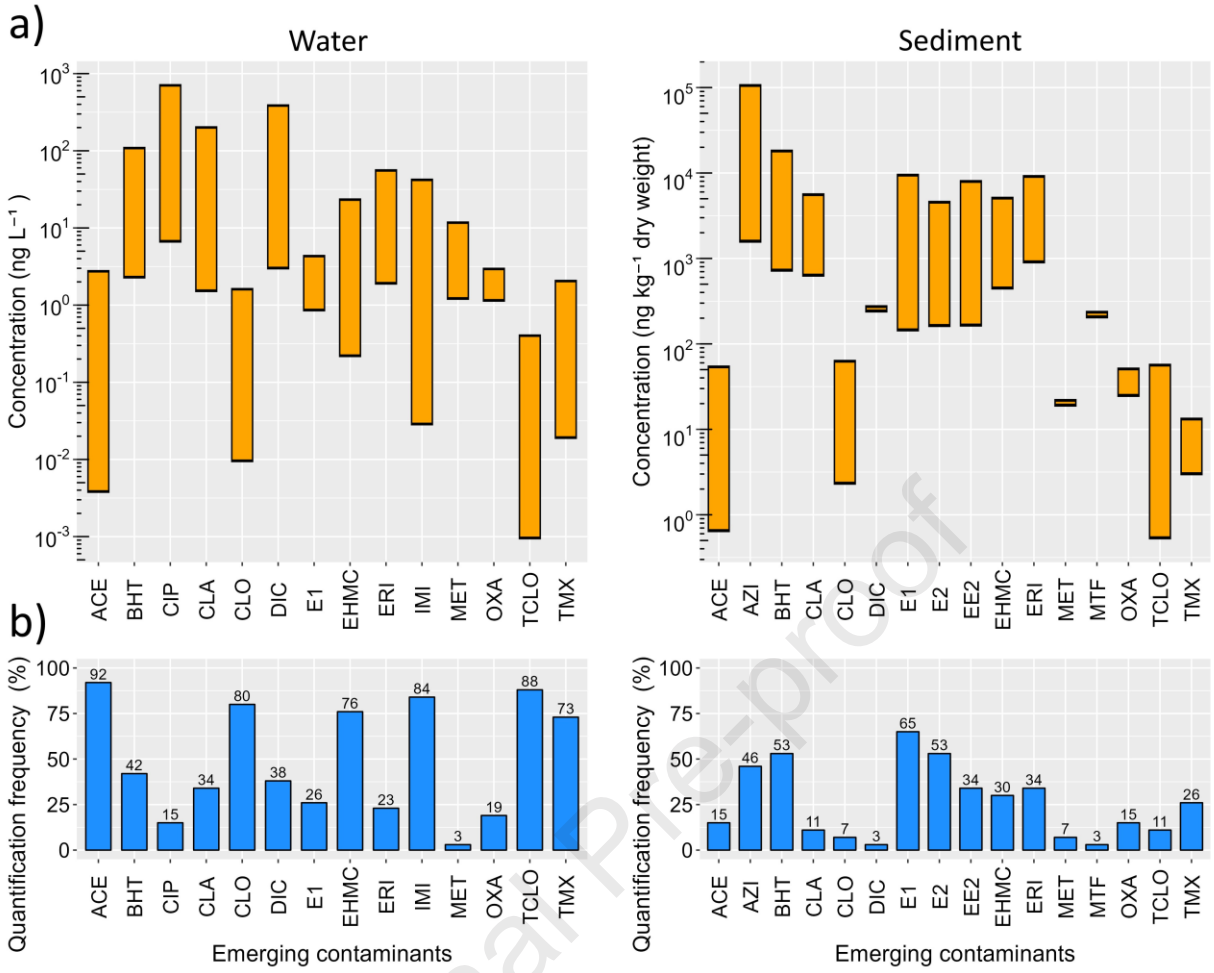

Figure 2. Concentration range (a) and quantification frequency (b) of the contaminants of emerging concern investigated in this study. ACE: Acetamiprid; AZI: Azithromycin; BHT: 2,6-Di-*tert*-butyl-4-methylphenol; CIP: Ciprofloxacin; CLA: Clarithromycin; CLO: Clothianidin; DIC: Diclofenac; E1: Estrone; E2: 17β-Estradiol; EE2: 17α-Ethynylestradiol; EHMC: 2-Ethylhexyl-4-methoxycinnamate; ERI: Erythromycin; IMI: Imidacloprid; MET: Methiocarb; MTF: Metaflumizone; OXA: Oxadiazon; TCLO: Thiacloprid; TMX: Thiamethoxam.

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HIGHLIGHTS

- The first investigation of twenty CECs in water and sediment of the Venice Lagoon
- The most frequently quantified contaminants in water were neonicotinoids and EHMC
- Estrogens and BHT had the higher quantification frequencies in sediment samples
- The major emission sources turned out to be tributary rivers and treated wastewater
- The study provides baseline knowledge to draft a Watch List for the Venice Lagoon

Declaration of interests

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

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: