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Research article

Modelling the impacts generated by reclaimed wastewater reuse in agriculture: From literature gaps to an integrated risk assessment in a One Health perspective

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ABSTRACT

The reuse of reclaimed wastewater is increasingly recognized as a viable alternative water source for irrigation. Its application, whether direct or indirect, impacts several interconnected compartments, including groundwater, surface water, soil, crops, and humans. Reclaimed wastewater provides essential resources for crops, like water and nutrients. However, it also introduces pathogens, and contaminants of emerging concern (CECs), defined as chemicals that may pose risks to human health and ecosystems but are not yet fully regulated, such as pharmaceuticals and personal care products, among others. Additionally, reclaimed wastewater may contain antibiotic-resistant bacteria (ARBs) and disinfection by-products (DBPs), all of which present potential health and environmental risks. Therefore, regulatory bodies stress the need for preventive risk assessments to ensure safe reuse.

This paper critically reviews available models for assessing the impacts of reclaimed wastewater reuse in agriculture. It identifies gaps in current modelling approaches and outlines future research directions. Key areas requiring further investigation include the fate and transfer of CECs, ARBs and DBPs, and the co-occurrence of multiple risks in such interconnected systems, especially in the indirect reuse. To address these gaps, we proposed a simplified approach to integrate three types of risk associated with CECs in indirect reuse, focusing on risks posed by antibiotics and other pharmaceuticals: human health risk, environmental risk and risk from antibiotic resistance development. This approach aids in identifying the most critical endpoints within the One Health approach, supporting (i) CECs prioritization in regulations based on their critical endpoints and (ii) the adoption of CEC-specific mitigation measures.

1. Introduction

The growing urbanization and the increasing establishment of water-demanding lifestyles has boosted water withdrawals. Besides, climate change exacerbates water scarcity. The convergence of these two issues emphasizes the pressing need for implementing policies for a sustainable water management. Agriculture is the most water-intensive sector (Mojid et al., 2021), and reuse of reclaimed wastewater has been recognized as a reliable alternative to conventional freshwater sources for irrigation (Jaramillo and Restrepo, 2017).

Reclaimed wastewater might be loaded with a variety of contaminants, including pathogens, such as bacteria, viruses and parasites, which can directly cause diseases in humans and animals, and contaminants of emerging concern (CECs), defined as a broad category of chemicals that have been detected in the environment and may pose risks to human health or ecosystems but are not yet fully regulated (Kumar et al., 2022). They include chemicals such as pharmaceuticals, personal care products, endocrine disruptors, pesticides, per- and polyfluoroalkyl substances, among others (NORMAN network website). Additionally, antibiotic resistant bacteria (ARB) and antibiotic resistant genes (ARGs), which develop resistance due to the presence of antibiotics in the wastewater, pose significant public health challenges, while disinfection by-products (DBPs), formed during wastewater disinfection processes, may include potentially toxic compounds, like trihalomethanes and nitrosamines. Finally, conventional contaminants such as heavy metals, salts, organic matter and suspended solids can be present in reclaimed wastewater. This mixture of contaminants complicates the management of reclaimed wastewater for irrigation (Yalin

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et al., 2023).

Based on where the wastewater treatment plant (WWTP) effluent is discharged, the agricultural reuse can be (i) indirect, when the effluent is discharged into a surface water recipient and irrigation water is derived downstream the point of discharge, or (ii) direct, when the effluent is directly used for crops irrigation, through a dedicated distribution network, without any dilution with freshwater (Kesari et al., 2021). Understanding this distinction is crucial, as it directly influences the quality of the irrigation water. In fact, in case of direct reuse, the irrigation water quality corresponds exactly to the quality of the WWTP effluent, enabling straightforward quality control by managing effluent quality. Conversely, indirect reuse poses greater complexity in controlling the irrigation water quality, since it depends on diverse factors, including effluent and freshwater qualities, dilution factor achieved by the receiving surface water and hydrological conditions (Jeong et al., 2016).

In both cases, it emerges that the agricultural reuse of reclaimed wastewater inherently connects water in numerous compartments (e.g., WWTP, surface water, groundwater, soil, crop), leading to a series of impacts, either positive or negative, which need to be evaluated. As for positive impacts, besides alleviating the water stress, the reuse of reclaimed wastewater provides a source of nutrients (e.g., nitrogen and phosphorus) to enhance agricultural productivity. Conversely, the presence of a wide range of contaminants (e.g. CECs, ARB, DBPs, heavy metals) in WWTPs effluent, even after extensive treatments, favors the cross-contamination of different compartments (Delli Compagni et al., 2020). For example, contaminants can accumulate in soil, causing salinization and changes to the soil properties (Khaskhoussy et al., 2022). From the soil, these contaminants can either be uptaken and accumulated by crops, potentially affecting their growth and entering the food chain (Seyoum et al., 2022a), or contaminate groundwater, where aquifers are present (Dahmouni et al., 2022), with consequences on the safety of drinking water supplies. Finally, the consumption of crops contaminated by pathogens, heavy metals and CECs, could imply a not negligible risk for human health (Penserini et al., 2023). Beyond direct health impacts, the social perception of reclaimed wastewater reuse, as well as the associated costs and energy requirements for the implementation of reuse, especially in direct reuse scenarios, are also important to be considered.

The One Health approach (WHO, 2022) underscores the interconnectedness of human, animal, and environmental health. This perspective is crucial in the context of agricultural reuse of reclaimed wastewater, as it recognizes that contaminants in wastewater can simultaneously affect multiple compartments. Recognizing these interconnected risks, the European Union has established quality standards for reclaimed wastewater intended for direct reuse in irrigation, setting four quality classes based on physical, chemical, and microbiological criteria (EU Commission, 2020). Although this regulation emphasizes the adoption of preventive risk assessments, the specific methods for integrating multiple, co-occurring risks across interconnected systems remain undefined. For example, environmental risk assessments are being increasingly applied to WWTP effluent discharge (Ianes et al., 2023). These assessments often refer to regulations such as the EU Watch List (Cortes et al., 2022), which identifies specific CECs that must be monitored. However, current risk assessment procedures often consider individual risks in isolation, which is insufficient for the holistic management required by the One Health approach (Ardiyanti et al., 2024a). Hence, it becomes fundamental to understand the status of available models for impacts assessment, especially for the integrated risk quantification models.

This literature review first aims to present an overview of the available models to assess the impacts of reclaimed wastewater reuse in agriculture, focusing on the connections among modelled impacts, involved compartments, and targeted variables. This review outlines the existing primary gaps, emphasizing key features and areas of application of models adopted for impacts evaluation, and delineating future directions for research in this field. Secondly, based on the review outcomes, we propose a simplified, yet holistic risk assessment approach aligned to the One Health perspective to evaluate the co-occurring implications of reclaimed wastewater indirect reuse. This approach integrates risks that are often assessed separately. In details, we simultaneously estimate three types of risks related to distinct endpoints: human health risk, environmental risk and risk of antibiotic resistance development. Our approach was applied to 6 pharmaceuticals, including three antibiotics, based on the availability of data in the reviewed papers. The goal is to highlight the critical need for a comprehensive regulation that effectively protect both ecosystems and human health. In this perspective, the proposed approach might be used to identify the most vulnerable endpoints and inform the adoption of targeted contaminant-specific mitigation measures.

2. Conceptualization of the reclaimed wastewater reuse system and studies' selection criteria

A conceptual framework was defined to describe the reclaimed wastewater reuse system, visualized in Fig. 1. This framework permits an easy visualization of the three key aspects addressed in this work, focusing on (i) the compartments involved in the agricultural reuse system, (ii) the available models for the impacts assessment, and (ii) the targeted models' variables, which account directly an impact or are proxy of an impact.

The compartments correspond to the physical boundaries for the impact assessment, and they are differentiated in six categories: (i) WWTP, (ii) environment (intended as the natural water system), (iii) irrigation system, (iv) soil, (v) crop and (vi) humans.

Impact models are the tools to evaluate one or more specific impacts of reclaimed wastewater reuse. In total, based on models found to be applied in the literature on reclaimed wastewater reuse in agriculture, ten categories were identified, discerning between quantity-based and quality-based models. Quantity-based impact models assess the impacts related to the volume of reclaimed wastewater provided by WWTPs for irrigation. These models estimate how much the use of reclaimed wastewater affects freshwater availability, economy, energy consumption and public health within a specific area. The analysis is typically conducted through: (i) water mass flow analysis, (ii) Life Cycle Assessment (LCA), (iii) cost analysis, (iv) energy consumption estimation, and (v) social analysis. Conversely, quality-based impact models analyze the impacts associated to reclaimed wastewater quality, studying the effects (vi) of treatment processes, (vii) on soil and (viii) crop, or estimating (ix) the environmental risk and (x) the human risk. They model the fate of contaminants across the compartments using indicators, like concentrations or derived values (e.g., Sodium Absorption Ratio as proxy for salinity). In addition, they also evaluate the specific effect generated by the water quality on the involved compartment.

The model variables represent those quantities targeted by the considered models, that are: (i) water volume for the quantity-based impact models, and content of (ii) pathogens (i.e., bacteria, viruses, protozoa and helminths), (iii) CECs (i.e., pharmaceuticals, personal care products, endocrine disrupting chemicals, pesticides, per- and polyfluoroalkyl substances, plasticizers and transformation products) (iv) ARBs and ARGs (from now on referred as ARBs category), (v) DBPs, (vi) heavy metals, (vii) nutrients, (viii) salinity and (ix) conventional contaminants (i.e., organic matter and suspended solids) for the quality-based impact models.

