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Research article

Emissions of pharmaceuticals and plant protection products to the lagoon of Venice: development of a new emission inventory

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ABSTRACT

Estimating the emissions of chemical pollutants to water is a fundamental step for the development and application of effective and sustainable management strategies of water resources, but methods applied so far to build chemicals inventories at the European or national scale show several limitations when applied at the local scale. The issue is particularly relevant when considering contaminants of emerging concern (CECs), whose environmental releases and occurrence are still poorly studied and understood.

In this work, an approach to estimate water emissions of nine active pharmaceutical ingredients (APIs) and ten most applied plant protection products (PPPs) is presented, considering proxy indicators (e.g., sales data and census information). The application area is the lagoon of Venice (Italy), a complex transitional environment highly influenced by anthropic pressures (e.g., agricultural and industrial activities, animal breeding, and wastewater discharge). The presented approach can be tailored to the information available for any local scale case study.

Data on annual regional sales of PPPs and APIs were integrated with georeferenced demographic and economic statistics (such as census and land-use information) to estimate chemicals emissions to surface water and groundwater. A sensitivity and uncertainty analysis identified the main factors affecting emissions estimates, and those contributing more significantly to results uncertainty.

Results showed the highest estimated emissions of APIs for antibiotics (i.e., amoxicillin, clarithromycin, azithromycin, and ciprofloxacin) used for humans and animals, while most of hormones' emission (i.e., 17- α-ethinylestradiol and 17-β-estradiol) derived from animal breeding. Regarding PPPs, glyphosate and imidacloprid emissions were one to two orders of magnitude higher compared to the other chemicals.

Uncertainty and sensitivity analysis showed that the variability of each parameter used to estimate emissions depends greatly both on the target chemical and the specific emission source considered. Excretion rates and removal during wastewater treatment were major key parameters for all the target pharmaceutical compounds, while for PPPs the key parameter was their loss into the natural waters after application.

1. Introduction

Water resources are of utmost importance for both the environment and human life (Katusiime and Schütt, 2020), but anthropogenic drivers such as urban development, agricultural activities, industrial production, and the consequent wastewater discharge and emissions of xenobiotic chemicals have led to severe degradation of the global water supply (Akhtar et al., 2021; Calgaro et al., 2019; Wada and Bierkens, 2014). The development of effective and sustainable strategies for the management of water resources aimed at protecting human health and ecosystems (Khatri and Tyagi, 2015) requires the identification and quantification of pollutants' emission and the prediction of environmental concentrations of parent compounds and their transformation products. In this context, the identification of contaminants of emerging concern (CECs), for which available monitoring data is insufficient or of inadequate quality, has become a fundamental issue (Geissen et al., 2015).

To assess the actual risk across the EU waters, the Environmental Quality Standards Directive 2013/39/EU (EC, 2013) calls for the periodic creation of a "Watch List" identifying a set of pollutants (maximum 14) for launching an *ad-hoc* EU-wide monitoring program, lasting up to four years. The inclusion of chemicals into the Watch List may follow

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several criteria, including a procedure relying on a risk-based prioritization of candidate substances at the European scale (Carvalho et al., 2015; Cortes et al., 2020; Robert et al., 2018) through the quantification of predicted environmental concentrations (PECs), the identification of measured environmental concentrations (MEC), and the derivation of predicted no-effect concentrations (PNEC) and human acceptable or tolerable daily intake values.

For EU-scale exposure assessments, the estimation of PECs using predictive chemical fate models starts from the collection of data about the tonnage (of use, manufacture, and import), that have been submitted under the REACH regulation (which are, however, covered by confidentiality constraints) (Cortes et al., 2020). Although this approach is appropriate at the European scale, it can be hardly adopted if the assessment is carried out at different scales (i.e., national, regional, or local), where pollutants' loads to surface waters at higher spatial and/or temporal scale are considered and site-specific information to estimate emissions might not be accessible.

In addition, while EU Member States (MS) are solicited to provide annual inventories of the emissions of priority substances, such as the European Pollutant Release and Transfer Register (E-PRTR) established by Regulation 2006/166/EC, and the emission inventory at the river basin district scale (EC, 2012) set up according to the Water Framework Directive provisions (EC, 2000), the reporting of the release for other hazardous substances (such as to the WISE-SOE (Water Information System Europe – State of the Environment database) (EC, 2020a) is still uneven and incomplete across EU, and publicly available datasets are rather scarce (Pistocchi et al., 2019).

Furthermore, while pollutants' loads to specific water bodies (e.g., lakes, lagoons, and coastal areas) can also be estimated based either on their concentration in each tributary and the respective water discharge flow (Steen et al., 2001) or by back-estimation based on influent concentrations of wastewater treatment plants (WWTPs) in the case of active pharmaceutical ingredients (APIs), those approaches require rather extensive monitoring activities (Chen et al., 2019).

In this context, it becomes evident that the derivation of water emissions data turns into a challenge in the case of CECs, due both to the scarcity of monitoring data and the rather limited knowledge about the environmental properties and behaviour of some of these pollutants (Carvalho et al., 2015). Therefore, local or regional studies often require the development of *ad-hoc* approaches, depending on the specific spatial and temporal resolution of available data and the possibility to derive or extrapolate water emission estimates from "proxy" indicators, such as sales information or surveys (Chen et al., 2019; Leclerc et al., 2019).

Transitional water bodies are of particular concern as sensitive, and often unique, ecosystems that are threatened by several anthropic stressors (e.g., agricultural and industrial activities, animal breeding, and discharges from WWTPs due to urban settlements).

In this work we present the development of an emission inventory for nineteen CECs, selected from the 1st and the 2nd Watch List (EC, 2018, 2015), aimed at setting the background for their fate and exposure modelling in the Venice lagoon (Italy), with the final aim to select a list of chemicals to be further monitored in this area by means of a specific risk-based prioritization exercise.

The lagoon of Venice is one of the largest coastal transition environments in the Mediterranean Sea and is located in a highly populated area where anthropogenic pressures (e.g., chemical industry, urban settlements, tourism, and glass manufacturing) increased over the last century, thus resulting in chemical pollution and eutrophication phenomena (Micheletti et al., 2011). While different monitoring programs have been conducted to manage the presence of priority substances (CVN, 2010; EC, 2000; EMD, 2009), the lagoon is not included in the screening monitoring of Watch List contaminants set by National authorities (ISPRA, 2017), therefore the environmental occurrence and behaviour of CECs has been only rarely investigated (Pojana et al., 2004; Vecchiato et al., 2016) and is still poorly understood.

In detail, the main aim of this work is to define a procedure for quantifying emissions for two categories of CECs, namely active pharmaceutical ingredients (APIs) and plant protection products (PPPs), specifically tailored to the availability of information (e.g., market statistics, and realistic use patterns) at the case-study level. The development of this water emission inventory made use of GIS-based tools in combination with demographic and economic statistics to estimate emissions at the resolution required by the study. Moreover, the work includes a critical evaluation of the proposed approach to provide support for future exposure modelling studies on CECs in the environment and the establishment of more effective management strategies for these chemicals also for other catchments where only limited monitoring data is available.

2. Materials and methods

2.1. Study area

The lagoon of Venice, located in the northern Adriatic Sea and part of the Veneto Region territory (Italy), is the largest transitional water system of the Mediterranean Sea (Madricardo et al., 2019; Sfriso et al., 2019) as well as one of the UNESCO World Cultural and Natural Heritage sites (Fig. 1). The lagoon can be hydrodynamically considered as a 3-component system composed by its drainage basin, the lagoon itself, and the adjacent Adriatic Sea (Molinaroli et al., 2007).

