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Review

Towards sustainable water reuse: A critical review and meta-analysis of emerging chemical contaminants with risk-based evaluation, health hazard prediction and prioritization for assessment of effluent water quality

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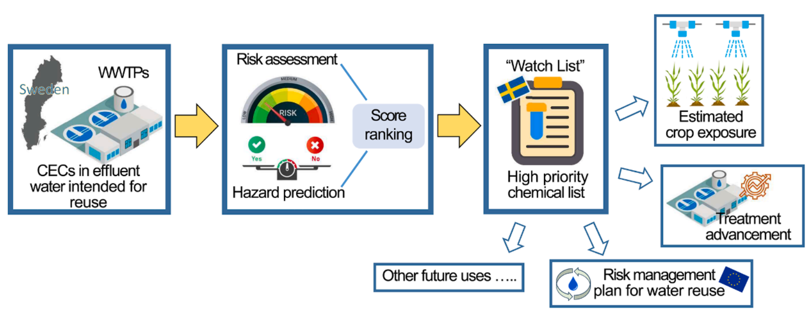
HIGHLIGHTS

- Compiled 682 chemicals, metals and (micro)plastics in wastewater intended for reuse.
- New, holistic quantitative methodology to assess, score and prioritize chemical CECs.
- Meta-analysis of chemical CECs with 14 ecological risk and health hazard features.
- List of chemical CECs in high to low priority for evaluating effluent water quality.
- High-priority chemicals are mainly pharmaceuticals with venlafaxine at the very top.

GRAPHICAL ABSTRACT



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ABSTRACT

Reuse of treated wastewater is necessary to address water shortages in a changing climate. Sustainability of wastewater reuse requires reducing the environmental impacts of contaminants of emerging concern (CECs), but it is being questioned as CECs are not regulated in the assessment of effluent water quality for reuse both nationally in Sweden and at the broader European Union level. There is also a lack of details in this topic on which CECs to be addressed and methodologies to be used for assessing their environmental impacts. A better understanding of the ecological risks and health hazards of CECs associated with wastewater reuse will assist in the development of effective regulations on water reuse, (inter)nationally, as well as related treatment/monitoring guidelines. This review provides a list of specific chemical CECs that hinder sustainable wastewater reuse, and also demonstrates a holistic quantitative methodology for assessing, scoring and prioritizing their associated ecological risks and health hazards posed to the environment and humans. To achieve this, we compile information and concentrations of a wide range of CECs (∼15 000 data entries) identified in Swedish effluent wastewater from domestic (blackwater, greywater, mixture of both) and municipal settings, and further perform a meta-analysis of their potentials for 14 risk and hazard features, consisting of ecological risk, environmental hazard, and human health hazard. The features are then scored against defined criteria including guideline

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values, followed by score ranking for prioritization. This finally produces a unique list of chemical CECs from high to low priority based on risk- and hazard-evaluations. Out of the priority chemicals, 30, mainly pharmaceuticals, had risk quotient ≥ 1, indicating ecological risk, 16 had environmental hazard being persistent and mobile, and around 60 resulted in positive predictions for at least four human health hazards (particularly skin sensitization, developmental toxicity, hepatoxicity, and carcinogenicity). The 10 highest-priority chemicals (final score 2.3–3.0 out of 4.0) were venlafaxine, bicalutamide, desvenlafaxine, diclofenac, amoxicillin, clarithromycin, diethyltoluamide, genistein, azithromycin, and fexofenadine. Potential crop exposure to selected chemicals following one year of wastewater reuse for agricultural irrigation was also estimated, resulting in a range of 0.04 ng/kg (fluoxetine) to 1160 ng/kg (carbamazepine). Overall, our work will help focus efforts and costs on the critical chemicals in future (waste)water-related studies, such as, to evaluate removal efficiency of advanced treatment technologies and to study upstream source tracing (polluter-pays principle), and also in supporting policymakers to better regulate CECs for sustainable wastewater reuse in the future.

1. Introduction

In the European Union (EU), more than 40 billion m^3 of wastewater are treated annually, of which less than 3 % is currently reused [1]. In Sweden, treated municipal wastewater is directly reused (mostly for irrigation) in only a few counties in central and southern Sweden [2]. In 2020, the total volume used for irrigation in Sweden was 73 million m^3 (https://www.statistikdatabasen.scb.se/). Reusing treated municipal wastewater is a potential way to deal with the challenge of water scarcity in many parts of the world, including Sweden, where the southern regions in particular has been experiencing water shortages in recent years [3]. Potential for increasing reuse of treated wastewater to six times the current level in the EU has been identified [4]. However, conventional municipal wastewater treatment plants (WWTPs) are not designed to remove organic micropollutants, most of which are considered contaminants of emerging concern (CECs) [5]. Therefore, CEC removal in wastewater treatment is partial at best [6-8], meaning that effluent water from municipal WWTPs is one of the main sources of CECs in the environment [9-11,5]. Spread of CECs to the environment with wastewater reuse poses threats to aquatic ecosystems, soils, and crops. Most CECs are not regulated or typically monitored [12,13], despite being frequently detected in wastewater and aquatic ecosystems. Chemical pollution is one component of the triple crisis, together with climate change and biodiversity loss [14], and has also been suggested as one of the planetary boundaries impacting the integrity of Earth system processes [15]. There is therefore a need for better knowledge of CECs at source (e.g., wastewater), their potential environmental pollution, and future mitigations, in line with the Swedish environmental quality objective of a 'non-toxic environment' [16].

In assessing treated water quality for reuse, minimum requirements defined by the EU [17] do not include CECs, but state maximum permissible concentrations for bacteria (e.g., *Escherichia coli*) and basic water quality parameters (biochemical oxygen demand, total suspended solids, etc.). CECs are mentioned only under additional requirements, which are applicable based on case-specific risk assessments. Proposed revisions to the EU Urban Wastewater Treatment Directive (UWWTD) (*COM(2022) 541 final*) [18] introduce the requirement of quaternary treatment aimed at removal of CECs, while emphasizing a precautionary and risk-based approach. Considering the ever-increasing number of CECs, prioritization of hazardous pollutants from high to low concern is a crucial prerequisite for environmental authorities in developing homogeneous, comprehensible, and enforceable effluent water quality standards and detailed quaternary treatment objectives and guidelines. Some efforts have already been made to prioritize CECs in different contexts, e.g., based on catchment susceptibility (e.g., Park & Park [19]) and occurrence in local-scale municipal WWTPs [20-22] or on-site wastewater treatment facilities [23]. A number of studies have also assessed risk of selected CECs for wastewater reuse (e.g., [24,25]). In addition, the EU directive on priority substances [26] lists 45 priority substances in the broader field of water policy, but not specific to WWTPs and wastewater reuse. Proposed revisions to the UWWTD include a list of 13 substances based on their ease of treatment or disposal.

In this review article, we aim to provide an overview of CEC occurrence in treated wastewater, characterize their ecological risks and health hazards to the environment and humans, and draw up a list of high-priority CECs for future water research and their implications for wastewater reuse in agriculture. We first performed a comprehensive literature review to compile information and occurrence data on CECs in treated domestic wastewater (mixture of blackwater and greywater, e.g., from onsite sewage facilities), municipal wastewater (centralized sewage systems from municipalities and urban areas), and treated greywater and blackwater from across Sweden. In a subsequent meta-analysis, we performed risk and hazard evaluations, scoring against defined criteria, and ranking to prioritize the CECs from high to low concern in effluent wastewater. We considered a broad spectrum of risk categories, with a total of 14 parameters covering ecological risks, probabilistic risk assessment, environmental health hazards, and human health hazards. The outcome is a unique holistic risk-based evaluation of CECs in assessing effluent wastewater quality for reuse. While this review focuses on literature in Sweden, our study's scope and workflow are highly beneficial to other countries in search for similar applications of water reuse (see Section 8). The workflow is also applicable to other contexts outside wastewater reuse. The list of high-priority CECs is critical for environmental authorities, policymakers, and the research community, to set directions for regulations, monitoring strategies, and treatment technologies in the future.

