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Comparing risk-based approaches to jointly assess environmental and human health risks and prioritize emerging contaminants in agricultural wastewater reuse

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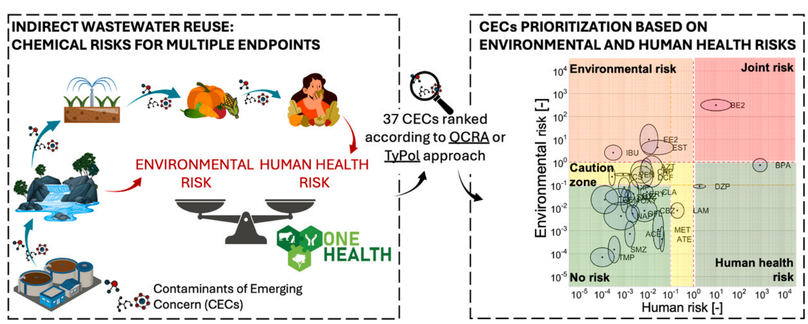
HIGHLIGHTS

- We prioritized CECs in agricultural wastewater reuse assessing jointly risks.
- Accounting for environmental and human health risk enables the One Health approach.
- Focusing on only one risk overlooks CECs displaying effects on different endpoints.
- CECs were prioritized even with missing concentration or toxicological data.
- CECs prioritization inform monitoring programs and regulatory control actions.

GRAPHICAL ABSTRACT



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ABSTRACT

Despite mitigating water scarcity, agricultural reuse of treated wastewater introduces contaminants of emerging concern (CECs) into ecosystems, posing risks to environment and human health. The large number of CECs complicates their comprehensive monitoring, especially due to analytical limitations and data gaps in toxicology. This study prioritizes CECs based on their environmental and human health risks, by applying two complementary methodologies: Quantitative Chemical Risk Assessment (QCRA) and TyPol, following the One Health framework. Unlike most existing approaches, which assess environmental or human risks separately, our study jointly considers both endpoints in an integrated assessment. QCRA enables contaminant-specific prioritization by integrating concentration data and toxicological thresholds to estimate probabilistic risk distributions. TyPol provides cluster-based prioritization by grouping CECs according to molecular properties, environmental behavior, and toxicological characteristics. Applied to 37 relevant CECs, both methodologies identified estrogenic compounds as high-priority for both endpoints, while macrolides exhibited a significant environmental risk. Other contaminants showed divergent prioritizations. QCRA provides contaminant-specific insights but relies on complete datasets, while TyPol demonstrated adaptability in scenarios with missing data, although with reduced precision. Together, these methodologies provide decision-makers with versatile tools to support

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regulatory actions, from monitoring programs to treatment strategies, advancing sustainable agriculture and public health protection.

1. Introduction

The increase of global population and the intensification of climate change are driving the urgent need for sustainable water management practices [5]. Agriculture accounts for nearly 70 % of global freshwater use [52], and increasing research efforts are focused on identifying strategies to reduce its water demand, with agricultural wastewater reuse emerging as an attractive option to alleviate pressure on primary freshwater resources [37]. However, a variety of contaminants are present in the effluent of wastewater treatment plants (WWTP) reaching irrigated crops in case of both direct and indirect reuse, representing a potential source of hazard [67]. Among these, contaminants of emerging concern (CECs), have gained increasing attention. CECs refer to a broad category of newly identified synthetic or naturally occurring chemicals detected in the environment at trace concentrations (ng L^{-1} or μg L^{-1}), potentially hazardous or recently determined to be hazardous to humans and ecosystems [35]. These include substances such as pharmaceuticals, personal care products, alkylphenols, and other industrial substances, among others [42]. One of the primary challenges in managing CECs is the uncertainty associated with their presence, detection, fate and (eco) toxicological effects [40]. Many CECs are present at concentrations below the limit of quantification (LOQ), leading to gaps in monitoring data [31]. Moreover, toxicological information is often incomplete or unavailable, further complicating risk assessments [4]. Finally, the growing number of CECs and their wide-ranging properties add complexity to the development of effective monitoring and regulatory frameworks [41]. Despite their potential risk, many CECs remain unregulated, though some have been incorporated into European water policies including the European Union (EU) Water Framework Directive [11], the Directive on the quality of water intended for human consumption [25], the new EU Proposal for the Urban Wastewater Treatment Directive [26] or the EU Watch List [22].

The risk posed by CECs depend not only on the contaminants themselves but also on the type of reuse. In direct reuse systems, reclaimed wastewater is applied directly to crops without dilution; on the other end, indirect reuse involves discharging treated effluents into natural water bodies, being the mixed water used after the point of discharge. Hence, in both cases, a human health risk arises, due to the potential crop contamination which causes contaminants to enter the food chain [51] . Environmental risk also arise, but through different pathways: in direct reuse, contaminants can accumulate in soil, impacting soil ecosystems and potentially being transferred into water bodies [29], whereas in indirect reuse, environmental risk is primarily associated with the contamination of surface water and the impact on aquatic ecosystems [34].

In this context, addressing both environmental and human health risks matches the principles of the One Health approach, promoted by the World Health Organization [66], which recognizes the interdependence of human, animal, and environmental health. When dealing with wastewater reuse, this approach is crucial for developing risk management strategies that simultaneously address environmental and human health protection, ensuring a more integrated and effective approach to the identification of contaminants to be prioritized for monitoring and reduction actions, among the hundreds of CECs entering the environment [3]. Several methodologies have been developed to prioritize CECs based on different criteria. Servien et al. [59] introduced the TyPol (Typology of Pollutants) methodology, which clusters compounds based on their molecular properties and environmental behavior, offering predictions for CECs environmental fate even in the absence of detailed data for individual compounds. Concentration-based approaches have also been widely adopted, as in García-Vara et al. [30] and Zhong et al. [68], which estimated the environmental risk based on CEC levels in reclaimed wastewater and surface water, respectively. Such studies reflect a broader trend in the context of wastewater reuse, where prioritization frameworks tend to focus primarily on environmental risk, while human health risk remains largely overlooked. In contrast, human health risk is more commonly addressed in drinking water prioritization frameworks, as shown by Rosenblum et al. [54], who prioritized CECs by estimating their concentrations and the associated human health risk due to drinking water consumption.

Efforts to integrate both risks emerged in Aemig et al. [2] and Servien et al. [58], who prioritized CECs by combining their concentration data with characterization factors (CFs), used as toxicological indicators in Life Cycle Assessment, to estimate environmental and human health impacts in the context of WWTP discharge of CECs into rivers. Similarly, the Quantitative Chemical Risk Assessment (QCRA) developed by Cantoni et al. [8], was applied with a simplified approach by Penserini et al. [48] for CECs prioritization, evaluating the likelihood of pharmaceutical concentrations to exceed toxicological thresholds associated with (i) environmental, (ii) antibiotic resistance, and (iii) human health risks in the context of indirect wastewater reuse. However, concentration-based approaches could not be applied in the absence of complete dataset, particularly when toxicological or concentration information were missing, leaving certain CECs unaddressed in risk prioritization efforts. Despite the availability of different prioritization methodologies, it still emerges a need for comprehensive tools capable of addressing both environmental and human health risks in a unified framework, even if data gaps are present. Current approaches often focus on one risk endpoint at a time or lack integration between environmental and human health considerations, limiting their usefulness for decision-making in wastewater reuse management.

This study aims to bridge this gap by developing a robust framework for the simultaneous environmental and human health risk-based prioritization of CECs in the context of agricultural wastewater reuse, offering risk-informed guidance to decision-makers in line with the One Health approach. To achieve this, we adopted and compared two risk-based prioritization methodologies, QCRA and an upgraded version of TyPol, since both methodologies enable to simultaneously assess environmental and human health risks but with two different approaches. These methodologies were applied to a set of 37 CECs considered relevant for agricultural wastewater reuse, due to their frequent detection in such systems and to their inclusion in water regulation directives. By examining the strengths and limitations of each approach in the ranking of the same set of CECs, this study aims to assess their performance in CECs prioritization and risk characterization. Finally, a scenario analysis was conducted to evaluate the procedures applicability and consistency when data gaps are present.

2. Materials and methods

2.1. Reuse case study conceptualization and CECs concentration data collection

We consider the indirect reuse of reclaimed wastewater in agriculture: CECs enter surface water through the discharged effluent and are then delivered to soil and crops through the irrigation water abstracted downstream the point of discharge. Therefore, surface water (after mixing with the effluent) and crops were selected as compartments of interest for shaping the fate of CECs to the final endpoint for which the risk is assessed: i) the aquatic ecosystem (e.g., fish, invertebrates, and algae) for environmental risk and, ii) the crop consumers for human health risk. Data required by QCRA and TyPol were retrieved from literature, considering only field monitoring and case studies reporting concentration data collected under representative conditions in the period 2010–2024; studies conducted in sites located near industrial effluents or significant sources of contamination were excluded. For crops, only fruits and vegetables were considered, being the crops with the highest availability of concentration data in the literature. Only concentration data in edible portions (leaves and fruits) were collected, as they are the best representative of human dietary exposure. The specific crop species analyzed for each contaminant are detailed in Table S2. Only concentrations measured in unpacked raw products, directly collected from crops or local markets, were included.

Among the hundreds of compounds belonging to CECs category, the set of contaminants to be investigated were selected based on two criteria: (i) their inclusion in European legislations regulating the monitoring of CECs in aquatic ecosystems [11,22,25,26], (ii) availability of concentration data in surface water, crops or soil within studies investigating the indirect reuse of reclaimed wastewater in agriculture from urban WWTPs, conducted under the representative conditions described above. 55 articles out of 90 consulted matched the criteria mentioned above, resulting in 51 candidate CECs.

However, 14 CECs were excluded because they lacked one or more of the input parameters required by QCRA or TyPol, leaving only 37 CECs with the complete data needed for the implementation of the two risk assessment procedures. The selected 37 CECs include 32 pharmaceuticals and 5 industrial compounds, differentiated as: (i) 11 antibiotics, (ii) 5 anti-inflammatories, (iii) 3 anti-hypertensives, (iv) 5 central nervous systems (CNS) medications, (v) 3 lipid regulators or diuretics, (vi) 2 stimulants or opioids, (vii) 3 hormones, (viii) 3 alkylphenols and 2 (ix) other industrial compounds. This screening framework determines the predominance of pharmaceuticals, compounds both included in EU water quality directives and supported by abundant occurrence data in agricultural wastewater reuse studies. Selected CECs are listed in Table 1, where raw concentration data ($C_{i,j}$) are reported for each CEC *i* and compartment *j*, together with the number of data available and the percentage of data below the LOQ. The 14 CECs excluded from the assessment are listed in Table S1, where the reason for the exclusion is reported.