The drainage basin of the lagoon covers about 2560 km^2 and ensures an average freshwater input of about 35.5 m^3/s, through the contribution of several natural rivers and artificially controlled channels (Zuliani et al., 2005). This area is subjected to several anthropogenic pressures due to its high population density (ca. 250 inhabitants per

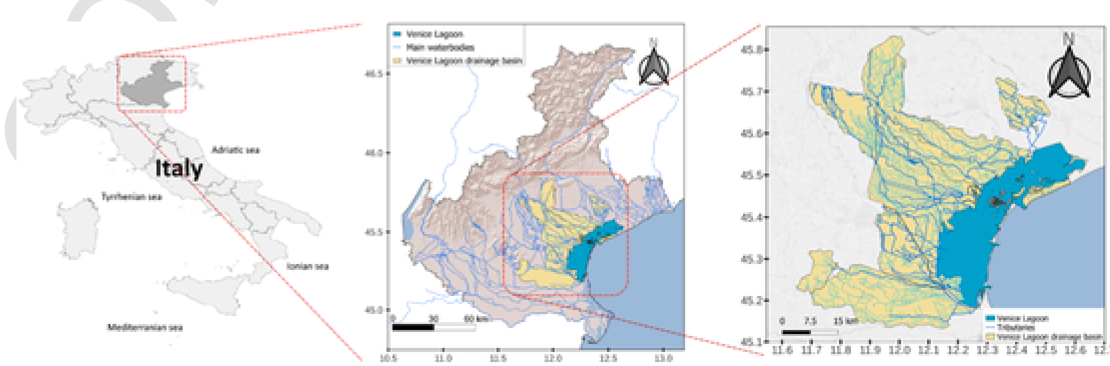

Fig. 1. Location of the case study catchment area in the Veneto region (northern Italy). The map of the right shows the surface waters contributing to the Venice lagoon drainage basin (the major rivers are highlighted in dark blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

km^2) and the extensive presence of agricultural and industrial activities (UNEP/MAP and Plan Bleu, 2020). In particular, since most of the drainage basin available surface (about 65%) (Veneto Region, 2020a) is used for agricultural purposes to grow a large variety of products (e.g., corn, sugarbeet, soy, wheat, grapes, barley, and vegetables), there is a widespread use of several classes of PPPs (e.g., herbicides, pesticides, and fungicides) which may end in the lagoon due to run-off or leaching to surface and groundwaters. Furthermore, the presence of both a highly developed animal breeding industry (UNEP/MAP and Plan Bleu, 2020) and densely populated areas in the drainage basin causes the discharge of many APIs into the lagoon, for example due to the discharge of effluents from wastewater and sewage treatment plants, improper disposal of unused or expired pharmaceuticals, or natural emissions from animals and people in the case of hormones (Fernandes et al., 2021).

In this context, chemical pollution due to the emission of organic (e.g., PCBs, PCDDs) and inorganic pollutants (e.g., heavy metals) (Dalla Valle et al., 2005; Giubilato et al., 2016; Sfriso et al., 2019; Sommerfreund et al., 2010; Zonta et al., 2005) have already been observed by several authors, while recent studies also reported the presence of several CECs in groundwater and freshwaters (ARPAV, 2019a; Vecchiato et al., 2016), emphasising the need to establish suitable management strategies.

2.2. Selected compounds

The chemical substances considered in this work have been selected from the the 1st and the 2nd Watch List (EC, 2018, 2015) due to the absence of systematic monitoring activities in Italy to investigate their presence in transitional waters. In detail, we focused on several APIs (Table 1) and PPPs (Table 2) due to their environmental relevance (Pojana et al., 2004) and the availability of sales data specific to the case study area that could be used as proxy indicators to quantify the emissions of these pollutants to the water compartment. Other chemicals that were a part of the Watch lists' monitoring programmes (e.g., 2-ethyl-hexyl-4-methoxycinnamate and 2,6-di-tert-butyl-4-methylphenol) were not considered in this study because sales data specific to the case study area was not available.

Table 1
Average of excretion factor (F_i), average removal efficiency by WWTPs treatment (R_i), average absorption factor for gel formulations (A_i), average sewer conversion of E2 to E1 (SC_i), and range of quantity of active compound corresponding to each dose (CF_i) for the APIs considered in this study. (N.A.: not available).

APIs	F_i	R_i	CF_i	A_i	SC_i
Hormones	-	–	mg·Dose⁻¹	–	–
17- β -estradiol (E2)	6.50E-01	8.20E-01	2.50E-02 - 2.00 E+03	–	2.80E-01
Estrone (E1)	2.50E-01	7.60E-01	N.A.	–	–
17- α -ethinylestradiol (EE2)	2.70E-01	7.40E-01	6.94E-04- 1.00 E+03	5.00E-01	–
Nonsteroidal anti-inflammatory drugs					
Diclofenac (DIC)	2.00E-01	3.70E-01	5.00 E+01–5.00 E+03	1.50E-01	–
Penicillin antibiotics					
Amoxicillin (AMO)	8.50E-01	7.80E-01	8.00 E+01–2.00 E+03	–	–
Quinolone antibiotics					
Ciprofloxacin (CIP)	4.60E-01	6.40E-01	2.00 E+00–1.00 E+03	–	–
Macrolide antibiotics					
Erythromycin (ERY)	2.60E-01	5.30E-01	3.00 E+01–1.30 E+03	–	–
Clarythromycin (CLA)	3.50E-01	4.70E-01	1.25 E+02–5.00 E+02	–	–
Azythromycin (AZY)	1.00E-01	4.20E-01	5.00 E+02–1.50 E+03	–	–

The references to the studies used to obtain these values are reported in Table S3, Table S4, and Table S5.

Table 2
Average fraction of the selected PPPs entering the water compartment through run-off, leaching, and drainage after application (*Li*), and area destined to agriculture in the Veneto Region (A_V) and in the Venice lagoon drainage basin (A_B).

PPPs	L_i
Insecticides	
Metaflumizone (MTF)	1.00 E-02[a]
Methiocarb (MTC)	1.00 E-02[a]
Herbicides	
Glyphosate (GLY)	1.12E-02
Triallate (TRI)	6.00E-03
Oxadiazon (OXA)	9.50E-03
Neonicotinoid insecticides	
Imidacloprid (IMI)	7.54E-02
Thiacloprid (TCLO)	1.00 E-02[a]
Thiamethoxam (TMX)	6.89E-03
Clothianidin (CLO)	1.00 E-02[a]
Acetamiprid (ACE)	1.00 E-02[a]
Area	
A_V	7.81 E+03 km^2
A_B	1.37 E+03 km^2

The references to the studies used to obtain these values are reported in Table S10.
a: Since no experimental data was found for MET, MTF, CLO, TCLO, and ACE the estimation ($L_i \approx$ 1.00E-02) for postemergence-applied PPPs reported by Spencer and Cliath *et al.* and Leclerc *et al.* was used (Leclerc et al., 2019; Spencer and Cliath, 1991).

2.2.1. Active pharmaceutical ingredients

APIs cover all classes of chemicals used primarily to prevent or treat human and animal diseases. Pharmaceuticals (e.g., antibiotics, analgesics and painkillers, cardiovascular drugs, blood lipid regulators, and antidepressants) are generally excreted and emitted into the sewerage system following use and can then be released into surface water bodies or enter terrestrial systems. Furthermore, veterinary drugs may be released directly in surface waters or indirectly during the land application of manure and slurry from live-stock facilities (Boxall et al., 2004; Sarmah et al., 2006). Once in the environment, APIs can be absorbed by and interact with living organisms, thus representing a potential risk for non-target organisms and for the whole ecosystem. For example, hormones might act as endocrine disruptors (Adeel et al., 2017), while antibiotics may significantly increase the proliferation of multi-resistant bacteria (Kümmerer, 2009).

In detail, the APIs selected in this study are reported in Table 1, and have been chosen as representative compounds for the most used drugs in Italy (i.e., hormones, penicillin antibiotics, quinolone antibiotics, macrolide antibiotics, and nonsteroidal anti-inflammatory drugs) (AIFA, 2019, 2018).

2.2.2. Plant protection products

PPPs are formulations mainly used to keep crops (or other useful or desirable plants) healthy and prevent them and their products from being destroyed by diseases and/or infestations (EC, 2009). They include herbicides, fungicides, insecticides, acaricides, molluscicides, plant growth regulators, repellents, and pesticides. (EC, 2020b). They are primarily used in agriculture but also forestry, horticulture, and for the management of both amenity areas and home gardens. Each formulation consists of one or more active substances, responsible for the properties of the PPP, as well as other substances called co-formulants. The toxicity of these chemicals towards humans and animals is quite lower with respect to that against target plants, but there are still direct and indirect toxic effects on non-target organisms that are not fully understood yet (Barbosa et al., 2016; Gupta, 2012).

