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Occurrence and removal of chemicals of emerging concern in wastewater treatment plants and their impact on receiving water systems

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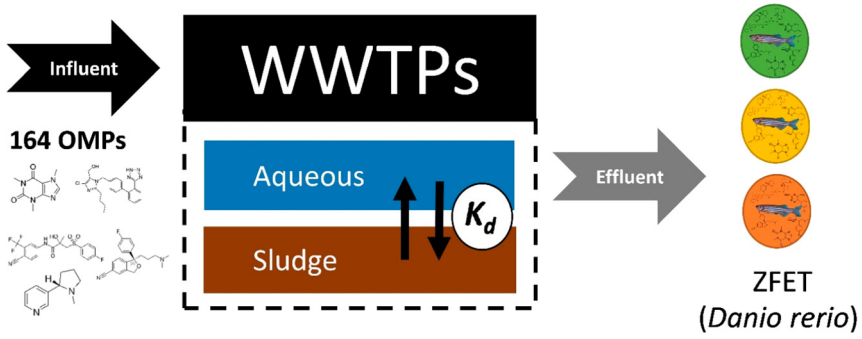
HIGHLIGHTS

- 164 CECs s were studied in 15 WWTPs and its recipients
- The zebrafish embryo toxicity tests were applied to WWTP and recipient samples
- Most target CECs were efficiently removed in the WWTPs
- The zebrafish embryos were not affected by the effluent and recipient samples

GRAPHICAL ABSTRACT



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ABSTRACT

Wastewater treatment plants (WWTPs) are considered the main sources of chemicals of emerging concern (CECs) in aquatic environments, and can negatively impact aquatic ecosystems. In this study, WWTP influent, effluent, and sludge, and upstream and downstream waters from the WWTP recipient were investigated at 15 locations for a total of 164 CECs, including pharmaceuticals, personal care products, industrial chemicals, per- and polyfluoroalkyl substances (PFASs), and pesticides. In addition, zebrafish (*Danio rerio*) embryo toxicity tests (ZFET) were applied to WWTP influent and effluent, and upstream and downstream waters from WWTP recipients. A total of 119 CECs were detected in at least one sample, mean concentrations ranging from 0.11 ng/L (propylparaben) to 64,000 ng/L (caffeine), in wastewater samples and from 0.44 ng/L (ciprofloxacin) to 19,000 ng/L (metformin) in surface water samples. Large variations of CEC concentrations were found between the selected WWTPs, which can be explained by differences in CEC composition in influent water and WWTP treatment process. The sludge-water partitioning coefficient (K_d) of CECs showed a significant linear correlation to octanol/water partition coefficient (K_{OW}) ($p < 0.001$), and thus could be used for predicting their fate in the aqueous and solid phase. The ΣCEC concentrations in WWTPs declined by on average 60%, based on comparisons of WWTP influent and effluent concentrations. The high concentrations of CECs in WWTP effluent resulted in, on average, 50% higher concentrations of CECs in water downstream of WWTPs compared with upstream. Some WWTP samples showed toxicity in ZFET compared with the respective control group, but no individual CECs or groups of CECs could explain this toxicity. These results could provide a theoretical basis for optimization of existing treatment systems of different designs, and could significantly contribute to protecting recipient waters.

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1. Introduction

Contamination of the aquatic environment by chemicals of emerging concern (CECs), such as pharmaceuticals, personal care products, industrial chemicals, per- and polyfluoroalkyl substances (PFASs), and pesticides, has raised strong concerns due to their potential bioaccumulative and toxic characteristics (Meyer et al., 2019; Petrie et al., 2015; Sörengård et al., 2019). This rising concern derives from the widespread and growing use of CECs, but is also a consequence of improvements in analytical techniques enabling detection of such substances at trace levels (Dürig et al., 2019). Hundreds of thousands of tons of CECs are dispensed and consumed annually worldwide and continuously released into the environment, albeit at low concentrations (Gago-Ferrero et al., 2017; Petrie et al., 2015). CECs can be detected in various environmental matrixes in trace concentration levels ranging from few ng/L to several μg/L in water, sediments and biota (Dürig et al., 2020; Golovko et al., 2020; Rehrl et al., 2020). Their fate and transport are complex and dependent on numerous factors, such as production volume, consumption, disposal, removal and transformation at wastewater treatment plants (WWTPs), stability (Caliman and Gavrilescu, 2009; Debska et al., 2004; Fedorova et al., 2014; Golovko et al., 2014; Luo et al., 2014; Petrie et al., 2015). CECs are now ubiquitous in groundwater and surface water across the globe (Caliman and Gavrilescu, 2009; Gago-Ferrero et al., 2015; Jones-Lepp and Stevens, 2007; Rogers, 1996; Rostvall et al., 2018; Yang et al., 2017) and occur in complex mixtures which can have adverse effects on the aquatic environment and its organisms (Carlsson et al., 2006; Carlsson et al., 2013). For example, there are about 3000 different substances, used in human medication in the EU, which are not regulated and often have shown to be environmental persistent and are of toxicological concern (Fent et al., 2006). Adverse effects that are frequently associated with the occurrence of CECs in the aquatic environment are increasing antibiotic resistance of microorganisms, acute or chronic toxicity, negative effects to non-target organisms, uncertainties regarding transformation products and metabolites and endocrine disrupting effects (Daughton and Ternes, 1999).