The CECs concentration data for each compartment ($C_{i,j}$) were used to estimate their statistical distributions, following the procedure detailed in section S1.1. Since a high percentage of concentration data was lower than the LOQ, the Maximum Likelihood Estimation method for left-censored data (MLE_{LC}) [7] was applied to fit statistical distributions including censored data, not to lose the information hidden in censored data, that might significantly impact the risk estimation. From each $C_{i,j}$ statistical distribution, 1000 values were sampled independently and used to derive the concentrations required for the estimation of environmental or human health risk.

2.2. QCRA approach

The QCRA methodology applied in this study was originally developed by the authors [8], to evaluate the human health risk associated with exposure to CECs through the consumption of crops irrigated with reclaimed wastewater mixed with surface water, accounting for variability and uncertainty in both exposure levels and toxicological thresholds [49]. In the present work, the methodology was extended to also assess the environmental risk related to the presence of CECs in surface water in the context of wastewater reuse.

QCRA builds on established risk assessment procedures designed to quantify environmental and human-health risks through the calculation of Risk Quotient (RQ) [13] and Benchmark Quotient (BQ) [56] indicators, respectively. QCRA is structured in three sequential steps: (i) exposure assessment, where the level of CECs to which the aquatic ecosystem or crop consumers are exposed is determined, (ii) hazard assessment, where toxicological safety thresholds for the environment or the human health are collected from the latest toxicological scientific opinions available, and (iii) risk characterization, where the results from the previous steps are combined to estimate the risk index distributions for the environment and the human health.

2.2.1. Exposure assessment

For environmental risk, the concentration in surface water was considered as the exposure concentration ($C_{EXP,i} = C_{i,SW}$). For human health risk, the exposure level for crop consumers corresponded to the CEC exposure dose ($Dose_{EXP,i}$) [$\mu g_i\ kg_{bw}^{-1}\ day^{-1}$] calculated as:

$$Dose_{EXP,\ i} = C_{i,CROP} \times IR \tag{1}$$

where $C_{i,CROP}$ is the concentration in crops, and IR is the intake rate [$g_{CROP}\ kg_{bw}^{\ -1}\ day^{-1}$]. The IR was determined by dividing the daily consumption of fruits and vegetables by the average body weight, assumed constant and equal to 60 kg for adults [15]. Food consumption data were sourced from the European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database [14]. Only unprocessed fruits and vegetables referred to adult consumers were considered, resulting in an average daily consumption of 126.28 g_{CROP} day^{-1}.

For those CECs for which the number of data for $C_{i,CROP}$ was not sufficient to estimate their statistical distributions (15 out of 37, see Table 1), $C_{i,CROP}$ were derived from concentrations in soil ($C_{i,SOIL}$), as follows:

$$C_{i,CROP} = C_{i,SOIL} \times BCF_i \tag{2}$$

where BCF is the bioconcentration factor [($mg_i\ kg_{CROP}^{-1}$) ($mg_i\ kg_{SOIL}^{-1}$) $^{-1}$], describing the uptake of a chemical from soil into the edible parts of crops. $C_{i,SOIL}$ and BCF values were collected from literature following the same criteria described in Section 2.1 (Table 1) and their statistical distributions were calculated as detailed in section S1.1. However, BCFs were available only for 6 of the 15 CECs (see Table 1), thus, crop concentrations distributions were ultimately fitted for 28 out of 37 CECs. A summary of the best fitting distributions and the respective parameters determined for the 37 CECs is reported in Table S3.

2.2.2. Hazard assessment

For the environmental risk, the toxicological safety threshold is the Predicted No Effect Concentrations (PNEC) [$\mu g_i\ L^{-1}$], representing the contaminant concentration observed to be safe for the most sensitive aquatic species in available toxicological studies, implying that no adverse effect is expected to occur for the most vulnerable organisms in freshwater ecosystems [27]. The lowest PNECs referred to freshwater were collected from [43] for a precautionary approach. For human health, the toxicological safety threshold is the reference dose (RfD) [$\mu g_i\ kg_{bw}^{-1}\ day^{-1}$], which represents the contaminant dose that does not result in the exceedance of the tolerable exposure over the consumer lifetime [17]. RfD values were collected consulting the most recent toxicological evaluations and are summarized in Table 1, with references detailed in Table S2.

2.2.3. Risk characterization

The risk index, namely the RQ and the BQ for, respectively, environment and human health, were calculated as:

$$RQ_i = \frac{C_{EXP,i}}{PNEC_i} \tag{3}$$

$$BQ_i = \frac{Dose_{EXP,i}}{RfD_i} \tag{4}$$

Both environmental and human health risk assessments are characterized by dimensionless risk outputs, which allow to identify comparable threshold values for the two procedures. Generally, RQ or BQ lower than 0.1 indicates the absence of significant concern, between 0.1 and 1 indicates that further investigation might be warranted, and

Table 1
Summary of the 37 CECs considered in this study. For each CEC, the abbreviation and the CAS number are reported. For each compartment, it is reported the number of available data, the percentage of data below the LOQ, the concentrations range and mean and the BCFs, if necessary. Toxicological parameters are expressed in terms of: CF_{ECO} [PDF m^3 d kg_i^{-1}], CF_{HT} [DALY kg_i^{-1}], PNEC [μg L^{-1}], RfD [μg kg_{bw}^{-1} d^{-1}]. The references for concentrations, BCFs and RfDs are listed in Table S2.

				SW compartment			Crop compartment			Soil compartment				Toxicological parameters			
CEC group	CEC name	CEC ID	CAS number	# of data	Data below LOQ [%]	Concentration[a] [μg L^{-1}]	# of data	Data below LOQ [%]	Concentration[a] [μg kg^{-1}]	# of data[b]	Data below LOQ[b] [%]	Concentration[a] [μg kg^{-1}]	BCF[a] [-]	PNEC[c]	RfD	CF_{ECO}[d]	CF_{HT}[d]
Antibiotics	Azithromycin	AZT	83905–01–5	15	13.3	0.17 (<0.001–2.35)	17	76.5	27.83 (<0.5–100)	-	-	-	-	0.019	1.7	3.25E+05	4.16E-06
	Clarithromycin	CLA	81103–11–9	17	0.0	0.14 (0.00042–2.4)	22	81.8	33.25 (<0.3–107.7)	-	-	-	-	0.12	1.4	2.91E+05	4.23E-06
	Ciprofloxacin	CIP*	85721–33–1	35	0.0	0.39 (0.00002–13.56)	18	83.3	-	10	0	90.01 (0.17–730)	0.23 (0.09–0.53)	0.089	7.1	6.51E+03	3.11E-06
	Erythromicyn	ERY	114–07–8	33	0.0	0.61 (<0.0011–9.19)	44	86.4	6.83 (<0.5–33.5)	-	-	-	-	0.3	4.4	2.94E+06	2.76E-06
	Lincomycin	LIN **	154–21–2	18	16.7	0.16 (<0.003–2.84)	13	92.3	-	-	-	-	-	3.95	10	1.22E+05	6.42E-06
	Metrodinazole	MDZ **	443–48–1	6	0.0	0.08 (<0.0015–0.35)	9	100.0	-	-	-	-	-	33.1	0.068	5.38E+02	2.27E-07
	Ofloxacin	OFL	82419–36–1	36	0.0	0.28 (<0.022–8.77)	13	53.8	2.38 (0.44–18.5)	-	-	-	-	1.39	1.9	4.26E+04	3.97E-06
	Oxytetracycline	OXY *	79–57–2	25	0.0	0.30 (0.00068–2.79)	0	-	-	9	0	51.84 (2–212)	0.095 (0.08–0.11)	0.43	3	4.54E+04	4.4E-06
	Trimethoprim	TMP	738–70–5	26	0.0	0.05 (0.00031–0.52)	49	53.1	4.46 (<0.01–63.9)	-	-	-	-	120	5.7	3.32E+03	2.77E-06
	Sulfamethoxazole	SMX	723–46–6	37	0.0	0.26 (0.00012–11.92)	59	64.4	3.68 (<0.1–15)	-	-	-	-	0.6	5.7	1.57E+04	4.7E-07
	Sulfamethazine	SMZ	57–68–1	24	4.2	0.11 (0.00003–1.19)	39	61.5	1.36 (<0.022–4.2)	-	-	-	-	30	10	6.23E+04	1.77E-06
Anti-inflammatories	Acetaminophen	ACE	103–90–2	13	7.7	0.20 (<0.00013–2.38)	42	78.6	2.42 (<0.2–4)	-	-	-	-	46	4.64	2.48E+02	4.8E-07
	Diclofenac	DCF	15307–86–5	23	0.0	0.78 (0.0009–18.74)	33	54.5	14.58 (<0.05–140)	-	-	-	-	0.05	1.4	6.00E+03	3.76E-04
	Ibuprofen	IBU	15687–27–1	19	0.0	1.02 (0.0010–31.32)	23	69.6	2.28 (<1–13.82)	-	-	-	-	0.011	11.43	7.86E+02	1.68E-06
	Ketoprofen	KET **	22071–15–4	12	8.3	0.03 (<0.0034–0.078)	22	95.5	-	-	-	-	-	2.1	5	2.95E+04	1.11E-06
	Naproxen	NAP	22204–53–1	16	0.0	0.43 (0.00027–1.01)	30	86.7	8.26 (<0.1–34.4)	-	-	-	-	1.7	7.1	6.44E+03	1.65E-06
Anti-hypertensives	Atenolol	ATE	29122–68–7	9	0.0	0.17 (0.0004–0.55)	33	81.8	4.09 (<0.1–15)	-	-	-	-	150	0.36	7.27E+04	2.2E-06
	Metoprolol	MET	37350–58–6	5	0.0	0.22 (0.00009–0.77)	27	63.0	4.47 (<0.5–15)	-	-	-	-	8.6	0.36	5.57E+04	3.49E-06
	Valsartan	VAL **	137862–53–4	8	0.0	0.90 (<0.0037–7.47)	10	90.0	-	-	-	-	-	560	0.057	4.53E+02	4.55E-06
CNS medications	Carbamazepine	CBZ	298–46–4	25	0.0	0.49 (0.0004–11.56)	133	0.8	46.76 (<0.01–1300)	-	-	-	-	2	2.86	2.60E+03	2.32E-06
	Citalopram	CIT **	59729–33–8	5	0.0	0.03 (0.0006–0.12)	9	66.7	-	-	-	-	-	16	0.114	1.87E+07	1.55E-05
	Diazepam	DZP	439–14–5	6	16.7	0.02 (<0.0003–0.125)	38	65.8	10.95 (<0.05–80)	-	-	-	-	0.29	0.0057	8.31E+04	3.77E-06
	Lamotrigine	LAM	84057–84–1	5	0.0	0.22 (0.0015–1.2)	53	45.3	39.44 (<0.2–500)	-	-	-	-	8	0.3	2.01E+05	7.43E-06
	Venlafaxine	VEN	93413–69–5	5	0.0	0.25 (0.014–0.57)	56	30.4	2.78 (<0.1–20)	-	-	-	-	0.88	1.07	1.02E+04	8.68E-06

