Science of the Total Environment 900 (2023) 165735

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Quantitative and qualitative approaches for CEC prioritization when reusing reclaimed water for irrigation needs – A critical review

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ARTICLE INFO

Editor: Jay Gan

Keywords:
Contaminants of emerging concern
Irrigation
Prioritization
Qualitative and quantitative approaches
Reclaimed water
Reuse

ABSTRACT

The use of reclaimed water for irrigation is an option that is becoming increasingly widespread to alleviate water scarcity and to cope with drought. However, reclaimed water, if used for irrigation, may introduce Contaminants of Emerging Concern (CECs) into the agroecosystems, which may be taken up by the crops and subsequently enter the food chain. The number of CECs is steadily increasing due to their continuous introduction on the market for different uses. There is an urgent need to draw up a short list of potential high priority CECs, which are substances that could be taken up by plants and accumulated in food produce, and/or that could have negative effects on human health and the environment. This review presents and discusses the approaches developed to prioritize CECs when reclaimed water is (re-)used for irrigation. They are divided into quantitative methodologies, which estimate the risk for environmental compartments (soil and water), predators and humans through equations, and qualitative methodologies, which are instead conceptual frameworks or procedures based on the simultaneous combination of data/information/practices with the judgment of experts. Three antibiotics (erythromycin, sulfamethoxazole and ciprofloxacin), one estrogen (17-α ethinylestradiol) and one analgesic (ibuprofen) were found on at least two priority lists, although comparison among studies is still difficult. The review remarks that it is advisable to harmonize the different methodologies in order to identify the priority CECs to include in monitoring programs in reclaimed water reuse projects and to ensure a high level of protection for humans and the environment.

1. Introduction

Contaminants of emerging concern (CECs) comprise a vast array of pollutants as chemicals or microorganisms that pose a potential, perceived or real risk to the environment and/or human health (UNEP, 2017). The list of CECs may change due to the development of novel analytical techniques, leading to the detection of chemicals or microorganisms that occur at very low concentrations in water, the production of new synthetic industrial compounds and the awareness of the negative impacts of known compounds on the environment and human health. Examples of CECs are pharmaceuticals and personal care products, hormones, metals, perfluorinated compounds or their derivatives, antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARGs) (Jeong et al., 2023; Pastorino and Ginebreda, 2021; Sousa et al., 2018). Some CECs are consumed by humans and, after they have been metabolized, they are excreted in urine and/or feces as unchanged compounds, or their metabolites, and are released into the municipal sewage network. Similarly, industrial effluents with CECs may be discharged into the sewer and conveyed to the municipal wastewater treatment plants (WWTPs). These plants have been designed to remove easily-degradable organic compounds occurring at high concentrations (mg L^{-1}) and not to remove CECs which are mostly found at trace concentrations (ng L^{-1} to μg L^{-1}). Consequently, CECs are reported to be frequently detected in the treated effluent (Sousa et al., 2018; Verlicchi et al., 2012). Only in a few countries, (among them, Switzerland), end-of-pipe treatments (ozonation and sorption onto activated carbon) have been adopted to guarantee the removal of a selection of common CECs found in wastewater (Micropoll strategy https://micropoll.ch/en/faq/swiss-micropollutant-strategy/). In others, such as the Netherlands, Finland, Germany, Sweden, and Denmark studies were carried out to evaluate treatments able to remove a selection of micropollutants from a secondary effluent as well as their investments and operational costs (EurEau, 2019). At EU level, the proposal currently under discussion for a Directive concerning urban wastewater treatment mentions the need

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https://doi.org/10.1016/j.scitotenv.2023.165735
Received 29 May 2023; Received in revised form 18 July 2023; Accepted 21 July 2023

for a quaternary treatment (ozonation and/or filtering with activated carbon or advanced techniques like nano-filtration membranes) to reduce the content of organic micropollutants (EC COM 541 final, 2022; EC SWD 541 final, 2022), which is supported by recent findings (Pistocchi et al., 2022).

With regard to small wastewater treatment plants in rural areas whose final effluent is released in a river characterized by a low dilution factor, nature-based solutions (NBSs) represent alternative and valid polishing options (Venditti et al., 2022) as they are able to remove a wide spectrum of micropollutants (Verlicchi et al., 2013; Verlicchi and Zambello, 2014). NBSs are the subject of many ongoing projects aiming at identifying the optimal operational conditions in removing CECs, including ARB and ARGs (among them HYDROUSA, https://www.hydrousa.org/about-the-project/, and NATURE, https://www.natureproject.eu/).

In the case of appropriate polishing treatments, the final effluent might be adequate for agricultural irrigation. Its reuse could overcome the difficulties caused by (fresh) water scarcity and drought events, which are consequences of climate change. The reuse practice is in agreement with the European Union (EU) Water Framework Directive (EU Directive, 2000/60/EC) and, above all, the recent European minimum requirements for water reuse (EU Regulation, 2020/741). It is aligned with some of the Sustainable Development Goals (SDG 2 and 6) included in the 2030 Agenda for Sustainable Development (United Nations A/RES/70/1, 2015) and the EU communication 'Closing the loop – An EU action plan for the Circular Economy' (EC COM 614 final, 2015).

It is necessary to guarantee the high quality of the reclaimed water as irrigated crops might bioaccumulate residual contaminants, included CECs, in their tissues and contribute to their introduction into the food chain (Christou et al., 2017a; Shi et al., 2022). This is clearly remarked in the One Health Approach which recognizes that human health is directly connected with animals, plants and the environment (Prata, 2022).

Due to the large number of CECs occurring in water, it is not feasible to monitor them all, therefore, a short list would be advisable to identify priority substances that may cause a significant risk to or via the aquatic environment. Some authors have proposed the estimation of the risk quotient (RQ) to evaluate the level of risk regarding specific targets. The RQ is based on the evaluation of the ratio between the maximum environmental concentration (MEC) and the lowest predicted no-effect concentrations (PNEC) (EC and European Chemicals Bureau, 2003), and some authors have also proposed another additional RQ calculated as the 95th percentile of all MEC values (MEC_{95}) (Slobodnik et al., 2012; Tousova et al., 2017; von der Ohe et al., 2011).

Within this framework, the current paper presents and discusses the available approaches for the prioritization of CECs in reclaimed water that is reused for irrigation (other water reuse has been excluded). A systematic review is developed regarding the (few) quantitative and qualitative methodologies found in the literature. It finally remarks on the main areas where there is a lack of knowledge and where future research efforts should be made. This will help collect any missing data to confirm currently-identified CECs or add new ones. It will also be useful to harmonize the methodologies by combining the different issues addressed in the overviewed approaches. Monitoring programs including CECs when reclaimed water is reused will ensure a higher level of protection not only for the environment, but also for animals and human health.

2. Framework of the review

Data collection was focused on existing methodologies that describe how to define a priority list of CECs in reclaimed water in the context of its reuse for irrigation. A literature search of papers published in international journals was developed using the publication database Scopus (www.scopus.com), without setting any limitations regarding time interval since this topic has been covered only recently. In fact, most of the past proposals of prioritization referred to cases of groundwater recharge or the safeguarding of surface water bodies, when treated effluents are released (among them Guo et al. (2021) and Köck-Schulmeyer et al. (2021)). The combinations of the applied keywords were: "reclaimed water reuse irrigation" AND ("CEC" OR "micropollutants" OR "contaminants of emerging concern"); and "reclaimed water prioritization" AND "contaminants of emerging concern". Among the almost 100 studies found, only 6 focus on the proposal to develop methodologies for building a priority list of CECs in reclaimed water used for irrigation in agriculture (Delli Compagni et al., 2020; Fu et al., 2019; Muñoz et al., 2009; Revitt et al., 2021; Verlicchi et al., 2023) or in urban green spaces (Lyu et al., 2019). If the methodologies are equation-based procedures, they are defined quantitative; if they present a conceptual framework and/or consist of score-based procedures they are considered qualitative. In overviewing the quantitative methodologies (Section 3), the current study first presents the variables characterizing each CEC, each methodology is based on, and the equations adopted for their estimation (Section 3.1). It then presents how they measure the CEC risk that is the effect of the CEC on the environment (soil and/or water) and/or on the organisms (terrestrial predators and/or humans (Section 3.2) and how they select the priority CECs (Section 3.3). Each methodology develops starting from a group of CECs preselected with reference to some relevant case studies (Table 1). On the basis of specific criteria, it ranks the preselected CECs (in descending order) and defines the thresholds to identify the priority ones. The final lists obtained by the different methodologies are then compared in order to identify the common CECs.

Section 4 presents and discusses the qualitative approaches and in particular it highlights the rationale behind their development and outlines the main steps leading to the selection of the priority CECs.

A final analysis is carried out on the main strengths and weaknesses of all the overviewed methodologies (Section 5) in order to highlight the main fields requiring further research efforts (Section 6).

3. Quantitative methodologies

Three quantitative methodologies have been proposed to prioritize the CECs to monitor in projects of the reuse of reclaimed water for irrigation: Muñoz et al. (2009), Lyu et al. (2019) and Delli Compagni et al. (2020). In the following, they are divided into two steps: the first concerns the selection of the variables characterizing each CEC and the equations for its estimation; the second consists of the development of a procedure or an aggregation function accounting for the selected variables aiming at measuring the effect of the CEC on the environment (soil and/or water ecosystems) and on the organisms (terrestrial predators and/or humans), representing the CEC risk. The lists of priority CECs found in the three cases include substances with the highest risk, or those of great concern with reference to one or more of the selected variables.

3.1. Variables and equations for their estimation

The variables which characterize each approach are summarized in Fig. 1 and their description and analysis are provided in the following subsections, including the auxiliary equations and correlations useful for their estimation.

3.1.1. Muñoz et al., 2009

Specifically, Muñoz et al. (2009) proposed a methodology to prioritize CECs in the case of a direct reuse in agriculture. It considers the effects reclaimed water exposure has on soil organisms as well as the poisoning of terrestrial predators which consume the irrigated crop. Their methodology is based on the Technical Guidance Document on Risk Assessment at a local level (EC and European Chemicals Bureau, 2003). It starts with the estimation of the CEC concentration in the soil due to the application of treated wastewater (TWW) by means of Eq. (1):

Table 1
Preselected CECs in the WWTP effluents in the different case studies.