In detail, the PPPs selected in this study are reported in Table 2, and they have been chosen due to their wide use as herbicides and insecticides in Italy (ISPRA, 2020), as well as for the availability of sales data at the local scale.

2.3. Emissions inventories

Calculating the emissions of each specific class of chemicals may require a tailored method for the estimation, to account for the specific production and use patterns and to make the best use of available data (e.g., sales data, market statistics, and data on product uses), especially if specific local emission inventories are not readily available (Leclerc et al., 2019; Sala et al., 2015). In the following paragraphs, the methodologies defined for emission estimation of APIs and PPPs are detailed.

2.3.1. Active pharmaceutical ingredients

Several authors have already reported the paucity of monitoring data regarding the emissions of APIs to freshwater at the European, national, and local level (Leclerc et al., 2019; Sala et al., 2015), therefore it has been preferred to derive these emissions from national or regional sales data, taking into account both the partial elimination in the human body and removal in wastewater treatment plants of these compounds, since emission of pharmaceuticals are closely related to local population density, consumption level, and scale of livestock and poultry breeding industries (Chen et al., 2019). In detail, the use of active ingredients in pharmaceuticals authorised in Europe is monitored by the European Medicines Agency, and information is available through an online database (EMA, 2020), where for each ingredient the list of pharmaceutical products on the European market can be identified. Furthermore, the quantity of consumed pharmaceutical products is monitored by each Member State. In particular, in Italy the Italian Agency for Pharmaceutical Products (AIFA) hosts the national Observatory on the use of Pharmaceuticals (OsMED), which releases annual estimates of pharmaceuticals consumption with a focus on the regional scale (AIFA, 2009).

2.3.1.1. Emissions of APIs from human treatment. Regional records on the annual quantity of drug packages (i.e., DP_i) sold through hospitals and pharmacies affiliated with the National Healthcare System were collected. This data was combined with the number of doses per drug package (i.e., ND_i) and quantity of active compound corresponding to each dose (i.e., CF_i mg/Dose) (information reported within AIFA national drug database (AIFA, 2020)) to estimate the total quantity of each API annually sold in the Veneto Region (i.e., $Q_{APIi\text{-}V}$, mg) (Eq. (1)) (Sinnott et al., 2016; WHO, 2017).

$$Q_{APIi-V} = DP_i \cdot ND \cdot CF_i \tag{1}$$

Starting from data on the quantity of drugs annually dispensed by the Italian Healthcare Service in the Veneto Region, the quantity of each API used in the area corresponding to the lagoon drainage basin (Q_{APIi-B}) was estimated by assuming the API's consumption to show the same spatial distribution as the population (Eq. (2)) (Le Corre et al., 2012; Ort et al., 2010). The population towards which each drug is targeted in the Veneto region and in the case study region (P_{i-V} and P_{i-B}, respectively) (Table S1) was obtained based on the most common uses of each pharmaceutical (Harrison and Bonnar, 1980; Kwon, 2016; Kwong and Lindsay Grayson, 2017; Parnham et al., 2014; Rodvold, 1999; Standing et al., 2009; Washington and Wilson, 1985) and by scaling the most recent national census data (De Rossi, 2015; ISTAT, 2012a; Veneto Region, 2019) to the area of interest by mean of GIS-based spatial analysis tools (QGIS® software, version 3.8.3-Zanzibar).

$$Q_{APIi-B} = Q_{APIi-V} \cdot \left(P_{i-B}/P_{i-V}\right) \tag{2}$$

Moreover, it has been already reported that APIs are usually released into the environment either from WWTP plants that treat urban wastewater or by direct emission from settlements that lack such facilities (Barbosa et al., 2016), as in the case of the city of Venice (Libralato et al., 2012). For this reason, the fraction of each chemical removed during wastewater treatment (i.e., removal efficiency, R_i) and the fraction of each active compound excreted after consumption (i.e., excretion factor, F_i) are required for emissions estimation (Table 1). In addition, since DIC and E2 are included also in products for topical use, these formulations were treated separately and an additional term for their absorption (i.e., A_i) was used (Table 1).

Since no information was found in the literature for R_i referring to the WWTPs situated in the Venice lagoon drainage basin, the arithmetic average of the values reported in other studies was used for each chemical to account for diversity between the studied installations. In particular, Table 1 reports the average values, while detailed information is available in the Supporting Information (Table S2, Table S3, and Table S4).

In addition, several studies on the emission of hormones reported that a significant fraction (ca. 28%) of E2 discharged into the sewer system can be converted to E1 due to degradation processes (Fleming et al., 2016; Heffley et al., 2014), therefore an additional term (i.e., sewer conversion, SC_{E2}) was considered while estimating emissions of these two hormones.

Since excretion factors have an inter-individual variation due to metabolic differences, when more than one F_i was reported in literature, arithmetic average values were used (Table S3), and the same approach was also used to account for the variation of A_i caused by the differences in the gel formulation and individual metabolism (Table S4).

Furthermore, since Venice historical centre and the surrounding islands are not served by WWTPs (Libralato et al., 2012), the population of the case study area was divided (Leclerc et al., 2019) into two groups: (1) Venice and the nearby islands and (2) areas served by WWTPs (Table S1).

The quantity of each API sold in the Venice lagoon drainage basin corresponding to each population group was calculated by using Eq. 3:

$$Q_{APIi-B\ (Group\ j)} = Q_{APIi-B} \cdot \%_{Group\ j} \tag{3}$$

where $\%_{Group\ j}$ represents the fraction of the Veneto Region target population which resides in the case study area.

Furthermore, the emission of each API for Group (1) was estimated by applying Eq. 4, while for Group (2) Eq. 5 was used.

$$E_{i\ Group\ (1)-Pharma} = \left(Q_{APIi-B\ (Group\ (1))} \cdot F_i\right) + \left(Q_{APIi-B\ (Group\ (1))-Gel} \cdot A_i \cdot F_i\right) \tag{4}$$

$$E_{i\ Group\ (2)-Pharma} = \left(Q_{APIi-B\ (Group\ (j))} \cdot F_i \cdot \left(1 - R_i\right)\right) + \left(Q_{APIi-B\ (Group\ (j))-Gel} \cdot A_i \cdot F_i \cdot \left(1 - R_i\right)\right) \tag{5}$$

In addition, to account for the transformation of E2 to E1 within the sewer system (i.e., $E_{E2\ to\ E1}$) (Fleming et al., 2016; Heffley et al., 2014) the emission of E2 corresponding to Group 2 was multiplied for SC_{E2} (Eq. 6) and the result was deducted from the overall E2 emission to WWTPs and was considered as an emission of E1 into WWTPs.

$$E_{E_2\ to\ E_1} = \left[\left(\left(Q_{E_2-B\ (Group\ (2))}\right) + \left(Q_{E_2-B\ (Group\ (2))-Gel} \cdot A_i\right)\right) \cdot F_i\right] \cdot SC_{E_2} \tag{6}$$

Finally, the total emission of each API (i.e., $E_{i-Pharma\ Tot}$) discharged into the Venice lagoon drainage basin caused by the use of pharmaceutical products was calculated as the sum of all population groups' contributions:

$$E_{i-Pharma\ Tot} = E_{i\ Group\ (1)-Pharma} + E_{i\ Group\ (2)-Pharma} \tag{7}$$

2.3.1.2. Emissions of APIs from sources other than human treatment. In addition to emissions caused by the human consumption of medicines, APIs can also be introduced into the environment because they are used for livestock treatment (i.e., DIC, AMO, CIP, ERY, CLA, and AZI) or are naturally produced by both animals and people (i.e., E1 and E2) (EC, 2011; Heffley et al., 2014; Johnson and Williams, 2004). Furthermore, since the use of hormonal drugs in livestock farming has been banned in Europe starting from 2003 (EC, 2003), no emission of EE2 from animal husbandry was considered.