2. Meta-analysis

A meta-analysis workflow adapted from Löffler et al. [27] was developed based on occurrence and on risk and hazard assessment of chemical contaminants (Fig. 1). The assessment divides risk and hazard into three compartments: 1) ecological risk based on ecotoxicological data; 2) environmental hazard through persistence, mobility, and bioaccumulation potential; and 3) human health hazard by a combination of various adverse health effects. Based on this, we developed a novel scoring and ranking system to prioritize chemical contaminants in wastewater.

2.1. Data compilation

We used English and Swedish keywords to search for scientific articles (peer-reviewed) and grey literature in four different search engines (Web of Science, Scopus, Google Scholar, DiVA Portal) (Tables S1 and S2 in Supplementary Information (SI)). We retrieved scientific articles through search strings with three specific groups of keywords (Table S2): i) keywords for focusing the search on the Swedish context, ii) keywords for contaminants (e.g., pharmaceuticals), and iii) keywords for wastewater streams (e.g., sewage, greywater, etc.). Each group featured the Boolean operator 'OR' between the keywords within the group and the Boolean operator 'AND' between the groups (Table S2). We tested the search string systematically to determine the most effective formulation prior to finalization. We performed a quality check using names of some individual contaminants instead of contaminant groups, e.g., using "ciprofloxacin" instead of "pharmaceuticals", to assess how well keywords for contaminant groups captured studies using individual names. We found no additional studies, confirming the adequacy of the search strings. We also evaluated the search results with relevant key articles well-known to the authors. Duplicate literature was removed. Documents in Swedish were translated to English using Google Translate. Only literature published from January 2000 to October 2022 was included, as much relevant research has emerged in recent years. We then performed abstract screening on the retrieved scientific literature with the aid of Rayyan [28] to eliminate irrelevant articles that were not within the three groups of interest (Table S2). Any relevant articles found during the selection process through snowballing, i.e., using references citied in an article to identify additional relevant articles, were also added. Extracted information and data included contaminant name and group, concentrations in influent and/or effluent, detection/quantification limits, numbers of samples, wastewater type, treatment plant details (name, city and county), and sampling methods. In assessment of full texts, we divided hits (both scientific articles and grey literature) into three different categories: i) wastewater, ii) sludge, and iii) pilot studies with new technologies. This paper pertains to the first group, i.e., wastewater.

2.2. Data pre-processing

In order to perform an appropriate, robust risk assessment, we focused on substances in our dataset that fulfilled two criteria: 1) at least 20 quantifiable data points (effluent concentrations excluding non-detects) and 2) quantifiable frequency of more than 50 %. This resulted in 128 contaminants, comprising 119 chemical contaminants, five metals, and four linear alkylbenzene sulfonate (LAS) compounds (Table S3 in SI). Data pre-processing included screening for potential duplicates due to naming differences. Substances identified by Chemical Abstracts Service (CAS) number but appearing under different chemical names were merged under one of the names. We then used CAS number of each substance to retrieve their respective SMILES from the ChemSpider database (http://www.chemspider.com/). Due to lack of unique CAS numbers, we excluded the four LAS compounds in our dataset from further risk and hazard evaluations. Where branched and linear per- and poly-fluoroalkyl substances (PFAS) were reported separately, we combined their concentrations (e.g., linear- and branched-perfluorooctanesulfonic acid (PFOS) were reported jointly as PFOS), for consistency with most other reports.

2.3. Ecological risk assessment

We performed an ecological risk assessment for each chemical by comparing the measured concentrations in wastewater treatment effluent against predicted no-effect concentrations (PNECs). We collected ecotoxicological data for chemicals from curated expert sources, such as the European Chemicals Agency [29], the Swedish FASS pharmaceuticals database [30], the US EPA ECOTOX database [31], the Pesticides Properties Database [32], and the scientific literature.

We derived PNECs according to European guidelines for chemical risk assessment (Table S4 in SI) [33,34]. Briefly, we applied an appropriate assessment factor [33] to ecotoxicity data for the most sensitive species. We used chronic ecotoxicity data from standard test species for algae, daphnids, and fish by preference, but also acute data and data for non-standard species depending on data availability. For data-poor chemicals where no empirical data were available, we obtained quantitative structure activity relationship (QSAR) data (ECOSAR, 2023) and applied an assessment factor of 1000 to the acute toxicity value for the most sensitive species.

For each chemical, we calculated the conventional ecological risk quotient (RQ):

$$RQ = \frac{MEC_{eff,\max}}{PNEC} \quad (1)$$

where $MEC_{eff,max}$ is measured environmental concentration, taken as the maximum effluent concentration in the dataset, and PNEC is the predicted no-effect concentration. With this assessment, we focus on the scenario where effluent water is directly reused such as for agricultural irrigation. This also supports a worst-case scenario (conservative approach) of protecting the health of ecosystems given that effluent water could be discharged to recipient water bodies. Hence, dilution of effluent water is not considered in our ecological risk assessment, reflecting the direct reuse and worst-case scenarios, and also because dilution can vary widely [35,36] and determining specific dilution factors is impractical for the scope of this study.

We also considered two more risk parameters, namely frequency of exceedance (FoE) and extent of exceedance (EoE) [37,38]. FoE reveals the frequency of measured effluent concentrations exceeding PNEC

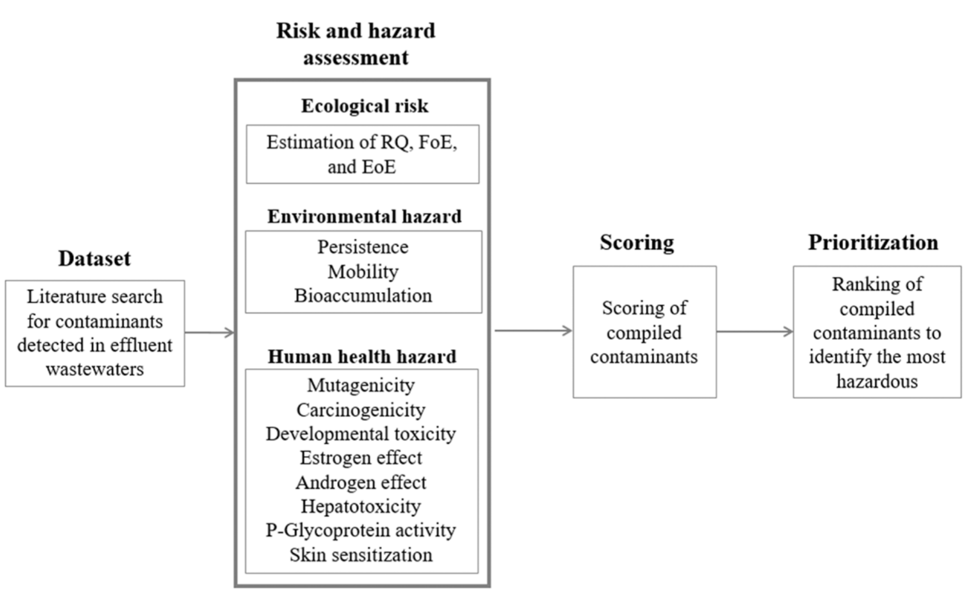

Fig. 1. Meta-analysis workflow, comprising literature search, risk and hazard assessment, scoring, and prioritization of substances. RQ: risk quotient; FoE: frequency of exceedance; EoE: extent of exceedance.

values (Eq. 2), while EoE resembles an RQ with effluent concentrations at the 95th percentile (Eq. 3):

$$FoE = \frac{n}{N} \quad (2)$$

$$EoE = \frac{MEC_{eff,95\%tile}}{PNEC} \quad (3)$$

where n is number of data points (i.e., effluent concentrations) above PNEC, N is total number of data entries (i.e., quantifiable and non-quantifiable data points), and $MEC_{eff,95\,\%tile}$ is measured effluent concentration of a chemical contaminant at the 95th percentile of the dataset.