Scopus database was used for collecting studies written in English and published in the period 2017–2023 from peer-reviewed journals. The resulting articles were filtered off after the analysis of title, abstract and conclusions, resulting in 268 articles, which were hence analyzed through the following conceptual pipeline: for each study, the type of reclaimed wastewater reuse (direct or indirect) was indicated; each study was classified assigning one or more categories as a function of (i) compartments, (ii) impact models and (iii) targeted variables addressed

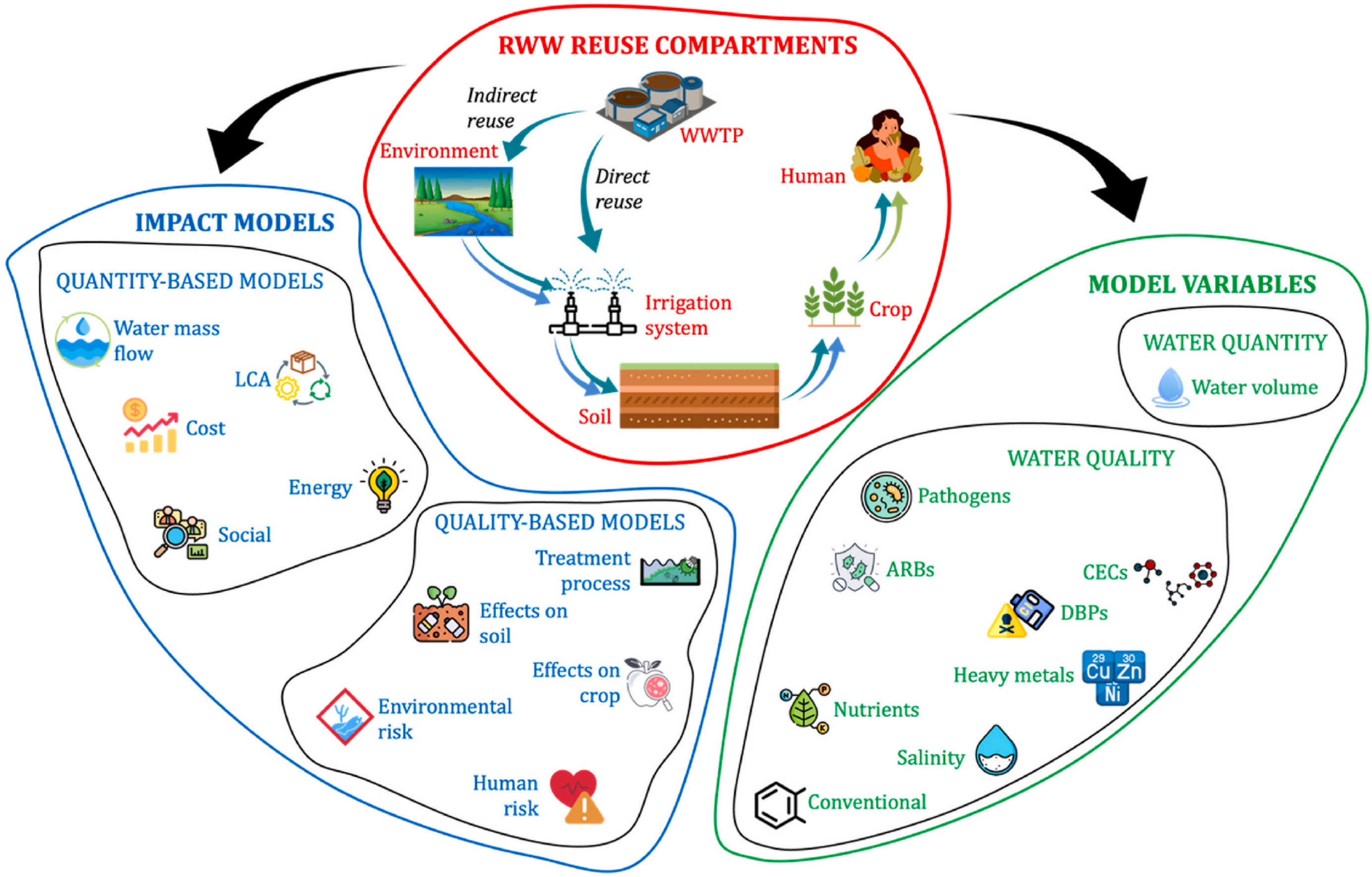

Fig. 1. Schematic overview of the conceptual framework for a reclaimed wastewater reuse system: involved compartments (in red), available models for impacts assessment (in blue), and targeted models' variables (in green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

by the study. Only studies with at least one category for each feature in Fig. 1 (compartment, model, variable) were further considered, leading to 165 articles.

3. Models for impacts assessment of reclaimed wastewater reuse

A summary of the main features of the models is reported in Table 1, indicating the total number of articles available for each of them, the evaluated impacts, and the compartments and target variables most frequently included in the studies reviewed.

3.1. Quantity-based impacts models

As shown in Table 1, all the quantity-based models primarily focus on (i) water volume as the main targeted variable, and (ii) WWTPs and the environment as the main involved compartments. Models relying on water mass flow primarily assess the impacts in terms of water volumes that can be delivered by WWTPs. These models solve water mass flow balances to evaluate how the water volume can meet crop irrigation water requirement (Vivaldi et al., 2022) or alleviate water scarcity by reducing withdrawals from freshwater sources (Abd-Elaty et al., 2022). They are often utilized in decision-support systems for regional water reuse planning, matching and optimizing water needs and sources in a given area (Wang et al., 2019).

LCA models provide a comprehensive framework to assess the environmental sustainability of the whole life cycle of reclaimed wastewater reuse in agriculture. When coupled with Life Cycle Cost analysis, LCA can provide also an assessment of the economic feasibility of such practice (Canaj et al., 2021a). LCA models include various types of impacts, which can be customized depending on the impact of interest: in the case of reclaimed wastewater reuse in agriculture, the commonly studied impacts are climate change potential, water depletion, eutrophication potential, toxicities (e.g., toxicity for humans, environment, marine ecosystem) and ozone depletion (Moretti et al., 2019). Hence, despite being quantity-based models, LCA models enable the calculation of risks, and humans are often included among the studied compartments, as shown in Table 1. However, the primary function of LCA models applied to reclaimed wastewater reuse is the sustainability evaluation of this practice, while they display limitations in accurately and comprehensively quantifying environmental and human health risks. These limitations include the loss of spatial, temporal, dose-response, and threshold information variations in modeling choices (Klöpffer and Curran, 2014), requiring the use of additional risk assessment models.

Cost models aim at assessing the economic viability and cost-effectiveness of reclaimed wastewater reuse, focusing on its implementation, maintenance and optimization. They frequently employ Cost Benefit Analysis (CBA) to compare the infrastructure capital and operating costs of the reuse project with its associated benefits, which usually correspond with savings related to water recovery (Bolinches et al., 2022). Scenario-based modeling is employed too, to simulate costs under different conditions to support stakeholders in the decision-making (Golfam et al., 2021).

Energy models are adopted to assess the energy balance resulting from the implementation and operation of reclaimed wastewater reuse in agriculture. They quantify the energy required for both the reclamation treatment processes (Mendret et al., 2019) and the agronomic practices (Yenkie et al., 2019). These models strive to optimize the direct

Table 1
Summary of models' main features and number of available studies for each model: assessed impacts, compartments and variables most frequently addressed, defined as in Fig. 1.