WWTPs have been shown to be the main sources of CECs in the aquatic environment (Sörengård et al., 2019). Removal of CECs by WWTPs generally depends on their physico-chemical properties (Rostvall et al., 2018). Previous studies have found that removal of CECs by conventional WWTPs is not sufficient, and that CECs can pass through WWTPs and enter water systems (Gago-Ferrero et al., 2017; Golovko et al., 2014; Sörengård et al., 2019). While the final effluent is discharged into surface waters, the remaining residual sludge may be incinerated, disposed at landfills, which can for instance lead to percolation into groundwater, or applied as fertilizer to agricultural areas, which pose a risk of run-off into water bodies (Luo et al., 2014; Yang et al., 2017). WWTP effluents have a high impact on the occurrence of CECs in the water system, in particular in recipients with low or varying water flows or recipients receiving wastewater from several or large WWTPs (Blum et al., 2018; Gago-Ferrero et al., 2017). More knowledge is needed on their removal efficiency in WWTPs and impact on recipient water.

In order to assess risks of CECs in the aquatic environment, combined use of analytical chemistry and toxicological bioassays is a suitable approach, especially when evaluating complex chemical mixtures such as whole effluents and surface water samples. The combination of chemical and toxicity evaluation is needed to fully understand the risks caused by the presence of CECs in the aquatic environment. The zebrafish (*Danio rerio*) embryo toxicity test (ZFET) has been used in various such applications, including toxicity testing of mixtures of CECs and sewage effluents (Menger et al., 2020; Pohl et al., 2020).

The aim of the present study was to assess the occurrence and removal of 164 CECs in WWTPs and their impact on the receiving water systems, using chemical characterization and toxicological evaluation. Specific objectives were to: i) evaluate the removal efficiency of CECs in 15 WWTPs in Sweden based on WWTP influent, effluent, and sludge; ii) assess the impact of the WWTPs on the recipient water system comparing upstream and downstream waters from the WWTP recipients; and iii) evaluate the toxicological effects of CECs in WWPT influent and effluent and recipient water using ZFET. The ZFET was used for toxicological screening of water samples in combination with chemical characterization of CECs to identify potential environmental impacts of the WWTPs to the recipient water system.

2. Material and methods

2.1. Target CECs and chemicals

The target CECs were selected based on their occurrence and ubiquity in the aquatic environment, as well as their production and consumption volume (Caliman and Gavrilescu, 2009; Debska et al., 2004; Luo et al., 2014; Petrie et al., 2015). The 164 CECs targeted comprised: pharmaceuticals ($n = 96$), pesticides ($n = 34$), PFASs ($n = 10$), parabens ($n = 3$), industrial chemicals ($n = 9$), personal care products ($n = 4$), stimulants ($n = 3$), vitamins ($n = 2$), a drug ($n = 1$), a fatty acid ($n = 1$) and an isoflavone ($n = 1$). Native standards were acquired from Sigma-Aldrich (Sweden). Isotopically labeled standards (ISs) ($n = 26$) were obtained from Wellington Laboratories (Canada), Teknolab AB (Kungsbacka, Sweden), Sigma-Aldrich, and Toronto Research Chemicals (Toronto, Canada). All analytical standards used for analysis were of high purity grade (>95%). Detailed information about native standards and ISs can be found elsewhere (Gago-Ferrero et al., 2017; Sörengård et al., 2019).

Ultrapure water was generated by a Milli-Q (MQ) Advantage Ultrapure Water purification system and filtered through a 0.22 μm Millipak Express membrane and an LC-Pak polishing unit (Merk Millipore, Billercia, MA). Methanol, acetonitrile, and formic acid of high analytical grade were acquired from Sigma-Aldrich (Sweden).

2.2. Sampling

Influent and effluent wastewater samples were collected as 24-h or one-week composite samples from 15 WWTPs in Sweden during June 2018 (Table S1 in Supporting Information (SI)). The WWTP sites were selected based on a report by the Swedish Environmental Protection Agency (SEPA), which identified WWTPs with potentially large impacts on the receiving water body (Wallberg et al., 2016). Surface water samples (0.1 m below the water surface) were collected (as grab samples) in the recipient of WWTPs (both downstream and upstream of the WWTP effluent entry point). All samples were collected into 1-L high-density polyethylene bottles, immediately frozen, and stored frozen (−20 °C) until analysis. Sludge samples were collected from dewatered sludge at 14 WWTPs (Table S1 in SI).

2.3. Sample preparation for chemical analysis

Procedures used for preparation of water and sludge samples for instrument analysis are described in detail elsewhere (Fedorova et al., 2014; Golovko et al., 2016). In brief, the wastewater and river water samples were spiked with the IS mixture to achieve a concentration of 50 ng/L. The water samples were then filtered through a syringe filter (0.45 μm, regenerated cellulose; Minisart® RC, Sartorius, Germany) and 10 mL aliquots were analyzed using a two-dimensional liquid chromatography (LC/LC) method coupled to tandem mass spectrometry (MS/MS).