2.3.1.2.1. Emissions of E1 and E2 from people. The approach reported by Heffley and co-workers (Eq. 8) (Heffley et al., 2014) to estimate the natural emission of E1 and E2 from people was adapted thought the elaboration of literature and national census data (De Rossi, 2015; ISTAT, 2012a) by means of GIS-based spatial analysis tools (QGIS® version 3.8.3-Zanzibar).

$$\begin{aligned} E_{i-People} = & \sum_{j=A}^{D} Class_{j\ (Group\ (1))} \cdot EX_{i,j} \\ & + \sum_{j=A}^{D} \left(Class_{j\ (Group\ (2))} \cdot EX_{i} \cdot \left(1 - R_i\right)\right) \end{aligned} \tag{8}$$

Population in the Venice Lagoon drainage basin, excluding prepubescent individuals (i.e., 14 years of age and under) due to extremely low oestrogen excretion concentrations (Fleming et al., 2016), was divided into four categories due to different excretion rates of E1 and E2 (Table 3 and Table S5): pregnant females (i.e., Class A), menstruating females (i.e., women between 13 and 49 years old, Class B), menopausal females not taking hormone replacement therapy (HRT) (i.e., women over 50 years old, Class C), and males (i.e., Class D). The excretion rates ($EX_{i,j}$) for the four demographic profiles used in this study are also reported in Table 3. Since the contribution of menopausal females on HRT has already been accounted for from E1 and E2 sale data, recent trends in HRT use in Italy (i.e., ca. 6% of menopausal females) were estimated by comparing the results reported by Manzoli and colleagues (Manzoli et al., 2004) (ca. 13.5% of menopausal females) for the 1997–2001 period with the overall sales of HRT drugs in Italy between 2000 and 2018 (AIFA, 2019; Donati et al., 2012), to account for the decrease of HRT caused by concerns over its associations with cancer and heart diseases (Heffley et al., 2014).

Table 3
Per capita mean excretion rates (EXi,j) and per animal mean excretion rates (EXi,k) of E1 and E2.

Population	E1	E2
	$\mu g \cdot day^{-1}$	
Class A (Pregnant females)	5.50 E+02[e]	3.93 E+02[e]
Class B (Menstruating females)	1.17 E+01[e]	3.20 E+00[e]
Class C (Menopausal females not on HRT)	1.80 E+00[e]	1.00 E+00[e]
Class D (Males)	2.60 E+00[e]	1.80 E+00[e]
Swine - Sow	4.11 E+02[a]	1.63 E+01[a]
Swine - Piglet	1.00 E+00[b]	5.00 E+00[b]
Swine - Others	2.25 E+01[a]	1.00 E+01[a]
Beef cattle	1.11 E+03[c]	3.75 E+02[c]
Dairy cattle	8.38 E+02[d]	3.42 E+02[c]
Sheep	1.26 E+01[a]	3.00 E+00[c]
Poultry	8.30 E-01[a]	3.50 E+00[c]

a: from Zhang et al. (2014); b: from Liu et al. (2012); c: from Johnson et al. (2006); d: from Lange et al. (2002): e: from Heffley et al. (2014).

2.3.1.2.2. Emissions of E1 and E2 from animal husbandry. Emissions of E1 and E2 from animals (i.e., swine, cattle, sheep, and poultry) were estimated by adapting the approach reported by Zhang and colleagues (Zhang et al., 2014) (Eq. 9) based on the mean excretion rates ($EX_{i,k}$) reported in Table 3 and on animal population data (AP_k) for each municipality of the lagoon drainage basin retrieved from the Italian National Zootechnical Registry (Italian Health Ministry, 2020) and elaborated by mean of GIS software. Data on livestock breeding method (i.e., proportion of intensive breeding, S_k) was obtained for the Veneto Region from the Italian National Zootechnical Registry (Table S6) (Italian Health Ministry, 2020). Scattered breeding waste was assumed to be generally discharged directly without any treatment and the fraction of the wastes generated from intensive breeding subjected to treatment (e.g., storage tanks or sedimentation tanks as biological treatment) before discharging into the receiving environment (i.e., θ) was assumed equal to the fraction of farms equipped with waste treatment facilities in each municipality of the Venice Lagoon drainage basin based on the elaboration of national census data (ISTAT, 2012b) (Table S7).

$$\begin{aligned} E_{i-Animals} = & \sum_{k,i} AP_k \cdot EX_{i,k} \cdot S_k \cdot \theta \cdot \left(1 - R_i\right) \\ & + \sum_{k,i} AP_k \cdot EX_{i,k} \cdot S_k \cdot (1 - \theta) \\ & + \sum_{k,i} AP_k \cdot EX_{i,k} \cdot \left(1 - S_k\right) \end{aligned} \tag{9}$$

2.3.1.2.3. Emissions of antibiotics from animal husbandry. The use of antibiotics for animal treatment has been recognized as one of the main sources of these chemicals' emissions to the water compartment (Borck Høg and Korsgaard, 2016; WHO, 2014), but data on their sale and use for this purpose at the local or regional level is often scarce or completely unavailable (Maggio et al., 2020), therefore it is necessary to resort to estimations. In this work, we relied on generic estimations of animal *vs* human use reported at the national level for a specific class of compounds (e.g., macrolide antibiotics and fluoroquinolones antibiotics) that have been used to obtain a rough estimate for the selected substances.

In particular, JIACRA estimated that in 2014 the use of macrolides and fluoroquinolones antibiotics in Italy for human treatment accounted roughly for 30% and 70% of their respective total consumption. In addition, the same authors reported that approximately 65% of the total penicillin antibiotics consumption in Europe in the same year was used for human consumption (JIACRA, 2017). In particular, AMO, CIP, ERY, CLA, and AZI are mostly used for the treatment of pigs, cattle and poultry (Borck Høg and Korsgaard, 2016), which constitute the majority of the livestock raised in our case study area (Italian Health Ministry, 2020). For these reasons, the data obtained on the human consumption of these antibiotics in the Veneto Region (Q_{APIi-V}) was used to obtain an approximate estimate of their consumption for livestock treatment.

The average annual amount of antibiotics used for each animal (45 $mg \cdot PCU^{-1}$ for cattle, 148 $mg \cdot PCU^{-1}$ for poultry, and 172 $mg \cdot PCU^{-1}$ for pigs) reported by Van Boeckel and co-workers (Van Boeckel et al., 2015) was used to normalize livestock population (AP_{kn}) with respect to antibiotic consumption, and the consumption of these APIs (Eq. 10) in each municipality (Q_{APIi-M}) was considered to be directly proportional to the ratio of raised livestock *vs* Veneto total livestock population (A_{kn-M}/A_{kn-V}) (See Supporting Information for details).

$$Q_{APIi-M} = Q_{APIi-V} \cdot \left(AP_{kn-M}/AP_{kn-V}\right) \tag{10}$$

Furthermore, the estimation reported by Peng et al. ($F_{antibiotics} \approx$ 0.60) (Peng et al., 2016) was used to adapt Eq. 9 to account for the different ways antibiotics are administered, and therefore excreted from livestock.

The use of DIC in Italy has been authorized for pigs and cattle (Kolar et al., 2014), but no information on the consumption of this API for animal use was found in the literature, thus emissions of this chemical from veterinary drugs could not be estimated.

Finally, the total emission of each API into the Venice lagoon drainage basin was calculated as the sum of the discharges from people and animals (Eq. (11) and Fig. 2).

$$\mathrm{E_{i-Tot}} = \mathrm{E_{i-Pharma\ Tot}} + \mathrm{E_{i-People}} + \mathrm{E_{i-Animals}} \qquad 11$$

2.3.2. Plant protection products

To safeguard the environment and human health, as well as to guarantee a sustainable management of water resources, the estimation of PPPs' emissions into the environment is fundamental to carry out the needed risk and impact assessments (PPR, 2013). However, there is no systematic collection of emission data based on the actual use of these chemicals either at the European or national level, causing the need to use other proxy indicators, such as sales data (Eurostat, 2019) or a combination of information on the harvested area with typical pesticides use patterns by crop and country (Leclerc et al., 2019).