We performed probabilistic risk assessment [39] to supplement the ecological risk assessment and to visualize the ranked data points of a chemical contaminant in relation to the PNEC value (Fig. S1 in SI). For this, we numerically ranked reported concentrations in ascending order and assigned percent rank *j* using the Weibull model (Eq. 4), where *i* is the numerical rank assigned and *n* is the number of data points. We used linear regression to fit percent rank against the effluent concentrations (probability and log-normal scale, respectively). We used regression coefficients (slope and intercept) to estimate the centile values corresponding to PNECs (Eq. 5), from the environmental concentrations, where x represents the respective PNEC.

$$j = \frac{i * 100}{n + 1} \quad (4)$$

$$\text{centile value} = ((\text{slope} * \log(\text{x})) + \text{intercept}) \quad (5)$$

2.4. Prediction of environmental hazards

We used the VEGA *in silico* platform (version 1.2.3) [40] to predict persistence, mobility, and bioaccumulation as environmental hazard indicators for each chemical contaminant, as previously applied [27]. We predicted chemical persistence in water (half-life) using the model IRFMN (version 1.0.1). We estimated water solubility using the model IRFMN (version 1.0.2), organic carbon-water partition coefficient (K_{oc}) using Opera (version 1.0.1) and bioaccumulation using bio-concentration factor (BCF), estimated by CAESAR (version 2.1.15).

2.5. Prediction of human health hazards

Considering potential human exposure to chemicals in wastewater reuse via different pathways, such as occupational exposures for farmers during wastewater irrigation in agricultural settings [41-43] and human consumption of edible, raw crops with residual wastewater after irrigation [44], we performed a prediction of human health hazards for the selected chemical contaminants. The approach was adapted from Bruks et al. [45,46], Löffler et al. [27], and Menger et al. [47], who used *in silico* approaches for predicting mutagenicity, carcinogenicity, developmental toxicity, skin sensitization, estrogen receptor effect, androgen receptor effect, hepatoxicity, and P-glycoprotein activity as proxies for human health hazards. We performed this using the VEGA software and the models Mutagenicity (Ames test) Consensus model (v.1.0.4), Carcinogenicity model (CAESAR) (v.2.1.10), Developmental Toxicity model (CAESAR) (v2.1.8), Estrogen Receptor-mediated effect (IRFMN-CERAPP) (v.1.0.1), Androgen receptor-mediated effect (IRFMN-COMPARA) (v.1.0.1), Hepatoxicity model (IRFMN) (v.1.0.1), P-Glycoprotein activity model (NIC) (v1.0.1), and Skin Sensitization model (CAESAR) (v.2.1.7).

For both the environmental and human health hazard predictions, we evaluated model performance considering inclusion of our 119 selected chemical contaminants in the respective training and test datasets, based on CAS numbers or SMILES structures. Most models included between five and 48 of our ranked chemical contaminants (Table S5 in SI). However, there was only one in the skin sensitization model and none in the P-glycoprotein activity model, so estimates of these should be treated with caution. Given the variability in SMILES notation, where the same chemical can be represented in multiple ways, the evaluation results (Table S5) indicate minimum number of chemicals included.

2.6. Scoring and prioritization

The last step of our meta-analysis was to score the parameters against criteria based on ecological risk assessment, environmental hazard, and human health hazard (Table 1). We applied a binary score of either 1 or 0 to all parameters except FoE, which we left in numerical form due to lack of reliable criteria for scoring. We assigned a score of 1 for RQ > 1 and EoE > 1, otherwise a score of 0. In accordance with REACH regulation guidelines, we scored persistence, mobility, and bioaccumulation as follows: a score of 1 was assigned for persistence when the half-life in water exceeded 40 days, for mobility when solubility was above 0.15 mg/L and log $K_{oc} \leq 4.5$, and for bioaccumulation when log BCF surpassed 3.3; otherwise, a score of 0 was assigned. For each human health hazard parameter, a score of 1 indicated a positive prediction, whereas a score of 0 denoted a negative outcome.

The overall score of the ecological risk assessment ($Score_{Eco}$) was calculated as:

$$Score_{Eco} = \frac{Score_{RQ} + Score_{EoE}}{2} + FoE \quad (6)$$

The overall score of predicted environmental hazard ($Score_{EH}$) was estimated as:

$$Score_{EH} = \frac{\sum_{i=1}^{3} n_i}{3} \quad (7)$$

where n_i represents the scores for persistence, mobility, and bioaccumulation.

The overall score of human health hazard ($Score_{HH}$) was calculated as:

$$Score_{HH} = \frac{\sum_{i=1}^{8} n_i}{8} \quad (8)$$

where n_i represents scores for mutagenicity, carcinogenicity, developmental toxicity, skin sensitization, estrogen receptor effect, androgen

Table 1
Parameters and related scoring criteria for chemical contaminants in the meta-analysis. RQ: ecological risk quotient; EoE: extent of exceedance; FoE: frequency of exceedance; K_{oc}: organic carbon-water partition coefficient; BCF: bio-concentration factor.

	Parameter	Risk/hazard (score 1)	No risk/hazard (score 0)
Ecological risk	RQ	> 1	< 1
	EoE	> 1	< 1
	FoE	Not applicable	Not applicable
Environmental hazard	Persistence (half-life in water)	> 40 days	< 40 days
	Mobility (solubility and log K_{oc} (log L/kg))	> 0.15 mg/L and ≤ 4.5	< 0.15 mg/L and ≥ 4.5
	Bioaccumulation (log BCF) (log L/kg wet weight)	> 3.3	< 3.3
Human health hazard	Mutagenicity	Positive	Negative
	Carcinogenicity		
	Developmental toxicity		
	Skin sensitization		
	Estrogen receptor effect		
	Androgen receptor effect		
	Hepatoxicity		
	P-glycoprotein activity		

receptor effect, hepatoxicity, and P-glycoprotein activity.

A final score of each chemical contaminant was obtained:

$$Final\ score = \quad Score_{Eco} + Score_{EH} + Score_{HH} \tag{9}$$

We then ranked the final score of each chemical contaminant in descending order, to result in a risk-based prioritization. $Score_{Eco}$, with a maximum score of 2, had a higher weighting on the final score than $Score_{EH}$ and $Score_{HH}$, which had a maximum score of 1 each. The maximum final score was 4, representing the highest concern, and the minimum was 0, indicating the lowest concern.

Amlodipine besylate is not a single chemical compound, but rather comprises two distinct structures [48]. We conducted environmental and human health hazard prediction for each structure separately, with the score representing the average of these two evaluations.