(*continued on next page*)

Table 1 (*continued*)

CEC group	CEC name	CEC ID	CAS number	SW compartment: # of data	SW compartment: Data below LOQ [%]	SW compartment: Concentration[a] [µg L^{-1}]	Crop compartment: # of data	Crop compartment: Data below LOQ [%]	Crop compartment: Concentration[a] [µg kg^{-1}]	Soil compartment: # of data[b]	Soil compartment: Data below LOQ[b] [%]	Soil compartment: Concentration[a] [µg kg^{-1}]	Soil compartment: BCF[a] [-]	Toxicological parameters: PNEC[c]	Toxicological parameters: RfD	Toxicological parameters: CF_{ECO}[d]	Toxicological parameters: CF_{HT}[d]
Lipid regulators/ Diuretics	Bezafibrate	BZF **	41859–67–0	8	0.0	0.85 (0.00001–15.06)	34	97.1	-	-	-	-	-	2.29	2.9	4.29E+03	1.1E-05
	Furosemide	FUR **	54–31–9	6	0.0	0.15 (0.002–0.86)	12	91.7	-	-	-	-	-	31.3	2.5	1.35E+05	1.93E-06
	Gemfibrozil	GEM *	25812–30–0	17	0.0	0.39 (0.00019–7.78)	28	96.4	-	7	0	14.32 (0.008–58)	1.62[e] (-)	0.5	8.57	2.93E+04	2.84E-06
Stimulants/ Opioids	Caffeine	CAF	58–08–2	18	0.0	2.01 (0.0002–39.81)	81	33.3	13.5 (<0.1–169)	-	-	-	-	1.2	1.2	5.49E+02	6.39E-07
	Codeine	COD **	76–57–3	5	0.0	0.07 (0.0096–0.15)	16	93.8	-	-	-	-	-	7.19	0.86	3.83E+05	1.93E-05
Hormones	17a-ethinylestradiol	EE2*	57–63–6	92	15.2	0.20 (<0.00005–17.11)	0	-	-	13	61	0.88 (0.18–1.73)	5.37 (0.44–16.5)	0.00004	0.003	1.05E+07	3.97E-05
	17b-estradiol	BE2*	50–28–2	24	8.3	0.20 (<0.000034–2.68)	0	-	-	13	53	1.13 (0.65–1.66)	145 (36–850)	0.0004	0.05	5.63E+07	2.62E-05
	Estrone	EST*	53–16–7	18	0.0	0.73 (0.0002–13.63)	0	-	-	14	14	10.93 (0.27–60.14)	49.4 (0.6–178)	0.0036	0.07	4.12E+05	1.54E-05
Alkylphenols	4-nonylphenol	NP	104–40–5	10	0.0	0.31 (0.0001–1.10)	36	0.0	110.04 (2.23–3537)	-	-	-	-	0.25	3.94	9.21E+04	4.42E-06
	4-tert octylphenol	OCT **	140–66–9	15	0.0	0.07 (0.0002–0.35)	0	-	-	-	-	-	-	0.47	1	2.87E+05	5.53E-06
	Bisphenol A	BPA	80–05–7	23	0.0	0.27 (0.0006–3.07)	15	0.0	110.8 (4.9–363.3)	-	-	-	-	0.24	0.0002	4.38E+03	1.2E-07
Other industrial compounds	Benzotriazole	BTZ	95–14–7	11	0.0	1.11 (0.004–3.7)	23	62.5	19.6 (<0.2–90)	-	-	-	-	19	17	9.25E+03	2.62E-07
	Triclosan	TCS	3380–34–5	13	0.0	0.09 (0.00048–0.53)	20	55.0	6.05 (<1–18.46)	-	-	-	-	0,11	83	2.58E+06	9.25E-07

[*] CEC for which crop concentration data were not sufficient to estimate their statistical distributions, thus crop concentration data were derived from concentrations in soil.
[**] CEC for which neither crop concentration data nor BCF values where sufficient to estimate their statistical distributions, thus crop concentration data were not derived.
[a] Data are reported as mean values with ranges in brackets.
[b] Data refer exclusively to soil concentration data.
[c] NORMAN website.
[d] EPLCA website.
[e] For GEM, only a single BCF value was reported.

higher than 1 indicates the presence of a risk [56]. A Monte Carlo method was applied, which allowed for the propagation of the uncertainties related to the estimated distributions of $C_{EXP,i}$ and $Dose_{EXP,i}$ into 1000 RQ and BQ values, respectively. The obtained values were used to fit probability distributions of RQ or BQ. From the probabilistic distributions it is possible to extrapolate the probability of RQ or BQ higher than threshold values (0.1 and 1). Both these risk statistical parameters express the percentage of the total area underlying the probability density curve that is above the RQ or BQ value of 0.1 and 1. For each CEC, the estimated probabilities of RQ or BQ higher than threshold values are reported in Table S4.

2.2.4. Contaminants risk-based ranking methodology

For this ranking, the 75th percentile values of the RQ or BQ distributions were compared with the risk threshold values defined in Section 2.2.3. Based on these comparisons, CECs were ranked into 4 classes:

i. Both RQ and BQ 75th percentiles higher than 1, indicating the most hazardous CECs that pose simultaneous risks to the environment and human health, that need to be prioritized.
ii. Only one of either RQ or BQ 75th percentile exceeds 1, representing hazardous CECs for which only one endpoint is at risk. The prioritization in this case depends on the case-specific vulnerability of the affected endpoint.
iii. At least one of RQ or BQ 75th percentile higher than 0.1, suggesting that while these CECs do not present an immediate risk, they warrant further investigation.
iv. Both RQ and BQ 75th percentiles lower than 0.1, indicating CECs that do not pose any risk and are considered substantially safe.

2.3. TyPol approach

The TyPol approach, originally developed by the authors [59] and later refined in subsequent work [58] to estimate the potential impacts of CECs on the aquatic environment and the human health, was adopted in this study and integrated within a broader risk-based prioritization framework. The original TyPol methodology clusters CECs based on two types of parameters: molecular descriptors (MDs, input variables) and environmental parameters (EPs, target variables), capturing their environmental behavior. TyPol is based on a Partial Least-Squares (PLS) approach, that models the relationship between the input variables and the target variables. Then it builds a hierarchical clustering on the components of the PLS which allows to cluster the CECs that share common behaviors. In this work, this methodology was upgraded by incorporating also toxicological parameters (TOX) as additional target variables, enabling the simultaneous consideration of environmental and human health risks in the clustering process. In addition, differently from Servien et al. [58], which focused on assessing the risk for individual CECs, here environmental and human health risk distributions are calculated for each cluster, and clusters are then ranked according to these risk distributions highlighting the highest priority groups of CECs.

The risk-based prioritization framework based on TyPol consists here of four main steps, instead of the original two: (i) selection of the clustering variables (i.e., MDs, EPs and TOX) relevant to this case study, (ii) clustering of compounds based on these variables, (iii) estimation of the environmental and human health risks distributions for each cluster, and (iv) cluster risk-based ranking methodology.

2.3.1. Selection of the clustering variables

MDs and EPs were selected based on the environmental processes considered relevant for the specific case study, i.e., environmental and human health risks due to indirect reuse of reclaimed wastewater. The same set of 40 MDs detailed by Servien et al. [59], was adopted here. These MDs can be differentiated between constitutional, geometric, and topological descriptors, commonly referred to as 2D descriptors (35 out of 40 MDs), or in quantum-chemical descriptors, commonly referred to as 3D descriptors (5 out of 40 MDs).

The environmental processes of interest include dissolution, volatilization, adsorption, degradation, and bioaccumulation. Each of these environmental processes can be described by different EPs: (i) water solubility (S_w) for dissolution, (ii) vapor pressure (P_{vap}) for volatilization from soil and plant, and Henry's law constant (K_H) for volatilization from water, (iii) octanol-water partition coefficient (K_{ow}) for adsorption, (iv) half-life (DT_{50}) for degradation, and (v) bioaccumulation factor (BAF) to consider the impacts on the organisms. The database for MDs and EPs is regularly updated and now gathers more than 800 compounds including pesticides, persistent chemicals, pharmaceuticals and their transformation products [58].

TOX were included to integrate risk-related information directly into the clustering process. Specifically, PNECs, RfDs, and characterization factors (CFs), were considered as additional clustering variables. CFs are toxicological indicators adopted within Life Cycle Assessment to convert environmental emissions of compounds into potential impacts in terms of toxicity for environment and human health. CFs are typically calculated within USEtox® software [53], as detailed in section S.1.2. For environmental toxicity, a CF for ecotoxicity (CF_{ECO}) is estimated, expressed as a potentially disappeared fraction of species per kg of emitted substance [PDF m^3 d kg_i^{-1}], indicating the daily volume of organisms potentially disappearing due to the presence of a compound in an environmental compartment. CF for human toxicity (CF_{HT}) is expressed in terms of Disability-Adjusted Life Years per kg of emitted substance [DALY kg_i^{-1}], indicating the number of years lost due to illness, handicap, or premature death specific to the compound presence. Both CF_{ECO} and CF_{HT} were collected from the EF3.1 database made available by the European Platform on LCA [20] and are reported in Table 1. A summary of the MDs, EPs and TOX considered in this study is reported in Table S5.

2.3.2. TyPol clustering procedure

TyPol applies a sequence of statistical methods to classify each CEC in a group of compounds having similar MDs, EPs and TOX, thus, potentially a similar environmental and toxicological behavior. Specifically, a Partial Least Squares regression (PLS) [1] is used to find the multidimensional directions in the observable variables (i.e. MDs) space that explain the maximum multidimensional variance direction in the predicted variable (i.e. EPs and TOX) space. The optimal number of components to perform clustering was selected using the PRESS (Prediction Sum of Squares) criterion. In addition, PLS can deal with missing values by using the NIPALS (Non-linear Iterative Partial Least Squares) algorithm, which allows performing PLS (and clustering) without removing the individuals with missing values and without estimating these missing values [44]. After the PLS analysis, a hierarchical clustering algorithm [65] is used and the final number of clusters is chosen after comparison of the heights of the dendrogram.