Model type	Model	# available studies	Impacts	Compartments	Variables	References
QUANTITY-BASED	Water mass flow analysis	44	• Freshwater sources depletion • Required irrigation water fulfilment • Regional-scale water management	WWTP, Environment	Water volume	(Vivaldi et al., 2022; Abd-Elaty et al., 2022; Wang et al., 2019; Canaj et al., 2021a; Moretti et al., 2019), (Bolinches et al., 2022; Golfam et al., 2021; Mendret et al., 2019; Yenkie et al., 2019; Jeong et al., 2020; Chhipi-Shrestha et al., 2019), (Arena et al., 2020), (Vergine et al., 2017), (Tran et al., 2017), (Gormaz-Cuevas et al., 2021; Penserini et al., 2024; Foglia et al., 2021), (Canaj et al., 2021b; Canaj et al., 2021c; Jeuland et al., 2021; López-Serrano et al., 2021; Paul et al., 2021; Pronk et al., 2021; Shakeri et al., 2021; Soltani-Gerdefaramarzi et al.; Zolfaghary et al., 2021; Al-Shutayri and Al-Juaidi, 2019; Azeb et al., 2020; Dehaghi and Khoshfetrat, 2020; Di Maria et al., 2020; Oertlé et al., 2020; Oubelkacem et al., 2020; Paul et al., 2020; Zimmermann and Fischer, 2020; Busari et al., 2019; Giannoccaro et al., 2019; Goodwin et al., 2019; Pan et al., 2019; Romeiko, 2019; Akhoundi and Nazif, 2018; Ansari et al., 2018; Geem et al., 2018; Büyükkamaci and Karaca, 2017; Shiu et al., 2017)
	LCA	17	• Global warming potential • Eutrophication potential • Toxicities • Freshwater sources depletion • Environmental sustainability	WWTP, Environment, Human	Water volume	(Canaj et al., 2021a), (Moretti et al., 2019), (Chhipi-Shrestha et al., 2019), (Foglia et al., 2021), (Canaj et al., 2021b), (Canaj et al., 2021c), (Azeb et al., 2020), (Di Maria et al., 2020), (Oertlé et al., 2020), (Pan et al., 2019; Romeiko, 2019; Akhoundi and Nazif, 2018), (Geem et al., 2018; Büyükkamaci and Karaca, 2017; Shiu et al., 2017; Xu et al., 2020; Dong et al., 2017)
	Cost analysis	36	• Cost-effectiveness	WWTP, Environment	Water volume	(Canaj et al., 2021a), (Moretti et al., 2019), (Bolinches et al., 2022; Golfam et al., 2021; Mendret et al., 2019; Yenkie et al., 2019), (Chhipi-Shrestha et al., 2019), (López-Serrano et al., 2022), (Arena et al., 2020), (Vergine et al., 2017), (Tran et al., 2017), (Gormaz-Cuevas et al., 2021; Penserini et al., 2024; Foglia et al., 2021), (Canaj et al., 2021b), (Canaj et al., 2021c), (López-Serrano et al., 2021), (Paul et al., 2021), (Zolfaghary et al., 2021), (Dehaghi and Khoshfetrat, 2020; Di Maria et al., 2020; Oertlé et al., 2020; Oubelkacem et al., 2020; Paul et al., 2020; Zimmermann and Fischer, 2020; Busari et al., 2019; Giannoccaro et al., 2019), (Pan et al., 2019), (Akhoundi and Nazif, 2018), (Geem et al., 2018), (Büyükkamaci and Karaca, 2017), (Xu et al., 2020), (Delanka-Pedige et al., 2020; Aznar-Crespo et al., 2019; Zabala et al., 2019; Montemurro et al., 2017; Ferreira et al., 2020)
	Energy analysis	19	• Energy balance • Energy recovery	WWTP, Environment	Water volume	(Canaj et al., 2021a), (Moretti et al., 2019), (Mendret et al., 2019), (Yenkie et al., 2019), (Chhipi-Shrestha et al., 2019), (Arena et al., 2020), (Vergine et al., 2017), (Foglia et al., 2021), (Canaj et al., 2021b), (Canaj et al., 2021c), (Azeb et al., 2020), (Pan et al., 2019; Romeiko, 2019; Akhoundi and Nazif, 2018), (Büyükkamaci and Karaca, 2017), (Shiu et al., 2017), (Dong et al., 2017), (Delanka-Pedige et al., 2020), (Ferreira et al., 2020)
	Social analysis	18	• Public acceptance and awareness • Stakeholders engagement	WWTP, Environment, Human	Water volume	(Wang et al., 2019), (Jeong et al., 2020; Chhipi-Shrestha et al., 2019; López-Serrano et al., 2022), (Arena et al., 2020), (Dehaghi and Khoshfetrat, 2020; Di Maria et al., 2020; Oertlé et al., 2020), (Zimmermann and Fischer, 2020), (Goodwin et al., 2019), (Akhoundi and Nazif, 2018), (Aznar-Crespo et al., 2019), (Zabala et al., 2019), (Deh-Haghi et al.; Deh-Haghi et al., 2020; Sohail et al., 2021; Almanaseer et al., 2020; Mahjoub et al., 2022)
QUALITY-BASED	Treatment process performance	39	• Process management and optimization	WWTP, Crops	Pathogens, Nutrients, Conventional	(Seyoum et al., 2022a), (Abd-Elaty et al., 2022), (Truchado et al., 2021), (Leiva et al., 2019), (Vergine et al., 2017), (Tran et al., 2017), (Agnelo et al., 2020), (Penserini et al., 2024; Foglia et al.,

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Table 1 (*continued*)

Model type	Model	# available studies	Impacts	Compartments	Variables	References
			• Release of contaminants			2021; Ben Mordechay et al., 2021), (Contreras et al., 2017), (Gonzales-Gustavson et al., 2019), (Guadie et al., 2021), (Giannoccaro et al., 2019), (Pan et al., 2019), (Geem et al., 2018), (Büyükkamaci and Karaca, 2017), (Xu et al., 2020; Dong et al., 2017; Delanka-Pedige et al., 2020), (Ferreira et al., 2020), (Mahjoub et al., 2022; Ben Mordechay et al., 2022; Pitoro et al., 2022; Yang et al., 2021; Zaouri et al., 2021; Deepnarain et al., 2020; Hong et al., 2020; Kulkarni et al., 2020; Oliveira et al., 2020; Sharma et al., 2020; Marano et al., 2019; Martínez-Piernas et al., 2019b; Tripathi et al., 2019; Peña et al., 2019; Vergine et al., 2020; Libutti et al., 2018; Nahim-Granados et al., 2021; Moulia et al., 2023)
	Effects on soil	73	• Salinization • Soil structure degradation • Microbial community structure and activity • Contaminants cumulation	WWTP, Soil, Crops	Pathogens, CECs, Heavy metals, Nutrients, Conventional, Salinity	(Delli Compagni et al., 2020; Khaskhoussy et al., 2022; Seyoum et al., 2022a; Dahmouni et al., 2022), (Shah et al., 2022; Rezapour et al., 2021; Guedes et al., 2022; Liang et al., 2022; Hashem et al., 2022), (Gholipour et al., 2022), (Petousi et al., 2019), (de Santiago-Martín et al., 2020), (Moazeni et al., 2017), (Vergine et al., 2017), (García-Valverde et al., 2023; Bueno et al., 2022; Agnelo et al., 2020), (Seyoum et al., 2021), (Ben Mordechay et al., 2021), (Christou et al., 2017), (Revitt et al., 2021), (Franklin et al., 2018; Natasha et al., 2021; Gatta et al., 2018), (Beltrán et al., 2020), (Bakari et al., 2022; Meffe et al., 2021; Liu et al., 2020; Guadie et al., 2021; Tariq, 2021), (Romeiko, 2019), (Ansari et al., 2018), (Ferreira et al., 2020), (Ben Mordechay et al., 2022), (Sharma et al., 2020), (Marano et al., 2019), (Tripathi et al., 2019), (Libutti et al., 2018), (Moulia et al., 2023; Ben Mordechay et al., 2018; Franklin et al., 2022; Farhadkhani et al., 2020; Seyoum et al., 2022b; Abi Saab et al., 2021; Chaganti et al., 2021; de Carvalho et al., 2021; Feder, 2021; Gallego et al., 2021; Bigott et al., 2022; Kampouris et al., 2021; Musazura and Odindo, 2021; Njimat et al., 2021; Shahriar et al., 2021; Werfelli et al., 2021; Wu et al., 2021; Ababsa et al., 2020; D'Alessio et al., 2020; Hussain and Qureshi, 2020; Mendes Reis et al., 2021; Erel et al., 2019; Li et al., 2019; Obayomi et al., 2019; Beneduce et al., 2017; Liu et al., 2018; Sallach et al., 2018; Picó et al., 2019; shamsizadeh et al., 2021; Sunyer-Caldú et al., 2022; Mkhinini et al., 2019; Jahany and Rezapour, 2020; Mehmood et al., 2019; Farhadkhani et al., 2018)
	Effects on crop	108	• Salinization • Phytotoxicity • Contaminants uptake and cumulation	WWTP, Soil, Crops	Pathogens, CECs, Heavy metals, Nutrients, Conventional	(Delli Compagni et al., 2020; Khaskhoussy et al., 2022; Seyoum et al., 2022a; Dahmouni et al., 2022), (Vivaldi et al., 2022), (Moretti et al., 2019), (Golfam et al., 2021), (Truchado et al., 2021; Shah et al., 2022; Rezapour et al., 2021), (Liang et al., 2022; Hashem et al., 2022; Leiva et al., 2019; Gholipour et al., 2022; Petousi et al., 2019; Verlicchi et al., 2023; de Santiago-Martín et al., 2020; Moazeni et al., 2017; Margenat et al., 2017), (Arena et al., 2020), (Vergine et al., 2017), (García-Valverde et al., 2023; Bueno et al., 2022; Agnelo et al., 2020), (Penserini et al., 2024), (Ben Mordechay et al., 2021), (Christou et al., 2017), (Natasha et al., 2021; Gatta et al., 2018; Martínez-Piernas et al., 2019a), (Masciopinto et al., 2020), (Beltrán et al., 2020; Gonzales-Gustavson et al., 2019; Troldborg et al., 2017; Bakari et al., 2022; Meffe et al., 2021; Liu et al., 2020; Guadie et al., 2021; Tariq, 2021), (Canaj et al., 2021b), (Canaj et al., 2021c), (López-Serrano et al., 2021), (Paul et al., 2021), (Soltani-Gerdefaramarzi et al.), (Zolfaghary et al., 2021), (Azeb et al., 2020), (Dehaghi and Khoshfetrat, 2020), (Oubelkacem et al., 2020; Paul et al., 2020; Zimmermann and Fischer, 2020; Busari et al., 2019), (Romeiko, 2019), (Ansari et al., 2018), (Xu et al., 2020), (

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Table 1 (*continued*)