3. Overview of the literature search and dataset

Of the peer-reviewed scientific articles, we focused on year 2000–2022, resulting in 1406 records, out of which 139 were selected after abstract screening. We evaluated relevance for a final selection of 57 articles (41 % of 139 articles, plus one more added by snowballing). The search for grey literature resulted in 85 records, of which 27 (32 %) were of relevance to this study (Table S6). Relevant terms that appeared with the highest frequency in the scientific articles included 'environment', 'sludge', 'chemical', 'analyte', and 'treatment process' (Fig. 2A, larger circles). Terms such as 'micropollutant', 'chemical', 'benzotriazole', and 'biocide' appeared more frequently in recent years (Fig. 2A, yellow to yellowish-green circle). The records were more or less evenly distributed over the study period (Fig. 2B). The highest number of records within one year was eight, in 2017. The most represented journal was *Science of the Total Environment*, with 12 articles, followed by *Water Research* (7), *Chemosphere* (5), and *Water Science & Technology* (5) (Fig. 2C).

Data extracted from the selected literature covered all 21 counties of Sweden (Fig. S2), with approximately 15 000 data points (including quantifiable data points and non-quantifiable values, "not analyzed",

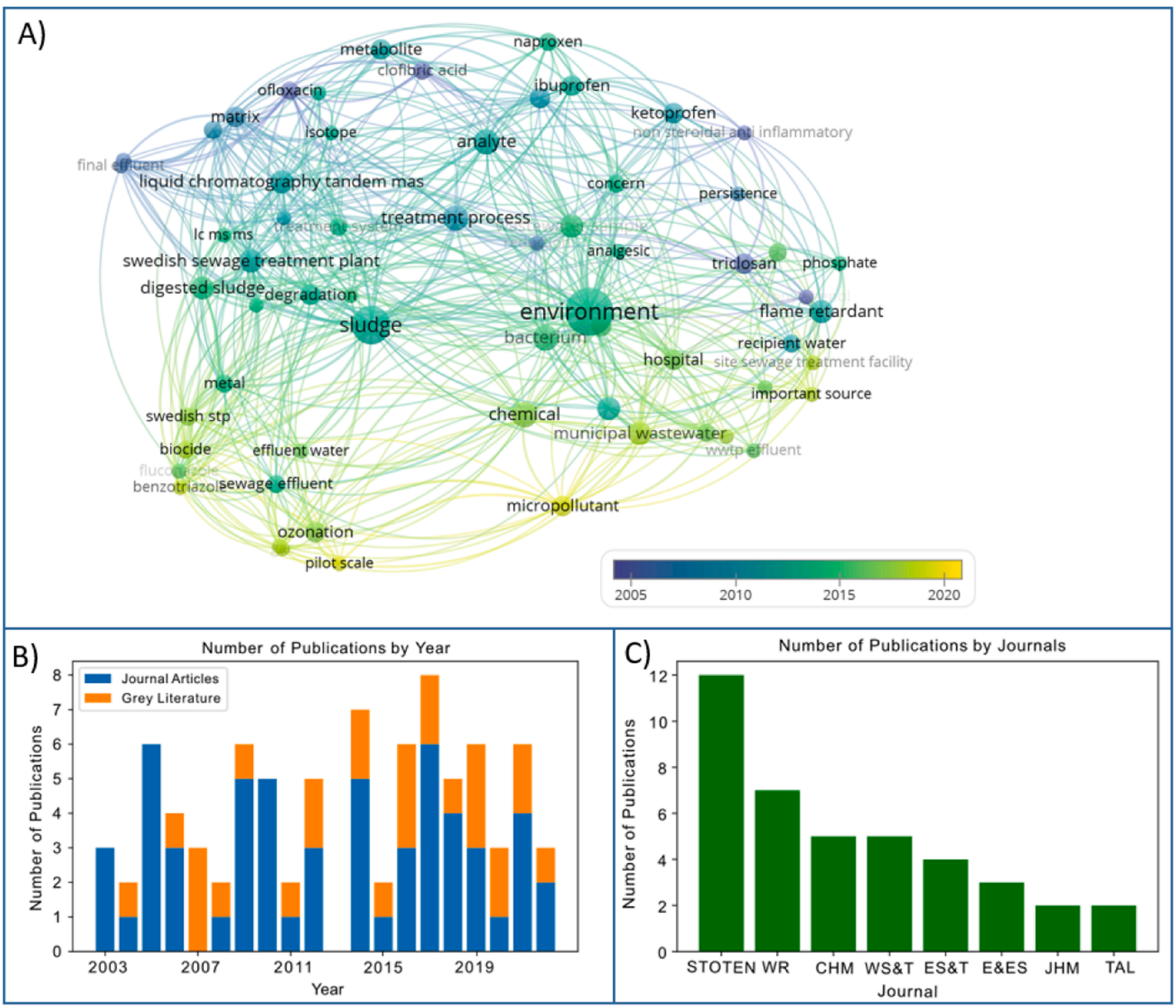

Fig. 2. (A) Overlay visualization of occurrence of terms in the title and abstract of selected scientific articles (size of circles and labels represent weight based on occurrence, lines represent co-occurrences); (B) chronological distribution of the selected literature; and (C) number of relevant scientific publications by journal (STOTEN: *Science of the Total environment*; WR: *Water Research*; CHM: *Chemosphere*; WS&T: *Water Science and Technology*; ES&T: *Environmental Science & Technology*; E&ES: *Ecotoxicology and Environmental Safety*; JHM: *Journal of Hazardous Materials*; TAL: *Talanta*).

and entries with no data in the source literature) on contaminant concentrations in influent and effluent wastewater. Counties with a larger population, e.g., Stockholm, Västra Götaland, and Skåne in central and southern Sweden, generally had higher numbers of data points (Fig. S2). Measurements on municipal wastewater (14 440 data points) dominated the data, while data points for domestic wastewater (289), greywater (214), and blackwater (142), represented only four, two, and one county, respectively.

4. Occurrence of CECs in wastewater

Of the 730 substances compiled from the literature, 682 were reported with concentration units in mass per volume (e.g., μg/L) (Table S7). The others were microplastics (see SI for a brief description of the risk of microplastics in wastewater reuse), antimicrobial resistance genes, or expressed as estrogenic effects. Additionally, 52 substances without effluent data points ("not analyzed" and entries with no data in the source literature) were removed from the 682 substances. Of the 630 compiled substances (Table S8), a total of 128 contaminants (Table S3) met the criteria of > 20 quantifiable data points of effluent concentration and > 50 % quantifiable frequency, including five metals (see SI for brief description of the risk of metals in wastewater reuse) and four LAS compounds. On exclusion of these, 119 chemical contaminants remained for further risk characterization and prioritization.

Diclofenac (175 data points, quantifiable frequency 93 %) was reported most frequently in effluent wastewater (Table S8), followed by ibuprofen (130 data points, quantifiable frequency 85 %), naproxen (122 data points, quantifiable frequency 99 %), trimethoprim (122 data points, quantifiable frequency 96 %), and oxazepam (120 data points, quantifiable frequency 99 %). A total of 160 contaminants showed 100 % quantifiable frequency, of which 131 had less than 20 quantifiable data points and 60 had only one quantifiable data point in the dataset (Table S8). Based on their median influent and effluent concentrations in the dataset, removal efficiency of the 119 chemicals was generally highly variable, with some almost completely removed (e.g., caffeine) and others either not removed at all (e.g., perfluoroheptanoic acid) or present in higher concentrations in effluent than in influent (e.g., metronidazole-OH (Fig. 3). Metronidazole-OH, sparfloxacin, and mefenamic acid were the bottom three CECs in the dataset in terms of removal efficiency, while salicylic acid, caffeine, and nicotine were the top three (Fig. 3).