The sludge samples were prepared using an ultrasonic-based solvent approach, for which detailed information can be found elsewhere (Golovko et al., 2016). The sludge samples were air-dried overnight in a clean fume hood. Before extraction, an IS mixture ($c = 10$ ng/g dw sludge) was added to 2 g dry sludge sample. Then 4 mL of acetonitrile and water (1/1, *v*/v, 0.1% formic acid) were added to the air-dried sludge

and the samples were ultrasonicated for 15 min. The supernatant was filtered through a syringe filter (0.45 μm, regenerated cellulose, VWR, Sweden) into 10-mL vials. The step was repeated with a second extraction solvent mixture (acetonitrile, 2-propanol, and water (3/3/4 v/v/v with 0.1% formic acid)). The two supernatants were combined, mixed well, and 1 mL of the extract was used for analysis.

2.4. Instrumental analysis of CECs

The water and sludge samples were analyzed by a DIONEX UltiMate 3000 ultra-high pressure liquid chromatography (UPLC) system (Thermo Scientific, Waltham, MA, USA) coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ QUANTIVA, Thermo Scientific, Waltham, MA, USA) (for details, see text in SI).

2.5. Quality control

The performance of the method was assessed with regard to its linearity, limit of quantification (LOQ), precision, and blanks (for details see text and Table S2 in SI). The physico-chemical properties of all target compounds detected ($n = 164$) are shown in Table S3 in SI.

2.6. Fish embryo toxicity tests

Samples of influent and effluent from four WWTPs and water samples from their recipients (i.e., upstream and downstream of the WWTPs) were toxicologically evaluated using the ZFET ($n = 24$ per treatment). The testing included measurements of lethal and sublethal responses in developing zebrafish embryos from fertilization up to 6 days of age (for details, see text and Table S4 in SI) (Carlsson et al., 2013). In addition, screening for acute toxicity using ZFET was performed on influent and effluent samples from seven WWTPs and water samples from their recipients.

The extraction of the water samples (1 L) was done using solid phase extraction system (SPE-DEX, Horizon Technology, Salem, NH, USA) using HLB extraction disks (Atlantic HLB-H Disks, diameter 47 mm; Horizon Technology, Salem, NH, USA). In total, 1 L of the water sample (influent, effluent and recipient waters) was automatically filtered and loaded on the SPE disk which was pre-conditioned with methanol (50 mL, 25 mL × 2) followed by Millipore water (25 mL × 2). Next, the SPE disk was washed with 5% methanol (25 mL × 2) and then Millipore water (25 mL × 2). The SPE disk was dried with nitrogen for 10 min at room temperature and finally eluted with methanol (25 mL × 3). The TurboVap Classic II system (Biotage, USA) was used for the evaporation until 0.5 mL at 40 °C in the 200 mL evaporation tube, which was then rinsed with ethanol. The samples were further concentrated with solvent exchange to 0.5 mL of ethanol. Finally the extract was concentrated and the solvent was changed to dimethyl sulfoxide (DMSO) (concentration factor 2000).

The extracts were kept frozen at −20 °C until the day of exposure. Each extract was diluted by mixing 20 μL of the extracted sample with 20,000 μL of carbon-filtered tap water in Petri dishes, resulting in 0.1% solvent concentration in the exposure solution (concentration factor two times the original water concentration). The embryos were observed using stereo and inverted microscopes (Leica EZ4D and Olympus CKX41) at 24, 48, and 144 h post-fertilization (hpf) for specific endpoints in three categories; lethal categorical, sublethal categorical, and sublethal continuous (Table S1 in SI). The hatching time for each embryo was recorded by a time-lapse camera (Canon EOS 500D) that photographed the plates automatically every hour between 48 and 144 hpf. The hatching time for each individual embryo was determined by visual examination of the time-lapse photos. At 144 hpf, embryo behavior was evaluated using an automated computerized video recording system (ViewPoint Zebrabox®, ViewPoint, France). The swimming activity of each embryo in the 96-well plates was automatically recorded in alternating dark and light phases. The assessment of swimming activity began with 10 min of acclimation in light, followed by three alternating 5-min dark and light intervals. The data on swimming activity were evaluated in terms of three variables: total swimming distance in darkness (mm/15 min), total swimming distance in light (mm/15 min), and total swimming distance (mm/30 min).

2.7. Evaluation and statistics

The removal efficiency of individual CECs in the WWTPs was calculated as:

$$Removalefficiency[\%] = \left(\frac{([Influent]-[Effluent])}{[Influent]}\right) \times 100 \quad (1)$$

The sludge/water partitioning coefficient (K_d [L/ kg]) was calculated as:

$$K_d[L/\ kg] = \frac{c_s}{c_{aq}} = \frac{c_{sludge}}{c_{effluent}} \quad (2)$$

where c_s is the CEC concentration in the sludge (c_{sludge}) and c_{aq} is the CEC concentration in the aqueous effluent phase (c_{sludge}).