Model type	Model	# available studies	Impacts	Compartments	Variables	References
						Aznar-Crespo et al., 2019), (Montemurro et al., 2017), (Deh-Haghi et al.), (Deh-Haghi et al., 2020), (Almanaseer et al., 2020), (Ben Mordechay et al., 2022), (Pitoro et al., 2022), (Zaouri et al., 2021), (Deepnarain et al., 2020), (Sharma et al., 2020; Marano et al., 2019; Martínez-Piernas et al., 2019b; Tripathi et al., 2019), (Libutti et al., 2018), (Nahim-Granados et al., 2021), (Ben Mordechay et al., 2018), (Farhadkhani et al., 2020; Seyoum et al., 2022b; Abi Saab et al., 2021), (de Carvalho et al., 2021; Feder, 2021; Gallego et al., 2021; Bigott et al., 2022), (Musazura and Odindo, 2021), (Shahriar et al., 2021), (Werfelli et al., 2021), (D'Alessio et al., 2020; Hussain and Qureshi, 2020; Mendes Reis et al., 2021; Erel et al., 2019; Li et al., 2019; Obayomi et al., 2019; Beneduce et al., 2017; Liu et al., 2018; Sallach et al., 2018; Picó et al., 2019; shamsizadeh et al., 2021; Sunyer-Caldú et al., 2022), (Mehmood et al., 2019; Farhadkhani et al., 2018; Alcaide Zaragoza et al., 2022; Khan et al., 2022; Shtull-Trauring et al., 2022; Ben Hassena et al., 2018, 2021; Renai et al., 2021; Amoah et al., 2020; Perulli et al., 2019; Sofo et al., 2019; Ashrafi et al., 2017; González García et al., 2019; Rekik et al., 2017; Pedrero et al., 2018; Njuguna et al., 2019; Alvarez-Holguin et al., 2022)
	Environmental risk	13	• Risk for the environment	WWTP, Environment	CECs, Heavy metals, Nutrients	(Delli Compagni et al., 2020), (Canaj et al., 2021a), (Moretti et al., 2019), (Verlicchi et al., 2023), (Foglia et al., 2021), (Franklin et al., 2018), (Canaj et al., 2021b), (Canaj et al., 2021c), (Azeb et al., 2020), (Pan et al., 2019), (Romeiko, 2019), (Büyükkamaci and Karaca, 2017), (Shiu et al., 2017)
	Human risk	45	• Risk for human health	WWTP, Crops, Human	Pathogens, CECs, Heavy metals	(Delli Compagni et al., 2020), (Penserini et al., 2023), (Canaj et al., 2021a), (Moretti et al., 2019), (Gholipour et al., 2022), (de Santiago-Martín et al., 2020), (Moazeni et al., 2017), (Rebelo et al., 2020), (García-Valverde et al., 2023), (Bueno et al., 2022), (Foglia et al., 2021), (Christou et al., 2017), (Revitt et al., 2021), (Fonseca-Salazar et al., 2021), (Natasha et al., 2021; Gatta et al., 2018; Martínez-Piernas et al., 2019a), (Masciopinto et al., 2020; Contreras et al., 2017; Beltrán et al., 2020; Gonzales-Gustavson et al., 2019; Troldborg et al., 2017; Bakari et al., 2022; Meffe et al., 2021; Liu et al., 2020; Guadie et al., 2021; Tariq, 2021), (Canaj et al., 2021b), (Canaj et al., 2021c), (Azeb et al., 2020), (Di Maria et al., 2020), (Pan et al., 2019), (Romeiko, 2019), (Büyükkamaci and Karaca, 2017), (Shiu et al., 2017), (Dong et al., 2017), (Deepnarain et al., 2020), (Nahim-Granados et al., 2021), (Farhadkhani et al., 2020), (Shahriar et al., 2021), (Hussain and Qureshi, 2020), (Mehmood et al., 2019), (Amoah et al., 2020), (Njuguna et al., 2019), (Owusu-Ansah et al., 2017)

and indirect energy usage, promote renewable energy integration, and recover energy throughout the process.

Lastly, social models focus on analyzing interactions, behaviors and perceptions of diverse stakeholders involved in agricultural reuse, including farmers, policy-makers and consumers. These models often integrate social indicators (e.g., cultural factors, income level), through multi-criteria analysis to quantify the impacts (Jeong et al., 2020). A key aspect of social models is their emphasis on the human compartment, as they aim to understand and address the social implications of wastewater reuse in agriculture. Thus, along with LCA models, social models address impacts on humans despite being quantity-based models (Table 1). Notably, the variable of primary interest in these models is frequently the quantity of water reused, since it is recognized as a pivotal factor influencing the social implications of agricultural wastewater reuse (Chhipi-Shrestha et al., 2019). Stakeholders are usually engaged through surveys, aiming at developing effective communication and education campaigns to promote public acceptance (López-Serrano et al., 2022).

3.2. Quality-based impacts models

Treatment process models focus on the quality of the wastewater as a function of the reclamation treatment train. They are used to optimize and manage the treatment processes aiming at (i) controlling the release of different types of contaminants, to minimize potential harm to the compartments downstream the point of discharge (Rizzo et al., 2020), (ii) guaranteeing that reclaimed wastewater meets the required standards for safe irrigation (Truchado et al., 2021).

Models estimating the effects on soil of reclaimed wastewater reuse are aimed at the assessment of several impacts, since each contaminant released in soil determines a different effect. A high level of inorganic constituents in reclaimed wastewater, determining wastewater salinity, may lead to soil salinization (Shah et al., 2022). Organic and inorganic constituents, such as organic matter and ions, can determine deterioration of soil hydraulic properties (Rezapour et al., 2021). The potentially harmful contaminants, such as pathogens, heavy metals, CECs, ARBs and DBPs can cumulate in soil and alter the soil microbial community structure and activity (Guedes et al., 2022). Nutrients contained in reclaimed wastewater may lead to fertilization enhancement of soil, or instead to a nutrient overdosage (Liang et al., 2022).

The modelled effects on crops of reclaimed wastewater reuse are similar to the ones modelled for soil. Reclaimed wastewater contains both conventional nutrients (nitrogen, phosphorus and potassium) as well as micronutrients that together enhance crops growth and yield (Hashem et al., 2022). However, chemicals such as heavy metals, CECs, and DBPs can be uptaken from the soil and accumulate in different parts of the plant (i.e., root, leaves or steam), leading to phytotoxicity and hindering crop growth (Leiva et al., 2019). Pathogens and ARBs, on the other hand, are generally not uptaken into the plant tissue, but can adhere to the surface, posing risks primarily for crops consumed raw (Gholipour et al., 2022). When exposed to saline conditions, crops may experience an osmotic stress, resulting in yield loss and lower product quality (Petousi et al., 2019).

Environmental risk models are used to assess the potential risk that contaminants may pose to the environment. In the case of agricultural wastewater reuse, the environmental risk is estimated for the receiving surface water, quantifying the adverse effects on the ecosystem and the impacted species (Verlicchi et al., 2023).

Human risk models are applied to quantify human health risks for both hazardous chemicals (de Santiago-Martín et al., 2020) and microorganisms (Moazeni et al., 2017), deriving from the consumption of crops irrigated by reclaimed wastewater.

4. Studies classification between direct and indirect reuse

An essential aspect to consider when the impacts of agricultural wastewater reuse are modelled is the distinction between direct and indirect reuse, since it strongly affects the quality of irrigation water. Fig. 2 delineates the partition of the collected articles between direct and indirect reuse.

It clearly emerges that the direct reuse is the dominant focus, accounting for the 84% (139 out of 165 articles) of the considered studies. However, this does not align with the actual reality of reclaimed wastewater reuse practices. In fact, most surface water streams are employed *de facto* for indirect irrigation, especially due to the increasing number of WWTPs discharging their effluents in the natural water network (Margenat et al., 2017); while still a limited, and only recently growing, number of WWTPs are applying direct reuse (Alcalde-Sanz et al., 2014). Consequently, the indirect reuse of reclaimed wastewater remains an understudied practice.

This research gap arises due to two main reasons. Firstly, the direct wastewater reuse is easier to replicate at lab- or pilot-scale with respect to the indirect one (Rizzo et al., 2020). Secondly, most of the currently suggested and regulated water quality standards (Rebelo et al., 2020) refer to the direct wastewater reuse, making it a more compelling subject for researchers and practitioners. Indirect reuse is often not considered as a wastewater reuse, but it is rather implemented as an unplanned reuse. In fact, many studies do not specify the type of reuse under investigation, while no studies were conducted to compare the impacts resulting from direct and indirect reuse, highlighting a disparity between the extensive application of this practice and the gap pointed out in literature. The fact that only direct reuse is regulated may inadvertently encourage the widespread application of indirect reuse, which is unregulated. Stakeholders would find it more convenient to comply with the conventional water quality standard for discharge in surface water, from which the irrigation water is derived, rather than complying with more stringent water quality standards for reuse, and providing an *ad hoc* infrastructure for delivering reclaimed wastewater to crops (Angelakis and Snyder, 2015).