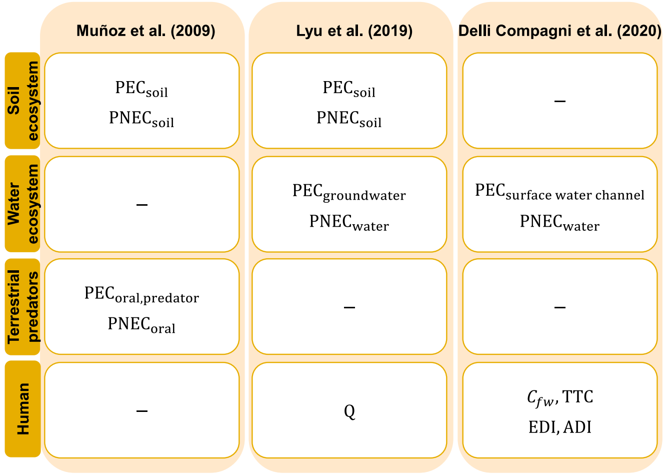
		 Case A: Alcalá de Henares (Spain)	 Case B: El Ejido (Spain)	 Beijing (China)	 Milan (Italy)
		Muñoz et al., 2009	Muñoz et al., 2009	Lyu et al., 2019	Castiglioni et al., 2018a, 2018b
CECs	Class	Mean concentrations, ng L^{-1}			
17α-Estradiol	Hormone	–	–	18.25	–
17α-Ethinylestradiol	Hormone	–	–	38.53	–
17α-Hydroxyprogesterone	Hormone	–	–	0.07	–
17β-Estradiol	Hormone	–	–	10.22	–
19-nor-4-Androstene-3,17-diol	Hormone	–	–	0.09	–
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (2,3,7,8-TCDD)	Dioxin	0.55	0.5	–	–
21 α-Hydroxyprogesterone	Hormone	–	–	0.73	–
4-n-nonylphenol	Surfactant	–	–	150.56	–
4-tert-Octylphenol	Surfactant	–	–	51.3	–
6α-Methyl-hydroxyprogesterone	Hormone	–	–	0.93	–
Androstenedione	Hormone	–	–	7.59	–
Androsterone	Hormone	–	–	0.61	–
Atenolol	Beta-blocker	4800	15,000	–	–
Benzophenone-3	UV-filter	84	79	–	–
Benzyl butyl phthalate	Plasticizer	–	–	390	–
Bezafibrate	Lipid regulator	–	–	15.27	–
Bis(2-ethylhexyl) Phthalate	Plasticizer	–	–	2490.65	–
Bisphenol A	Plasticizer	–	–	34.01	–
Caffeine	Stimulant	880	5500	160.65	–
Carbamazepine	Psychiatric drug	110	260	139.85	245
Cd	Heavy metal	22	140	–	–
Chloramphenicol	Antibiotic	–	–	12.3	–
Ciprofloxacin	Antibiotic	2000	710	17.64	–
Citalopram	Psychiatric drug	–	–	3.67	–
Clarithromycin	Antibiotic	–	–	–	465
Clofibric acid (clofibrate metabolite)	Lipid regulator	–	–	59.71	–
Clozapine	Psychiatric drug	–	–	20.67	–
Cortisol	Hormone	–	–	0.73	–
Cortisone	Hormone	–	–	0.26	–
Dexamethasone	Anti-inflammatory	–	–	0.01	–
Dibutyl phthalate	Plasticizer	–	–	6559.73	–
Diclofenac	Anti-inflammatory	360	1700	227.86	469
Diethyl phthalate	Plasticizer	–	–	606.44	–
Difloxacin	Antibiotic	–	–	0.2	–
Dimethyl phthalate	Plasticizer	–	–	833.58	–
Dioctyl phthalate	Plasticizer	–	–	788.89	–
Diuron	Pesticide	43	450	–	–
Enrofloxacin	Antibiotic	–	–	0.55	–
Erythromycin	Antibiotic	890	570	268.48	–
Estriol	Hormone	–	–	13.47	–
Estrone	Hormone	–	–	26.88	5.6
Fenofibric acid (fenofibrate metabolite)	Lipid regulator	4700	17,000	–	–
Fleroxacin	Antibiotic	–	–	8.86	–
Fluoxetine	Psychiatric drug	270	77	–	–
Furosemide	Diuretic	–	–	–	554
Galaxolide	Synthetic musk	1800	8300	827	–
Gemfibrozil	Lipid regulator	1000	6800	65.3	–
Hexachlorobenzene	Pesticide	140	10	–	–
Hg	Heavy metal	390	n.d.	–	–
Hydrochlorothiazide	Diuretic	1800	3000	–	–
Ibuprofen	Anti-inflammatory	540	4700	–	59.8
Indomethacine	Anti-inflammatory	–	–	49.4	–
Josamycin	Antibiotic	–	–	0.81	–
Ketoprofen	Anti-inflammatory	–	–	76.83	–
Lindane	Pesticide	2.1	8.3	–	–
Lomefloxacin	Antibiotic	–	–	25.11	–
Medroxyprogesterone acetate	Hormone	–	–	0.33	–
Mefenamic acid	Anti-inflammatory	–	–	23.95	–
Megestrol acetate	Hormone	–	–	0.19	–
Metoprolol	Beta-blocker	–	–	149.43	–
N,N-diethyl-meta-toluamide (DEET)	Pesticide	–	–	422.12	–
N-acetyl-4-amino-antipyrine (4-AAA) (dipyrone metabolite)	Anti-inflammatory	4200	12,000	–	–
Nalidixic acid	Antibiotic	–	–	65	–

(*continued on next page*)

Table 1 (*continued*)

		 Case A: Alcalá de Henares (Spain)	 Case B: El Ejido (Spain)	 Beijing (China)	 Milan (Italy)
		Muñoz et al., 2009	Muñoz et al., 2009	Lyu et al., 2019	Castiglioni et al., 2018a, 2018b
CECs	Class	Mean concentrations, ng L^{-1}			
Ni	Heavy Metal	21,000	270	–	–
Norfloxacin	Antibiotic	–	–	87.12	–
Ofloxacin	Antibiotic	–	–	568.9	–
Paracetamol	Anti-inflammatory	–	–	–	22.6
Pb	Heavy metal	390	1700	–	–
Pentabromodiphenyl ether	Polybromodiphenyl ether	0.25	n.d.	–	–
Perfluorooctane sulfonate	PFOS	–	–	–	6.9
Perfluorooctanoic acid	PFOA	–	–	–	12.2
Prednisolone	Hormone	–	–	0.48	–
Prednisone	Hormone	–	–	0.01	–
Progesterone	Hormone	–	–	1.4	–
Propranolol	Beta-blocker	–	–	4.85	–
Roxithromycin	Antibiotic	–	–	149.78	–
Spiramycin	Antibiotic	–	–	5.47	–
Sulfadiazine	Antibiotic	–	–	227.53	–
Sulfamerazine	Antibiotic	–	–	18.37	–
Sulfamethazine	Antibiotic	–	–	4.96	–
Sulfamethoxazole	Antibiotic	180	550	719.49	74.7
Sulfapyridine	Antibiotic	–	–	202.31	–
Sulpiride	Psychiatric drug	–	–	107.13	–
Testosterone	Hormone	–	–	0.79	–
Tetrabromodiphenyl ether	Polybromodiphenyl ether	1.2	0.2	–	–
Tonalid	Synthetic musk	290	900	109.17	–
Triclosan	Antiseptic	340	310	–	240
Trihexyphenidyl	Anti-Parkinson drug	–	–	0.27	–
Trimethoprim	Antibiotic	–	–	313.31	–
Tylosin tartrate	Antibiotic	–	–	1.11	–
Number of selected CECs		27	27	67	13

"–" = CEC not included in the selection of the case study; n.d. = not detected.



	Muñoz et al. (2009)	Lyu et al. (2019)	Delli Compagni et al. (2020)
Soil ecosystem	PEC_{soil} $PNEC_{soil}$	PEC_{soil} $PNEC_{soil}$	–
Water ecosystem	–	$PEC_{groundwater}$ $PNEC_{water}$	$PEC_{surface\ water\ channel}$ $PNEC_{water}$
Terrestrial predators	$PEC_{oral,predator}$ $PNEC_{oral}$	–	–
Human	–	Q	C_{fw}, TTC EDI, ADI

Fig. 1. Overview of the variables selected for the different compartments (water and soil) and targets (humans and terrestrial animals) in the quantitative methodologies under review for the prioritization of CECs when reclaimed water is reused for irrigation (Muñoz et al., 2009; Lyu et al., 2019; Delli Compagni et al., 2020). Legend: PEC = Predicted Environmental Concentration; PNEC = Predicted No-Effect Concentration; Q = total emission in air; C_{fw} = concentration in the edible part of the crop; TTC = Threshold of Toxicological Concern; EDI = Estimated Daily Intake; ADI = Admissible Daily Intake.

$$PEC_{soil} = \frac{D_{irr}}{k} - \frac{D_{irr}}{k} \bullet e^{-365 \bullet m \bullet k} \tag{1}$$

where PEC_{soil} is the predicted CEC concentration in the soil at the beginning of year m (mg kg_{wwt}^{-1} with the pedex wwt meaning wet weight), assuming a null initial concentration of the CEC and continuous irrigation; D_{irr} the TWW daily flux to the soil through irrigation (mg kg_{wwt}^{-1} d^{-1}), estimated by Eq. (2); and k the CEC-specific first-order rate constant for removal from topsoil (d^{-1}), calculated according to Eq. (3).

$$D_{irr} = \frac{C_{TWW} \bullet APPL_{water}}{DEPTH_{soil} \bullet RHO_{soil}} \tag{2}$$

In Eq. (2), C_{TWW} is the concentration of the CEC in the TWW (mg L^{-1}); $APPL_{water}$ the wastewater irrigation rate (L m^{-2} d^{-1}); $DEPTH_{soil}$ the mixing depth of soil (m); and RHO_{soil} the bulk density of (wet) soil (1700 kg_{wwt} m^{-3}).

$$k = k_{volat} + k_{leach} + k_{bio_{soil}} \tag{3}$$

According to Eq. (3), the CEC removal rate constant k depends on three main processes: volatilization, leaching and soil biodegradation, respectively estimated by the CEC pseudo-first order rate constant for volatilization k_{volat} (d^{-1}) (Eq. (4)), for leaching to deeper soil layers k_{leach} (d^{-1}) (Eq. (5)), and for biodegradation in soil $k_{bio\ soil}$ (d^{-1}). This last term is a function of the CEC half-life in soil ($t_{1/2,soil}$) found in online databases, such as the Hazardous Substances Data Bank (HSDB) integrated into PubChem (https://pubchem.ncbi.nlm.nih.gov/) and the FOOTPRINT pesticide-properties database (http://sitem.herts.ac.uk/aeru/ppdb/en/), or in the literature, or is estimated using the

Estimation Programs Interface Suite (EPI Suite) developed by EPA's and Syracuse Research Corp (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface).