5. Risk and hazard evaluations

Of the 119 chemical contaminants selected for risk assessment, 30 had RQ ≥ 1 (Table S9). These were mainly pharmaceuticals (26), together with a few chemicals for non-medical use (food additive (1), personal care products (insect repellant (1), antimicrobial agent (1)), and an industrial chemical (1). Clarithromycin showed the highest RQ (390), and EoE of 78 (Table S9). The highest concentration of clarithromycin (780 ng/L) was measured in effluent from WWTP Ön in Umeå [49]. For comparison, the PNEC of clarithromycin is 2 ng/L. Venlafaxine and diclofenac also had high RQ (114 and 108, respectively) and EoE > 1. The highest effluent concentration of diclofenac (3900 ng/L) was detected at Kungsängsverket WWTP in Uppsala [49]. The highest venlafaxine concentration (8110 ng/L) was measured in effluent from oxidation and ammonia treatment of blackwater, in Södertälje municipality [50]. For EoE > 1, the number of contaminants was reduced from 30 to 24 (Table S9), with bezafibrate, carbamazepine, codeine, metoprolol, thiabandazole, and tramadol no longer showing ecological risks. The highest concentrations of carbamazepine and metoprolol were measured in treated blackwater [50] and the highest concentration of thiabendazole in domestic wastewater treated in soil beds [51], which may explain the difference between maximum concentration and 95th percentile effluent concentration. However, the highest concentrations of bezafibrate, codeine, and tramadol were measured in effluent from municipal wastewater treatment plants. Use of grab samples, instead of composite samples, may have resulted in exceptionally high concentrations of bezafibrate [23] and codeine [52]. In addition to sampling method, size and features of the WWTP and sampling season can also explain the differences [53]. FoE of these chemicals ranged between 0.01 (metoprolol and carbamazepine) and 0.97 (bicalutamide) (Table S9). This means that some were almost always present in concentrations above their respective PNEC, e.g., bicalutamide, fexofenadine, and diclofenac (Figs. S1A and S1B), while others were rarely encountered in effluent concentrations above their respective PNEC, e.g., bezafibrate, carbamazepine (Fig. S1A), codeine (Fig. S1B), metoprolol (Fig. S1C), and tramadol (Fig. S1D). Bicalutamide scored highest for overall ecological risk ($Score_{eco}$=1.97) followed by fexofenadine, diclofenac, venlafaxine, and amoxicillin (Fig. 4, Table S9).

For environmental hazards, the majority (92 out of 119) of the selected CECs exceeded the threshold for at least one of the three criteria (persistent, mobile, bioaccumulative), resulting in $Score_{EH}$ of 0.33 (Fig. 4, Table S10). There were 17 chemicals with $Score_{EH}$ = 0.67, of which 16 were predicted to be persistent and mobile but not bioaccumulative, while one (perfluorohexanesulfonic acid) was predicted to be mobile and bioaccumulative, but not persistent over 40 days. PFOS was the only chemical with $Score_{EH}$ = 1 (Fig. 4; Table S10), meaning that it met the criteria of being persistent, mobile, and bioaccumulative, which is consistent with its well-known properties [54]. A $Score_{EH}$ of 0 was observed for 10 chemicals, i.e., they had values below the threshold for the three environmental hazard criteria.

For human health hazards, around half of the 119 chemicals resulted in $Score_{HH}$ ≥ 0.5, with positive predictions for at least four of the

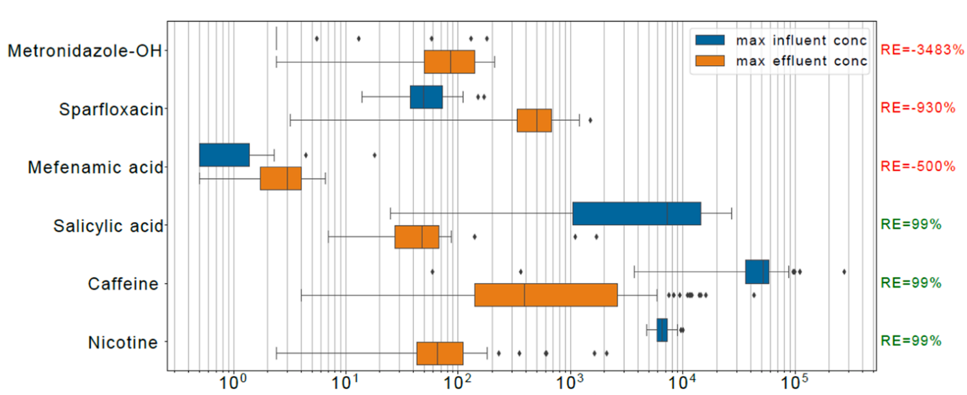

Fig. 3. The top three chemicals in the dataset in terms of removal efficiency (RE, green) and the bottom three (red), calculated based on median maximum influent and effluent concentrations in each row (report) in the compiled dataset. See Fig. S3 for RE of other contaminants, including metals and linear alkylbenzene sulfonate compounds.