Several methodologies based on the life cycle assessment approach have been developed and applied to estimate the emission of specific classes of PPPs at the European and national level (Renzulli et al., 2015; Schmidt Rivera et al., 2017), by using information available in dedicated databases (e.g., AGRIBALYSE database) (Asselin-Balençon et al., 2020) or by using aggregated sales data (Eurostat, 2019) available at the European and national level (Eurostat, 2019). Nonetheless, these approaches showed several limitations when applied at the local scale and to specific chemicals, since they tend to completely or partially ignore local conditions, such as specific use patterns for the treatment of particular crops or other characteristic management practices (Nitschelm et al., 2018).

To account for this lack of data, the inventories of the PPPs sold under each regional authority administrative domain (ARPAV, 2019b) can be combined with the information reported on the database that each Member State (IEM, 2018) must update and maintain on the available PPPs on the national market (e.g., formulation information) in compliance with European Directive 1272/2008 (EC, 2008) to obtain more realistic emissions estimates. Furthermore, while this information could be used as input for local scale crop-specific leaching models (Giannouli and Antonopoulos, 2015; Utami et al., 2020), these tools also require very specific information (e.g., soil morphology, hydrological models and crop-specific land use) that may not be available.

Due to the lack of the necessary information for the case study area, these models could not be applied, therefore the following approach based on literature data and regional sales data was used.

The load of each selected PPP (E_{PPPi}, kg·year^{-1}) bearing on the lagoon of Venice was estimated using Eq. 12:

$$\mathrm{E_{PPPi}} = \left[\mathrm{Q_i}\cdot \mathrm{f_i}\cdot \left(\mathrm{A_B}/\mathrm{A_V}\right)\right]\cdot \mathrm{L_i} \qquad 12$$

where f_i is the fraction of the active substance present in each commercial product, Q_i (kg•year^{-1}) is the total amount sold and hypothetically applied in the administrative area at the regional level (in our case study in the Veneto Region), A_B/A_V (km^2) is the ratio between the area dedicated to agriculture in the Veneto Region (A_V, km^2) and the area dedicated to agriculture in the Venice lagoon's drainage basin (A_B, km^2), and L_i is the fraction of chemical entering the water compartment through run-off, leaching, and drainage after application of the PPP (Kobierska et al., 2020). The rest of the applied PPP is assumed not to enter the water compartment due to adsorption to the soil, uptake within plants, and degradation.

The fraction of each PPP entering the water compartment in a year (L_i) has been estimated by taking data from the literature on the amount of chemical emitted into the environment by leaching into groundwater ($L_{\ i-leached}$), by surface run-off ($L_{\ i-run-off}$), by drainage ($L_{\ i-drainage}$), or a combination of these phenomena (Table S9)· thus applying Eq. 13:

$$\mathrm{L_i} = \left(\mathrm{L_{\ i-leached}} + \mathrm{L_{\ i-run-off}} + \mathrm{L_{\ i-drainage}}\right) \qquad 13$$

Since no experimental data was found for MET, MTF, CLO, TCLO, and ACE, the estimation ($L_i = 0.01$) for postemergence-applied PPPs reported in the literature by several authors (Leclerc et al., 2019; Spencer and Cliath, 1991) was applied.

A summary of the data input for each PPP emission to the water compartment is given in Table 2, while detailed information is reported in the Supporting Information (Table S9). The values reported in Table 2 on the area dedicated to agriculture in the Veneto Region and in the Venice lagoon's drainage basin were obtained through the elaboration of the Veneto Region technical map (Veneto Region, 2020b) (Fig. S1) by mean of GIS-based spatial analysis tools, using the QGIS® software (version 3.8.3-Zanzibar).

2.4. Uncertainty and sensitivity analysis of the adopted models

Even though the use of predictive models has been widely recognized as a valid tool in several emission inventory studies (Lim et al., 2011; Lindim et al., 2016; Verlicchi et al., 2014; Zhang et al., 2014, 2015), the use and adaptation of average values, literature or default data as an alternative to more site-specific information that may not be readily available leads to an intrinsic and inevitable uncertainty in the computed emissions. Furthermore, the presence of extreme values or trends in the selected input data may also significantly influence the estimated results, thus care must be taken in data selection (e.g., searching for outliers). For this reason, sensitivity and uncertainty analyses were carried out on all emission estimation models to quantify and compare the influence of each parameter on the calculated emissions values for both PPPs and APIs.

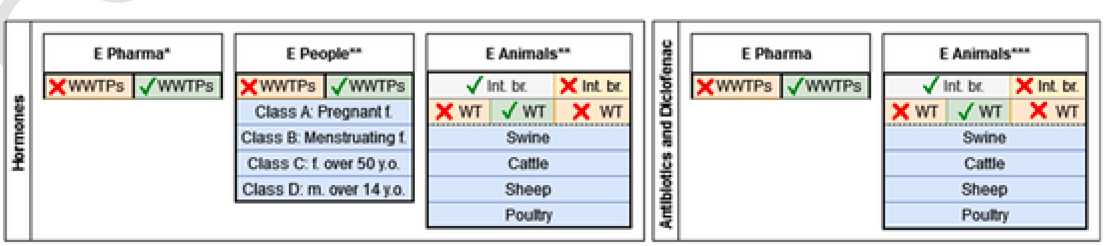

Fig. 2. Summary of the contributions considered to estimate the selected APIs' emissions. Int br.: Intensive breeding; WT: Waste treatment; WWTPs: Wastewater treatment plants; *: Not available for E1; **: Applied only for E1 and E2; ***: Not available for DIC. Green checkmarks and red crosses indicate if an emission is subjected to the specified treatment or not, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In detail, sensitivity analysis was carried out as to account also for the difference in the ranges of variation determined for each parameter by calculating a sensitivity coefficient ($S_{i,m}$), applying the approach reported by Mackay and colleagues (Eq. 14) (Mackay et al., 2014).

$$S_{i,m} = \left[\left(\Delta E_{MAX/MIN}\right)/E_i\right] \;/\; \left[\left(\Delta m_{MAX/MIN}\right)/m_i\right] \qquad 14$$

where $\Delta m_{MAX/MIN}$ is the variation range of the *m-th* parameter and $\Delta E_{MAX/MIN}$ is the resulting perturbation of the emission of the *i-th* chemical (E_i).

The uncertainty associated with the variability of each parameter was estimated by the possible fluctuations of E_i (i.e., $V_{i,m}$) expressed by the change of the *m-th* parameter (Eq. 15), where $E_{i\ new}$ corresponds to the emission of each chemical calculated by using the minimum and maximum value of each parameter (as reported in SI, Tables S10–S14) (Verlicchi et al., 2014).

$$V_{i,m} = \left[\left(E_{i\ new} - E_i\right)/E_i\right] \cdot 100 \qquad 15$$

For these analyses only one parameter was changed within its defined range, while the others remained constant. The following variations were considered.

- The total human and animal populations (i.e., P_V, and A_k), the fraction of the area included into the drainage basin of the municipalities situated on the edge of the case study area, and the areas dedicated to agriculture in Veneto and in the Venice lagoon's drainage basin (i.e., A_V and A_B) were assumed to vary between −10% and +10% with respect to the assumed value (Verlicchi et al., 2014). Each Group population was also assumed to vary between −10% and +10% of the assumed value, then the contribution of each Group to the total drainage basin population was calculated with respect to the new total drainage basin population.
- For PPPs sales a percentage variation of ±20% with respect to the reported value was assumed to account for the difference between sales and actual application within the Veneto Region (EEA, 2022).
- The value of $L_{i-total}$ was assumed to vary between the maximum and minimum reported values (Table S9) for GLY, IMI and TMX. For the other PPPs mean/maximum and mean/minimum ratios equal to those of GLY (0.2 and 12, respectively) were used.
- The interval assumed for APIs consumption variation was of ±30% for antibiotics (Verlicchi et al., 2014) and ±25% for DIC (Aldekoa et al., 2013). Since oestrogens are used for birth control and hormone replacement therapy (HRT), they require long term adherence to prescribed doses to ensure effectiveness, thus a consumption variation of ±10% was hypothesized (Heffley et al., 2014).
- The removal efficiency R_i, excretion factor F_i, sewer conversion factor SC_{E2} and absorption coefficient A_i were assumed to vary between the minimum and maximum values found in the literature, following the approach reported by Verlicchi and coworkers (Verlicchi et al., 2014). Since only one value was found for F_{AMO} a ±37% variation coefficient was used, which is commonly considered to be a reasonable high-biased uncertainty estimate (Chen et al., 2018).
- The excretion factor for antibiotics used for treatments of livestock was assumed to vary between 0.30 and 0.90, as reported by Peng et al. (2016).
- The excretion rates of E1 and E2 from people and animals were assumed to vary within the intervals reported in the literature (Table S11 and Table S12).