For chemical evaluation, octanol/water partition coefficient (K_{OW}) of the compounds was acquired from EPI Suite™ model (v. 4.11, USEPA, USA) (Table S3 in SI). Partial Least Squares (PLS) using SIMCA 14.0 software was used to identify relationships between the modeled physico-chemical characteristics of the CECs (predictor variables (X)) and their removal efficiencies and partitioning behavior (response variables (Y)). The same PLS model was used to relate the measured chemical composition (X) and ZFET score (from 0 to 3) (Y). Compounds with no identified physiochemical characteristics and with concentrations <LOQ were ignored. For a good PLS, R^2X (PC1) should exceed 0.3 to explain enough of the variation in the data, and R^2Y (PC2) should not exceed 0.4 because the risk of over-fit. After identifying important variables, relationships between these variables were analyzed with Pearson correlation, with significance level set to $p < 0.05$.

The toxicity data were analyzed using R Studio Version 1.1.463 (RStudio, Inc.). One-way ANOVA with Dunnet's post hoc test was used to analyze the continuous ZFET endpoints. The binary data were analyzed using the Fisher exact test. One-way ANOVA with pairwise comparison was used to analyze the behavioral endpoints.

3. Results and discussion

3.1. Occurrence of CECs in wastewater influent and effluent, and in sludge

Of the 164 target CECs analyzed in wastewater influent and effluent, 119 contaminants were detected in most sample, including pharmaceuticals, personal care products, industrial chemicals, PFASs, pesticides, parabens, stimulants, and vitamins (Tables S5 and S6 in SI). The dominant groups were NSAIDs (nonsteroidal anti-inflammatory drug), stimulants, antidiabetic drugs, and industrial chemicals, which were present at the highest concentrations in WWTP influent and effluent (Fig. 1). Mean CEC concentrations detected for individual compounds in wastewater samples showed high variation, ranging from ng/L to mg/L. Given this wide range of concentrations, a noteworthy finding was that a group of only 20 CECs was responsible for 70% of the combined concentration of pollutants in WWTP influent and effluent (Tables S5 and S6 in SI). These compounds were not only present in high concentrations, but had a high frequency of detection (>50%) (Fig. 2). The CECs included three industrial chemicals (tetraethylene glycol, pentaethylene glycol monododecyl ether (laureth-5) and di-(2-ethylhexyl)phosphoric acid (DEHPA)), 15 pharmaceuticals (salicylic acid, diclofenac, losartan, valsartan, venlafaxine, oxazepam, lamotrigine, carbamazepine, tramadol, HCTZ, theophylline, furosemide, ranitidine, bicalutamide, and metformin), and the stimulants caffeine and nicotine (Tables S5 and S6 in

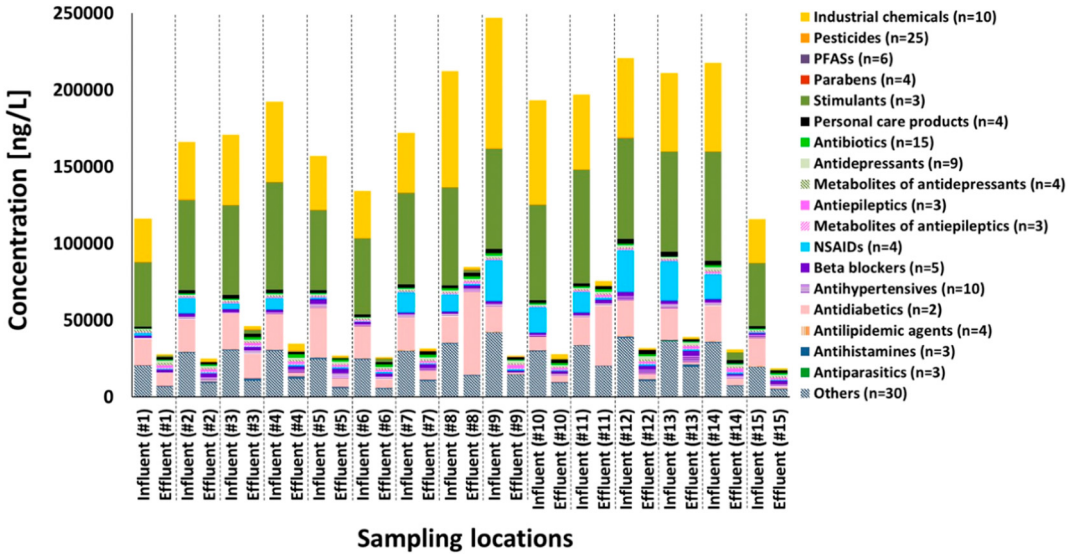

Fig. 1. Combined concentrations of chemicals of emerging concern (CECs) in samples of influent and effluent from wastewater treatment plants in Sweden. NSAIDs – nonsteroidal anti-inflammatory drugs, PFASs – *per*- and polyfluoroalkyl substances.