Unlike traditional QSAR approaches [12], which build single-endpoint models from molecular structure alone, TyPol is an inherently multivariate tool having several target variables. This allows TyPol to model a global behavior around a chemical process, rather than predict just a specific endpoint. Some approaches combining QSAR with life-cycle assessment have been recently defined (*inter alia*, [62,63]) but they have essentially a predictive purpose, whereas the main goal of TyPol is in clustering of substances by shared fate and hazard profiles, laying the groundwork for the subsequent cluster-level risk assessment and ranking.

2.3.3. Estimation of clusters environmental and human health risks distributions

Environmental and human health risk assessments are not directly included in TyPol, but they are usually performed subsequently to the clustering, with an independent approach based on CFs [2,58]. The calculation methods for CF_{ECO} and CF_{HT} (section S.1.2) already incorporate all the factors regulating the transport and fate of CECs in the environment, including the exposure route for humans. Thus, to correctly assess both risks, it is necessary to consider the concentration of CECs within the same initial compartment, which is SW in this case. The environmental risk ($RISK_{ECO}$) and human health risk ($RISK_{HT}$) were then estimated, according to Aemig et al. [2], by multiplying the median concentration of CECs ($C_{50,i,SW}$) in SW by CF_{ECO} and CF_{HT}, respectively, as follows:

$$RISK_{ECO,i} = CF_{ECO,i} \times C_{50,i,SW} \quad (5)$$

$$RISK_{HT,i} = CF_{HT,i} \times C_{50,i,SW} \quad (6)$$

As a result, $RISK_{ECO}$ is expressed as PDF d, while $RISK_{HT}$ is expressed as DALY m^{-3}.

In addition, differently from Servien et al. [58], which focused on assessing the risks for individual CECs *i*, the risk assessment was extended to a cluster-based approach. Once that CECs were assigned to their specific cluster, for each cluster *k,* the risk distribution ($RISK_{ECO,k}$ and $RISK_{HT,k}$) was determined by aggregating the median risk values ($RISK_{ECO,i}$ and $RISK_{HT,i}$) of all the CECs within that cluster.

2.3.4. Cluster risk-based ranking methodologies

After calculating the environmental and human health risk distribution of each cluster (i.e., $RISK_{ECO,k}$ and $RISK_{HT,k}$), a sequence of non-parametric statistical tests was applied to translate these distributions into statistically significant priority tiers. First, the non-parametric Kruskal-Wallis test was used to determine if there were statistically significant differences between risk distributions of the different clusters [46]. When Kruskal-Wallis test indicated at least one significant difference (p-value lower than α=5 %), the post-hoc Dunn's test for pairwise comparison [10] was used Fare clic o toccare qui per immettere il testo. to identify which clusters diverge in risk levels. Finally, a hierarchical clustering algorithm was applied, employing a dissimilarity matrix and a hierarchical tree [50], to group clusters into three statistically distinct tiers: high, medium, and low priority.

This analysis ensures that each priority level reflects data-driven differences in the underlying risk distributions, resulting in the identification of three ranking levels, according to which each cluster was assigned to its ranking class. Detailed steps and parameters are provided in Section S.1.3.

2.4. Missing data handling for risk estimation

In TyPol, CECs are assigned to clusters even when not all the clustering parameters (i.e., MDs, EPs and TOX) are available. This enables to attribute the median values of the assigned cluster to the CEC for the calculation of $RISK_{ECO}$ and $RISK_{HT}$, which would otherwise not be possible in cases where single parameters are missing. A scenario analysis was conducted to explore the potential of the TyPol approach in assessing the risk for a CEC when concentration or toxicological data are incomplete. Three scenario were tested, each based on different combinations of available input parameters for the considered CEC (i.e., $C_{50,SW,}$ CF_{ECO} and CF_{HT}) to estimate the risk using Eqs. 5 and 6. The same clusters were maintained across all three scenarios, which were derived based only on MDs and EPs. This approach was necessary because, when CFs are missing, it is not possible to include also TOX in the clustering process.

In the baseline scenario (BL), we assumed both concentration and CFs for the CEC are available, allowing risk calculation for each CEC using its specific concentration and CFs, as described in Section 2.3.3. In the NO-CONC scenario, we simulated a case where concentration data might be unavailable for some CECs. To account for this, risk was estimated for all CECs by using their specific CFs while replacing individual concentrations with the cluster median, calculated from all CEC concentrations within the same cluster. Similarly, in the NO-CF scenario, we simulated the absence of toxicological data, and estimated risk for all CECs using their specific concentration values while replacing missing CFs with the cluster median. In all scenarios, after the risk estimates, clusters were ranked following the statistical approach outlined in Section 2.3.4. Here below are summarized the contaminant-specific values or cluster-specific median values adopted for calculating the CEC-specific risk in each scenario of data availability:

– BL: $C_{50,i,SW}$ of the analyzed CEC and $CF_{ECO,i}$ or $CF_{HT,i}$ of the analyzed CEC;
– NO-CONC: $C_{50,k,SW}$ of the cluster and $CF_{ECO,i}$ or $CF_{HT,i}$ of the analyzed CEC;
– NO-CF: $C_{50,i,SW}$ of the analyzed CEC and $CF_{ECO,k}$ or $CF_{HT,k}$ of the cluster.

3. Results and discussion

3.1. Contaminants concentration distributions

The estimated concentration distributions for SW and crops are shown in Fig. 1. Concentrations for the nine CECs that could not be quantified in crops are displayed only for SW. No significant trends emerge among different groups of CECs, and, since the data for SW and crops were derived from independent studies conducted at different locations, no direct correlation can be assumed between these two compartments. Most CECs exhibit a wide variability, with concentrations ranging from 10^{-10} to 10^{1} μg L^{-1} for SW, where the highest variability is observed, and from 10^{-4} to 10^{4} μg kg^{-1} in crops. This variability reflects the differing occurrences, behaviors, and transport mechanisms of CECs across environmental compartments, but also challenges in measuring them accurately. In fact, many CECs are characterized by high percentages of left-censored data, particularly in crops, where 66 % of the data falls below the LOQ (Table 1). This limitation of the analytical methods does not imply a lack of risk but rather indicates the challenge in detecting low concentrations, regardless of the compound toxicity [49].

3.2. QCRA risk distributions

Feeding the concentration distributions (Fig. 1) into the risk assessment procedure allows for better accounting of the uncertainties and variability associated with CECs. Fig. 2 presents the environmental and human health risk distributions, expressed as RQ and BQ respectively.

It can be noted that the variability in concentration distributions is reflected in the wide range of RQ (10^{-11} to 10^{5}) and BQ (10^{-8} to 10^{4}) values. The results show that environmental risks are statistically higher than human health risks for 18 CECs (64 % of cases: BE2, EE2, EST, IBU, AZT, NP, CAF, VEN, DCF, TCS, CIP, CLA, ERY, BTZ, SMX, GEM, OXY, NAP), statistically lower for 5 CECs (BPA, DZP, LAM, MET, ATE), and that they do not present a statistical difference for 5 CECs (CBZ, OFL, ACE, SMZ, TMP). These findings have important implications for indirect water reuse. Given that the environmental risk was found to be higher in the majority of cases, it is crucial to adopt an integrated One Health approach that considers both ecological and human health impacts, rather than focusing solely on the human health risk. This broader perspective enables a more comprehensive and precautionary evaluation of indirect reuse implementation, ensuring that environmental risk is not overlooked in decision-making processes.

For the environmental risk, four CECs (BE2, EST, EE2, IBU) exhibit a probability of RQ higher than the risk presence threshold P(RQ > 1) higher than 75 %. An additional four CECs (BPA, AZT, NP, CAF) shows a P(RQ > 1) higher than 25 %, while DCF, TCS, ERY and CIP exceed the risk presence threshold in more than 5 % of the distribution. For human health risk, BPA and BE2 present a P(BQ > 1) higher than 75 %, while DZP surpasses the risk threshold in more than 25 % of the distribution, and EST in 5 % of the distribution. Additionally, LAM, NP and EE2 have a low P(BQ > 1) (i.e., < 5 %) but still show a notable probability of exceeding the warning threshold of 0.1 P(BQ > 0.1), equal to 72.2 %,

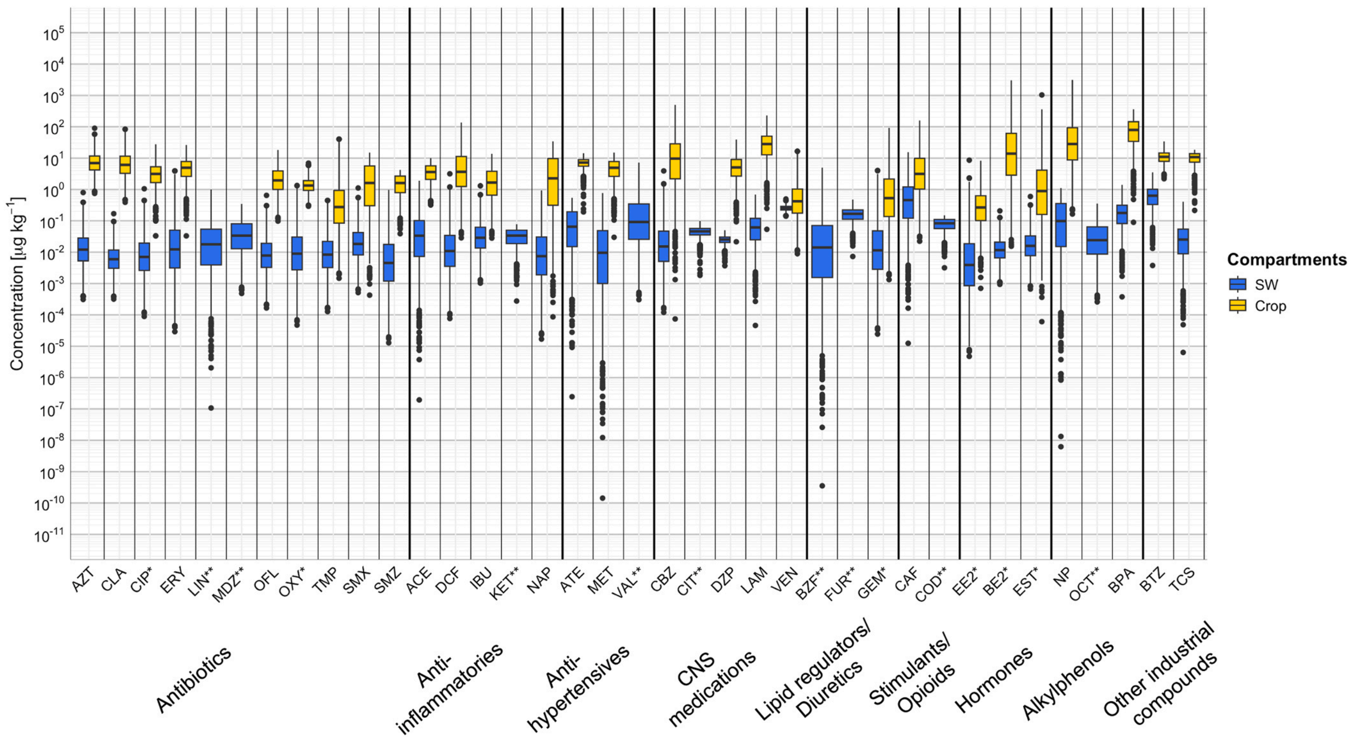

Fig. 1. (a) Estimated concentration distributions in SW and crop compartments differentiated per CECs: concentrations in SW and crop are expressed respectively in [µg L^{-1}] and [µg kg^{-1}]. For CECs marked with a "*", crop concentration was estimated from concentration in soil. For CECs marked with a "**", crop concentration was not estimated.