The cost of dedicated infrastructures coupled with the territorial context are crucial aspects to consider, since they greatly influence the type of reuse and the allocation of economic resources. Such infrastructures are suitable only where the territory does not already provide a network of irrigation channels that can be utilized. In fact, in

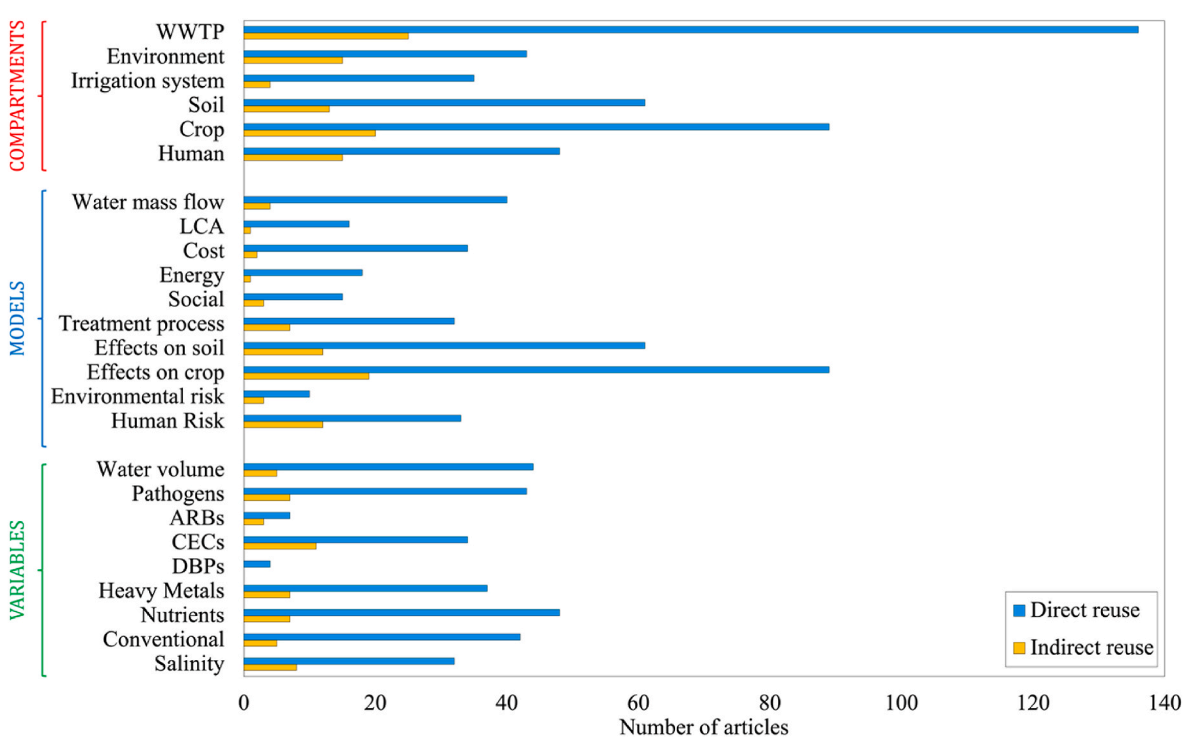

Fig. 2. Number of articles mentioning the analyzed categories, differentiated per direct or indirect reuse.

these latter cases, the reuse often shifts from direct to indirect, because these irrigation channels are already supplied with natural waters. When the proportion of natural water reduces in favor of reclaimed wastewater, also pushed by climate change consequences, the reuse is brought back towards a direct reuse, which skips yet regulations. Thus, economic resources are more likely to be employed for the WWTPs upgrade rather than for the creation of transport infrastructure. Two examples are Lombardy and Apulia regions in Italy: in Lombardy, where more than 37,000 km of irrigation channels are present, reclaimed wastewater is often indirectly reused due to the existing natural channels (Pistocchi et al., 2018), while in Apulia, where no irrigation channels are present, many cases of direct reuse are reported (Vivaldi et al., 2022), (Arena et al., 2020), (Vergine et al., 2017). Therefore, the choice of reuse type strictly depends on the local territory characteristics. Additionally, stakeholders are often unaware about the actual use of the surface water downstream the point of effluent discharge, and this might lead to overlook the potential implications of an unplanned reuse (Helmecke et al., 2020). This highlights the need for regulatory alignment in water quality standards for both direct and indirect reuse. The EU Watch List (Cortes et al., 2022) could serve as a starting point for developing more uniform regulations governing indirect reuse, ensuring that the same monitoring and risk management practices are applied across both direct and indirect reuse scenarios. Such regulatory alignment is essential to bridge the gap between practice and research, and to encourage the implementation of comprehensive risk assessments that consider both reuse types.

Moreover, there is a growing concern on how climate change can affect freshwater availability and quality (Ianes et al., 2023). However, among articles addressing indirect agricultural wastewater reuse, only (Tran et al., 2017) examined how the contaminants in the WWTP effluent and in the aquatic environment may be altered by drought, focusing on how treatment trains may be upgraded to reduce contaminants concentrations. This represents an important gap, demanding further research, being reclaimed wastewater reuse a viable alternative water source for agriculture, to mitigate the current and projected water scarcity.

5. Trends in categories combinations: consolidated aspects and gaps to be filled

Given the complexity of connections between compartments (see Fig. 1), there is a large variety of impacts that need to be quantified for providing a comprehensive overview of pros and cons of agricultural wastewater reuse. Hence, a heatmap of the available literature studies is here presented in Fig. 3 to visualize, through the categories introduced in Section 2, (i) which compartments and to which extent are considered, (ii) which variables are targeted in literature, and (iii) how the various models are combined. For each cell, the heatmap reports the number of articles in which the corresponding paired categories are considered simultaneously, while along the diagonal the total number of studies evaluating the individual categories are reported.

Regarding the analyzed compartments, from the top-left part of the diagonal, it can be noted that most of the studies consider respectively WWTP (161 out of 165 articles) and Crop (109 out of 165 articles) compartments. This was somehow expected since the impacts assessment of reclaimed wastewater reuse in agriculture must necessarily consider WWTP and crops characteristics. However, the other interconnected compartments (environment, irrigation system, soil and humans) are analyzed in less than half of the studies, with numbers ranging from 39 to 74 studies per compartment. Neglecting these compartments and their interconnections does not allow for a comprehensive understanding of the impacts, both positive and negative, nor helps in identifying long-term strategies to maximize positive impacts and minimize negative ones. For instance, beyond water and nutrient supply, positive impacts include potential groundwater recharge, which is closely linked to the irrigation system used. In anticipation of increasingly prolonged drought periods, groundwater might act as a natural reservoir (Humberto et al., 2018). Thus, ignoring the broader context and these additional benefits can lead to incomplete impact assessments and suboptimal strategies.

For the targeted variables, from the bottom-right part of the diagonal, it emerges that most of them, such as conventional contaminants (e.g., heavy metals, nutrients, etc.), pathogens and CECs, are relatively well-addressed in the literature, with 40–55 studies per variable. The uniform consideration of these variables across studies demonstrates a mature understanding of their behavior in different compartments, such as soil, crops, and groundwater, and the risk they pose to human health through food chain transfer. For instance, CECs have been the focus of extensive modeling efforts (*inter alia*, (García-Valverde et al., 2023), (Bueno et al., 2022)), leading to a robust body of work that evaluates their persistence in the environment, bioaccumulation potential, and ecotoxicological impacts. Among them, pharmaceuticals were the most frequently studied, appearing in 35 out of 45 studies on CECs. On the other hand, the positive effects of nutrients are frequently compared to the negative ones of heavy metals or salinity in soil and crop models (Agnelo et al., 2020).

Despite this comprehensive coverage, notable gaps remain in the literature concerning ARBs and DBPs, for which only, respectively, 10 and 4 studies out of 165 were carried out, pointing out a lack of applications addressing these variables. However, these contaminants are topics of growing interest inevitably related to the reclaimed wastewater reuse, since WWTPs are the major contributors for their presence into the environment (Albolafio et al., 2022). Specifically, ARBs and antibiotic resistance genes (ARGs) monitoring poses a specific challenge due to their extensive breadth and high measurement cost, associated with the complexity in correlating their presence with established monitoring targets (e.g., *Escherichia coli*) (Seyoum et al., 2021). The concern for DBPs is raised due to the high level of disinfection efficacy demanded by direct reuse regulations. The regulatory limit for *E. coli* is set at 10 CFU mL^{-1} (EU Commission, 2020), in contrast with the 5,000 CFU mL^{-1} allowed for discharge into surface water (UWWTD 91/271), which eventually would apply in case of indirect reuse. Meeting this standard requires using substantial dosages of disinfectants, which, in case of chemical disinfection, can lead to the formation of DBPs. DBPs pose significant risks to aquatic ecosystems, particularly in cases of indirect reuse where treated water may eventually reach natural water bodies (Cui et al., 2021). For humans, DBPs raise concerns about their potential accumulation in the edible parts of crops (Christou et al., 2019). This underscores the critical importance of including both these variables in agricultural wastewater reuse studies. In addition, it highlights the necessity of considering the interconnections of the entire system, especially for certain types of contaminants that have the most substantial negative impacts on both human health and the environment. Addressing this gap is essential to develop comprehensive strategies that ensure the safe and sustainable reuse of reclaimed wastewater in agriculture.