$$\frac{1}{k_{volat}} = \left(\frac{1}{kasl_{air} \bullet K_{air-water}} + \frac{1}{kasl_{soil-air} \bullet K_{air-water} + kasl_{soil-water}}\right) \bullet K_{soil-water} \bullet DEPTH_{soil} \tag{4}$$

$$k_{leach} = \frac{Finf_{soil} \bullet RAIN_{rate}}{K_{soil-water} \bullet DEPTH_{soil}} \tag{5}$$

In Eqs. (4) and (5), $kasl_{air}$ is the partial mass transfer coefficient at the air-side of the air-soil interface (120 m d^{-1}); $kasl_{soil\text{-}air}$ the partial mass transfer coefficient at soil air-side of the air-soil interface (0.48 m d^{-1}); $kasl_{soil\text{-}water}$ the partial mass transfer coefficient at soil water-side of the air-soil interface (4.8×10^{-5} m d^{-1}); $K_{air\text{-}water}$ the air-water equilibrium distribution constant ($m^3\ m^{-3}$) expressed by Henry's Law (Eq. (6)); $K_{soil\text{-}water}$ the soil-water partition coefficient ($m^3\ m^{-3}$) derived from Eq. (7); $Finf_{soil}$ the fraction of rainwater that infiltrates into soil; and $RAIN_{rate}$ (m d^{-1}) the precipitation rate, assumed equal to 700 mm $year^{-1}$.

$$K_{air-water} = \frac{H}{R \bullet T} \tag{6}$$

where H is Henry's law constant (Pa $m^3\ mol^{-1}$); R the universal gas constant (8.314 Pa $m^3\ mol^{-1}\ K^{-1}$) and T the temperature at the air-water interface (285 K).

$$K_{soil-water} = Fair_{soil} \bullet K_{air-water} + Fwater_{soil} + Fsolid_{soil} \bullet \frac{K_{d,soil}}{1000} \bullet RHO_{solid} \tag{7}$$

where $Fair_{soil}$ is the air fraction in soil (0.2 $m^3\ m^{-3}$); $Fwater_{soil}$ the water fraction in soil (0.2 $m^3\ m^{-3}$); $Fsolid_{soil}$ the solids fraction in soil (0.6 $m^3\ m^{-3}$); RHO_{solid} the density of solid phase (2500 kg m^{-3}); and $K_{d,soil}$ the solid-water partition coefficient for soil (L kg^{-1}) which can be obtained by Eq. (8).

$$K_{d,soil} = K_{oc} \bullet f_{oc,soil} \tag{8}$$

where K_{oc} is the organic carbon-water partition coefficient of CEC (L kg^{-1}) evaluated by means of the EPI Suite or by experimental investigations and $f_{oc,soil}$ the fraction of organic carbon in soil (0.02 kg kg^{-1}).

The proposed method then evaluates for each CEC the concentration in soil organisms (the earthworms, representing the predators' food) by means of Eq. (9):

$$PEC_{oral,predator} = \frac{BCF_{earthworm} \bullet C_{porewater} + PEC_{soil} \bullet F_{gut} \bullet CONV_{soil}}{1 + F_{gut} \bullet CONV_{soil}} \tag{9}$$

where $PEC_{oral,predator}$ is the CEC concentration in the earthworms' tissue and the CEC concentration on the soil present in the earthworms' gut (mg kg_{wwt}^{-1}); $BCF_{earthworm}$ the bioconcentration factor for the earthworms' tissue on a wet weight basis estimated by Eq. (10), (Jager, 1998) (L kg_{wwt}^{-1}); $C_{porewater}$ the CEC concentration in soil pore-water calculated by Eq. (11) (mg L^{-1}); F_{gut} the fraction of gut loading in earthworms (0.1 $kg_{dwt}\ kg_{wwt}^{-1}$ with the pedex dwt meaning dry weight); and $CONV_{soil}$ a conversion factor for soil concentration wet-dry weight soil ($kg_{wwt}\ kg_{dwt}^{-1}$) defined by Eq. (12).

$$BCF_{earthworm} = \frac{0.84 + 0.012 \bullet K_{ow}}{RHO_{earthworm}} \tag{10}$$

where K_{ow} is the CEC octanol-water partition coefficient and $RHO_{earthworm}$ the earthworm density (1 $kg_{wwt}\ L^{-1}$).

$$C_{porewater} = \frac{PEC_{soil} \bullet RHO_{soil}}{K_{soil-water} \bullet 1000} \tag{11}$$

$$CONV_{soil} = \frac{RHO_{soil}}{Fsolid_{soil} \bullet RHO_{soild}} \tag{12}$$

According to Muñoz et al. (2009), if toxicity data (EC50, LC50 or NOEC) are available for soil organisms (a producer, a consumer and/or a decomposer), $PNEC_{soil}$ (mg kg^{-1}) is evaluated according to Eq. (13) and results from the experimental value TOX_{soil} divided by an assessment factor (AF_{soil}), which is defined according to Table S1.

$$PNEC_{soil} = \frac{TOX_{soil}}{AF_{soil}} \tag{13}$$

Otherwise, if toxicity data are not available, $PNEC_{soil}$ is calculated from $PNEC_{water}$, using the equilibrium partitioning method according to the EC and European Chemicals Bureau (2003) (Eq. (14)):

$$PNEC_{soil} = \frac{K_{soil-water}}{RHO_{soil}} \bullet PNEC_{water} \bullet 1000 \tag{14}$$

$PNEC_{water}$ (mg L^{-1}) is derived from the literature or, according to the EC and European Chemicals Bureau (2003), is the result of aquatic toxicity data (L(*E*)C50 or NOEC) divided by the same AF used for the soil compartment (Table S1). The toxicity data for fish, daphnia, and algae are found in the literature or are estimated using the ECOSAR model (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model).

$PNEC_{oral}$ (kg kg_{food}^{-1}) derives from toxicity studies referring to the dietary and oral exposure of higher members of the food chain which ingest organisms from lower trophic levels containing accumulated CEC in their tissues (secondary poisoning). It is evaluated by Eq. (15), where TOX_{oral} (kg kg_{food}^{-1}) is the available toxicity data for birds ($LC50_{bird}$, $NOEC_{bird}$) or mammals ($NOEC_{mammal,food,chr}$) and AF_{oral} is reported in Table S2. Results from long-term studies are preferred to predict the secondary poisoning effects on bird and mammal populations, using NOECs for mortality, reproduction, or growth.

$$PNEC_{oral} = \frac{TOX_{oral}}{AF_{oral}} \tag{15}$$

3.1.2. Lyu et al., 2019

Lyu et al. (2019) developed a methodology which is based on the effects of the reuse of reclaimed water on soil and groundwater organisms, as well as humans due to the aerosolization of CECs into the air during sprinkler irrigation. Their proposal refers to the irrigation of urban green spaces, but it could also be extended to the agriculture irrigation. The HYDRUS-1D model (Šimůnek et al., 2016) was used to evaluate CEC concentrations in soil (PEC_{soil}) and groundwater ($PEC_{groundwater}$), and the period of simulation was set to 10 years to guarantee stationary conditions in the solute transport in soil. The parameters required by the model are initial and boundary conditions (10–15 mm h^{-1} of irrigation rates), soil hydraulic properties (bulk density and saturated hydraulic conductivity), solute transport parameters (half-life $t_{1/2}$, Henry's law constant H, organic carbon-water distribution coefficients K_{oc}), and root distribution (depending on the turf grasses development). Additionally, the total amount of CECs emitted into the air (Q, µg) over 10 years (3650 days) of irrigation with reclaimed water is estimated by Eq. (16).

$$Q = Q_1 + Q_2 \tag{16}$$

where Q_1 (µg) is the emission of each CEC into the air by aerosolization of reclaimed water due to sprinkler irrigation (Eq. (17)) and Q_2 (µg) the emission of CECs by volatilization.

$$Q_1 = \sum_{n=1}^{3650} Q_{A,n} = \sum_{n=1}^{3650} C_{TWW,n} \bullet q_n \bullet A_n \tag{17}$$

where $Q_{A,n}$ is the amount of CEC emitted into the air by reclaimed water aerosolization on the *n*-th day (µg d^{-1}); $C_{TWW,n}$ the CEC concentration in treated wastewater (reclaimed water) on the n-th day (μg L^{-1}); q_i the sprinkling flow rate on the n-th day (L d^{-1}); A_n the atomization efficiency factor of reclaimed water on the n-th day given by Eq. (18); and n the days in the 10 years of observation.

$$log_{10}A_n = 0.031 \bullet T_n + 0.000096 \bullet u_n \bullet W_n - 3.1 \tag{18}$$

where T_n is the temperature on the n-th day (°C); u_n the wind speed on the n-th day (m s^{-1}); and W_n the light intensity on the n-th day (W m^{-2}).

The model was validated by means of measured CEC concentrations; a statistical analysis showed that the predictions of the models could be accepted.

To estimate the PNEC in soil for CECs (μg kg^{-1}), the methodology by Lyu et al. (2019) followed the equilibrium partition method (Eq. (14)) considering only the solid fraction (Eq. (19)).

$$\text{PNEC}_{soil} = K_{d,soil} \bullet \text{PNEC}_{water} \tag{19}$$

$K_{\text{d,soil}}$ (L kg^{-1}) is obtained by Eq. (8) where K_{oc} is evaluated by the EPI Suite and $f_{\text{oc,soil}}$ is assumed equal to 0.713 %, 0.568 %, 0.478 %, and 0.278 % for the 0–20, 20–40, 40–60, and 60–300 cm layers of the soil profile, respectively, according to Wang et al. (2013).

$\text{PNEC}_{\text{water}}$ (μg L^{-1}) is calculated, according to the European Medicines Agency guideline (EMEA, 2006), by an assessment factor equal to 1000 applied to the lowest L(*E*)C50 (for fish, daphnia and algae) found in the literature or estimate by the ECOSAR model.

3.1.3. *Delli Compagni et al., 2020*

Delli Compagni et al. (2020) proposed a methodology consisting of a model able to evaluate the environmental and human health risks of reclaimed water directly reused for the irrigation of different crops and to rank the CECs. The model considers that the TWW is released into a dedicated open channel which conveys it to the crops for irrigation. The channel only contains the TWW and is modelled by means of the IUWS_MP library (Vezzaro et al., 2014) as a sequence of segments each corresponding to a continuous stirred reactor tank consisting of two compartments (bulk water and sediments) where CECs are subjected to biotic and abiotic processes as well as sorption to particles and colloids.

The CEC behavior in soil and plants is simulated by a coupled soil-plant model (CSPM) which includes a first model that simulates the movement of the water and the dissolved CECs through the soil and a four-compartment model which simulates CEC uptake and translocation through xylem and phloem flows in plant tissues (roots, stem, leaves and fruits) (Trapp, 2004, 2009; Trapp and Horobin, 2005).