SI). The CEC concentrations detected in this study were comparable to those in other studies, which detected mainly pharmaceuticals, personal care products, and stimulants in wastewater and sludge samples (Gobel et al., 2005; Kasprzyk-Hordern et al., 2009; Lajeunesse et al., 2012; Yang et al., 2017). For example, Fick et al. (Fick et al., 2011) performed a screening study in Sweden for 101 pharmaceuticals in wastewater, surface water, sludge, and biota samples, and reported similar concentration levels to those found for most pharmaceuticals analyzed in the present study.

For individual CECs, the highest concentrations were found for metformin (up to 54,000 ng/L), caffeine (64,000 ng/L), and nicotine (9600 ng/L) in wastewater influent and effluent. Metformin is by far the most frequently prescribed antidiabetic drug worldwide and in Sweden (Lindim et al., 2016). It has been shown that metformin is not completely metabolized in the human body (Krentz and Bailey, 2005), and is excreted unchanged and therefore released into the environment via wastewater (Briones et al., 2016; Lindim et al., 2016; Scheurer et al., 2009). Caffeine is widely consumed with food and it has been suggested that it could serve as a suitable wastewater indicator for river water, as presence of this compound in river water can be a strong indication of wastewater contamination (Glassmeyer et al., 2005). Nicotine is among the most widely used stimulants (besides caffeine) and is included in tobacco, snuff, and other smoke-free tobacco products containing nicotine (Ramström and Foulds, 2006) and widely detected in the environment (Gago-Ferrero et al., 2017; Sörengård et al., 2019; Yang et al., 2017). Furthermore, high concentrations of some metabolites were found in effluent wastewater, such as metronidazole-OH at up to 160 ng/L (metabolite of metronidazole), desmethylcitalopram at up to 100 ng/L (metabolite of citalopram), desmethylvenlafaxine at up to 1600 ng/L (metabolite of venlafaxine), and three of the main metabolites of the antiepileptic drug carbamazepine: D-H-CAR (up to 580 ng/L), carbamazepine 10,11-epoxyde (up to 400 ng/L), and oxcarbazepine (up to 33 ng/L) (Tables S5 and S6 in SI). The occurrence of the metabolites in the wastewater could originate from human excreted metabolites or parent compounds can undergo biotransformation during wastewater treatment (Caliman and Gavrilescu, 2009; Debska et al., 2004; Luo et al., 2014; Petrie et al., 2015). These results show that it is important to monitor pharmaceutical metabolites/

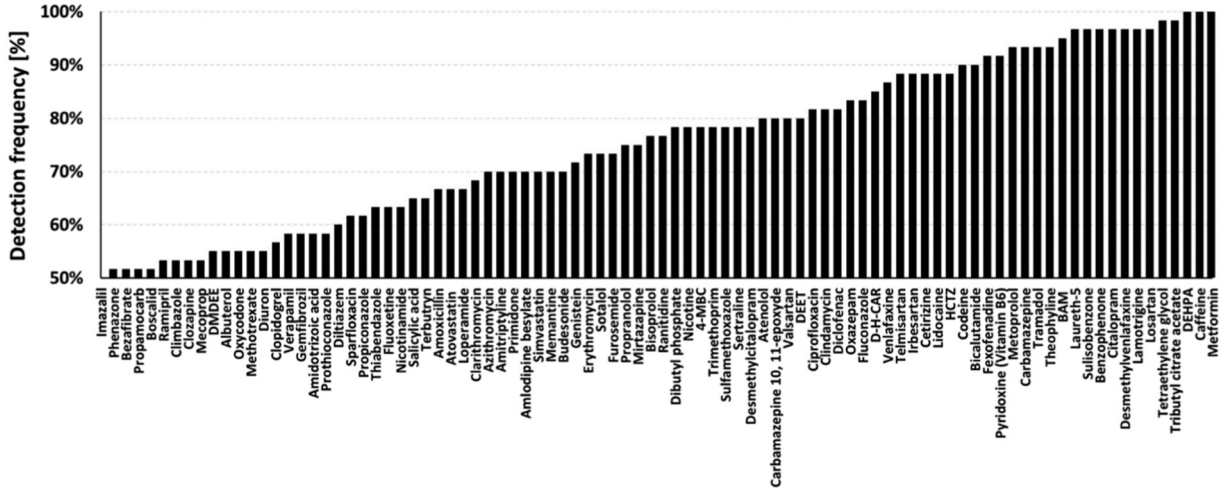

Fig. 2. Detection frequency of chemicals of emerging concern (CECs) present at frequency of detection >50% in samples of influent and effluent from wastewater treatment plants and in surface water samples from Sweden. DMDEE – 2,2-dimorpholinyldiethyl-ether, 4-MBC – 3-(4-methylbenzylidene)camphor, DEET – N,N-diethyl-m-toluamide, D-H-CAR – 10,11-Dihydro-10-hydroxycarbamazepine, HCTZ – hydrochlorothiazide, BAM – dichlorobenzamide, DEHPA – di-(2-ethylhexyl)phosphoric acid.