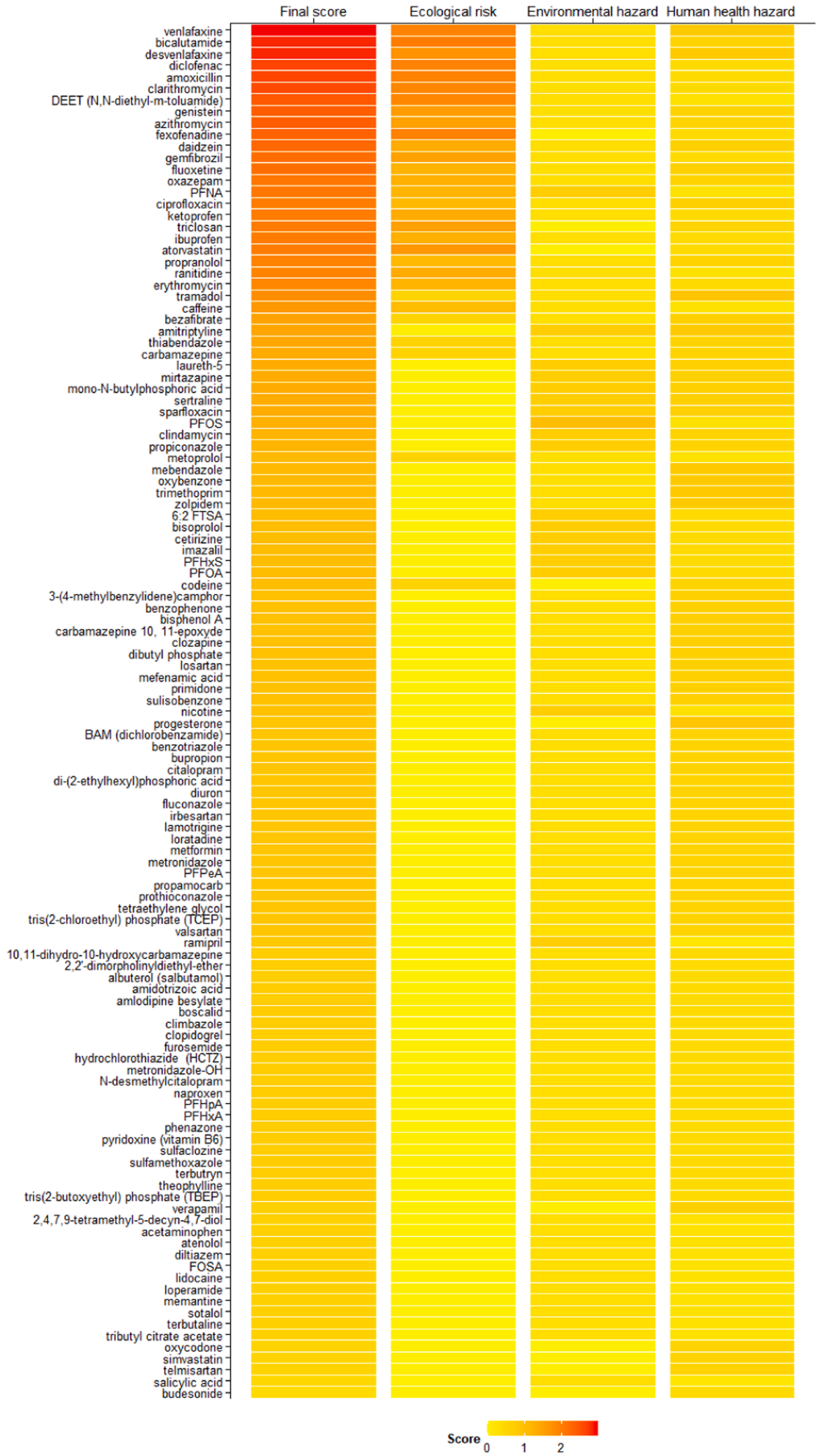

Fig. 4. Final risk and hazard scores for high-priority chemical contaminants of concern (CECs) in effluent water, based on scores from evaluations of ecological risks ($Score_{Eco}$), environmental hazards ($Score_{EH}$), and human health hazards ($Score_{HH}$). See Table S12 for individual scores.

adverse health effects (Fig. 4, Table S11). Progesterone (a steroid hormone) and tramadol (an opioid) had the highest $Score_{HH}$, 0.88. These two chemicals had positive predictions for seven out of the eight parameters (predicted negative only for mutagenicity). Steroid hormones have been linked with a number of serious human health risks, including cancer [55]. Tramadol has been shown to cause an increase in genotoxic and cytotoxic risk [56]. There were 59 chemicals with $Score_{HH}$ of 0.5–0.75, meaning positive prediction for four to six adverse health effects, most commonly skin sensitization, developmental toxicity, hepatoxicity, and carcinogenicity. Of 50 chemicals with a positive prediction of carcinogenicity, nine also showed positive mutagenicity prediction, which was obtained for a total of 20 chemicals. Ramipril and salicylic acid showed the lowest $Score_{HH}$ (0.12), with a positive prediction only for hepatotoxicity and developmental toxicity, respectively. Salicylic acid has also been termed a developmental toxicant by European Commission Scientific Committee on Consumer Safety [57].

6. Prioritization of chemicals of concern

After ranking the final score, we obtained a list of 119 chemicals prioritized from high to low concern for future evaluation of effluent wastewater quality (Fig. 4, Table S12). The largest contaminant group in the list is pharmaceuticals (69 of the 119 chemicals). Concerns over the risks associated with different classes of pharmaceuticals have increased in recent years [58,59], as reflected in their frequent appearance in the dataset on which we based our priority list. Of the maximum score of 4, the top 10 CECs (venlafaxine, bicalutamide, desvenlafaxine, diclofenac, amoxicillin, clarithromycin, DEET, genistein, azithromycin, and fexofenadine) had a final score of 2.3–3.0, followed by another eight chemicals (daidzein, gemfibrozil, fluoxetine, oxazepam, PFNA, ketoprofen, ciprofloxacin, and triclosan) with a final score of 2.0–2.3. These are mainly pharmaceuticals (15 out of 18), together with two personal care products (one insect repellant, one antimicrobial agent) and an industrial chemical. The four antibiotics in the top 18 had risk quotients of antimicrobial resistance (RQ_{AMR}) and EoE of, respectively: 1.1 and 0.96 for amoxicillin, 3.1 and 0.74 for clarithromycin, 0.68 and 0.35 for azithromycin, and 17 and 2 for ciprofloxacin, based on PNEC of resistance selection from a previous study [60]. For the other six antibiotics among the 119 chemicals, $RQ_{AMR} > 1$ was observed only for metronidazole (1.12) and trimethoprim (3.13), which had EoE of 0.6 and 0.62, respectively. Based on $PNEC_{AMR}$ of metronidazole, its transformation product, OH-metronidazole, also included in the priority list, showed RQ_{AMR} of 1.7, EoE of 1.3, and FoE of 0.29, suggesting that about one-third of the effluent concentration data points exceeded the PNEC value with its maximum and 95th percentile effluent concentrations, posing a risk of antimicrobial resistance selection.

The 13 suggested chemicals in the proposed revision of the EU UWWTD (COM(2022) 541 final) include diclofenac (non-steroidal anti-inflammatory drug), clarithromycin (antibiotic), and venlafaxine (serotonin-norepinephrine reuptake inhibitor), which were among the top-10 priority chemicals on our list, and six others with lower ranking on our list (final score 0.71–1.3) (Table S12). These six chemicals are: benzotriazole (corrosion inhibitor and industrial chemical), carbamazepine (anticonvulsant), citalopram (selective serotonin reuptake inhibitor), hydrochlorothiazide (diuretic), irbesartan (angiotensin II receptor antagonist), and metoprolol (beta-blocker). The remaining four chemicals proposed for UWWTD (amisulpride, candesartan, and two methylbenzotriazole isomers) were not on our list of high-priority CECs. Amisulpride was not obtained in our literature search, meaning that it had not been a target compound for measurement in the period covered by our dataset. Candesartan concentrations were reported in influent wastewater only, while the two methylbenzotriazole isomers were not reported separately (only as methylbenzotriazole).

In addition, 31 of our selected 119 chemicals are included in the priority list of 53 compounds posing ecological risks for recipient aquatic environments [61]. This suggests consistent impacts of effluent wastewater with these chemicals on surface water bodies. Twelve of the chemicals in the priority list had centile values below 50, indicating a 50 % probability of effluent concentrations above their PNEC (Table S13).

7. Implications for wastewater reuse

There are many avenues for wastewater reuse such as agricultural irrigation, industrial uses (e.g., as cooling water), urban applications (e.g., cleaning, firefighting, construction, in-building uses, landscape irrigation), and environmental applications (e.g., surface water replenishment and groundwater recharge) [62,63]. Among these, agriculture sector is the largest global consumer of freshwater [64]. In Sweden, reusing treated municipal wastewater for crop irrigation can benefit Swedish farmers, especially in regions where severe water shortages are experienced during the growing season [2]. The EU promotes wastewater reuse for agricultural irrigation through its regulatory framework [17]. We therefore aimed to provide a general overview of how maximum chemical concentrations in the effluent water, as reported in the literature, could translate to crop concentrations in the context of wastewater reuse. We obtained data on total production and yield of all crops from the Statistics Sweden (https://www.statistikdatabasen.scb.se/) for the year 2022 and calculated their land area. Swedish agricultural production is mainly rainfed [65] and water reuse for irrigation is seasonal.