2.5. Validation of emission estimation results

The emissions to the water compartment estimated for IMI, GLY, and OXA were compared to the respective load calculated by combining monitoring data on the concentration of these contaminants detected during the studied period (i.e., 2016–2019) in the tributaries of the Venice Lagoon (Collavini et al., 2005; Zuliani et al., 2005) (ARPAV, 2022) with each river average annual water flow, thus applying Eq. (16) (Montuori and Triassi, 2012; Steen et al., 2001; Svendsen et al., 2015):

$$E_{PPPi,t} = \overline{C_{i,t}} \cdot \overline{W_t} \qquad 16$$

where $E_{PPPi,t}$ is the load of the *i-th* PPP for the *t-th* tributary (kg•year^{-1}), $\overline{C_{i,t}}$ is the mean annual concentration detected (kg•m^{-3}) (ARPAV, 2019a), and $\overline{W_t}$ is the mean annual flow of water (m^3•year^{-1}) (CVN, 2020). The position of the water sampling and flow measurement stations is reported in Fig. S1. To calculate each tributary's PPP average concentration the samples that were below the limit of detection (LOD) were assigned a value of LOD/2 (Masiá et al., 2013). If more than 70% of the samplings where below the LOD, the load was assumed to be below the estimated value (Collavini et al., 2005; CVN, 2020).

Since no data or wastewater samples were available to estimate the load of APIs into and out of the WWTPs situated in the Venice Lagoon for the period of interest, it was not possible to directly validate the emission estimations of pharmaceuticals obtained in this study. However, a comparison with data reported for other Italian or European case studies was carried out to obtain a preliminary assessment of the accuracy of our work.

3. Results and discussion

Annual emissions of the selected APIs and PPPs for the case-study area are presented in this section, with the corresponding annual loads to the lagoon of Venice that have been estimated for the first time in this paper. Furthermore, sensitivity and uncertainty analysis were applied to identify the main factors affecting each emission estimation, and those contributing to most uncertainty in the results, respectively.

3.1. Pharmaceuticals

3.1.1. Emissions estimation

Based on the elaboration of the collected sales data of pharmaceutical products, for the whole Veneto region the highest annual sale quantities of the investigated APIs (corresponding to the maximum consumed quantities) resulted to be those of AMO (15,472 kg year^{-1}), CIP (1704 kg year^{-1}), and CLA (1286 kg year^{-1}), while the sales of the non-steroidal anti-inflammatory drug DIC (550 kg year^{-1}) were similar to those of AZI (759 kg year^{-1}) (Table S15). On the other hand, the use of ERY, E2, and EE2 was several orders of magnitude lower (4.8, 2.0, and 0.02 kg year^{-1}, respectively) than the other APIs. Finally, no data was available on the sale of E1 because this chemical is considered as a raw material for the preparation of other formulations and therefore its sold quantity is not tracked by the regional register.

The highest water emissions associated with the use of medicines containing the selected APIs for the case-study area (i.e., $E_{i-Pharma}$) were calculated for AMO (836 kg year^{-1}) and CIP (83 kg year^{-1}), and the lowest ones for hormones (i.e., E1, E2, and EE2) and ERY (Fig. 3, Table S16, Table S17, and Table S20). Similar results about pharmaceutical emission inventories, showing a widespread use and, therefore, a higher release of antibiotics with respect to other APIs into the environment have been reported for other areas of Italy (Al Aukidy et al., 2012), Europe (Lindim et al., 2016; van der Aa et al., 2011), and China (Zhang et al., 2015).

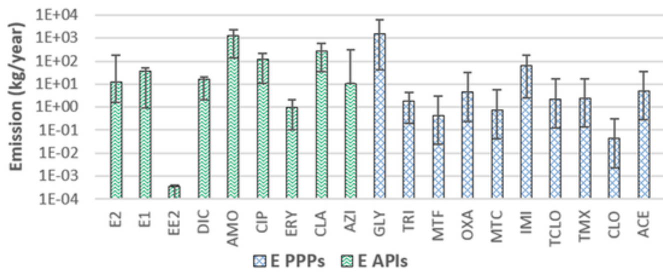

Fig. 3. Mean annual emission of the selected PPPs (E PPPs) and APIs (E APIs) to the lagoon of Venice for the investigated period. Error bars represent the overall uncertainty of each target chemical emission.

The results showed also that Venice historical centre and its surrounding islands contributed to a significant fraction (ca. 8–30%) of E_{Pharma} for all the target pharmaceutical compounds, despite accounting for about 5% of the total target population residing within the lagoon drainage basin (ISTAT, 2012a). Since these settlements are not served by WWTPs, these results show the importance of proper wastewater treatment to minimize negative impacts on the environment, especially in the case of particularly sensitive ecosystems such as transitional waterbodies.

Furthermore, while the release into the environment of the selected hormones attributable to pharmaceutical products was quite limited, the emissions of E1 and E2 due to natural excretion from both people and animals (i.e., E_{People} and $E_{Animals}$) (Table S18 and Table S19) were between one and three orders of magnitude higher. In detail, dairy and beef cattle breeding accounted for about 85% of E1 and E2 emissions, while people contributed only to about 3% of the total amount (13.0 and 36.1 kg year^{-1} for E1 and E2, respectively), showing the importance of proper animal waste treatment and management, especially in places characterized by a developed livestock industry. Similarly, the results showed that animal treatment contributed significantly (≈40–80%) to the overall emission of most of the other target APIs, especially in the case of macrolide antibiotics. This outcome confirms the need to monitor and limit the consumption of these substances for both human and animal treatment in order to minimize the onset of phenomena that could pose severe risks to both the human health and the environment such as spread of antibiotic resistant bacteria (European Medicines Agency, 2019; JIACRA, 2017, 2015). On the other hand, since no information on the veterinary use of DIC in the Veneto region was available or could be estimated from the quantity used for human treatments and literature data, the emission (16.5 kg year^{-1}) reported in Fig. 3 and Table S20 for this chemical is likely to be an underestimation, highlighting the need for more comprehensive datasets on the quantity of APIs used for veterinary applications at the local or regional scale (Maggio et al., 2020).

Although our approach for pharmaceuticals could not be validated due to the lack of appropriate monitoring data, the obtained results showed a similar "population to emission ratio" for the selected APIs as those reported by several authors for other areas of Italy (Cardini et al., 2021; Lindim et al., 2016; Riva et al., 2015; Verlicchi et al., 2014). On the other hand, while emissions of pharmaceutical compounds from people and animal treatment were taken into account, emissions form APIs' production sites could not be estimated, which may significantly contribute to the release of these substances in the environment, especially in the case of countries where the treatment of industrial effluents is still limited (Larsson, 2014). This could be accounted for by both considering the number of industrial plants dedicated to APIs production in the selected study area and by relating production tonnage to the emission into the environment. Unfortunately, self-reported data from industry or monitoring data from authorities are often scarce or completely unavailable, thus highlighting the urgent need for wider monitoring of API emissions from manufacturing (Larsson, 2014). Furthermore, since a significant amount of time may pass between sale and consumption of the pharmaceuticals with long shelf lives (e.g., analgesics), data referring to at least one or two years is recommended (Tembhare et al., 2019; Zilker et al., 2019).