The methodology proposed by Delli Compagni et al. (2020) takes into consideration: the sorption of ionized monovalent acidic and basic CECs, variable environmental conditions (namely sunlight intensity, air temperature, wind speed, pH and temperature in the water and soil), a dynamic pattern of irrigation mode (i.e. the flow rate for irrigating the crops varies over the day) and crop rotation in the same field within the same year.

Long-term simulations (> 1 year) were performed to obtain: the PEC of CECs at the end of the surface water channel ($\text{PEC}_{\text{surface water channel}}$, ng L^{-1}), the PEC of CECs in each of the different parts of the plant (roots, stem, leaves and fruits, μg kg_{dwt}^{-1}) leading to the corresponding bioconcentration factor related to the different crops BCF_{crop} (g_{dwt} g_{dwt}^{-1}) and the CEC mass leached into the groundwater (mg m^{-2} $season^{-1}$). The proposal by Delli Compagni et al. (2020) also includes a Monte-Carlo based uncertainty analysis to study the uncertainty propagation on the predicted concentration of each CEC in the surface water channel, and on the CSPM model predictions. High uncertainties were shown for weakly acidic CECs, possibly due to degradation in soil and the pH variations inside the plants.

Regarding the ecotoxicological parameters, the $\text{PNEC}_{\text{water}}$ (ng L^{-1}) for each CEC was obtained from literature data. With regard to human health associated with the dietary intake of crops irrigated with reclaimed water, two different approaches were followed. The first is based on the CEC concentration in the fresh weight of the edible part C_{fw} and on the threshold of toxicological concern (TTC); the second is based on the estimated daily intake (EDI) and the admissible daily intake (ADI).

C_{fw} (μg kg_{dwt}^{-1}) is an output of the CSPM model; TTC (μg kg_{bw}^{-1} d^{-1}) is defined as the level of daily oral exposure to a chemical over a lifetime considered to be of no appreciable risk to human health (American Chemistry Council, 2020). In the absence of chemical-specific toxicity data, and a low chemical concentration, a TTC value can be used as a surrogate to carry on risk evaluations and risk-based decision making. For these reasons, TTC may be adopted when edible crops are irrigated with reclaimed water containing low concentrations of CECs that have not been widely investigated. The TTC values and compound classification were determined using the Cramer classes decision tree implemented in Toxtree software (Patlewicz et al., 2008). In this way, compounds are classified as having genotoxic potential, or as one of the three structural classes (I, II, and III) reported in Table S3.

Regarding the second approach, ADI (μg kg_{bw}^{-1} d^{-1}) is evaluated by means of Eq. (20).

$$\text{ADI} = \frac{NOAEL}{SF} \tag{20}$$

where NOAEL (μg kg_{bw}^{-1} d^{-1}) is the highest CEC concentration at which no adverse effect occurs (called no adverse effect level) and SF is a safety factor considering different contributions: (i) interspecies differences; (ii) intra-species differences, (iii) severity of the adverse effect and (iv) quantity and quality of the scientific data. It may vary in the range 10–10,000. Quite often the value of 100 is used by regulatory bodies, resulting from the following assumptions: 10 accounts for uncertainties in inter-species extrapolation, 10 for uncertainties in intraspecies variability, and 1 for the consistent quantity and good quality of available data. The resulting SF is given by their product ($\text{SF} = 10 \times 10 \times 1$). Guidelines for the selection of the SF can be found in enHealth (2012).

In the case of pharmaceuticals with no NOAEL available, ADI is assessed assuming the lowest pharmaceutical daily dose divided by body weight (70 kg) and an appropriate SF (equal to 1000 according to Prosser and Sibley (2015) and Christou et al. (2017b)). Delli Compagni et al. (2020) assume the ADI values proposed by Prosser and Sibley (2015), Malchi et al. (2015), EFSA (2008), Environment Protection and Heritage Council of Australia (2008) and EMEA (1999).

The EDI values (μg kg_{bw}^{-1} d^{-1}) are assessed by means of Eq. (21) proposed by Prosser and Sibley (2015):

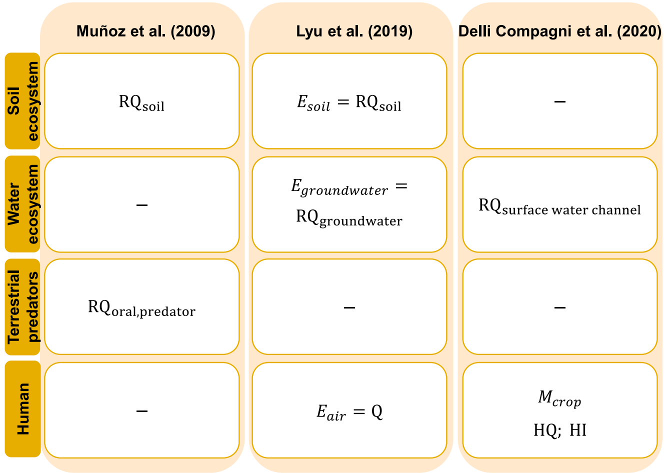
$$\text{EDI} = \frac{C_{fw} \bullet DIR_{person}}{BW_{person}} \tag{21}$$

where BW_{person} is the body weight, equal to 70 kg for an adult, 12 kg for a toddler and 5 kg for an infant (EFSA, 2012), and DIR_{person} (g_{dwt} d^{-1}) the crop daily intake rate per person (variable for infant, toddler and adult and provided by the national data base, such as National Cancer Institute (2014)).

3.2. *Risk assessment for the environment, human health and other organisms*

The priority lists of CECs were defined on the basis of specific target criteria which may refer to soil and (surface and ground) water, terrestrial predators or human (health), and which vary in the different methodologies. Fig. 2 summarizes the different approaches and reports the different target criteria. It emerges that for ecosystem j (soil or water), RQ is the common approach and is calculated for each CEC i according to Eq. (22) as the ratio between its PEC and the corresponding PNEC in the specific ecosystem j.

$$\text{RQ}_{i,j} = \frac{\text{PEC}_{i,j}}{\text{PNEC}_{i,j}} \tag{22}$$



	Muñoz et al. (2009)	Lyu et al. (2019)	Delli Compagni et al. (2020)
Soil ecosystem	$\mathrm{RQ}_{\mathrm{soil}}$	$E_{soil} = \mathrm{RQ}_{\mathrm{soil}}$	–
Water ecosystem	–	$E_{groundwater} = \mathrm{RQ}_{\mathrm{groundwater}}$	$\mathrm{RQ}_{\text{surface water channel}}$
Terrestrial predators	$\mathrm{RQ}_{\mathrm{oral,predator}}$	–	–
Human	–	$E_{air} = \mathrm{Q}$	M_{crop} HQ; HI

Fig. 2. Overview of the criteria assumed in the different methodologies for CEC prioritization in reclaimed water used for irrigation (Muñoz et al., 2009; Lyu et al., 2019; Delli Compagni et al., 2020). Legend: RQ = Risk Quotient; E = effect value; Q = total emission in air; M_{crop} = maximum admittable daily amount of edible crop; HQ = Hazard Quotient; HI = Hazard Index.

Regarding the risk for human health or other organisms, the methodologies propose different approaches that are discussed below.

3.2.1. *Muñoz et al., 2009*

Specifically, Muñoz et al. (2009) evaluate RQ in soil and in predators' food to assess the effects of CEC exposure to soil organisms and, in particular, to earthworms when reusing reclaimed water for irrigation. The risk characterization ratio for the soil compartment is $\mathrm{PEC_{soil}/PNEC_{soil}}$, whereas that for the predators' food is $\mathrm{PEC_{oral,predator}/PNEC_{oral}}$. All of these variables have already been discussed.

3.2.2. *Lyu et al., 2019*

Lyu et al. (2019) evaluate the environmental risk of each CEC for the different compartments $j = 1,2,3$ (1 = soil, 2 = groundwater, 3 = air) according to the related *effect values* E_j calculated on the basis of CEC concentration and toxicity, or CEC total emission. In particular, E_{soil} corresponds to the RQ in the soil (= $\mathrm{PEC_{soil}/PNEC_{soil}}$), $E_{\mathrm{groundwater}}$ to the RQ in groundwater (= $\mathrm{PEC_{groundwater}/PNEC_{water}}$). Finally, E_{air}, representing human risk, was set equal to the total CEC emission (Q), defined by Eq. (16). Following the procedure outlined by Li et al. (2019), Lyu et al. (2019) assign a score to each of the three effect values by means of a utility function S. With regard to the CEC i and the compartment j, the score $S_{\mathrm{i,j}}$ is equal to 0 if the $E_{\mathrm{i,j}}$ is <1, otherwise $S_{i,j}$ is defined by Eq. (23):

$$S_{i,j} = \frac{logE_{i,j} - min\left(logE_{i,j}\right)}{max\left(logE_{i,j}\right) - min\left(logE_{i,j}\right)} \tag{23}$$

where E_{ij} is the effect value for CEC i in the compartment j regarding the whole model prediction period. The minimum and maximum of log E_{ij} refer to the data set collection of effect values based on the PEC values provided by the HYDRUS-1D model applied for the selected period of 10 years (as reported in Section 3.1). Finally, Lyu et al. (2019) aggregate the three scores for each CEC i into an overall score ($S_{\mathrm{i,overall}}$) according to Eq. (24):

$$S_{i,overall} = \sum_{j=1}^{3} S_{i,j} \bullet W_{i,j} \tag{24}$$

where $W_{\mathrm{i,j}}$ is the weight for the score $S_{\mathrm{i,j}}$ referring to CEC i and compartment j which was assumed equal to 1/3 for the three compartments as in Li et al. (2019).

3.2.3. *Delli Compagni et al., 2020*

Delli Compagni et al. (2020) propose the ratio $\mathrm{PEC_{surface\ water\ channel}/PNEC_{water}}$ to evaluate RQ in surface water for each CEC and two different approaches to assess the human health risk associated with dietary intake. The first approach was based on TTC defined for each CEC making it possible to evaluate the corresponding maximum admittable daily amount of edible crop M_{crop} (Eq. (25)), expressed in kg d^{-1}, an individual can ingest in their lifetime without having adverse effect due to that CEC.

$$M_{crop} = \frac{\mathrm{TTC} \bullet BW_{person}}{C_{fw}} \tag{25}$$

For each CEC, the M_{crop} value has to be compared with the typical daily consumption of the crop by individuals of different ages (thus weight) to find out if the amount usually consumed is greater or less than the maximum admittable quantity.