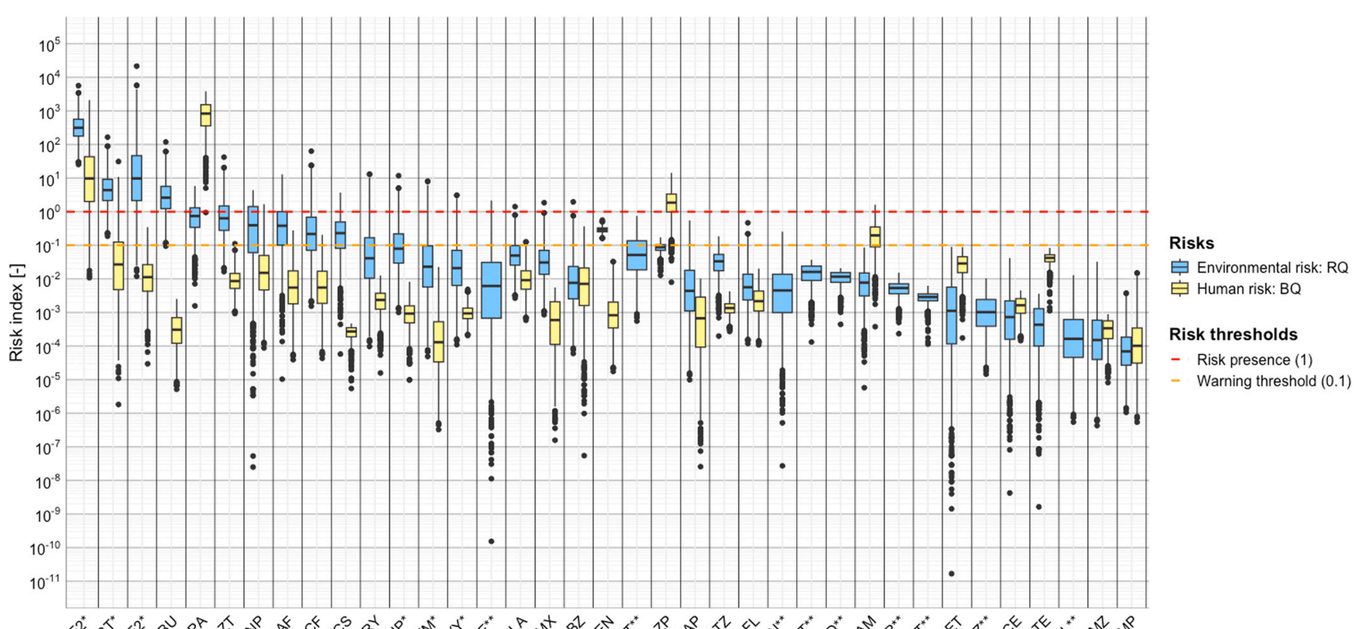

Fig. 2. Estimated RQ and BQ distributions respectively for the environment and the human health endpoints. For CECs marked with a "*", crop concentration was estimated from concentration in soil. For CECs marked with a "**", crop concentration was not estimated.

14.3 % and 6.3 %, respectively. Most CECs (15/37 for RQ and 21/28 for BQ) exhibit less than 5 % probability of falling below the warning thresholds value of 0.1, indicating a limited risk for these compounds. However, for nine CECs (BZF, OCT, LIN, KET, COD, FUR, CIT, MDZ, VAL), human health risk could not be assessed due to a lack of concentration data in crops, soil, and/or missing BCFs. This highlights a critical gap in the literature, as the absence of these data prevents a complete risk characterization. Notably, some of these CECs (BZF, OCT, LIN) exceed at least the environmental risk warning threshold, suggesting a potential concern for human health as well. Conversely, for BE2, although crop concentrations were either unavailable or below the LOQ, it was possible to estimate human health risk from concentrations in soil and BCFs. Given that BE2 poses a significant risk even at low, often undetectable, concentrations, addressing these knowledge gaps is essential to improve risk assessment accuracy and inform regulatory actions.

These findings align with prior studies such as Delli Compagni et al. [9], who reported elevated RQ values for BE2 and EE2, with median RQ values exceeding 1, followed by TCS, CLA, EST and IBU, having lower median RQs, but higher than 0.1. Similarly, Servien et al. [58] identified BE2 as a key contributor to environmental impacts, alongside with cypermethrine (not evaluated in this study). Regarding the human health risk, the significant concern posed by BPA is consistent with Penserini et al. [49], which highlighted the elevated health risk associated with BPA due to its widespread presence in crops irrigated with wastewater. In addition, EFSA [18,19] re-evaluation of the public health risk related to the presence of BPA in foodstuffs substantially lowered BPA's tolerable daily intake from 2 μg kg_{BW}^{-1} d^{-1} [16] to 0.2 ng kg_{BW}^{-1} d^{-1} . Moreover, the EU Commission banned its use in all food-contact materials as of January 2025 [23], underscoring the alignment of BPA prioritization with recent regulatory action. Malchi et al. [38] also emphasized the potential human health risk associated with LAM, while to the best of authors knowledge, no comparable studies addressing the human health risk from DZP via crop consumption were identified. By comparing Fig. 1 and Fig. 2 it becomes clear that relying solely on concentration data might be misleading. High concentrations do not necessarily translate to high risks. For example, some CECs with elevated concentrations in crops, such as NP or CBZ, show a relatively low risk due to their low toxicological hazards. Conversely, contaminants such as BE2 and DZP may appear non-threatening when only their concentrations are considered but display a significant risk when TOX are included.

This highlights the added value of a risk-based approach. By incorporating toxicological thresholds (PNECs, RfDs), a risk-based assessment ensures that the most harmful contaminants receive priority attention, offering insights into their actual impact on both environmental and human health.

3.2.1. QCRA ranking of contaminants in a One Health perspective

To enable simultaneous classification of CECs based on both environmental and human health risks, Fig. 3 presents these risks using ellipses, where the median values of the RQ and BQ distributions define

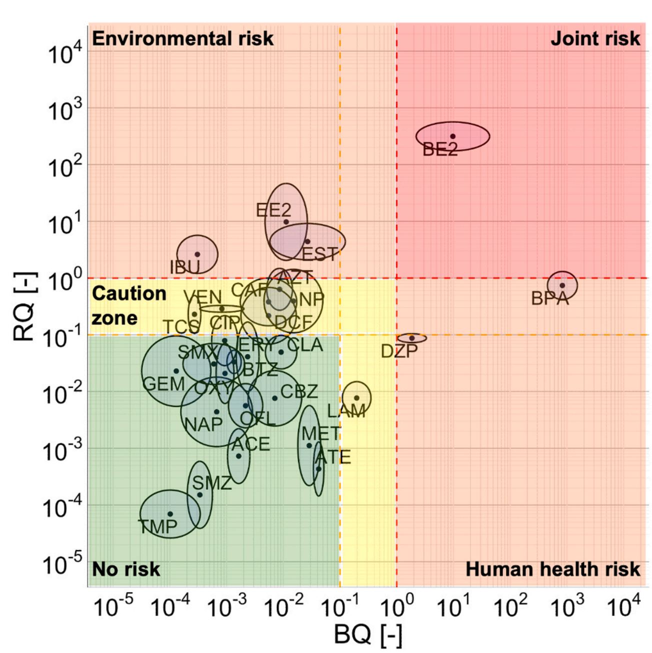

Fig. 3. Ellipses plot of the CECs-related environmental and human health risks, expressed as RQ and BQ, respectively. The colored zones indicate the level of priority required for each CECs, based on the different risk thresholds.

the center of each ellipse, while their interquartile ranges (25th and 75th percentiles) define the width of the ellipses along both axes. This approach aligns with the One Health framework, ensuring that contaminants are prioritized not only based on single endpoints but through an integrated perspective. Additionally, it provides a comprehensive risk ranking that reflects not only the median risk levels but also the variability within the distribution. The dashed lines represent the warning and risk presence thresholds, and they enable to classify CECs into four distinct risk zones (Section 2.2.4). CECs with the 75th percentile risk value below 0.1 for both endpoints fall into the no-risk zone (green). CECs with the 75th percentile risk value between 0.1 and 1 are categorized into the caution zone (yellow), with further differentiation based on whether human or environmental risk predominates. CECs exceeding 1 in either RQ or BQ occupy the environmental or human health risk zone (orange), respectively, while those exceeding 1 in both risks are placed in the joint-risk zone (red). BE2 and BPA are the only CECs located in this joint-risk zone, indicating their high prioritization need for both environmental and human health risks. Other CECs like EE2, EST, and IBU present high environmental risks (RQ > 1) but low human risks (BQ < 0.1), while DZP shows the opposite trend.