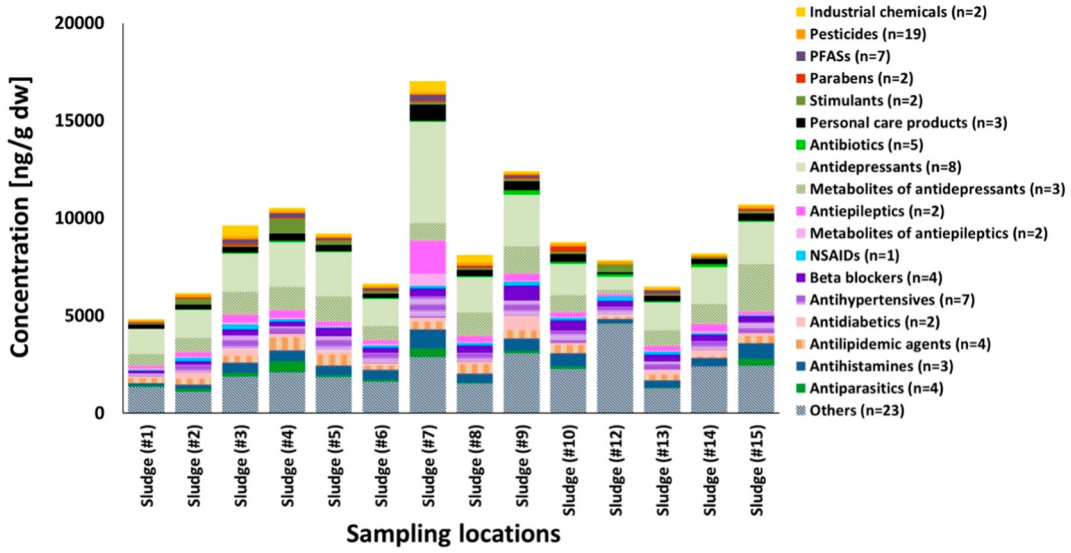

Fig. 3. Combined concentrations of chemicals of emerging concern (CECs) in 14 sludge samples from wastewater treatment plants. NSAIDs – non steroidal anti-inflammatory drugs, PFASs – per- and polyfluoroalkyl substances.

transformation products since their concentrations (Kasprzyk-Hordern et al., 2009; Petrie et al., 2015; Sörengård et al., 2019) and their toxicity potential (Caliman and Gavrilescu, 2009; Carlsson et al., 2013) can be higher than those of the parent compounds. For instance, a previous study reported that carbamazepine 10,11-epoxyde, the main active carbamazepine metabolite, might have potential biological effects in non-target species (Valdés et al., 2016).

Of the 164 target CECs, 103 were detected in sludge samples (Tables S5 and S7 in SI). Analysis of sludge showed large variations in concentrations between WWTPs (Fig. 3), which can be explained by differences in CEC composition in the influent water and in operating conditions at the WWTPs. Investigation of CECs in sludge is very important, because in Sweden 25% of sludge is used for agricultural purposes and 50% is used for landfilling or construction work (SEPA, 2013). The compounds with the highest frequency of detection (>90%) and high concentrations (>100 ng/g dw) in sludge were mainly pharmaceuticals such as lamotrigine, venlafaxine, propranolol, fluoxetine, carbamazepine, diclofenac, telmisartan, metoprolol, tramadol, cetirizine, clozapine, metformin, mirtazapine, amitriptyline, bicalutamide, losartan, fexofenadine, citalopram and its metabolite desmethylcitalopram, simvastatin, budesonide, sertraline and its metabolite norsertraline (Tables S6 and S7 in SI). Similar results have been reported in a Swedish screening study for metoprolol, mirtazapine, citalopram, amitriptyline, sertraline, and telmisartan (Fick et al., 2011). For instance, psychoactive compounds such as venlafaxine, fluoxetine, mirtazapine, amitriptyline, citalopram and sertraline have a lipophilic nature and therefore have high affinity to sludge (Horsing et al., 2011; Ivanová et al., 2018; Lajeunesse et al., 2012). The concentration levels in sludge obtained in this study are in agreement with previous studies on citalopram, fluoxetine and sertraline in sludge (Fick et al., 2011; Ivanová et al., 2018).

It should be mentioned that seven pesticides (chloridazon, fenpropimorph 4, dichlorprop (2,4-DP), fludioxonil, cyprodinil, mandipropamid, and difenoconazole) were found only in sludge samples. These pesticides have a relatively high K_{OW} ($K_{OW} > 3$, except chloridazon $K_{OW} = 1.1$), and can thus be expected to be mainly sorbed to soil, sediment, or sludge (Li, 2014) (Tables S3 and S6–7 in SI).