The second approach is based on the hazard quotient (HQ) that is the ratio between the amount of CEC ingested daily and the daily amount a person can ingest in their lifetime without causing an adverse health effect (Eq. (26)):

$$\mathrm{HQ} = \frac{\mathrm{EDI}}{\mathrm{ADI}} \tag{26}$$

The proposal also attempts to evaluate the risk of the cocktail of CECs, contained in the different crops daily ingested, by means of the hazard index (HI) defined by Eq. (27):

$$\mathrm{HI} = \sum\nolimits_{q=1}^{r} \sum_{i=1}^{p} \mathrm{HQ}_{i,q} \tag{27}$$

where p is the number of CECs in the cocktail and r is the number of crops daily ingested and q is the crop type.

This equation is a simplification of the model described in Evans et al. (2015) which is based on international estimated daily intakes (IEDIs) calculated on weight per person. IEDIs are defined in the Global Environment Monitoring System-Food contamination and assessment programme (GEMS/Food Database https://extranet.who.int/gemsfood/?DisplayFormat=1) for 13 cluster diets which are sets of countries grouped together on the basis of similar food consumption patterns.

Delli Compagni et al. (2020) assess the human risks by the two different approaches assuming for the C_{fw} for each CEC the median concentration and the 97.5th percentile in the studied crops (rice and wheat).

3.3. *Lists of priority CECs according to the different methodologies*

The methodologies described above were applied to prioritize CECs in TWW starting from a preselection of CECs which varied from case to case. Preselected compounds and their mean concentrations are reported in Table 1. Regarding Muñoz et al. (2009) two municipal WWTPs were considered: one located in Alcalá de Henares, central Spain, and the other in El Ejido, south-eastern Spain, (both based on activated sludge process). The 27 CECs were selected from >100 CECs monitored in a large quantity of Spanish (secondary) effluent within the framework of the project TRAGUA (www.consolider-tragua.com). The selection was performed on the basis of the occurrence and the impact on aquatic and terrestrial compartments and human health as described in Muñoz et al. (2008).

As per Lyu et al. (2019) the starting list contains 67 CECs detected in the secondary effluent of several municipal WWTPs in Beijing (China), mainly based on conventional activated sludge processes. Their concentrations are from previous investigations found in the literature by Lyu et al. (2019).

Finally, Delli Compagni et al. (2020) refer to 13 CECs selected based on their chemical and toxicological properties investigated from 80 CECs by (Castiglioni et al., 2018a, 2018b) in the secondary effluent of three municipal WWTPs in Milan (northern Italy) (2 conventional activated sludge systems and 1 biofilter).

The mean values refer to 24-h (time or flow proportional) composite samples of secondary effluent in the studies conducted in Spain and Italy, whereas in those performed in China, the mean values may refer to composite or grab samples. More details about the characteristics of the investigated WWTPs, their influent type, the corresponding water sampling frequency and mode as well as the monitoring periods are reported in Table S4.

The different proposals set thresholds for identifying the most critical CECs corresponding to those of priority (concern) which led to the lists reported in Fig. 3. Here CECs are ranked in descending order on the basis of their estimated risk for the corresponding environmental compartments, humans or animals (reported at the bottom of the figure).

3.3.1. *Muñoz et al., 2009*

Specifically, according to Muñoz et al. (2009), priority CECs for soil should be those with a $RQ_{soil} > 1$. Due to uncertainties related to a lack of experimental data for substance properties (e.g. soil-biodegradation rates or derivation of PNEC values in soil from structure-activity relationships for aquatic organisms), the authors lower the risk threshold from 1 to 0.1. The resulting lists contain 10 CECs for case study A (Alcalá de Henares WWTP) and 9 for case study B (El Ejido WWTP), with eight CECs in common but ranked in a different order. The substances present only in case study A are Ni and Hg, and the one only present in case study B is ibuprofen. Regarding the RQ for the oral predator, CECs are of priority if their $RQ_{oral\ predator} > 1$ and this identifies only diclofenac for the two cases which was already included in the lists regarding soil risk. These findings highlight that the priority compounds and their ranking are site-specific and in the absence of national guidelines or recommendations, an accurate analysis of the peculiarities of the study area is of relevant importance to identify the CECs to include in the list and in monitoring programs.

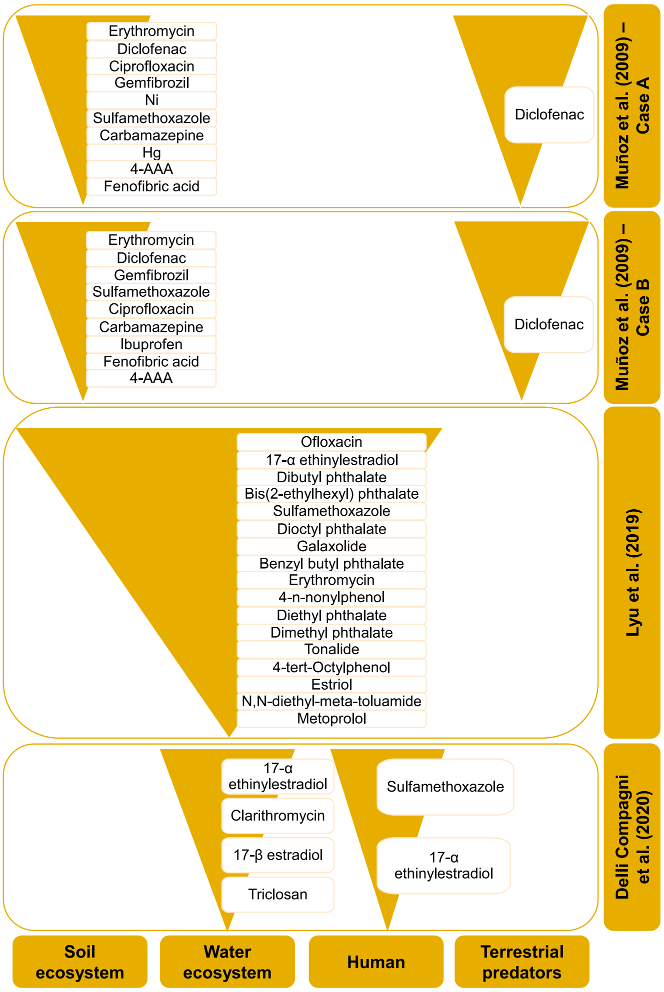


Fig. 3. Priority lists of CECs established in each case study, using the three quantitative methodologies (Muñoz et al., 2009; Lyu et al., 2019; Delli Compagni et al., 2020) to prioritize CECs in reclaimed water used for irrigation. The CECs are ranked in descending order according to the specific criteria.

3.3.2. *Lyu et al., 2019*

Lyu et al. (2019) divided CECs into three groups based on their $S_{i,overall}$ score: group I being $S_{i,overall} \geq 0.1$, corresponding to CECs of high priority; group II with $0.03 \leq S_{i,overall} < 0.1$ characterized by a moderate priority; and group III with $S_{i,overall} < 0.03$, with a low priority. The first group contains 17 CECs.

3.3.3. *Delli Compagni et al., 2020*

Delli Compagni et al. (2020) proposed an alert threshold of high risk for $RQ_{surface\ water\ channel} \geq 1$ and another one of medium risk for $0.1 \leq RQ_{surface\ water\ channel} < 1$. The CECs placed in the medium risk region are sulfamethoxazole, ibuprofen and estrone and those exceeding the high-risk threshold are clarithromycin, 17-α estradiol, 17-β estradiol, and triclosan.

With regard to the human risks, according to the TTC approach, it was found that the daily amount of edible crop (M_{crop}) of the two studied species, rice and wheat, required to exceed the corresponding TTCs showed unrealistic values (> 2 kg/day per person) for all CECs, with the only exception being sulfamethoxazole. For this CEC, M_{crop} for rice resulted equal to 10 g/day for infants and 50 g/day for adults, which might imply potential genotoxic effects from ingestion.

As to HQ, Delli Compagni et al. (2020) set a threshold at 0.1 to guarantee a higher level of prudence in human protection (Christou et al., 2017b; Prosser and Sibley, 2015). The CECs with an HQ exceeding the threshold are of concern. The results indicated a negligible risk for all the CECs, although an HQ (infants) of 0.3 was found for 17-α ethinylestradiol. A comparison with the TTC could not be done, since this latter approach is not valid for classes of compounds such as estrones (Kroes et al., 2004).

The threshold for HI was set at 1. The HI values were below 1, showing no potential risk for human health for the investigated CECs.

3.3.4. *Comparison*

The priority lists resulting from the discussed methodologies (Fig. 3) include CECs which differ in number and type. This is not only due to the different approaches, but also to the fact that each methodology is applied to a preselection of CECs detected in different study areas (Table 1), covering very different classes of substances. A comparison of the preselected CECs shows that there are only three in common: carbamazepine, diclofenac and sulfamethoxazole. Of these, only sulfamethoxazole appears in the priority lists of the four study areas (Fig. 3). In all the priority lists, at least one antibiotic is at the top (first three positions) of the ranking, confirming the high level of concern of this class of pharmaceuticals for soil, water, and humans, also regarding the consequent antibiotic resistance in the environment. In particular, erythromycin appears in the first position of the priority lists referring to two case studies that evaluate the risk of reclaimed water in the soil ecosystem (Muñoz et al., 2009) and it also appears in the nineth position of the priority list proposed by Lyu et al. (2019).

The estrogen 17α-ethinylestradiol is in the second position of the priority list by Lyu et al. (2019), and is in the priority lists proposed by Delli Compagni et al. (2020) to evaluate the risk for the water ecosystem and human health.

Finally, the complete list by Lyu et al. (2019) is longer than the other lists (17 CECs of different classes) as it derives from a wider array of CECs detected in the study area (Beijing).

4. Qualitative approaches

Qualitative approaches consist of *conceptual* frameworks able to establish a priority list among CECs in the case of a direct reuse of reclaimed water for agriculture needs. Three different proposals have been found in the literature: Fu et al. (2019), Revitt et al. (2021) and Verlicchi et al. (2023) and are presented and discussed herein.

4.1. Fu et al., 2019

Fu et al. (2019) outlined a tiered framework, which intends to estimate CEC mass flow which enters the soil by TWW and biosolids, and moves to the edible parts of the crops (Fig. 4). It consists of 4 priority/alert levels (1 being the highest and 4 the lowest) defined by: CEC mass flow into soil due to irrigation with reclaimed water and biosolid application (level 4); CEC availability in soil (level 3); CEC accumulation in (non-edible) roots (level 2) and CEC accumulation in edible organs (level 1).

Their approach starts with the development of a database of occurrence of CECs in TWW (C_{TWW}) and in biosolids (out of the scope of this review) which will be spread on the soil and the estimation of their mass flow rate associated with the amount of reclaimed water reused for agriculture needs. Then, it evaluates CEC persistence and sorption in soil through their half-life in soil, $t_{1/2,soil}$, and the solid-water partition coefficient for soil, $K_{d,soil}$, using experimental data, and descriptor-based and deep learning models.