This discrepancy between environment and human endpoints highlights the importance of this dual-risk approach, which provides critical insights, especially from a regulatory perspective. Other studies, such as García-Vara et al. [30] and Zhong et al. [68], based the CECs prioritization in reclaimed wastewater reuse systems exclusively on the environmental risk, evaluating CEC occurrence and ecotoxicity, without considering human health endpoints. Similarly, Meffe et al. [39] and Liu et al. [36] concentrated primarily on the human health risk due to the presence of CECs in indirect wastewater reuse systems, emphasizing exposure and risk related to human crop consumption pathways. These approaches, while valuable, may overlook CECs that pose a significant risk to one endpoint while seeming harmless in another. For instance, EE2, EST, IBU, AZT, NP, and CAF which may seem non-threatening from a human health perspective, present a substantial environmental risk, leading to potential ecosystem degradation if left unaddressed. Conversely, DZP human health impact may be understated if only the environmental risk is considered, and necessary interventions might not be implemented. Additionally, several CECs fall into the caution zone (yellow), requiring further assessment. In particular, for environmental risk, DCF, TCS, ERY, CIP, and VEN fall within this range, representing possible threats to aquatic ecosystems, while for human health risk, LAM exceeds the warning threshold. Meanwhile, CECs such as GEM, OXY, CLA, SMX, CBZ, NAP, BTZ, OFL, MET, ACE, ATE, SMZ, and TMP remain below the 0.1 threshold for both endpoints, ranking them in the no-risk zone (green) and suggesting limited concern under the evaluated conditions. By incorporating both RQ and BQ into the analysis, our method reveals critical insights otherwise lost in single-endpoint evaluations.

Importantly, the ellipses also indicate the level of uncertainty and variability in each risk dimension, ensuring that the risk-based CEC ranking reflects not only central values but also potential exceedances and variability. For instance, EST and EE2 exhibit similar median values, yet their interquartile ranges differ significantly between environmental and human health risks, with variability spanning more than an order of magnitude in one endpoint while remaining relatively narrow in the other. In contrast, compounds such as BPA and IBU display similar levels of variability across both risk dimensions, suggesting more consistent patterns across endpoints. Understanding these variability trends is crucial, as contaminants with highly uncertain risk distributions may require additional site-specific monitoring and targeted research to refine risk estimates. This comprehensive approach aligns with the One Health approach, facilitating more effective monitoring and management, particularly in wastewater reuse contexts, where CECs may pose differential risks to human health and the environment.

3.3. TyPol clustering

From the clustering procedure, four PLS components were selected. Results are reported only for the first two components, explaining 61 % of the variance in the MDs domain and 57 % of the variance in the EPs and TOX domain, while the resulting contributions of MDs, EPs and TOX to the four PLS components are illustrated in Figure S1. The first PLS component is primarily driven by MDs, with molecular size increasing from right to left. The second PLS component is influenced by TOX, with toxicity increasing from the upper right to the lower left. This is further supported by the correlation circle plot reported in Figure S2, illustrating the correlations between the different clustering variables and the first two PLS components. From the comparison of the dendrogram heights, five was indicated as the optimal number of clusters. Cluster sizes ranged from 3 to 22 compounds. Fig. 4 shows the individual factor map based on the first two PLS components. While some clusters may appear less distinct in this partial representation, their grouping becomes clearer when additional PLS components are considered, as in Figure S3. The range of variation for MDs, EPs and TOX within each cluster is provided in Figure S4.

Cluster 1 includes 4 CECs (ACE, BTZ, CAF, MDZ) from different categories, characterized by moderate molecular weight, limited aromatic and multiple bonds, and high S_W, P_{VAP}, and K_H, indicating high mobility in water and air, with a tendency for wide environmental distribution. The addition of TOX within the clustering emphasizes their lower hazard compared to other CECs, with moderate environmental persistence, but relatively low human and ecological toxicity (Figure S4).

Cluster 2 is the largest cluster with 22 CECs. It contains CECs from several categories (e.g., antibiotics, anti-inflammatories, industrial chemicals), with characteristics like moderate molecular weight and polarizability, high number of aromatic bonds and quite high P_{VAP}, K_H and K_{OW}, indicating their tendency to volatize, as well as their hydrophobicity and persistence potential. The distribution of CF_{ECO} and PNEC values suggests a moderate to high ecotoxicological potential for certain compounds within the cluster, while CF_{HT} and RfD values indicate a high variability in the human health risk (Figure S4). However, the broad range of molecular, environmental, and toxicological properties within this cluster implies that no single characteristic dominates.

Cluster 3 includes three macrolides (AZT, CLA, and ERY), characterized by very high molecular weight, a low number of hydrogen atoms, low values of S_W, P_{VAP} and K_H and moderate values of K_{OW} and BAF, indicating their tendency to persist in aquatic environments and soil, with moderate potential for bioaccumulation [57]. Notably, this is the cluster with the second-highest ecological toxicity, due to its low PNEC and high CF_{ECO} values.

Cluster 4 contains 5 CECs (CIP, COD, LIN, OFL, and OXY), primarily antibiotics and an opioid (COD). These CECs are characterized by high polarizability and relatively high connectivity indices, reflecting their complex molecular structure. Despite their high S_W, facilitating their dissolution and mobility in water, their low K_{OW} and BAF decrease their potential to be adsorbed to sediments, soils, and biotic tissues [28]. In terms of toxicological properties, CECs in this cluster exhibit moderate ecotoxicity and human health risk (Figure S4).

Finally, cluster 5 narrows to three estrogenic compounds (BE2, EE2, and EST), characterized by high molecular weight, multiple aromatic rings, and multiple bonds, making them chemically stable and resistant to degradation [47]. Their high K_{OW} increases their bioaccumulation potential, while high K_{OC} shows strong binding to organic matter in sediments and soils. The key distinction is their toxicological profile: estrogens have the lowest PNEC and highest CF_{ECO} values among the 37 selected CECs, indicating that even extremely low concentrations can pose ecological risk [6]. Furthermore, their low RfD and high CF_{HT} values also indicate a significant risk to human health, especially in terms of reproductive and developmental toxicity [9], justifying its distinct grouping based on toxicological considerations.

3.3.1. Ranking of clusters

The risk assessment has been applied to the clusters of CECs with similar MDs, EPs, and TOX characteristics, obtained in the previous step. The $RISK_{ECO,i}$ and $RISK_{HT,i}$ obtained for each CECs, reported in Figure S5, were grouped according to the clusters. The distributions of $RISK_{ECO,i}$ and $RISK_{HT,i}$ for the different clusters are shown in Fig. 5 where each boxplot represents a single cluster; besides, the median values of $RISK_{ECO,i}$ or $RISK_{HT,i}$ obtained for each CEC assigned to that cluster are also reported. The cluster ranking (see Section 2.3.4) shown in Fig. 5 with a color code, was obtained comparing the distributions of clusters $RISK_{ECO,k}$ or $RISK_{HT,k}$. A color scale was adopted to visualize the ranking, with red indicating the clusters to be prioritized, orange for those requiring further evaluation, and green for those of lower priority. Unlike the QCRA approach, which integrates and evaluates together environmental and human health risks (expressed as RQ and BQ), this analysis keeps the two endpoints separate, due to the different units of measurement of $RISK_{ECO}$ and $RISK_{HT}$.

Cluster 5, containing estrogenic compounds (BE2, EE2, and EST), emerges as the cluster with the highest risk, for both the environment and human health endpoints. The narrow range of risk distributions (around one order of magnitude) in both endpoints confirms that the clustering procedure consistently characterizes these CECs from a toxicological perspective, indicating that their endocrine-disrupting effects

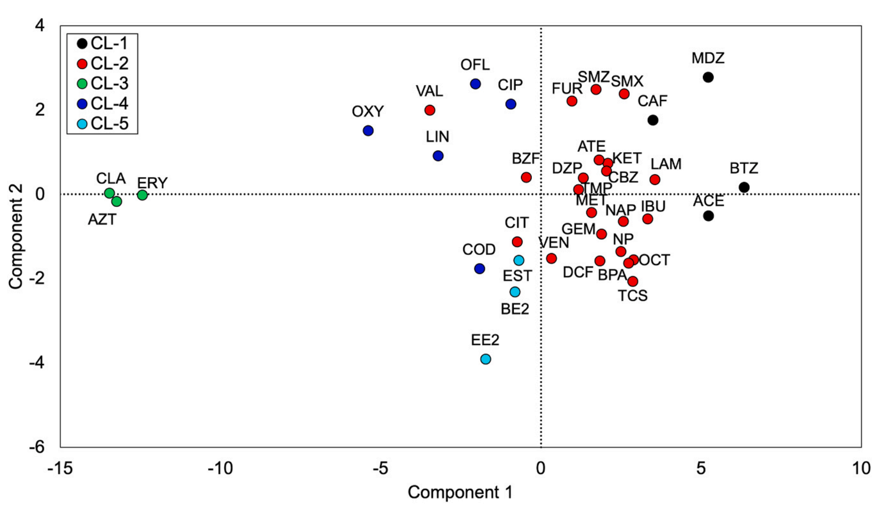

Fig. 4. Typol clustering of the 37 CECs in five clusters on the two main components of the PLS.

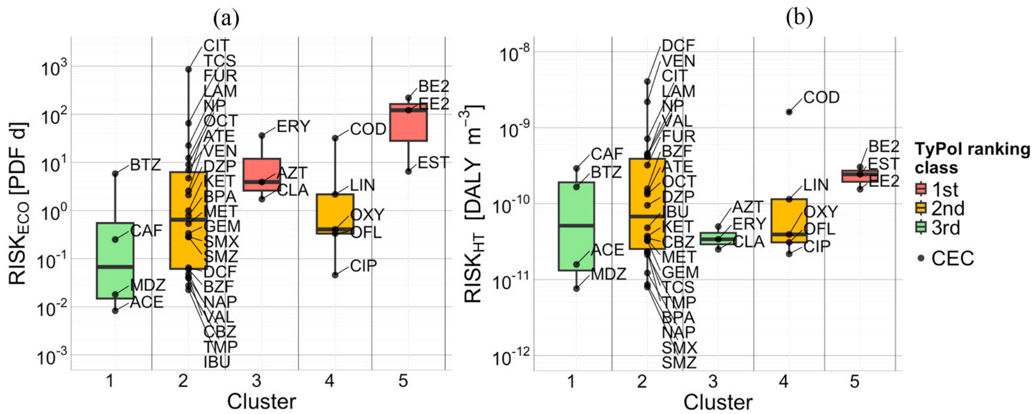

Fig. 5. Boxplots of (a) $RISK_{ECO}$, and (b) $RISK_{HT}$ for each cluster and their assigned ranking class.

require urgent attention, in line with the findings of many studies available in literature (inter alia, [60,61,64]). Given that both TyPol and QCRA confirm the human health risk associated with these compounds, the absence of direct measurements in crops remains a critical gap.

In contrast, cluster 3 (macrolides: AZT, CLA, and ERY) shows a different level of prioritization depending on the endpoint of interest. From an environmental perspective, it emerges as a cluster to be prioritized, together with cluster 5, while from a human health perspective, it is classified as a cluster with lower priority. This divergence between environmental and human health risks has been observed also by Oldenkamp et al. [45] and Huang et al. [33], who found macrolides to be of significant concern in aquatic systems due to their prolonged environmental presence and toxicity, while simultaneously classifying them displaying lower risk for human health.