We calculated predicted concentration of selected high-priority contaminants in soil (C_s) after irrigation with effluent wastewater, over one year, according to the approach previously used by Shahriar et al. [66]:

$$\frac{dC_s}{dt}M_s = V_wC_w - K_dM_sC_s - K_LK_{ws}AC_s - K_eAC_s - K_uM_pC_s \quad (10)$$

where dC_s is the change in concentration of a chemical contaminant in soil C_s (mg/kg) over a time step dt (days), M_s is the mass of soil (kg), V_w is the wastewater irrigation rate (L/day) calculated from effluent application rate of 1170 m^3/ha/year for an agricultural area (A) of 1 hectare in the Swedish context, C_w is the highest contaminant concentration in effluent wastewater (mg/L) in our dataset, K_d is the degradation rate constant (1/day), K_L is the leaching rate constant (L/m^2/day), K_{ws} is the water to soil partitioning coefficient (kg/L), K_e is erosion rate constant (kg/m^2/day), K_u is plant uptake factor, and M_p is plant biomass growth rate (kg/day, dry weight). K_e was considered as 0 assuming no erosion following Shahriar et al. [66], and area of the agricultural field (A) was taken as 1 hectare. Effluent application rate (1170 m^3/ha/year) was calculated from Sweden's total irrigation water use in the entire year 2020 (73.6 million m^3) (https://www.statistikdatabasen.scb.se/), which is based on Sweden's total agricultural area (62 893 ha). It should be noted that the application rate is an average figure for the entire year which considers seasonal variations in irrigation requirement. Sweden's total agricultural area was calculated from data on total production and yield of all crops in 2022 (https://www.statistikdatabasen.scb.se/). Total irrigated agricultural land was then estimated from total agricultural land area using share of irrigated agricultural land (1.7 %) in 2016 (https://data.worldbank.org/inidcator/). Values of all other parameters were taken from Shahriar et al. [66] (Table S14). With the values related to Swedish irrigation context and other parameters provided from Shahriar et al. [66], the predictions are then possible for carbamazepine, gemfibrozil, triclosan, fluoxetine, and naproxen in our list of priority chemicals.

We estimated the predicted chemical concentration in crops (C_p, ng/kg) based on its predicted concentration in soil (C_s) and plant uptake factor (Ku) [66]:

$$C_p = C_s \times K_u \quad (11)$$

In wastewater reuse for agricultural irrigation, the selected chemicals would result in predicted soil concentrations ranging from 0.15 ng/kg (fluoxetine) to 59 ng/kg (carbamazepine) after one year of irrigation (Fig. 5, Table S14). Naproxen also showed relatively higher predicted accumulation in soil (51 ng/kg) than triclosan (14 ng/kg) and gemfibrozil (11 ng/kg). Carbamazepine had the highest predicted concentration in crops (1160 ng/kg; dry weight), followed by triclosan (344 ng/kg), naproxen (181 ng/kg), gemfibrozil (111 ng/kg), and fluoxetine (0.04 ng/kg) (Fig. 5). Plant uptake of chemicals present in wastewater effluent is evident from findings in many laboratory and field studies [67-71]. For example, the approach used in this study gave estimates of carbamazepine in plants similar to cucumber stem and fruit (~1000 ng/kg, dry weight) concentrations, reported by Shenker et al., [72], with similar concentration (~3000 ng/L) (Table S14) in effluent water for irrigation. On the other hand, García et al., [73], using a dynamic plant uptake model, predicted substantially higher concentrations of carbamazepine (~2600000 ng/kg) and naproxen (~55000 ng/kg) in lettuce after irrigation with wastewater containing many times higher concentrations of these pharmaceuticals compared to our study (Table S14). Similarly, Polesel et al. [74] predicted lower concentrations of triclosan (30 ng/kg) in grain, with effluent water concentrations five times lower than our study (Table S14).

8. Concluding remarks and future perspectives

Under future climate change, compound droughts and heatwaves are projected to become more frequent [75]. Even in Sweden, a country with good historical access to water, low streamflow, declining levels of freshwater (e.g., lakes, groundwater), and precipitation deficits have been observed in recent decades [65,76]. This should act as an early warning signal to countries with similar climate conditions to Sweden to begin securing their water supply for the future. However, treated municipal wastewater is currently reused in only a few counties in Sweden, such as Gotland, Kalmar, Skåne, and Uppsala. Many other counties, including Västra Götaland, Södermanland, Jönköping, and Östergötland, have had to introduce irrigation bans due to water shortages in recent years [77–80]). More water for crop irrigation is expected to be needed in Sweden [65]. While reuse is not prohibited in Sweden but activities related to the processes necessary for reclamation are subject to notification to related authorities and application for permission, practices have not expanded in line with the around 1.2 billion m^3 of treated wastewater produced annually by municipal WWTPs in Sweden (https://www.statistikdatabasen.scb.se/) that can potentially be reused. One of the main reasons for the limited reuse rate is public and farmer concerns about the safety and sustainability of reusing treated wastewater due to the potential presence of hazardous substances in the effluent, which is similar to the perception that prevails regarding spreading sewage sludge in agricultural fields [81]. Uncertainty about future water quality regulations also hinders wastewater reuse [82].

Assessment of effluent water quality for reuse concerning presence of CECs and addressing their associated negative impacts on ecosystem health are not detailed in the EU Water Reuse Regulation [17]. Our review paper presents a novel risk-based evaluation and prioritization of the commonly-occurring CECs in treated municipal wastewater. In contrast, only 13 chemicals are listed in the EU's proposed revisions to the UWWTD [18] and these are based on ease of removal in the treatment process and ease of disposal, i.e., not risk-based. Even with good removal efficiency, residual chemical concentrations in effluent wastewater do not necessarily reflect negligible ecological risks. Our list of high-priority CECs in effluent wastewater is generally in line with other