After that, the proposal analyses the accumulation of these CECs in roots by quantitative structure−activity relationship-based (QSAR) models and/or deep learning models and identifies those compounds that can most enter into plant roots and translocate within plants. It then determines the metabolism rates and metabolites for CECs with a relevant uptake and translocation in edible roots, leaves and/or fruits. Finally, the proposal concludes with an estimation of the human exposure to the CECs and their metabolites characterized by a high risk as they are accumulated in edible parts. This prioritization scheme is at a conceptual stage and refinements are necessary also following the suggestions the authors provide. Despite this, it is useful for focusing on the main steps to follow to identify a short list of CECs to monitor for the assessment of the risk for human health.

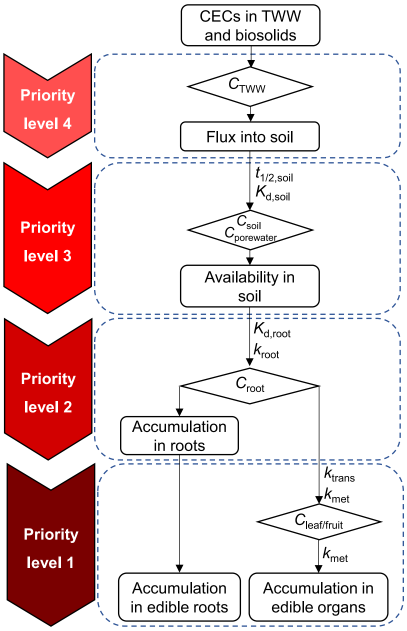


Fig. 4. Conceptual framework for the prioritization of CECs in reclaimed water used for irrigation in agriculture showing the different priority levels. Adapted from Fu et al. (2019). Legend: C_{TWW} concentration in treated wastewater, C_{soil} concentration in soil, $C_{porewater}$ water concentration in soil pores, $K_{d,soil}$ solid-water partition coefficient, $K_{d,root}$ solid-water partition for the root, k_{root} uptake into the root, k_{trans} translocation into the plant, and k_{met} in-plant metabolism.

4.2. Revitt et al., 2021

Revitt et al. (2021) developed another conceptual framework which combines data and (where unavailable) experts' judgment to support a qualitative evaluation of the risk due to the presence of CECs in the TWW used for agricultural needs. The framework is applied up to the "soil" receiving the TWW. The soil may act as CECs sink or source, depending on whether the CECs are retained (due to adsorption), react and form transformation products, become bioavailable for uptake by the plants, leachate toward groundwater or transfer to surface water via runoff. The risk is the CEC occurrence in the soil in a *bioavailable form.*

This approach considers the soil as the target receptor in the absence of CEC dose-response models and not widely understood cumulative exposures. Fig. 5 provides a schematic diagram of their proposal. The authors developed a qualitative risk assessment with scores allocated between 1 and 4 to estimate the likelihood of CEC occurrence and the magnitude of its impact. In particular, a score of 1 indicates the least likelihood/impact and a score of 4 corresponds to the highest likelihood/impact.

The likelihood of occurrence and the magnitude of impact depend on different key variables which may be listed in different forms (scenarios) as reported in Table 2.

On the one hand, the *likelihood of occurrence* refers to the *frequency* of occurrence of a CEC in the TWW and depends on: the source of wastewater, level of wastewater treatment, effect of TWW storage and distribution prior to its use, and soil irrigation technique. These key variables were selected based on the literature data and the experts' judgment provided by the NEREUS COST Action ESI 403 network (http://www.nereus-cost.eu).

On the other hand, the *magnitude of impact* focuses on the bioavailability of CECs in the soil if TWW is used for irrigation and depends on the CEC concentration in the TWW, CEC bioavailability/bioaccessibility in soil, and availability due to the addition of biosolids/manure to soil and ploughing.

Table 2 reports the assigned score for the different scenarios of each

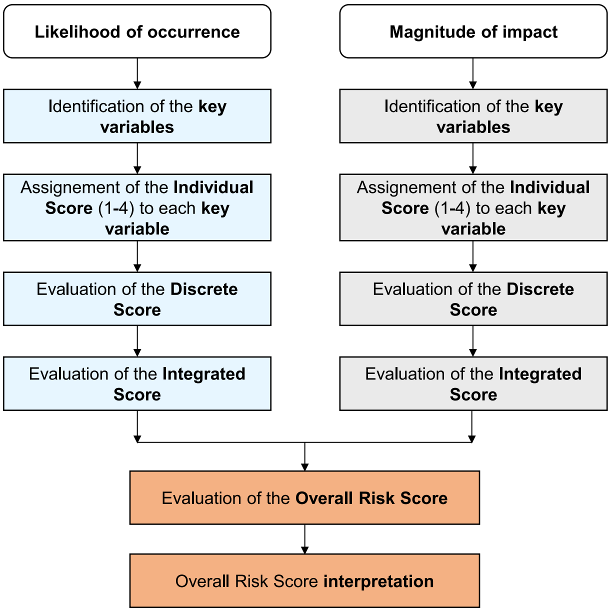


Fig. 5. Framework of the procedure suggested by Revitt et al. (2021) for CEC prioritization in the context of the reuse of reclaimed water.

Table 2
Individual scores for the different scenarios of each key variable defining the likelihood of occurrence and the magnitude of impact according to Revitt et al. (2021).

Individual Score	Likelihood of occurrence					Magnitude of impact			
	Score meaning	Key variables				Score meaning	Key variables		
		Source of wastewater	Level of wastewater treatment	Storage and distribution prior to use	Soil irrigation technique		CECs in treated wastewater [ng L^1]	CECs bioavailability/ bioaccessibility in soil	Addition of biosolids/ manure to soil and ploughing
1	Rare (lack of evidence but not impossible)	■ Rural	■ Tertiary (low formation of transformation products) ■ Tertiary (transformation products formation) ■ Secondary (membrane bioreactors) ■ Secondary (filter beds/ activated sludge)	■ Process breakdown (CEC degradation into non-toxic daughter products)	■ Drip ■ Sub-Surface	Very low (not available for uptake)	■ < 100	■ Limited movement ■ Limited availability for uptake	■ Biosolids/ composted animal manure application + no ploughing
2	Unlikely (uncommon but known to occur)	■ Municipal (residential sources)	■ Tertiary (transformation products formation) ■ Secondary (membrane bioreactors) ■ Secondary (filter beds/ activated sludge)	■ No process breakdown (or CEC degradation into toxic daughter products)	■ Surface ■ Spray/ sprinkler	Low (unlikely to be available for uptake)	■ ≥ 100 ≤ 1000	■ Ready movement ■ Limited availability for uptake	■ Biosolids/ composted animal manure application + ploughing
3	Possible (may occur sometimes)	■ Municipal (residential sources) ■ Municipal (industrial/ hospital sources with on-site treatment)	■ Secondary (membrane bioreactors) ■ Secondary (filter beds/ activated sludge)			Medium (may be available for uptake)	■ > 1000 ≤ 10,000	■ Limited movement ■ Ready availability for uptake	■ Animal manure application + ploughing or no ploughing
4	Likely (expected to occur)	■ Municipal (residential sources) ■ Municipal (industrial/ hospital sources with on-site treatment) ■ Municipal (industrial/ hospital sources without on-site treatment)	■ Secondary (filter beds/ activated sludge)			High (available for uptake)	■ > 10,000	■ Ready movement ■ Ready availability for uptake	■ No biosolids/ animal manure application + ploughing

key variable (Individual Scores). It emerges that for some sources of wastewater and wastewater treatment, different scores may be assigned depending on the related contributions to the wastewater (e.g. in the case of residential, hospital and industrial wastewater) and the removal capacity of the adopted technologies regarding the CEC under analysis.

The Discrete Score for the likelihood of occurrence and the magnitude of impact of a CEC reaching the soil is calculated by multiplying the Individual Scores assigned to each key variable. This step leads to a value (between 1 and 64) for the likelihood of occurrence and for the magnitude of impacts for each CEC.

The following phase consists of *rescaling* the obtained Discrete Scores into the corresponding Integrated Scores (variable between 1 and 4) according to the rules reported in Table 3.

Then, the Overall Risk Score assessment of a CEC is calculated by multiplying the two Integrated Scores just obtained. According to Revitt et al. (2021) (Overall Risk Score *interpretation*):

- an Overall Risk Score from 12 to 16 corresponds to the case of a CEC with a high probability of occurrence and bioavailability in the soil thus, resulting in a probable uptake;
- if it is in the range 9–11, this means it is probable that the CEC occurs and is bioavailable in the soil;

Table 3
Rules for rescaling the Discrete Score to the Integrated Score for the likelihood of occurrence and the magnitude of impact according to Revitt et al. (2021).

Discrete score	Integrated score
1–6	1
7–16	2
17–36	3
37–64	4

- when it is between 5 and 8 it means there is a limited possibility (unlikely) that the CEC occurs and is bioavailable in the soil;
- finally, when the Overall Risk Score is in the range 1–4 the CEC is present and bioavailable in the soil only in very rare instances.

According to this approach, the CECs with the highest Overall Risk Score are candidates to include in the priority list. The authors conclude that this must be considered a dynamic list as changes may occur due to the introduction of new products on the market, and the outcomes of chemical screening programs such as that of the European Chemical Agency identifying the “substances of very high concern” which has recently been updated (as reported in https://echa.europa.eu/es/-/echa-adds-nine-hazardous-chemicals-to-candidate-list).

4.3. Verlicchi et al., 2023

A third methodology was published very recently (Verlicchi et al., 2023): it was developed to support CEC monitoring program planning in a project of reclaimed water reuse for irrigation (SERPIC, https://www.serpic-project.eu/). It aims to identify a short list of relevant indicator CECs for the evaluation of their removal capacity by an additional polishing treatment, for the assessment of the risk for soil and crops, as well as for (surface and ground) water compartment, due to runoff and percolation. For the first time, in addition to organic CECs, it accounts for microbial CECs, which are ARB and ARGs. Fig. 6 shows the main issues related to this methodology. With reference to the area interested in the practice of reclaimed water reuse, it starts with the creation of a dataset of organic CECs present in the municipal secondary effluent (from a conventional activated sludge, CAS, system). Each of them is characterized by:

- Occurrence (O) in terms of the range of measured concentrations (from the literature and/or on site-investigations in the area of study);
- Persistence (P) defined as the resistance to be removed in municipal wastewater treatment plants (mainly based on CAS process). It is related to the observed range of removal efficiencies achieved in secondary treatments (from the literature and/or on site-investigations in the area of study);
- Bioaccumulation (B) in aquatic organism tissues expressed as Log K_{ow} (from the literature, online database (PubChem or ChemSpider http://www.chemspider.com/) and/or cheminformatics software (EPI Suite or Chemaxon https://chemaxon.com/));
- Toxicity (T) to aquatic life expressed in terms of $PNEC_{water}$ (from the literature, experimental investigations or online databases like NORMAN https://www.norman-network.com/nds/ecotox/), chronic values should be preferred (EC and European Chemicals Bureau, 2003).