3.2. Removal efficiency of CECs in WWTPs

Overall, removal efficiencies varied significantly between the 164 CEC compounds (Fig. 4). Medium removal efficiency was calculated for CECs that showed detection frequency > 50% ($n = 86$). Based on the removal efficiency tendencies in WWTPs, CECs were divided into two groups: positive removal efficiency ($n = 35$) and negative removal efficiency ($n = 48$). The ΣCEC concentration declined by on average 60% on comparing WWTP influent and effluent concentrations (Fig. 1). Similar results have been reported for most pharmaceuticals in a previous screening study (Fick et al., 2011). During wastewater treatment, CECs can be removed (i.e., positive removal efficiency) through microbial degradation or sorption to solids (Ternes et al., 2004), which are later removed with the sludge. Negative removal efficiency, i.e., higher CEC concentration in WWTP effluent compared with influent, can be explained by: i) degradation of precursors to target CECs (Jelic et al., 2011; Ternes et al., 2004); ii) partitioning to the aqueous phase of CECs sorbed to the solid phase (Jelic et al., 2011; Ternes et al., 2004); iii) influent and effluent samples representing different portions of wastewater, since the samples were collected at the same time but the WWTPs have different hydraulic retention times (Ort et al., 2010); iv) concentrations close to the detection limit, which have higher uncertainty; and v) analytical error (Ort et al., 2010).

Previous studies have reported relatively low removal efficiencies for most pharmaceuticals and personal care products in winter months, possibly owing to lower rates of microbial activity (Hedgespeth et al., 2012; Vieno et al., 2005). Degradation is assumed to be a minor factor and will be significantly reduced at lower temperatures. The negative removal values reported for some compounds (Gracia-Lor et al., 2012; Jelic et al., 2011) could be related to this effect. Similar seasonal differences in removal efficiencies have been reported elsewhere (Castiglioni et al., 2006; Ferguson et al., 2013; Hijosa-Valsero et al., 2010), leading to the general conclusion that treatment processes are more efficient during warmer periods. Another explanation for low or negative removal efficiencies can be that more water-soluble CECs (low K_d, low K_{OW}) may partition over time (under well-mixed conditions) to the aqueous phase, resulting in negative removal efficiency.

In the present study, carbamazepine and its metabolites showed negative removal efficiency, regardless of the treatment applied. The results concerning carbamazepine persistency and its ubiquitous occurrence confirm findings in previous studies (Joss et al., 2005). No significant overall removal was observed for most antibiotics (sparfloxacin, clindamycin, trimethoprim, erythromycin, azithromycin, clarithromycin, ciprofloxacin, amoxicillin, sulfamethoxazole, metronidazole and its metabolite) and antidepressants (citalopram and its metabolite desmethylcitalopram, sertraline, fluoxetine, venlafaxine and its metabolite desmethylvenlafaxine, oxazepam, mirtazapine, and

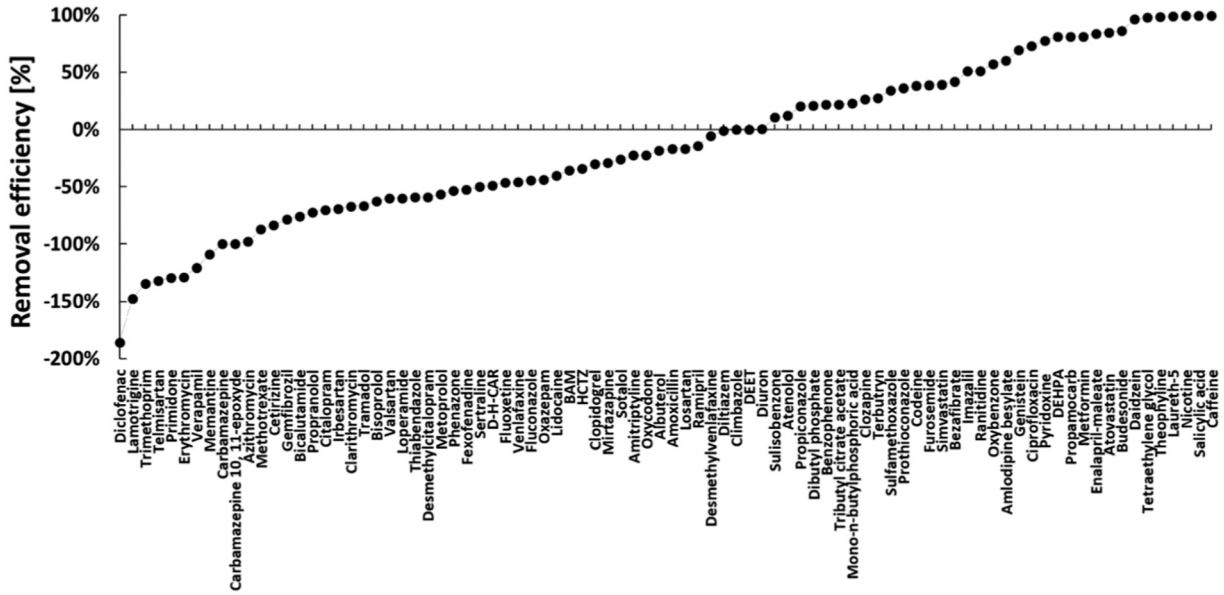

Fig. 4. Median removal efficiency of selected chemicals of emerging concern (CECs) with frequency of detection >50% in wastewater samples. D-H-CAR – 10,11-Dihydro-10-hydroxycarbamazepine (D-H-CAR), BAM – dichlorobenzamide, HCTZ – hydrochlorothiazide, DEET – N,N-diethyl-m-toluamide, DEHPA – di-(2-ethylhexyl)phosphoric acid.