Focusing on the models' combinations, quantity-based impact models are typically used for large scale planning, assessing impacts across extensive systems, from freshwater resources to the domestic water usage in cities. These models are frequently combined through Multi-Criteria Decision Analysis (MCDA) approaches to optimize the distribution of water volumes within the studied system, including wastewater as one of the considered water flows. In many cases, the optimal allocation of water volumes is obtained integrating also LCA, cost, energy or social impact models. In fact, they are applied in, respectively, 82%, 78%, 84% and 50% of the studies addressing water mass flow models. For example, in (Gormaz-Cuevas et al., 2021) the climate-induced water scarcity was addressed by formulating a multi-objective problem for the regional optimization of water extraction from natural sources and reuse, in which environmental and economic impacts are minimized. Occasionally reclaimed wastewater quality is also considered, but commonly quality parameters are

	WWTP	Environment	Irrigation system	Soil	Crop	Human	Water mass flow	LCA	Cost	Energy	Social	Treatment process	Effects on soil	Effects on crops	Environmental risk	Human risk	Water volume	Pathogens	ARBs	CECs	DBPs	Heavy metals	Nutrients	Conventionals	Salinity
WWTP	161																								
Environment	57	58																							
Irrigation system	38	9	39																						
Soil	72	10	18	74																					
Crop	108	31	32	59	109																				
Human	61	31	10	22	40	63																			
Water mass flow	43	38	9	3	20	20	44																		
LCA	17	16	4	1	6	15	15	17																	
Cost	35	28	3	2	17	17	29	13	36																
Energy	19	15	4	3	7	14	16	13	15	19															
Social	16	13	3	0	7	18	10	4	10	3	18														
Treatment process	39	10	6	12	20	10	9	6	11	7	1	39													
Effects on soil	71	9	18	73	58	21	3	1	2	3	0	12	73												
Effects on crops	107	30	32	58	108	39	20	6	17	7	7	20	58	108											
Environmental risk	13	13	5	3	7	11	10	10	7	10	0	3	3	7	13										
Human risk	45	19	7	22	32	45	11	12	8	11	1	9	21	31	11	45									
Water volume	47	39	10	3	23	25	44	15	32	16	15	9	3	23	10	11	49								
Pathogens	50	11	13	24	31	19	5	3	5	5	2	21	24	31	3	17	5	50							
ARBs	10	3	4	7	6	0	0	0	0	0	0	4	7	6	1	0	0	2	10						
CECs	44	15	8	30	35	22	7	7	6	8	1	9	29	34	10	20	7	9	4	45					
DBPs	4	0	3	3	4	0	0	0	0	0	0	2	3	4	0	0	0	3	0	0	4				
Heavy metals	43	15	8	23	31	21	10	8	7	8	4	7	23	31	7	18	10	13	1	11	1	44			
Nutrients	55	18	21	24	43	15	17	10	14	10	4	12	24	43	8	12	17	18	0	9	4	27	55		
Conventionals	47	13	14	24	26	12	12	9	10	9	4	18	24	26	6	9	12	21	0	9	3	24	31	47	
Salinity	39	9	13	24	30	9	9	4	4	4	2	10	24	30	4	7	9	12	0	7	3	19	27	23	40

4 – 161: Number of articles mentioning the single category (diagonal)

0 – 108: Number of articles mentioning the paired categories

Fig. 3. Heatmap reporting the paired combinations between the categories identified as in Fig. 1, grouped per compartments (in red), models (in blue) and variables (in green). In each cell, at the intersection of a row and column, is indicated, also by a gradient color scale, the number of articles addressing both the categories labeled in the row and column.

converted in indicators of other impacts. Two examples can be found in the studies of (Vivaldi et al., 2022) and (Penserini et al., 2024). In (Vivaldi et al., 2022) a set of quantitative indices was proposed, combining physical and operational features of both WWTPs and irrigation districts equipped for wastewater reuse, to quantify the reuse environmental benefits. In (Penserini et al., 2024) the economic savings resulting from direct reuse were estimated, combining effluent quality, crops requirements and characteristics of WWTPs and surrounding territory, in a prioritization framework. LCA models represent an exception because they already integrate the combination of different impacts, considering often also quality variables and risks. For example, in (Foglia et al., 2021), LCA was adopted for the assessment of environmental and economic impacts of a conventional WWTP compared to the impacts related to the WWTP upgrade for effluent reclamation.

Regarding the integration of quality-based impact models, they are often combined to model the transfer of contaminants between two or more compartments. For example, soil can accumulate compounds, blocking them from reaching crops, and, consequently, humans (Ben Mordechay et al., 2021). Conversely, the adopted irrigation system can affect the hazards related to specific compounds, as highlighted *inter alia* by (Hamilton et al., 2018) and (Aragüés et al., 2015). In (Hamilton et al., 2018) it was showed how the spray irrigation of reclaimed wastewater can increase the *Legionella pneumophila* risk for human health due to the formation of aerosols. While in (Aragüés et al., 2015) it was demonstrated that the improper management of the irrigation system can bring to soil salinization.

Regarding risk assessment models, if only studies performing exhaustive risk assessments are considered (excluding LCA studies), it emerges that only three studies applied an environmental risk assessment to reclaimed wastewater reuse. Being the indirect reuse the main responsible for the potential presence of an environmental risk, the lack of studies modelling the environmental risk is in accordance with the low number of studies addressing indirect reuse. Conversely, human risk is modelled more frequently than the environmental one (33 studies if LCA is not considered), but in no case these two risk assessment procedures were combined. A comprehensive risk-assessment framework that evaluates the impacts of the reclaimed wastewater reuse from the WWTP down to the final endpoints (environment or human health) is still missing. Such a framework would be useful in identifying the main contributors to the final estimated risk and it would support the prioritization of mitigation measures, indicating where and to which extent apply them.

6. Overview of the available risk assessment procedures

Risk assessment procedures are usually structured in four steps:

- problem formulation, to select the contaminant of interest and the target endpoint;
- exposure assessment, to identify exposure pathways and levels;
- hazard assessment, to determine dose-response relationships and toxicological reference concentrations;
- risk characterization, to estimate the magnitude of the risk through a risk index.

A preliminary distinction among risk assessment procedures regards the selected endpoint which can be either environmental (i.e., the natural water ecosystem) or human health. Depending on the selected endpoint, the contaminants of interest may differ.

In environmental risk assessment, target contaminants are usually chemicals (i.e., heavy metals, CECs, and DBPs). The exposed populations in these assessments typically include aquatic organisms (e.g., fish, invertebrates, and algae), and terrestrial wildlife (that may consume contaminated water or food) (Amiard and Amiard-Triquet, 2015). The exposure level corresponds to the measured environmental concentration (MEC) in natural water, while the toxicological reference concentration corresponds to the Predicted No-Effect Concentration (PNEC), determined through eco-toxicity studies. These studies estimate the concentration that is not expected to cause adverse effects on the specified organism over a given exposure period. For aquatic organisms, eco-toxicity studies typically measure effects on survival, reproduction, and growth, which are used to define the PNEC (Belanger et al., 2021).

For antibiotics, another threshold must be mentioned, since they may display an adverse effect directly or indirectly, through favoring the development of antibiotic resistance. In the latter case, the Predicted No-Effect Concentration for the antibiotic resistance development ($PNEC_{AR}$) is also considered, determined through the quantification of minimum inhibitory concentration data. These thresholds are critical for understanding at what concentrations antibiotics in the environment begin to select for resistant genes or bacteria (Bengtsson-Palme and Larsson, 2016).

In human health risk assessment, the targeted contaminants can be both chemicals or pathogens, typically characterized by, respectively, long-term chronic effects or short-term acute effects (Ardiyanti et al., 2024b), and the most common route of exposure is the oral ingestion due to crop consumption (Moazeni et al., 2017), (Christou et al., 2017). Then, exposure levels are estimated from the contaminants concentration in crops (C_{CROP}). For chemical hazard assessment, reference doses (RfD) are derived from toxicological studies as daily exposures levels that are not likely to have adverse health effects on the critical endpoint affected by the investigated substance during a person's lifetime (Baken et al., 2018). For microbial hazard assessment, dose-response relationships are used to correlate the pathogen dose and the probability and severity of adverse health effects (WHO, 2016), (Haas et al., 2014).

Finally, for both environmental and human health risk characterization, the type of approach can be qualitative, deterministic or probabilistic, in which the risk is quantified through, respectively, a qualitative index, a single precautionary value, or a statistical distribution. In particular, probabilistic approaches, as Quantitative Microbial Risk Assessment (QMRA) and Quantitative Chemical Risk Assessment (QCRA), permit to account for the uncertainties inherently present in each step of the risk assessment procedures (Ardiyanti et al., 2024b), (Zhiteneva et al., 2020). Estimating these uncertainties is crucial for understanding the reliability of the risk estimate, especially for contaminants for which the knowledge is not yet consolidated. Qualitative approaches do not have a reference procedure to rely on, but they are commonly adopted to derive risk matrices as outputs (Rebelo et al., 2020), (Revitt et al., 2021), (Fonseca-Salazar et al., 2021).