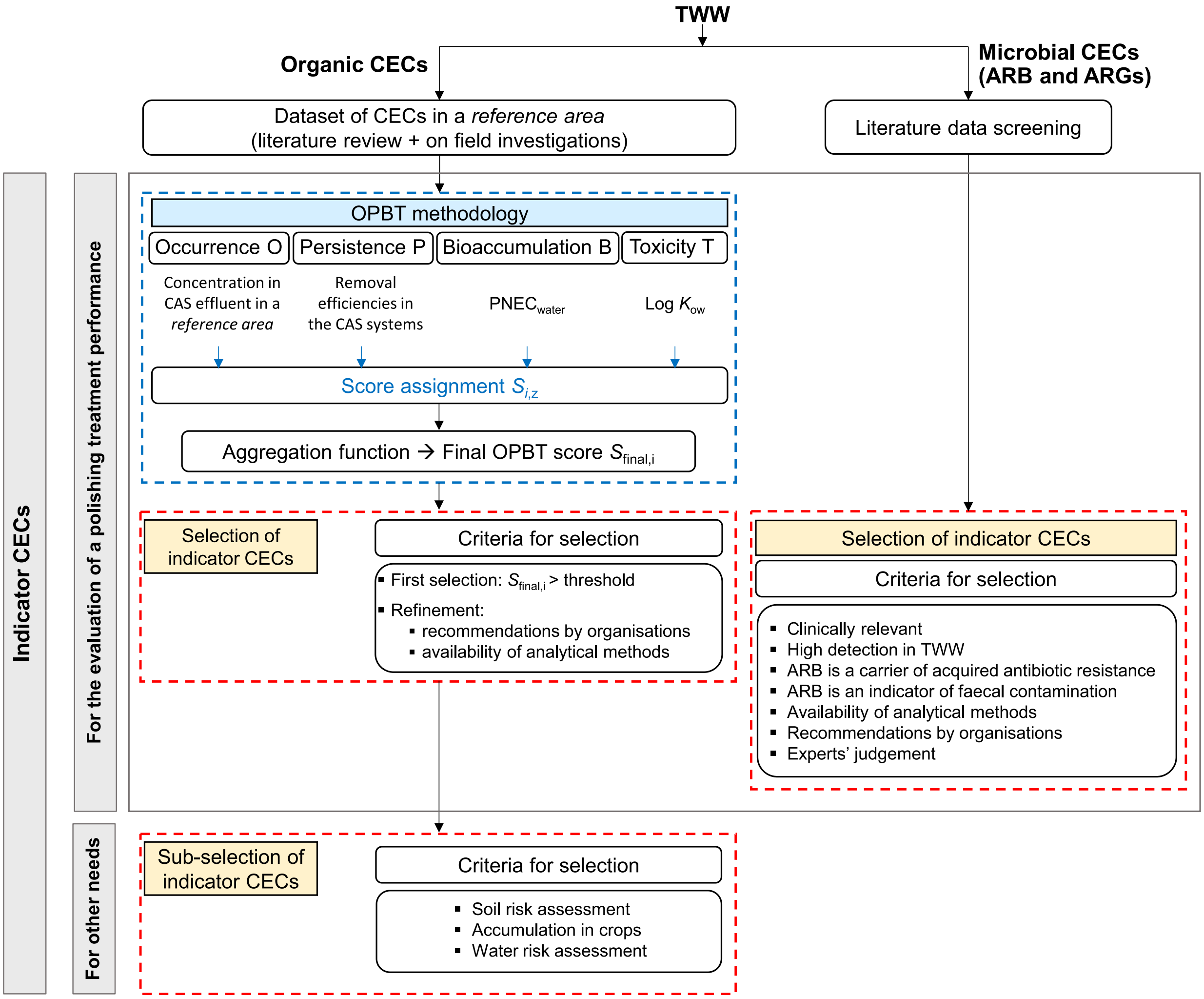


Fig. 6. Framework of the methodology developed by Verlicchi et al. (2023) to identify the priority organic and microbial CECs for the evaluation of the polishing treatment performance, the risk for soil and water and the accumulation in the crop.

Table 4
Score assigned to the four criteria of the OPBT methodology according to Verlicchi et al. (2023).

Score $S_{i,z}$	Occurrence O Concentration c (ng L^{-1})	Persistence P Removal R (%)	Bioaccumulation B Log K_{ow}	Toxicity T $PNEC_{water}$ (μg L^{-1})
1	$c < 50$	$R > 80$	Log $K_{ow} < 1$	$PNEC_{water} > 100$
2	$50 \leq c < 100$	$60 < R \leq 80$	$1 \leq$ Log $K_{ow} < 2$	$10 < PNEC_{water} \leq 100$
3	$100 \leq c < 500$	$40 < R \leq 60$	$2 \leq$ Log $K_{ow} < 3$	$1 < PNEC_{water} \leq 10$
4	$500 \leq c < 1000$	$20 < R \leq 40$	$3 \leq$ Log $K_{ow} < 4.5$	$0.1 < PNEC_{water} \leq 1$
5	$c \geq 1000$	$R \leq 20$	Log $K_{ow} \geq 4.5$	$PNEC_{water} \leq 0.1$
	No value available	No value available	No value available	No value available

For this reason, the methodology is called OPBT. Then a score ($S_{i,z}$) is assigned to each i-th CEC for the four criteria z, according to the thresholds reported in Table 4 which, regarding P, B and T, were in accordance with Daouk et al. (2015) and, regarding O, were set by the authors. The maximum value of concentrations and the average value of removal efficiency was assumed for each CEC.

Once the four criteria z are scored for each i-th CEC included in the dataset, and assuming the same weight (equal to 1) for each criterion, the final OPBT score ($S_{final,i}$) is obtained as the sum of the 4 assigned scores $S_{i,z}$ (Eq. (28)).

$$S_{final,i} = \sum_{z=1}^{4} S_{i,z} \tag{28}$$

The CECs are ranked according to the descending order of the final OPBT score: compounds with the highest $S_{final,i}$ are the potential candidates to be selected. The final list is also defined on the basis of recommendations by international organizations and networks, and availability of analytical techniques.

Regarding microbial CECs, the first step consists of a literature screening focusing on the ARB and ARGs present in secondary effluent in worldwide investigations. The selection is based on the criteria reported in Fig. 6.

The methodology was applied in the area of study including Spain, Portugal, Italy and South Africa. Regarding organic CECs, 349 compounds belonging to 39 different classes were preselected and it was decided that the final list had to include 25 substances. As to microbial CECs, starting from 22 ARB and 126 ARGs, 2 ARB and 3 ARGs were identified. The full list is reported in Table 5 with the CECs reported in alphabetical order.

Verlicchi et al. (2023) also proposed sub-lists of organic CECs (Table 5), starting from the whole list, for the assessment of the risk for soil, (surface and ground) water and crops. In particular:

- regarding the soil, they evaluated the $PNEC_{soil}$ by means of Eq. (19) for each of the 25 CECs and considered CECs with a value higher than 100 ng/kg as those of priority;
- regarding the water, they considered compounds with a $PNEC_{water} >$ 100 ng L^{-1} as CECs of priority;
- regarding the crops (potatoes and carrots in the SERPIC project), they considered the observed fate of CECs in the plants in terms of accumulation in the roots and translocation aboveground, based on the literature, and the expected fate depending on CEC charge and octanol-water distribution coefficient D_{ow} (accounting for K_{ow} and pK_a) according to (Bigott et al., 2020; Bueno et al., 2022; Keerthanan et al., 2021). The selected CECs are those found in the roots, characterized by a different charge.

A comparison with the priority lists from quantitative methodologies shows that ciprofloxacin, erythromycin and ibuprofen are common CECs for soil risk assessment, and sulfamethoxazole for human risk measured by accumulation in the crop.

5. Strengths, weaknesses and applications of the different methodologies

Table 6 summarizes the main strengths and weaknesses of the overviewed methodologies as well as the main uncertainties they are affected by.

The three quantitative approaches had a great impact on the scientific community as remarked by their number of citations (according to Scopus, on July 2023, 131 for Muñoz et al. (2009); 20 for Lyu et al. (2019) and 51 for Delli Compagni et al. (2020)). Only the approaches or the CEC selections defined by Muñoz et al. (2009) and Delli Compagni et al. (2020) were adopted in other investigations: this is the case of Jesse and Davidson (2019) for Muñoz et al. (2009) and of Narain-Ford et al. (2020) for Delli Compagni et al. (2020).

Regarding the qualitative approaches, Fu et al. (2019) was cited 89 times and the methodology adopted in 3 investigations (Ben Mordechay et al., 2021, 2022a, 2022b) Revitt et al. (2021) was cited 8 times and the approach adopted once (Beretsou et al., 2022) and finally the recently published Verlicchi et al. (2023) has not been yet mentioned.

Table 5
List of selected organic and microbial CECs for the reuse project by Verlicchi et al. (2023).

Selected CECs for the evaluation of polishing treatment performance	Sub-selected lists of CECs		
	Soil risk assessment	Accumulation in crops	Water risk assessment
Amoxicillin	Amoxicillin		Amoxicillin
Azithromycin	Azithromycin		Azithromycin
Bezafibrate			
Bisoprolol			
Bisphenol A		Bisphenol A	
Carbamazepine			
Carbamazepine 10,11 epoxide (metabolite)			
Ciprofloxacin	Ciprofloxacin		Ciprofloxacin
Clarithromycin	Clarithromycin		
Diclofenac			Diclofenac
Erythromycin	Erythromycin	Erythromycin	
Furosemide			
Gemfibrozil		Gemfibrozil	
Ibuprofen	Ibuprofen		Ibuprofen
Iopromide	Iopromide		
Irbesartan			
Nonylphenol		Nonylphenol	
Oxazepam			
Perfluorooctane sulfonic acid (PFOS)	PFOS	PFOS	PFOS
Sulfamethoxazole		Sulfamethoxazole	
Tetracycline	Tetracycline		Tetracycline
Tramadol			
Trimethoprim			
Valsartan			
Venlafaxine			
Escherichia coli			
Fecal coliforms			
16S rRNA			
sul1			
sul2			

Table 6
Strengths and weaknesses of the different methodologies.