Clusters 1, 2, and 4 show broader risk distributions, with differences ranging from 3 to 5 orders of magnitude within the same cluster. In Cluster 1, despite containing BTZ and CAF, which exhibit higher risk estimates (Fig. 5), the cluster remains consistently classified as low risk. This apparent discrepancy stems from the influence of ACE and MDZ, presenting low median values of $RISK_{ECO,i}$ or $RISK_{HT,i}$ (Figure S5). However, a key factor contributing to the elevated risks of BTZ and CAF is their notably higher C_{SW}. Their median, 25th and 75th percentile concentrations are among the highest across all CECs (Fig. 1), leading to significantly greater risk estimates despite their relatively low TOX values (Table 1). Clusters 2 and 4 include a broader spectrum of CECs with various risk levels. For instance, for cluster 2, the median $RISK_{ECO}$ of CIT is 3×10^4 times the TMP one, while the median $RISK_{HT}$ of DCF is 5×10^2 times the SMX, while for cluster 4, COD shows a median $RISK_{ECO}$ 7×10^2 times higher than the CIP one. This diversity leads to the classification of these two clusters as medium-risk clusters, even if they contain CECs that would have been considered high priority if evaluated individually, such as CIT, DCF, and COD (Figure S5).

The wider variation of estimated risks that is observed in clusters 1, 2, and 4 can also be attributed to the relatively lower influence of toxicological factors in the clustering process compared to other MDs and EPs. While TOX were included alongside MDs and EPs, their impact on cluster formation appears limited. This conclusion is supported by the analysis reported in Figures S6 and S7, where clustering was performed without TOX. Despite minor differences, the overall prioritization remained consistent, and the cluster structures did not change significantly, confirming the lower weight of toxicological factors in the clustering process. Furthermore, the broad risk distributions observed in the boxplots suggest that these clusters may not be as effective for identifying CECs that require targeted intervention. A practical approach to reducing this variability could involve assigning greater weight to toxicological factors during the clustering process. Alternatively, a post-clustering refinement step could help identifying higher-risk CECs within each broad cluster, thereby improving prioritization for risk management. Another key factor contributing to the wide risk distributions within these clusters is the role of CEC concentrations. Unlike MDs, EPs, and TOX, which guided the clustering, concentrations were not included as clustering variables, yet they directly influence risk estimation through their interaction with CFs, as described in Eqs. 5 and 6. This misalignment between clustering criteria and risk quantification variables likely contributes to the observed intra-cluster risk variability. Specifically, CECs with particularly high concentrations, such as BTZ and CAF in cluster 1, FUR and VEN in cluster 2, and COD in cluster 4 (Fig. 1), exhibit significantly higher risk estimates than other CECs within the same group, widening the intra-cluster risk range. Additionally, clustering outcomes are inherently influenced by the selection of CECs included in the analysis. A dataset with limited or highly diverse contaminants can increase variability within clusters. Expanding the clustering approach to validate its performance across a broader range of CECs or including additional contaminants with diverse profiles could enhance the robustness and applicability of this method.

3.4. Discussion of QCRA and TyPol outcomes

Both the QCRA and TyPol approaches offer valuable insights for prioritizing CECs based on their environmental and human health risks, though they lead to both converging and diverging outcomes. The diverse nature of these two risk assessment procedures makes the direct comparison of results challenging, yet both serve as complementary approaches in evaluating the CEC risk. QCRA procedure generates risk indices (RQ and BQ) specific for each CEC. This process allows to rank each CEC based on its exceedance of risk thresholds, independently from the other CECs. In contrast, TyPol procedure does not rely on risk thresholds, and it provides risk outputs associated with clusters. Consequently, clusters ranking reflects their relative risks based on the risk distribution of the CECs within them, making TyPol performance highly dependent on the selected set of CECs.

Fig. 6 illustrates these differences by integrating the results of both approaches, differentiated per environmental and human health risks. The boxplots represent the RQ (Fig. 6a) and BQ (Fig. 6b) distributions estimated through the QCRA, while the color coding for each compound comes from the three TyPol ranking classes according to, respectively, $RISK_{ECO}$ and $RISK_{HT}$. It can be observed that both QCRA and TyPol converge on the high prioritization of the estrogenic compounds contained in cluster 5, especially for the environmental risk, where all CECs significantly exceed the RQ threshold of 1. For human health risk, while TyPol ranks the entire cluster as high priority, QCRA enables to extrapolate a different but more detailed profile: BE2 would be classified as a CEC to be prioritized, while EST and EE2 as CECs that warrant further attention with, respectively, a probability of exceeding BQ= 1 equal to 5 % and a probability of exceeding BQ= 0.1 equal to 6.3 %. A comparable outcome is obtained for the macrolides assigned to cluster 3.

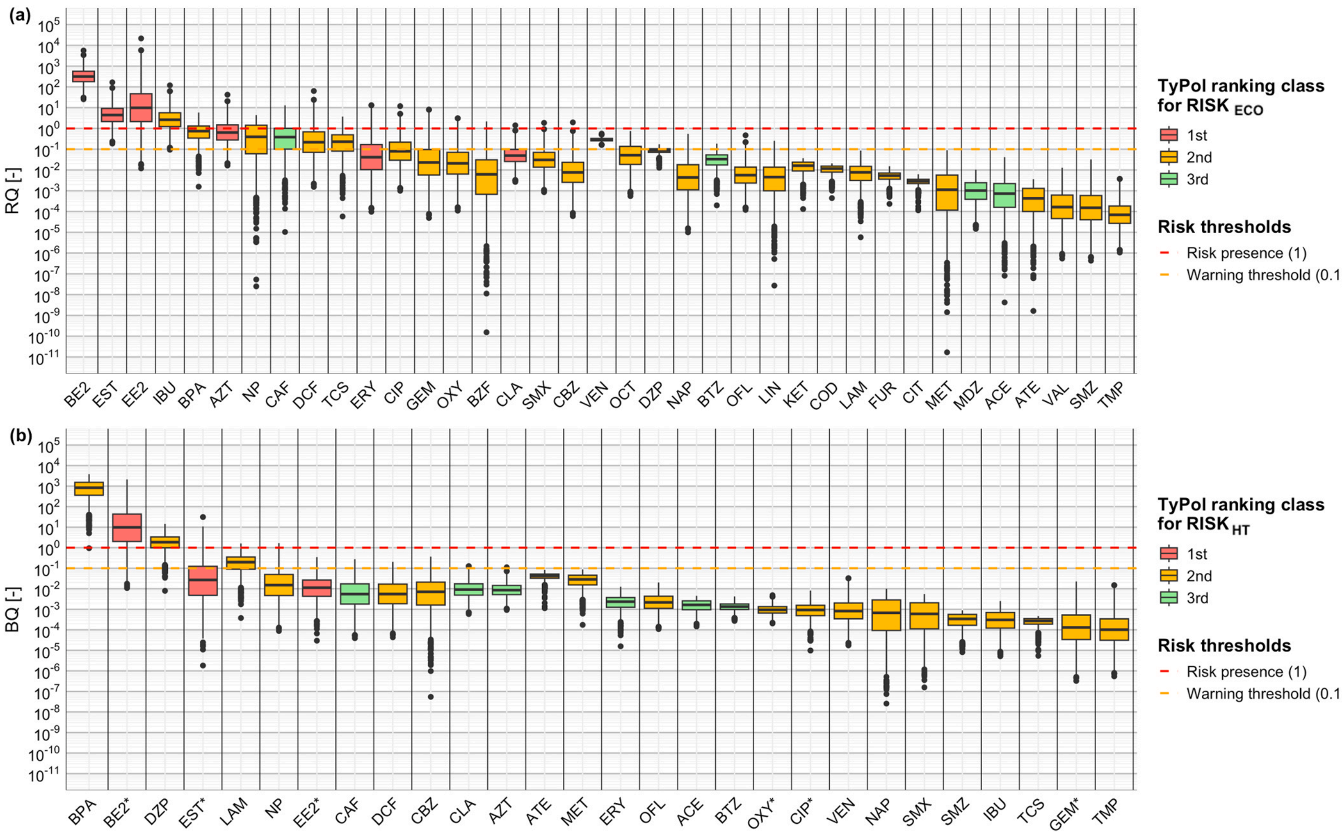

Fig. 6. RQ and BQ distributions sorted according to QCRA approach and filled according to TyPol ranking classes. Results are reported for (a) environmental and (b) human health risk-based prioritization.

Both procedures prioritize these CECs due to their environmental risk, while the risk to human health remains negligible. Once again, QCRA provides more details, indicating probabilities of exceeding an RQ of 0.1 for AZT (92.1 %), ERY (32.9 %), and CLA (24.2 %).

These prioritization outcomes align with current regulatory frameworks, in fact, both natural estrogens and macrolide antibiotics are under active consideration for being included into the revised WFD as enforceable Environmental Quality Standards (EQS) [24]. Although BE2, EE2 and EST no longer appear on the EU Watch List [22], the EU Commission [21] explicitly designates estrogenic hormones and macrolide antibiotics as priority families for group-based EQS (i.e. setting standards for entire substance families) to amend the EQS and Groundwater Directives. Furthermore, the EU Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) likewise advocates deriving provisional EQS for natural estrogens [55], formally recognized as endocrine disruptors, to protect environmental and the human health safety, further confirming their priority status in risk assessments.

However, discrepancies between the two approaches become more evident for low- and medium-risk clusters. For example, QCRA emphasizes the environmental risk posed by CAF, with a 75.1 % probability of exceeding an RQ of 0.1 and a 25.1 % probability of exceeding an RQ of 1, primarily driven by its high concentrations despite its low toxicity (Fig. 1 and Table 1). In contrast, TyPol assigns CAF to the low-risk cluster (cluster 1), due to its reliance on MDs, EPs, and TOX, minimizing the influence of concentration in favor of intrinsic compound properties. Consequently, CAF is grouped with MDZ and ACE, which exhibit limited risks (Fig. 5). This divergence in risk prioritization becomes even more pronounced in medium-risk clusters, such as cluster 2, which contains a heterogeneous mix of CECs with diverse characteristics. For instance, IBU is classified as highly environmentally toxic in QCRA, with a median RQ of 2.6 and an 80.3 % probability of exceeding RQ of 1, driven by its very low PNEC. However, in TyPol, IBU low environmental persistence is incorporated in the classification, resulting in a low CF_{ECO} value and, consequently, a lower prioritization. Similarly, for human health risk, further discrepancies arise with CECs like BPA, DZP, and LAM, all of which are classified as high-risk in QCRA due to their low RfD values, but as limited to no-risk CECs for TyPol.