Deterministic approaches conventionally consider the most precautionary values (i.e., maximum exposure concentration) to ensure the absence of risk in the most critical scenario. In the Environmental Risk Assessment (ERA), the maximum MEC is divided by PNEC or $PNEC_{AR}$ to estimate, respectively the Risk Quotient (RQ) (Verlicchi et al., 2023) and the Risk Quotient for antibiotic resistance development (RQ_{AR}) (Franklin et al., 2018) as follows:

$$RQ = \frac{MEC}{PNEC} \tag{1}$$

$$RQ_{AR} = \frac{MEC}{PNEC_{AR}} \tag{2}$$

In deterministic Chemical Risk Assessment (CRA) for human health, the maximum C_{CROP} is divided by RfD to obtain the Hazard Quotient (HQ) of a single contaminant (Natasha et al., 2021). When multiple contaminants are considered, the HQ values for each contaminant are summed up to obtain the Hazard Index (HI) (Gatta et al., 2018) as follows:

$$HQ_i = \frac{C_{CROP,i}}{RfD_i} \tag{3}$$

$$HI = \sum_i HQ_i \tag{4}$$

However, the use of a specific concentration value for the exposure assessment, for example the 50th, 75th, 90th percentile or the maximum concentration value, can strongly influence the risk estimation (Ianes et al., 2023). For chemicals, when limited toxicological data are available, human risk can be evaluated through the Threshold of Toxicological Concern (TTC) approach, in which chemicals are categorized into classes based on structural similarities and known toxicological data (e.g., Cramer classes I, II, and III) to set threshold exposure levels below which adverse effects are unlikely to occur (Christou et al., 2017), (Martínez-Piernas et al., 2019a).

Probabilistic approaches employ statistical indicators to determine the probability of risk. For chemicals, QCRA procedures are available to calculate the risk as a statistical distribution of the Benchmark Quotient (BQ), giving insights about estimation uncertainties (Cantoni et al., 2021), (Penserini et al., 2022). However, they have been primarily applied to evaluate risks associated to drinking water consumption, while only (Penserini et al., 2023) applied the QCRA to reclaimed wastewater reuse practices, estimating the probability of risk due to the consumption of crops irrigated with reclaimed wastewater. Conversely, QMRA are consolidated procedures quantifying the risk in terms of statistical distribution of Disability-Adjusted Life Year (DALY) and they are already frequently implemented for the risk evaluation of agricultural wastewater reuse (Masciopinto et al., 2020), (Contreras et al., 2017). Within this framework of diverse risk assessment procedures, Table 2 presents a summary of the mentioned available procedures, indicating their specific features (e.g., endpoint, inputs, outputs, etc.) and the number of studies that applied them to agricultural wastewater reuse.

It is interesting to note that articles are not uniformly distributed among the various types of risk assessment. Environmental risk assessment is mainly focused on chemicals by deterministic procedures and, if LCA studies are not considered, it is almost never applied to agricultural wastewater reuse (only three studies). Instead, human health risk assessment is performed more frequently in the agricultural reuse context, adopting different approaches depending on the contaminant of interest: for chemicals, the assessment is mainly deterministic (García-Valverde et al., 2023), (Beltrán et al., 2020), while for microorganisms the assessment is mainly probabilistic (Masciopinto et al., 2020), (Gonzales-Gustavson et al., 2019).

Table 2
Summary of the main features of risk assessment procedures applied to reclaimed wastewater reuse. The number of articles applying the specific type of risk assessment procedure is reported in brackets.

Endpoint	Risk source	Type of approach	Procedure	Exposure inputs	Toxicological inputs	Output	References
Environment (13)	CECs and heavy metals (12)	Deterministic (12)	ERA[a] (2)	Maximum MEC	PNEC	RQ	(Delli Compagni et al., 2020; Verlicchi et al., 2023)
			LCA (10)	Emission concentration from WWTP	CF_{ET}[b]	PDF[c]	(Canaj et al., 2021a; Canaj et al., 2021b; Canaj et al., 2021c; Foglia et al., 2021; Azeb et al., 2020; Moretti et al., 2019; Pan et al., 2019; Romeiko, 2019; Büyükkamaci and Karaca, 2017; Shiu et al., 2017)
	Antibiotics (1)	Deterministic (1)	ERA_{AR}[a] (1)	Maximum MEC	$PNEC_{AR}$	RQ_{AR}	(Franklin et al., 2018)
Human health (45)	CECs, including antibiotics, and heavy metals (32)	Qualitative (1)	Case-specific (1)	–	–	Risk matrix	(Revitt et al., 2021)
		Deterministic (30)	CRA (20)	Maximum C_{CROP}	RfD, Cramer class	HI, HQ, TTC	(Nahim-Granados et al., 2021; Guadie et al., 2021; Bakari et al., 2022; Bueno et al., 2022; Meffe et al., 2021; de Santiago-Martín et al., 2020; Shahriar et al., 2021; Natasha et al., 2021; Delli Compagni et al., 2020; Hussain and Qureshi, 2020; Liu et al., 2020; Gatta et al., 2018; Christou et al., 2017; Beltrán et al., 2020; García-Valverde et al., 2023; Tariq, 2021; Mehmood et al., 2019; Martínez-Piernas et al., 2019a; Njuguna et al., 2019; Troldborg et al., 2017)
			LCA (10)	Emission concentration from WWTP	CF_{HT}[d]	DALY	(Canaj et al., 2021a; Canaj et al., 2021b; Canaj et al., 2021c; Foglia et al., 2021; Azeb et al., 2020; Moretti et al., 2019; Pan et al., 2019; Romeiko, 2019; Büyükkamaci and Karaca, 2017; Shiu et al., 2017)
		Probabilistic (1)	QCRA (1)	Statistical distribution of C_{CROP}	Statistical distribution of RfD	BQ	(Penserini et al., 2023)
	Pathogens (16)	Qualitative (2)	Case-specific (2)	–	–	Risk matrix	(Fonseca-Salazar et al., 2021; Rebelo et al., 2020)
		Deterministic (3)	LCA (3)	Emission concentration from WWTP	CF_{HT}[d]	DALY	(Foglia et al., 2021; Büyükkamaci and Karaca, 2017; Dong et al., 2017)
		Probabilistic (12)	QMRA (12)	Statistical distribution of C_{CROP}	Dose-response model	DALY	(Dong et al., 2017; Deepnarain et al., 2020; Gonzales-Gustavson et al., 2019; Nahim-Granados et al., 2021; Gholipour et al., 2022; Farhadkhani et al., 2020; Hussain and Qureshi, 2020; Moazeni et al., 2017; Amoah et al., 2020; Masciopinto et al., 2020; Owusu-Ansah et al., 2017; Troldborg et al., 2017)

[a] Environmental Risk Assessment.
[b] Characterization factor for environmental toxicity.
[c] Potentially Disappeared Fraction.
[d] Characterization factor for human toxicity.

Anyway, even if the procedures for quantifying risk for chemicals and pathogens are well consolidated, there are no studies concurrently modelling the effects of both types of risk. (Troldborg et al., 2017) was the only study assessing the risks associated with the presence of both CECs and pathogens in wastewater for agricultural reuse. However, there was no integration nor comparison undertaken.

7. Integrated risk assessment approach

The abovementioned uneven state-of-the-art about risk assessment application to reclaimed wastewater reuse, makes it challenging to provide a comprehensive overview of the associated impacts in a One Health perspective, especially in the case of indirect reuse, where risks emerge for both the environment and human health.

Only (Delli Compagni et al., 2020) assessed the risk for both human health and environment in a case of indirect reclaimed wastewater reuse in agriculture, but no integration nor comparison of these two results was performed. The other existing studies estimating human health risk for indirect reuse, completely neglected the evaluation of the concurring environmental risk (de Santiago-Martín et al., 2020), (Bakari et al., 2022), (Meffe et al., 2021), (Liu et al., 2020), (Guadie et al., 2021), (Tariq, 2021).

To address this gap, we propose a simplified but holistic approach, in which human health, environmental and antibiotic resistance development risks due to CECs presence in reclaimed wastewater for indirect reuse are simultaneously estimated. Antibiotic resistance is addressed as a separate endpoint due to its dual impact on both human health and environmental ecosystems. ARBs and ARGs can spread through environmental pathways, leading to increased resistance in bacterial communities, which, in turn, poses significant threats to human health (Stanton et al., 2022). Typically, environmental risk assessments focus on the ecological impacts of contaminants on the aquatic ecosystem, while human health risk assessments focus on the adverse effects contaminants have when contacted by humans. However, both the approaches overlook the selection pressures exerted by low levels of antibiotics on microbial communities, which promote the development and dissemination of antibiotic resistance (WHO, 2024). This gap underscores the need to incorporate antibiotic resistance development within risk frameworks. Pharmaceuticals were selected as CECs of interest due to their ubiquitous presence in different compartments, their related risks potentially posed to human health and environment, and because, as pointed out from the literature review results, they are the most frequently addressed CECs in research focusing on wastewater reuse. Among these, antibiotics were specifically considered since they are the only class of contaminants capable of contributing to the development of antibiotic resistance. Studies were selected in this evaluation only if they met both the following criteria: (i) they calculated the human health risk associated to the consumption of crops irrigated through indirect reuse, and (ii) they provided contaminants concentration in the surface water collected and used for irrigation.

Only 4 articles out of 165 complied with the abovementioned criteria, namely (Delli Compagni et al., 2020), (de Santiago-Martín et al., 2020), (Meffe et al., 2021) and (Liu et al., 2020). We considered six pharmaceuticals, being the only ones in common among these articles: three pharmaceuticals, namely carbamazepine, diclofenac and ibuprofen, and three antibiotics, namely metronidazole, sulfamethoxazole and trimethoprim. The human health risks estimated by the articles authors and expressed as HQ, were directly taken and considered for the human health risk. In addition, two further types of risks occurring in the surface water used for irrigation were quantified: the environmental risk (RQ) was calculated from MEC and PNEC as in equation (1), while the risk for antibiotic resistance development (RQ_{AR}) was calculated from MEC and $PNEC_{AR}$ as in equation (2), in which MEC corresponds to the surface water concentration data reported by the considered studies. The PNEC and $PNEC_{AR}$ values of the selected pharmaceuticals were retrieved from literature, indicating threshold values for the development of, respectively, a chronic risk for the aquatic ecosystem and antibiotic resistance due to the selection of resistant bacterial strains.