Methodology	Strengths	Weaknesses
Muñoz et al., 2009 Aim: agricultural irrigation	1. The methodology is easy to apply, once the values of the different variables are known. 2. Regarding the environmental risk assessment, the methodology takes into account the simplified soil-food chain provided by the oral predators and the earthworms. In earthworms, which represent the food for the predators, CECs may accumulate in the tissues or may be in the gut due to the ingested soil where CECs may be present.	1. PECs for soil and for oral predator are estimated according to the equations suggested by EC and European Chemicals Bureau (2003) which contain many variables. Some of them could be difficult to estimate and literature values could be adopted. The uncertainty affecting the selected values depends on the variable and the source providing its value. 2. Human health risk is not considered. 3. CEC toxicity data, half-life in soil, K_{oc} may be obtained from experimental investigations and/or model estimations. Uncertainties affecting the corresponding values depend on the source and may be very different. 4. The methodology does not account for the CECs which may accumulate in the crops.
Lyu et al., 2019 Aim: green area irrigation	1. The proposed methodology takes into considerations the effects of the CECs occurring in the water, soil, and air. 2. The risk posed by the CECs is evaluated with respect to the environment and the human health (related to the amount of CECs in the air). 3. The model assigns the same weight to the score of the three effect values (referring to soil, groundwater, and air). It is possible to change the weight if the contributions have a different relevance. 4. The study carried out an uncertainty analysis.	1. It is not clear how the amount of CECs into air due to volatilization (Q_2) is evaluated. 2. The methodology is applied to the case of China. It should be difficult to apply it to other areas as many data are requested and they are not easy to find. 3. Toxicity data for human health were not included in this study due to the paucity of CECs intake by dermal contact, hand-to-mouth transfer, and breathing. 4. The uncertainty analysis points out that the values of CEC properties obtained by EPI Suite and toxicity data obtained by ECOSAR increase the uncertainty of the results. 5. If the same methodology is applied for the CECs selection in the case of the reuse in agriculture, it does not account for the CECs which may accumulate in the crops.
Delli Compagni et al., 2020 Aim: agricultural irrigation	1. The fate of the CECs in the soil is well modelled, as well as the translocation in the plant tissues. 2. The risk assessment for the human health is evaluated following two approaches: TTC from one side and EDI/ADI from the other side. By means of TTC, it is possible to assess the risk for not well investigated CECs. 3. The methodology can assess the risk due to the CEC cocktail contained in the crops daily ingested. 4. The model includes an uncertainty analysis of the CEC concentrations and transformation rates in the channel and a sensitivity analysis in order to evaluate which parameters mostly affect the results.	1. TWW are released into a dedicated open-air channel and conveyed to the irrigation field. In the case of rain event, the channel should receive land runoff and its quality may change. 2. The CEC selection should be different in the case of a TWW conveyed to the field to irrigate by a pipe (underground) instead of an open-air channel due to different biotic/abiotic processes occurring on the way to the field. 3. The channel is divided into segments depicted as continuous stirred tank reactors. This simplification does not take into account the real and complex scenario. 4. CEC concentrations in soil and crops depend on many parameters, according to the uncertainty and sensitivity analysis carried out by the study. Not always these parameters may be obtained from in situ investigations, and they instead come from literature, thus contributing in the uncertainties of the results.
Fu et al., 2019 Aim: agricultural irrigation	1. The study includes an in-depth description of the main steps to focus on the identification of priority CECs and in the missing information to develop them. 2. The model suggests accounting for CEC metabolites/transformation products during the degradation process once the CECs reach the soil with the irrigation water and once in the crops. 3. It proposes a procedure to assess the human risks due to the ingested edible parts of the crops.	1. It is still at a conceptual stage and does not provide the resulting short list of CECs for a specific study area. 2. The selection is based on the CEC bioaccumulation potential in crops and does not account for the environmental risk (regarding the soil and the water ecosystems).
Revitt et al., 2021 Aim: agricultural irrigation	1. It underlines that the list of priority CECs must be considered a dynamic list, to be updated over time and space. 2. It accounts for potential CEC transformation products during the tertiary treatment, the treated effluent storage and the distribution system.	1. The methodology is still at a conceptual stage, and the authors do not provide a short list of CECs referring to a specific case study. 2. The definition of the priority list will be the result of the combination of data and expert's judgment and thus it might change according to the expert's opinions. 3. The methodology does not investigate the types of transformation products, but it limits the analysis to a qualitative step, by assigning a different score in the case they are expected to be present or not. 4. The methodology limits the attention to the bioavailability of CECs in the soil and does not account for soil and water risk. 5. Moreover it does not evaluate the CEC bioaccumulation in crops and thus the consequent human risks due to crop ingestion.
Verlicchi et al., 2023 Aim: agricultural irrigation	1. It includes ARB and ARGs and metabolites products among the priority CECs. 2. The occurrence of the CEC is related to the (maximum) measured concentrations (composite samples) and not on the predicted concentrations in the study area. 3. The model assigns the same weight to the score of the four categories (occurrence, persistence, bioaccumulation and toxicity). It is possible to change the weight if the contributions have a different relevance.	1. It does not consider the human risk assessment, but only the (potential) CEC accumulation in the crops. 2. The methodology does not consider the frequency of occurrence in the study area to discriminate among the potential CECs. 3. The CEC environmental risk (for soil or water ecosystems) is associated to the CEC toxicity (PNEC in soil or water) and not to the corresponding CEC RQ that is the ratio between the environmental concentration (in soil or water) and the PNEC (in soil or water) of a compound.

6. Final remarks, conclusions and future needs for research

Most of the methodologies available in the literature to prioritize CECs focused on the assessment of the potential risk to the aquatic environment as reclaimed water has been used more often for groundwater recharge or directly released into surface water. Then, the number of studies aiming to propose methodologies to prioritize CECs in reclaimed water intended for agriculture irrigation is currently limited, despite recent European legislation promoting the reuse of reclaimed water (EU Regulation, 2020/741) and the draft of the Water Framework

Directive (EC COM 541 final, 2022) accounting for CECs in the final effluent. Otherwise, it is difficult to compare prioritized CECs among studies in order to reach a more solid conclusion mainly due to the lack of protocols to monitor representative CECs (generally selected on the basis of the available analytical techniques) and different procedures to estimate the risk. It emerged from the current review that antibiotics are the most relevant compounds for their potential adverse effects to the environment in the case of reuse of reclaimed water for irrigation and this finding underline the need to better investigate on ARB and ARGs in the reused effluent. Considering EU Directives, SDGs and circular economy principles, it is extremely important to find a holistic approach which would help ensure a high level of protection of environment, animal and human health when reclaimed water is used for agricultural purposes. There is an urgent need to establish a short list of priority CECs in reclaimed water since the number of CECs is continuously growing, with >204 million chemicals registered in the Chemical Abstract Service (https://www.cas.org/about/cas-content) and approximately 4000 new ones being registered every day (Carrizo et al., 2022; Kreuzinger et al., 2020). Based on the main gaps of knowledge identified, a list of recommendations is provided for the focus of future research:

- Monitoring investigations on the polished effluent should include not only pharmaceuticals, but also other classes of CECs, less investigated.
- Occurrence studies performed in reclaimed water for the direct reuse should be homogenized to monitor the same CECs, their metabolites and transformation products, and variability over the irrigation season. The analysis should include CEC biotic and abiotic transformation products, once in the soil. Additionally, analytical protocols for monitoring investigations should also consider ARB and ARGs.
- Frequency of occurrence in the reclaimed water should also be included among the selection criteria to focus on the CECs most frequently present or expected to be present.
- Persistence studies should relate to CECs resistant to removal in common WWTP (quite often CAS systems) in order to evaluate the most adequate polishing treatment of effluents directly reused in agriculture.
- Bioaccumulation studies in the adipose tissues of aquatic organisms or terrestrial predators would be of great importance.
- Toxicological studies, related to the potential risks of CECs to soil and water ecosystems, terrestrial predators, and human health should involve more CECs, including transformation products, ARB, and ARGs and different trophic levels. Likewise, toxicity data should account for the mixture of CECs and better investigate their potential synergistic, additive or antagonistic effects. Research efforts should fill the lack of dose response models (in human health risk assessment) and better understanding cumulative exposures.
- In-field investigations of the fate of CECs in the soil (sorption, soil/water partition, degradation) and in (different) crops (uptake, translocation, bioaccumulation and in-plant metabolism) are necessary to evaluate the potential risks to the environment and human health concerning reclaimed water used for agriculture. They should include real data on soil properties, climate conditions, target plant species, irrigation systems and cultivation practices. Moreover, studies should also monitor the effects of long-term water reuse in the same area.
- Uptake rates by crops should also be investigated for instance in terms of CEC bioconcentration factor (defined as the ratio between CEC concentration in root or leaf or fruit and its concentration in the growing medium).
- Other efforts should lead to the development of models able to predict spatial and temporal variations of CEC occurrence in TWW on the basis of the main influencing factors; CEC fate once in the soil and in the crops, also considering the effects of CEC mixtures. In addition, rapid screening tools, such as the use of plant cell cultures, could be exploited to evaluate plant uptake and metabolism potentials to exclude low priority CECs, thus narrowing the list of high-priority CECs as clearly remarked in Shi et al. (2022).
- Long-term monitoring for soil and crop matrices should be carried out in order to evaluate the effects of prolonged reclaimed water reuse practice in the same field on CEC accumulation in soil and crops, degradation/persistence in soil, and potential impacts on soil and (ground and surface) water, crops and human health. This would provide valuable insights into the environmental sustainability and long-term implications of reclaimed water irrigation practices.
- Finally, ongoing and future studies should provide details on the accuracy of the measured data with regard to sampling frequency and mode and chemical analysis. They should also carry out an uncertainty analysis related to the predicted parameters and/or variables and a sensitivity analysis in order to quantify and compare the influence on the predicted values of a variation of each of the factors included in the adopted model.

CRediT authorship contribution statement

Paola Verlicchi: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Engracia Lacasa:** Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Vittoria Grillini:** Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

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.

Acknowledgments

The authors would like to thank the EU and Bundesministerium für Bildung und Forschung, Germany, Ministero dell'Università e della Ricerca, Italy, Agencia Estatal de Investigación, Spain, Fundação para a Ciência e a Tecnologia, Portugal, Norges forskningsråd, Norway, Water Research Commission, South Africa for funding, in the frame of the collaborative international consortium SERPIC financed under the ERA-NET AquaticPollutants Joint Transnational Call (GA N° 869178). This ERA-NET is an integral part of the activities developed by the Water, Oceans and AMR Joint Programming Initiatives.

E. Lacasa would like to thank the Vicerrectorado de Profesorado y Desarrollo Profesional (University of Castilla-La Mancha (UCLM), Spain) for funding her research placement at the University of Ferrara (Italy) (UCLM resolution date: 19/05/2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.165735.

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