3.1.2. Sensitivity and uncertainty analysis

The results of the sensitivity analysis (Fig. 4 and Table S21) showed that E_{Pharma} was influenced the most by the variation of R_i, F_i, Q_{APIi-V}, and $P_{i\text{-}B}/P_{i\text{-}V}$. In particular, the model was more sensitive towards R_i variations for APIs that are more easily degraded during wastewater treatment, such as E1, EE2, AMO, and E2, while emission estimations for other pharmaceutical compounds were more dependent on F_i and Q_{APIi-V}.

Moreover, from the results reported in Fig. 4 and Table S21, it can also be seen that estimation of E_{People} was influenced mostly by R_i and by the number of people residing in the Venice lagoon drainage basin, especially of pregnant and menstruating females due their high daily excretion rates. In addition, the emission of E1 from people was also influenced by the variation of SC_{E2}, showing the importance of considering degradation processes as a source of this pollutant.

The sensitivity analysis also showed that emissions of all the target APIs due to animal breeding ($E_{Animals}$) were strongly influenced by parameters related to wastewater treatment (i.e., R_i, S_i, and θ), in particular for those chemicals with higher removal factors. In addition, the emissions of E1 and E2 were also strongly dependant on the emission rates from cattle, while the emission of antibiotics was sensitive to the excretion factor F_i and to the quantity used for human treatment, since it was used to estimate the quantity administered to animals due to the lack of more specific information. These results show the need to carefully monitor the consumption and excretion of these substances associated with animal breeding, as well as the importance of the treatment of animal waste before their application as fertilizers.

Based on the relative contribution of E_{Pharma}, E_{People}, and $E_{Animals}$ to the total emission of each target API, the factors related to animal breeding (i.e., S_i, and θ) showed high overall sensitivity coefficients in the case of E1, E2, ERY, CLA and AZY, whereas the total emission of EE2, DIC, CIP, and AMO was found to be more sensible towards the variation of parameters related to human consumption of medicines (i.e., F_i, and Q_{APIi-V}). Furthermore, since wastewater treatment is a process considered for all contributions, the model showed a high overall sensitivity toward the variation of R_i for all the target pharmaceuticals.

From the results of the uncertainty analysis reported in Fig. 5 and Table S21 it emerges that the variability of each API emission associated with the variation of each parameter changed greatly depending both on the target chemical and the specific emission considered. For example, the uncertainty related to the excreted fraction (i.e., F_i) of each target API from either people or animals caused the highest uncertainty on the overall release into the environment of DIC, ERY, CLA, CIP and AZY (between −98 and + 165% of the mean emission), but it was significantly less relevant in the case of E1, E2, EE2, and AMO, due to a combination of lower model sensitivity and better estimation of this parameter (Fig. 4, Table S13, and Table S21).

While the use of regional consumption data instead of national figures can lower the uncertainty related to the assumption of uniform consumption patterns (Oosterhuis et al., 2013), information obtained from the data used in this study does not take into account drugs dispensed to public hospital patients, over-the-counter (i.e., non-prescription) drugs (Ort et al., 2010) or improper disposal of unused medicines (e.g., flushing them down the toilet or throwing them out with the household waste) (Verlicchi et al., 2014). This led to a relevant uncertainty on the overall emission of AMO, CIP, ERY, CLA, AZY, DIC, and EE2 (between −30 and + 30%) but was almost negligible in the case of E1 and E2 since their emissions were estimated to be driven by animal excretions. In fact, the highest uncertainty related to the emis-

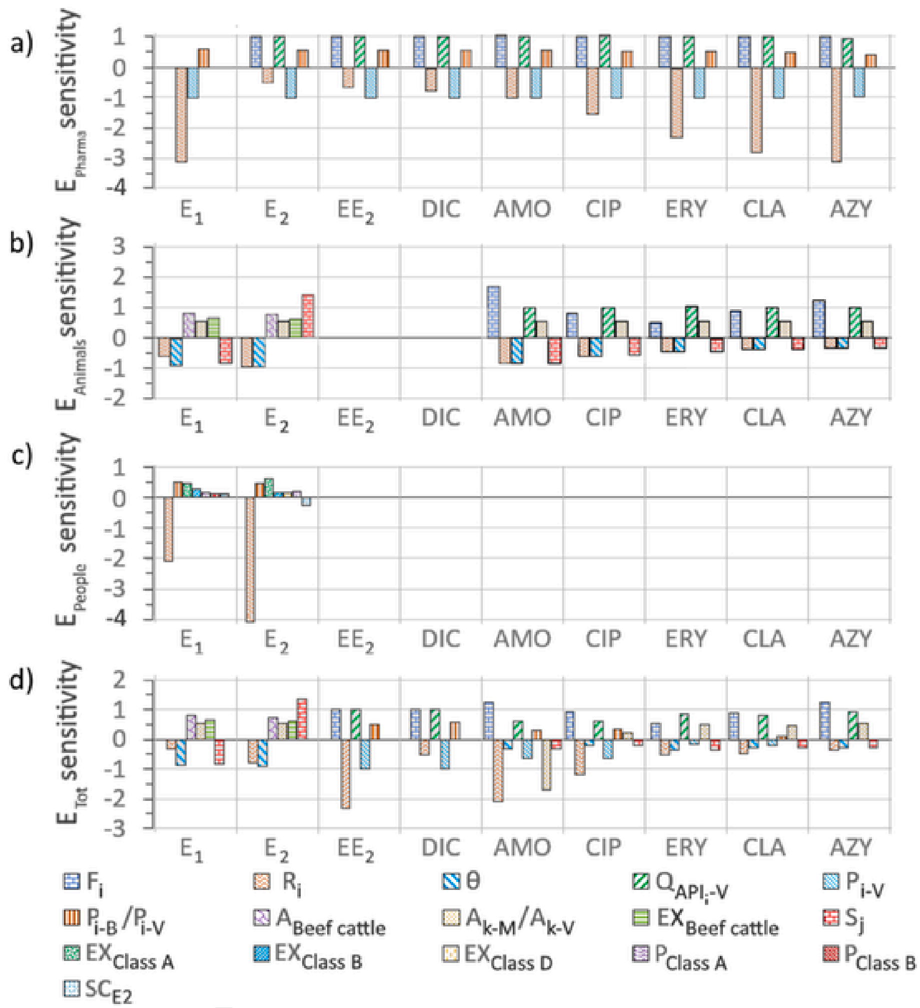

Fig. 4. Results of sensitivity analysis for the model used to calculate E_{Pharma} (a), $E_{Animals}$ (b), E_{People} (c), and E_{Tot} (d), showing the parameters that influenced each estimation the most.

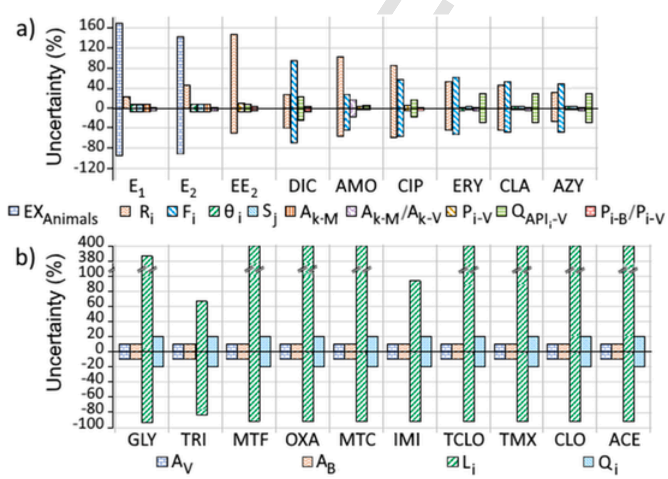

Fig. 5. Results of uncertainty analysis carried out by applying Eq. 14 showing the most relevant variations of APIs (a) and PPPs (b) mean annual emission due to each parameter uncertainty range (minimum/maximum).

sions of these two hormones turned out to be related to their excretion rates from cattle (between −95 and + 169%), showing the need for more accurate information on the metabolism of these chemicals in farm animals.