Risk indices (i.e., HQ, RQ, RQ_{AR}) equal to 0 correspond to an absence of risk, equal or above to 1 to a presence of risk, while values lower than 1 but higher than 0.1 indicate warning thresholds for potential risk occurrence (Penserini et al., 2022). A summary of the data retrieved from these studies to calculate environmental and antibiotic resistance development risks for each CEC is reported in Table 3, while the risks assessment results are shown in Fig. 4, where the three different risks are visualized together and differentiated per CEC.

HQ distributions shown in Fig. 4 represent the HQ estimated by the four studies for the selected pharmaceuticals. These results highlight that human health risk related to the indirect reuse of reclaimed wastewater, meaning the risk related to the consumption of crops irrigated with surface water in which reclaimed wastewater is discharged, is substantially lower than the warning threshold (HQ equal to 0.1) for all the considered pharmaceuticals. Thus, if only the human health risk is evaluated, as done in the original studies, it might be stated that the presence of these contaminants in the reclaimed wastewater reused for crop irrigation, after dilution with the natural surface water stream, does not pose any risk.

However, if environmental risk and risk of antibiotic resistance development associated with the pharmaceuticals concentration in the surface water are calculated, it becomes evident that they contribute significantly to the overall risk. In fact, RQ and RQ_{AR} are always statistically higher than the HQ and, in some cases, than the risk thresholds of 0.1 and 1. Hence, a presence of risk is established. Specifically, diclofenac and ibuprofen have RQ markedly higher than the threshold of 1, with estimated average RQs equal to, respectively, 5.1 and 9.4. The estimated RQ_{AR} distribution for metronidazole straddles the threshold of 1, having an average RQ_{AR} equal to 1.6. The estimated distributions of RQ and RQ_{AR}, for respectively, sulfamethoxazole and trimethoprim exhibit values exceeding the threshold of 0.1.

Thus, an increased attention would be recommendable for metronidazole and trimethoprim, in terms of regulatory measures or additional targeted monitoring campaigns. As for trimethoprim, it is the only pharmaceutical whose HQ distribution is significantly higher than the RQ one, but, on the other hand, it is slightly lower than the RQ_{AR}

Table 3
Summary of the data used for the calculation of environmental and antibiotic resistance development risks for each considered CEC. The concentrations in surface water (MEC) are reported as average and range in brackets, with the corresponding number of available concentration data, obtained from the considered studies. PNEC and $PNEC_{AR}$ values were retrieved in literature.

Class of CECs	CECs	CAS number	MEC [μg L^{-1}]	# available concentrations	PNEC [μg L^{-1}]	$PNEC_{AR}$ [μg L^{-1}]
Pharmaceuticals	CBZ	298–46-4	0.12 (0.11–0.15)	4	2[a]	–
	DCF	15,307–86-5	0.25 (0.16–0.32)	4	0.05[a]	–
	IBU	15,687-27-1	0.10 (0.003–0.18)	5	0.011[a]	–
Antibiotics	MET	443–48-1	0.20 (0.06–0.33)	3	33.1[a]	0.125[b]
	SMX	723–46-6	0.07 (0.006–0.13)	5	0.6[a]	16[b]
	TMP	738-70-5	0.06 (0.001–0.09)	3	120[a]	0.5[b]

[a] NORMAN website.
[b] Bengtsson-Palme and Larsson (2016).

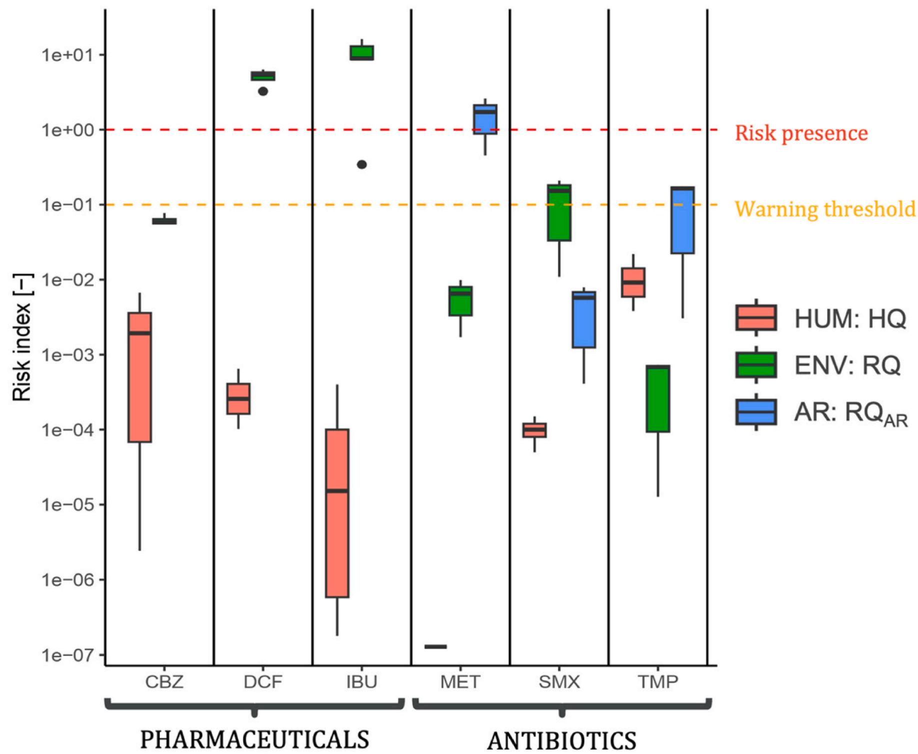

Fig. 4. Risk indices distributions for human health (HUM), environmental (ENV), and antibiotic resistance (AR) risks, across the analyzed pharmaceuticals: carbamazepine (CBZ), diclofenac (DCF), ibuprofen (IBU), metronidazole (MET), sulfamethoxazole (SMX) and trimethoprim (TMP). HQ values were estimated by the four studies analyzed, while RQ and RQ_{AR} were calculated within this work. Dashed lines indicate risk indices values equal to the warning thresholds (0.1) and risk presence threshold (1).

distribution.

This analysis underscores the importance of a holistic risk assessment employing a One Health approach. Instead of limiting the risk evaluation to the human endpoint, this approach assesses also the environmental and antibiotic resistance development risks for each pharmaceutical. This ensures that human health, environmental and antibiotic resistance development impacts are not only calculated but also contextualized within a broader framework, which helps determining contribution of each risk to the overall risk and identify the most critical endpoint. An important direct outcome of this One Health approach is the identification of the compounds responsible of the higher risk, supporting regulators and policy makers in an effective joint protection of humans and environment.

In the context of indirect reuse, integrating regulations on direct reuse, effluent discharge, and water body quality would be essential, as the latter two are directly correlated, and extending this procedure to a larger group of compounds would aid in establishing a prioritization framework for defining minimum water quality regulation standards. This integration would enhance the effectiveness of monitoring and managing the risks associated with reclaimed wastewater reuse, ensuring a more comprehensive protection of both human health and the environment.

8. Conclusions and remarks for future research directions

The review about models available to assess the impacts of reclaimed wastewater reuse in agriculture pointed out the main literature gaps, delineating areas for future research directions. In synthesis:

- Despite many surface water streams are used *de facto* for indirect and unplanned reuse of reclaimed wastewater, indirect reuse is not consistently analyzed as a formal practice. Thus, there is a lack of studies modelling the impacts of this practice.
- Only 10 and 4 articles out of 165 addressed in the last 7 years, respectively, antibiotic resistance and disinfection by-products as targeted variables. Given their presence in reclaimed wastewater and the raising concern regarding (i) the risk of development of antibiotic resistance and (ii) the trade-off between an adequate inactivation of pathogens and the formation of by-products through chemical disinfection, these are crucial contaminants to be considered.
- There is a lack of application of risk assessment procedures to reclaimed wastewater reuse. Only 3 articles (if LCA is not considered) quantified the environmental risk and only 1 article estimate both environmental and human health risk. In terms of human health, the risk procedures focus on individual class of contaminants, while it would be beneficial to estimate risks for both pathogens and chemicals.

To emphasize the importance of a holistic assessment in a One Health perspective, a simplified approach was proposed to simultaneously assess the human health, environmental and antibiotic resistance risks for pharmaceuticals deriving from indirect reclaimed wastewater reuse. The results provided valuable insights on the integrated quantification of overall risks, demonstrating that considering only the human health risk, would underestimate the overall risk and that more critical adverse effects (such as the environment and the potential development of antibiotic resistance risks) could be overlooked. Therefore, it is useful to identify the most critical endpoint for each CEC, aiming at prioritizing the regulation and the monitoring efforts.

CRediT authorship contribution statement

Luca Penserini: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Beatrice Cantoni:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Manuela Antonelli:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

All authors confirm the absence of any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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Data availability

Data will be made available on request.

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