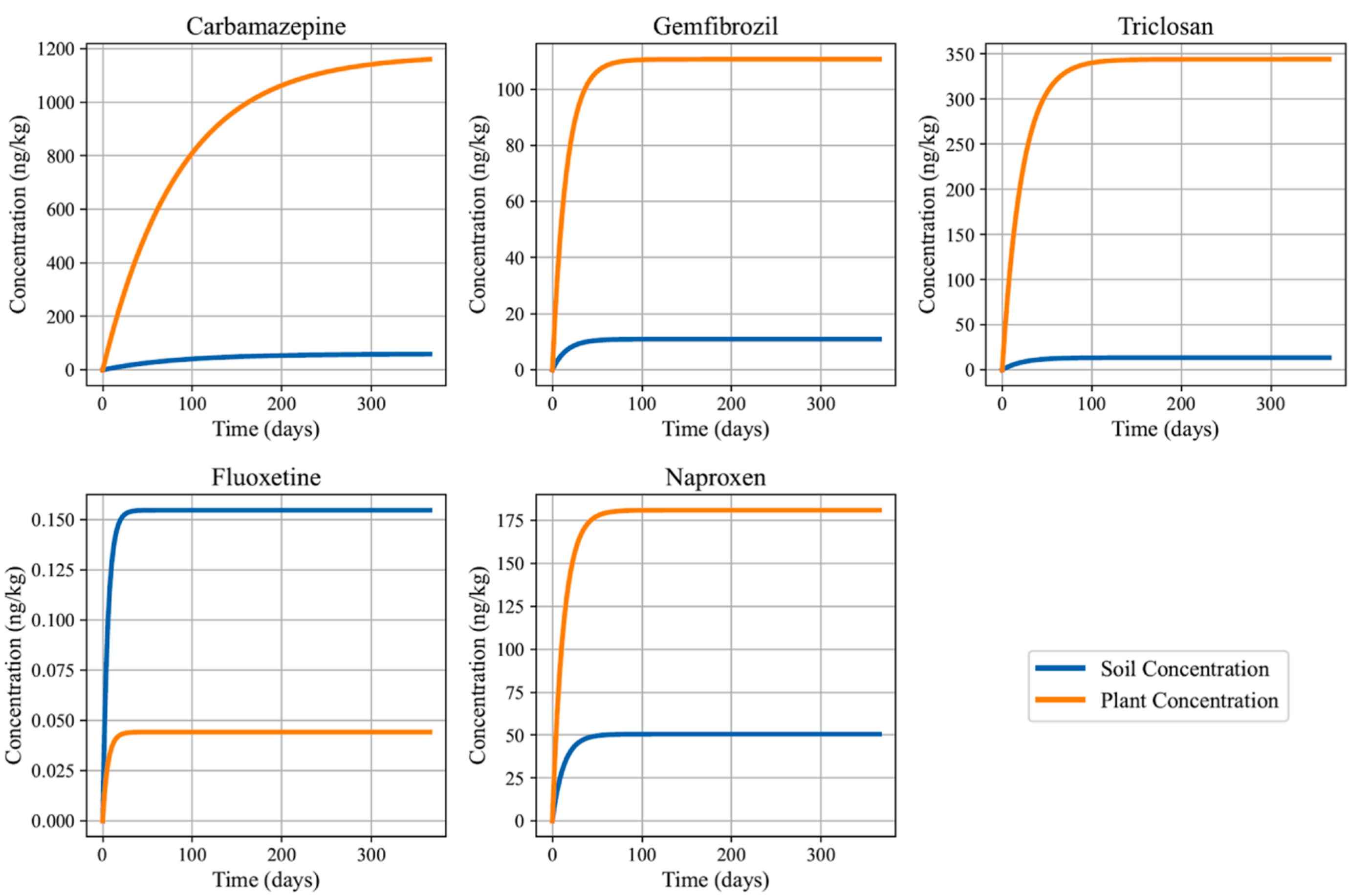

Fig. 5. Predicted concentrations of the selected chemicals of emerging concern (CECs) in soil and crops.

lists produced for e.g., surface water environments (e.g., [61]). A previous review of 70 regulations and guidelines worldwide for agricultural water reuse from across the world concluded that CECs are not comprehensively included in any of these [83]. In the EU, CECs had not been focused in the UWWTD regulation (*Directive 91/271/EEC*) on wastewater treatments implemented since 1991. The attention to addressing CECs in regulations related to wastewater treatment efficiency (*COM(2022) 541 final*) [18] and to effluent water for reuse [17] has only emerged and explored in recent years. While chemical contaminants in effluent wastewater intended for irrigation are not regulated in the EU, risk management plans concerning the exposure risks to the environment, human health, and animal health are required under certain site-specific conditions [17]. Despite these measures, significant shortcomings persist in ensuring safe reuse of effluent wastewater, primarily because regulatory frameworks often overlook the complex interactions and long-term ecological impacts of trace chemical residues. A step forward, as a potential future research direction, would be to define and enforce upper concentration limits for certain chemical contaminants in effluent water for reuse, similarly to e.g., the limits for PFAS and other chemicals set in drinking water directives for human health [84]. Our list of high-priority chemicals and the underlying methodology can be useful in establishment of upper limits and also for outlining the risk management plans required at least within the Swedish environment [17]. Our workflow, comprising a literature review and risk-based evaluation, can be applied to effluent wastewater reuse in other (EU) countries, to create a national list of high-priority chemicals, by simply replacing the keyword for 'country' in our search strings (Table S2). The high-priority chemical contaminants we identified can also serve as (additional/new) target compounds that: (a) should be considered for removal by advanced/quaternary wastewater treatments, besides those proposed in the EU's proposed revisions to the UWWTD; (b) would require upstream source tracing and potential control of releases; and (c) would be of high concern if entering water cycle, especially water bodies acting as sources of drinking water. Our ranking of CECs in order of risk can also help authorities, researchers, and non-scientific sectors prioritize efforts and costs on the related aspects, e.g., authorities could cost-effectively focus on the highly prioritized chemicals (e.g., the top-10) on our list for implementing risk management plans or determining effectiveness of quaternary treatment.

Only a few transformation products (e.g., OH-metronidazole, desvenlafaxine, *N*-desmethylcitalopram) are included in our list. These derived from five studies published 2018–2022 [85-89], demonstrating that the scientific literature has mainly focused on detection of parent compounds rather than transformation products. There is thus a knowledge gap regarding the risks posed by CEC transformation products in treated wastewater, suggesting a need for future research. Impacts of transformation products which cannot currently be assessed meta-analyses because of lack of data need to be considered in the future. In a previous study [27], we found that transformation products of three antibiotics in the top 10 chemicals in our list (i.e., amoxicillin, clarithromycin, and azithromycin) showed low to moderate risk and potential for development of antimicrobial resistance.

In addition to revealing the challenges arising from presence of CECs in treated wastewater, during the course of this review we also identified avenues for future research and development. Presence of CECs in wastewater effluent creates a need for development and implementation of advanced treatment technologies capable of removing a broad spectrum of CECs. Similarly, research should focus on extending hazard prediction models to include a broader range of chemical pollutants, for more reliable implementation and subsequent use in regulation. As demand for wastewater grows and more reuse projects are implemented, emphasis should also be placed on continuous and comprehensive monitoring of the system (wastewater, soil, crops) to determine the long-term environmental and health impacts. Such monitoring should include transformation products and active substances. Within Sweden, measurements of CECs need to be expanded to wastewater treatment plants, especially in counties with limited data on CECs (e.g., Västernorrland). Furthermore, improved management of CECs at sources upstream of WWTPs should be explored, e.g., through better management of unused pharmaceuticals, so that the incoming load to WWTPs is reduced. Lastly, risk arising from reuse of stormwater should be explored further. Municipal wastewater may or may not include stormwater depending on the wastewater collection systems (combined, partially-combined, or separate) and also, its reuse is often approached separately [90,91]. Stormwater harvesting and reuse can help in addressing the challenge of water scarcity as well as in mitigating the risks of floods and migration of hazardous pollutants from urban areas to the environment [90]. However, similar to effluent wastewater, stormwater can contain CECs [92]. Our risk assessment methodology can be used to create a similar risk-based list of priority chemicals in (treated and untreated) stormwater to identify treatment needs for reuse in situations where stormwater is separately collected.

Environmental implication

Sustainability of water reuse is hampered by the presence of harmful CECs with adverse ecological impacts. Recent EU regulation has delegated risk management to national environmental authorities to define detailed criteria for effluent water quality for reuse and assess related environmental impacts of CECs. Considering 14 features of ecological risks, environmental hazards and human health hazards, we present a holistic methodology with quantitative meta-analysis workflows to assess, score and prioritize the impacts of chemical CECs associated with effluent water reuse and a high-to-low priority list of chemicals, as the outcomes, to support environmental policymakers and researchers for sustainable wastewater reuse.

CRediT authorship contribution statement

Foon Yin Lai: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Cecilia Stålsby Lundborg:** Writing – review & editing, Methodology. **Paul Löffler:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Uzair Akbar Khan:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Karin Wiberg:** Writing – review & editing, Methodology. **Francis Spilsbury:** Writing – review & editing, Methodology, Investigation, Formal analysis.

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.

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(Uddevalla Kommun), and Lisa Reiter and Ingrid Bornfeldt Persson (Swedish Board of Agriculture).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.136175.

Data availability

Data will be made available on request.

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