The results also highlighted the need for a more comprehensive registration of the APIs administered for animal treatment both at the local and national scale (Maggio et al., 2020; van Dijk et al., 2021) by showing that a significant portion of the uncertainty attributed to the emissions of antibiotics could be ascribed to the use of class-specific cumulative sales estimations thanks to the absence of specific information on the use of each API in the breeding industry.

The parameters related to waste treatment were another relevant source of uncertainty found for the overall release estimation of all target APIs into the environment. In detail, *Ri* caused a high uncertainty, especially in the case of EE2, AMO, CIP and ERY (between −60 and + 147%), while θ and S_j were associated with a variation of the target antibiotic and hormone emissions of about ±10%.

Furthermore, since it is usually possible to accurately estimate the spatial distribution of human inhabitants and animals in a specific area under study (Verlicchi et al., 2014), the uncertainty associated with $P_{i\text{-}V}$, $P_{i\text{-}B}/P_{i\text{-}V}$, $A_{k\text{-}M}$, and $A_{k\text{-}B}/A_{k\text{-}V}$ is limited, and this was also reflected in the relatively low uncertainty associated with these parameters (Fig. 5 and Table S21).

3.2. Plant protection products

3.2.1. Emission estimation

Based on the PPPs sales data for the Veneto region, the use of GLY, MTF, OXA, MTC, TCLO, and TMX showed little change over the investigated period, while the sales of TRI, IMI, CLO, and ACE where much more variable (Table S22) (ARPAV, 2019b). The highest sales during the investigated period were found for GLY (434,182 kg year^{-1}) while other herbicides (i.e., OXA and TRI) were sold much less (2678 and 1678 kg year^{-1}, respectively). Sales data also showed that IMI, TMX, and ACE were the most used insecticides (5831, 1993, and 2870 kg year^{-1}, respectively), while MTC, MTF, and CLO were those sold the least (410, 240, and 33 kg year^{-1}, respectively). This trend was also reflected on the estimated annual water emission of PPPs to the Venice lagoon (Fig. 3 and Table S23), where the highest value was obtained for GLY (1350 kg year^{-1}) and IMI (61 kg year^{-1}), and the lowest for MTF, TRI, and CLO (0.43, 0.29, and 0.043 kg year^{-1}, respectively). In particular, the emission load was shown to depend not only on the amount of the compound sold, but also on the fraction entering the water compartment after application (L_i). For instance, the· L_i factor showed a variation of more than two orders of magnitude (e.g., between 0.0015 and 0.146 for GLY and IMI, respectively), similarly to what was reported by Räsänen *et al.* (Räsänen et al., 2015), causing compounds with quite different consumption rates to exhibit similar discharge, as is the case of TRI and MTF (Fig. 3 and Table S23).

The results obtained for GLY, IMI, and OXA also showed a good agreement with the loads calculated by using monitoring data and water-flow measurements (Table S24). In detail, since IMI and OXA concentration was always below the detection limit, their average load was calculated as <65 kg year^{-1} and <55 kg year^{-1}, respectively, while their estimated loads were 61 and 4.5 kg year^{-1}. Furthermore, since GLY was detected in all samples it was possible to obtain a more accurate estimation (1850 kg year^{-1}), showing that our approach underestimated the measured load of about 25%.

While other authors (Geng et al., 2021; Maggi et al., 2020) also used a combination of average application rates together with geographically-distributed data on agronomic practices, hydroclimatic variables, soil properties, and biogeochemical kinetics to estimate both national and global leaching rates of GLY to the water compartment, the application of these approaches at the local scale could require information that may be not available at the desired spatial and temporal scale.

The proposed approach regarding PPPs accounts for regional consumption patterns by using available regional sales estimations, which may not be always available, especially in the case of low- and middle-income countries (van den Berg et al., 2020). Moreover, the use of sales data as proxy indicator also requires information on the exact composition of each commercial product sold in the area of interest, and this may not be available in all cases due to confidentiality constraints (Galimberti et al., 2020). For these reasons, care must be taken when considering potential sources of information.

In addition, while the proposed methodology can be applied starting from sales data and generic land use information (i.e., agricultural *vs* non-agricultural land), the lack of experimental information on the release into ground/surface waters of several PPPs with respect of the applied quantity caused a high degree of uncertainty in the emissions estimation, especially in the case of CLO, ACE, MTC and MTF. For this reason, despite the complexity of the needed experimental activities, new studies on the release due to leaching, run-off, and drainage of herbicides and pesticides after application are fundamental.

3.2.2. *Sensitivity and uncertainty analysis*

Sensitivity and uncertainty analysis were carried out also on the model used to estimate PPPs emissions to quantify and compare the influence of each parameter on the calculated loads.

From the results reported in Table S24 it can be seen that, due to the simplicity of the approach adopted, the model used to estimate PPPs emissions showed the same absolute sensitivity coefficient ($S_{i,m}$ of 1.00) for all inputs parameters. In detail, positive variations of A_{Basin}, L_i, and Q_i caused an increase of the calculated emissions, while the increase of A_{Veneto} showed the opposite trend.

Furthermore, the results reported in Fig. 5 showed that the parameter causing the largest uncertainty for the calculated PPPs emissions is L_i, since it may vary by more than an order of magnitude (0.1–15.0%) thus causing a high level of uncertainty (from −93% to +400% of the mean emission value). This uncertainty can be attributed to the fact that this parameter is dependent on many factors, such as each PPP application method, the soil slope, hydrology, profile, texture, and composition, together with local meteorological conditions (e.g., rain, snow, and wind) following each product use. Also, it can be very difficult to obtain accurate measurements of water leaching, draining, and run-off during field studies over long periods of time. For these reasons, further studies are advisable to quantify this parameter more accurately, to increase the reliability of PPPs emission estimations.

On the other hand, the variation of the area devoted to agriculture in the Veneto region and the lagoon drainage basin caused a lower variation (ca. ±10% of the mean emission value) of E_{PPP} with respect to the uncertainty related to L_i due to the lower uncertainty associated with the mapping of land use.

4. Conclusions

In this study we demonstrated the feasibility of developing an emission inventory of APIs and PPPs for a local case-study using proxy indicators such as sales data and georeferenced demographic and land-use information. Where possible (i.e., for selected PPPs), comparison of the modelled chemical loads with those obtained from measured environmental concentrations in lagoon tributaries showed that our estimates are generally reliable, although important uncertainties were identified.

The results showed that most of the emissions of hormones and several antibiotics in the case study area could be attributed to animal breeding, highlighting the need to better trace the selling and use of these compounds to better focus on the management of wastes produced by these activities to reduce further degradation of surface and groundwater, as well as risks to the environment and human health.

Furthermore, sensitivity and uncertainty analysis showed that emission estimations could be significantly improved through further experimental investigations focusing on (i) measurement of APIs excretion rates from both humans and animals, (ii) measurements of APIs degradation rates during sewer transit and in WWTPs and (iii) new field studies on the leaching, drainage, and surface run-off and groundwater runoff of PPPs, especially in the case of those that are highly soluble in water.

While high-quality monitoring data for emissions estimations is preferable compared to a modelling approach (ECB, 2003), in the case of local scale studies focusing on a specific watershed, the use of the proxy indicators proposed by our methodology offers a viable compromise between the requirements for complex and high resolution data and estimation accuracy, especially when national or international data do not realistically represent the use/consumption patterns of the area of interest.

Furthermore, our methodology offers also valuable information for the preliminary apportionment of APIs and PPPs emissions to specific sources, activities, or areas, before the implementation of more complex and demanding monitoring programmes, thus facilitating a more effective and sustainable management of water resources.

Credit author statement

Loris Calgaro: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision Visualization; Writing – original draft; Writing – review & editing. Elisa Giubilato: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing. Lara Lamon: Conceptualization; Methodology; Writing – review & editing. Francesco Calore: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft. Elena Semenzin: Conceptualization; Investigation; Methodology; Writing – review & editing; Supervision; Funding acquisition; Project administration. Antonio Marcomini: Conceptualization; Methodology; Writing – review & editing; Supervision; Funding acquisition.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2022.117153.

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