The primary cause of these differences lies in the distinct methodologies and TOX adopted by each procedure. One key distinction is the concentrations used for risk assessments. QCRA uses $C_{EXP,SW}$ for the environmental risk and $C_{EXP,CROP}$ for the human health risk, focusing on direct human exposure through crop consumption. In contrast, TyPol applies the same concentration ($C_{EXP,SW}$) for both environmental and human health risks, as it evaluates the contaminants based on their presence in SW, the initial environmental compartment. Another important distinction is that in QCRA, PNEC and RfD are derived exclusively from dose-response data in toxicity studies, addressing only the toxicity of CECs. Conversely, in TyPol, CF_{ECO} and CF_{HT} integrate exposure-related factors, such as the fate and transport of CECs in the environment, since these are already considered in the calculation of CFs. As a result, MDs and EPs correlate more closely with CFs, which already account for environmental fate, rather than with specific TOX such as PNEC and RfD (Figure S2). Such wide variations within clusters reveal a limitation of the TyPol approach, where CECs with significantly different risk profiles are grouped together based primarily on their molecular and environmental characteristics, rather than on TOX. In contrast, QCRA provides a more consistent identification of high-risk CECs even within heterogeneous clusters. However, when MDs and EPs align with TOX, as seen with estrogenic compounds and macrolides, both approaches yield similar outcomes.

Although its strengths in prioritizing high-risk CECs, it must be reminded that a limitation of QCRA lies in its reliance on the availability of complete datasets to deliver accurate risk assessments, particularly for exposure concentrations, PNEC and/or RfD [4]. When these parameters are incomplete or unavailable, QCRA ability to perform CECs risk assessment is constrained, resulting in their exclusion from the analysis.

3.5. Missing data influence on risk estimation

While QCRA and TyPol provide valuable frameworks for risk prioritization, they both face challenges when working under data-limited conditions, as well as other prioritization methodologies reported in literature (*inter alia*, [30,32]). However, unlike QCRA, which requires complete toxicological and exposure data, TyPol offers more flexibility when working with incomplete datasets. By clustering CECs based on MDs and EPs, which are often more readily available than TOX and concentrations, it is possible to classify contaminants and use median cluster properties to evaluate risk.

A scenario analysis was performed to evaluate the consistency of CECs ranking under different data availability conditions (i.e., BL, NO-CONC, and NO-CF). BL represents the scenario where complete data are available, including both CEC-specific concentrations and CFs. NO-CONC and NO-CF simulate situations where, respectively, either concentration or CFs for a target CEC are unavailable, and median values from the respective cluster are substituted for the missing parameters.

The results, presented in Fig. 7, show the cluster rankings obtained in each scenario using the same color scale from Fig. 5, differentiating environmental and human health risks. To ensure comparability across scenarios, clustering was performed solely based on MDs and EPs, as the inclusion of TOX was not feasible when CFs were missing in the NO-CF scenario. This methodological choice allowed for a consistent risk evaluation across different data availability conditions. Despite the clusters being composed of the same CECs, the risk distributions for each cluster differ across the three scenarios, indicating that using CEC-specific or cluster-level median values influences the estimated risk of the individual CECs. However, the overall ranking of the CECs clusters remains consistent regardless of whether CEC-specific or cluster-level median values are used. This result is further supported in Figure S8, where the comparison between BL and NO-CONC scenarios, based on clustering that includes also TOX, shows no significant differences in cluster prioritization. These findings indicate that TyPol use of median values allows for effective ranking, even when individual data points are missing. However, it is important to note that the use of median values introduces some uncertainty in the risk estimates, particularly for contaminants with limited toxicological information [32].

The scenario analysis confirmed TyPol robustness in addressing data gaps which is particularly valuable in preliminary risk assessments, when comprehensive datasets are unavailable, especially for contaminants such as CECs. By integrating the strengths of both approaches, TyPol adaptability in data-limited contexts can complement QCRA detailed CEC-specific analysis, enhancing overall CECs prioritization based on both environmental and human health risks.

4. Study limitations and future perspectives

A limitation of this study is that the dataset was restricted to 37 CECs. These compounds were selected first for their regulatory relevance (listed in the most recent EU water quality directives) and second for their documented occurrence in agricultural wastewater reuse monitoring studies. These criteria excluded many high-concern classes of compounds whose distinct properties would challenge our methods, such as per- and polyfluoroalkyl substances (PFAS), whose extreme persistence and bioaccumulation demand specialized fate descriptors and exposure models, or pesticides, which often exhibit very low PNECs and distinct ecotoxicological profiles.

Similarly, all concentration data in this study were derived from indirect agricultural reuse via surface water mixtures applied to fruit and vegetable crops, which is a broadly diffused and established practice throughout Europe. Future work should test this framework under other irrigation pathways, such as direct reuse of treated effluent and managed aquifer recharge followed by groundwater abstraction for irrigation, each of which alters contaminants transport, soil-plant uptake factors and therefore requires recalibration of exposure parameters.

Finally, 14 CECs were omitted for lack of key inputs (MDs, EPs or toxicological thresholds), pinpointing specific data gaps that must be addressed before applying this dual-method approach to the full spectrum of CECs.

5. Conclusions

In this study, QCRA and TyPol, were adopted for the risk-based prioritization of CECs in the context of indirect wastewater reuse in

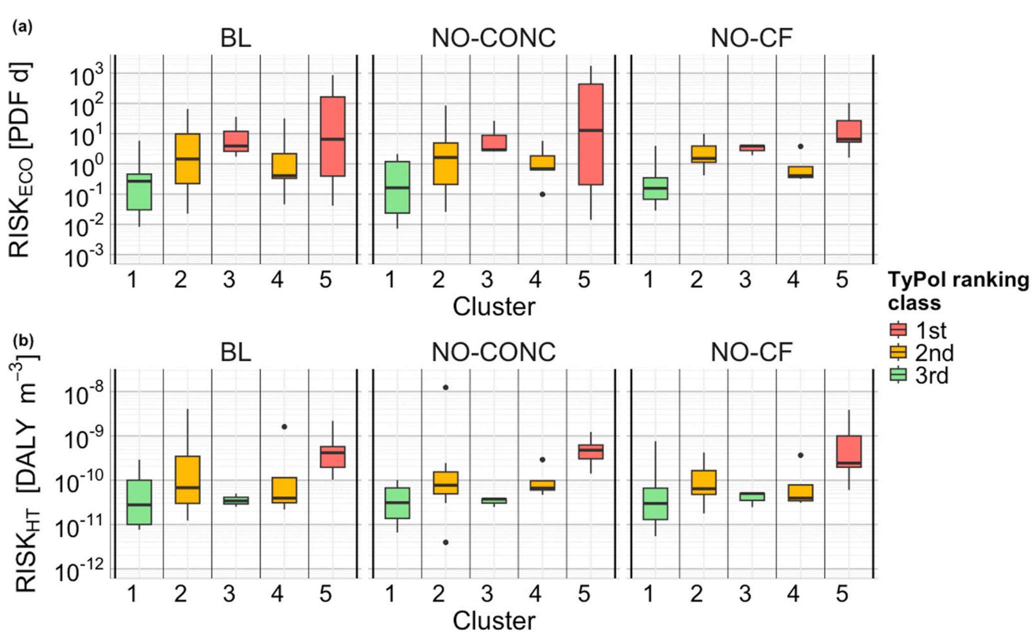

Fig. 7. Boxplots of (a) RISK$_{ECO}$ and (b) RISK$_{HT}$, differentiated by scenario and colored according to TyPol ranking classes.

agriculture procedures, addressing simultaneously environmental and human health risks, under a One Health approach. Both methods consistently pointed out estrogenic compounds (BE2, EE2, and EST) as CECs requiring prioritization due to their high risks. Macrolides (cluster 3), including AZT, ERY, and CLA, should also be prioritized due to their environmental risk, though their human health risk remain low. Conversely, BPA, IBU, and DZP (cluster 2), all of which exhibit significant risks in QCRA, were deprioritized in TyPol, while CAF (cluster 1), identified for closer attention for environmental risk in QCRA, is classified as a limited risk CEC in TyPol. These discrepancies highlight that TOX are underweighted in TyPol clustering compared to MDs and EPs, suggesting that refining the clustering process to prioritize toxicological data would improve the alignment between risk and cluster classifications, thereby enhancing TyPol effectiveness in risk assessment.

The strength of QCRA is its ability to address both environmental and human health risks within a single, integrated One Health framework. However, QCRA relies heavily on detailed toxicological data, which may not always be available or complete, limiting its applicability in data-scarce scenarios. By contrast, TyPol remains consistent in prioritizing CECs even when toxicological or exposure data are missing, as confirmed by the scenario analysis. This robustness makes it valuable in data-limited contexts. However, the reliance on cluster median values introduces uncertainty, especially for CECs with highly variable risk profiles. Expanding toxicological datasets for CECs and validating risk estimates through field monitoring programs are crucial next steps to ensure alignment with real-world exposure scenarios.

Despite these challenges, the integration of both methods offers a promising pathway for the comprehensive prioritization of CECs. QCRA detailed CEC-specific analysis complements TyPol broader cluster-based risk approach, ensuring that both environmental and human health risks are effectively managed. In conclusion, while both QCRA and TyPol provide useful frameworks for prioritizing CECs, their differing reliance on toxicological data versus MDs and EPs leads to distinct outcomes. Ultimately, the choice between the two methods depends on data availability. The results of this study support the potential for integrating both methodologies to improve the prioritization of CECs, especially as more CECs are identified and risk assessments require robust, adaptable tools.

Environmental implications

This study prioritizes CECs in treated wastewater aimed at agricultural reuse based on their environmental and human health risks, following the One Health approach, by using two complementary methodologies, also dealing with missing data about their presence and (eco)toxicology. Together, these methodologies provide a decision support tool (i) for decision-makers, to inform regulatory actions, from monitoring programs to treatment strategies, and (ii) for the scientific community, to identify the most critical data gaps that need to be addressed. Overall, this work supports the implementation of a unified and effective strategy for managing CECs, advancing sustainable agriculture and public health protection.

CRediT authorship contribution statement

Manuela Antonelli: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Beatrice Cantoni:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Alberto Desca:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Data curation. **Luca Penserini:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Rémi Servien:** Writing – review & editing, Validation, Supervision, Software, Methodology, Conceptualization. **Dominique Patureau:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Jérôme Mao:** Software, Resources. **Eric Latrille:** Software, Resources.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Beatrice Cantoni reports financial support was provided by AXA Research Fund. If there are other authors, they 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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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.140865.

Data availability

Data will be made available on request.

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