amitriptyline). Incomplete removal of these compounds during conventional treatment at WWTPs has been reported in several previous studies (Bendz et al., 2005; Gobel et al., 2007; Kasprzyk-Hordern et al., 2009). Analysis of the relationship between physiochemical characteristics of individual CECs (Fig. S1 in SI) and removal efficiency using the PLS model showed no significant correlation ($R^2X < 0.3$) (Fig. S1 in SI). For example, the structurally similar compounds sotalol and metoprolol (β blocker) showed similarly poor elimination, but another compound in this class, atenolol, exhibited much better removal. This is in agreement with the literature, where very few studies have found a correlation between physiochemical characteristics of CECs and removal efficiency (Rostvall et al., 2018). Thus, more research is needed to better predict removal efficiencies of CECs during wastewater treatment.

High concentrations of CECs were detected in sludge (Fig. 3), indicating that CECs can be removed from the wastewater stream via sludge, as reported previously (Camacho-Munoz et al., 2012). K_d value, which has been shown to be a good predictor for removal of CECs in WWTP (Pomiès et al., 2013), was calculated for 47 CECs (Table S2 in SI). The K_d value for most compounds showed a significant linear correlation with K_{OW} and was the best explanatory variable in a PLS plot ($R^2 = 0.32$; $p < 0.001$, Pearson correlation) (Fig. 5). Previous studies have discussed the role of the partitioning constant (Luo et al., 2014), suggesting that CECs with log $K_d < 2.5$ will mainly end up in the aqueous phase, while those with log $K_d > 3.2$ are more likely to partition to the solid phase. However, in this study there was no significant correlation

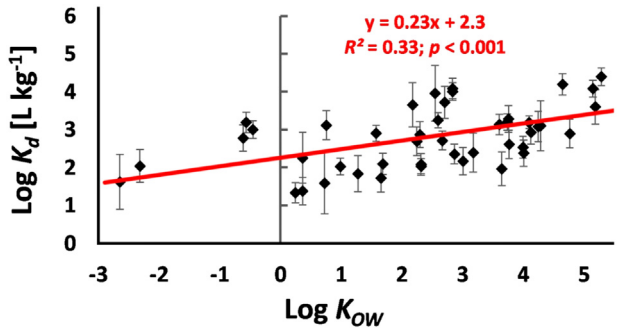

Fig. 5. Log partitioning coefficient (log K_d, L/kg) for chemicals of emerging concern (CEC) in sludge and wastewater (based on 48 CECs and 15 wastewater treatment plants) as a function of modeled log octanol/water partitioning coefficient (K_{OW}).

($R^2 = 0.077$, $p = 0.070$) between log K_d and removal efficiency (Fig. S1 in SI), which indicates that K_d value is not always a good predictor of removal efficiency. On the other hand, the linear model based on log K_{OW} presented in this study (Fig. 5) can be used as a simple tool for prediction of K_d values of new CECs and their fate in the aqueous and solid phase. Partitioning coefficient (log K_d) value is a critical parameter for prediction and modeling of the fate of individual CECs through WWTP as reported in a few studies (Luo et al., 2014; Pomiès et al., 2013). Here we present log K_d values for 47 CECs, information that can be used in future studies. The log K_d values for individual compounds ranged between 1.3 and 4.5, with a mean of 2.8 and a standard deviation of 0.83 (coefficient of variation (CV) = 30%). The K_d values for individual CECs were based on a minimum of four WWTPs (mean 13.3 ± 2.6 WWTPs) and the mean standard deviation was 0.36 ± 0.16 log units (CV = 14 ± 9.4%). This low variation in log K_d values for multiple WWTP indicates a high-quality assessment and good stability of the parameters. However, it should be noted that all WWTPs in this study had a similar (same order of magnitude) influent CEC profile (Figs. 1 and 3) and the same types of treatment steps, which should be considered when transferring the results to other WWTP conditions.

3.3. Impact of wastewater treatment effluent on the recipient water system

In surface water samples (upstream or downstream), 122 of the 164 target compounds were detected (Fig. 6, Tables S5 and S8 in SI). The highest concentration was observed for metformin (19,000 ng/L), followed by caffeine (3600 ng/L), sulisobenzone (1700 ng/L), and desmethylvenlafaxine (18,000 ng/L). In addition, 12 CECs (tetraethylene glycol, laureth-5, tributyl citrate acetate, DEHPA, pyridoxine, metoprolol, tramadol, codeine, citalopram, lamotrigine, BAM and losartan) were detected with >95% detection frequency in high concentrations. The frequent detection of these CECs can be explained by their universal use in many consumer products. Some of these compounds can be partly removed via natural attenuation (e.g., photodegradation), while other compounds (e.g., metoprolol, lamotrigine, and carbamazepine) are resistant to degradation and persistent in the environment. Metformin is one of the most frequently detected pharmaceuticals in surface water worldwide (Briones et al., 2016). Lindim et al. (Lindim et al., 2016) identified metformin, furosemide, gabapentin, atenolol, and tramadol as substances with high emissions to Swedish surface waters,

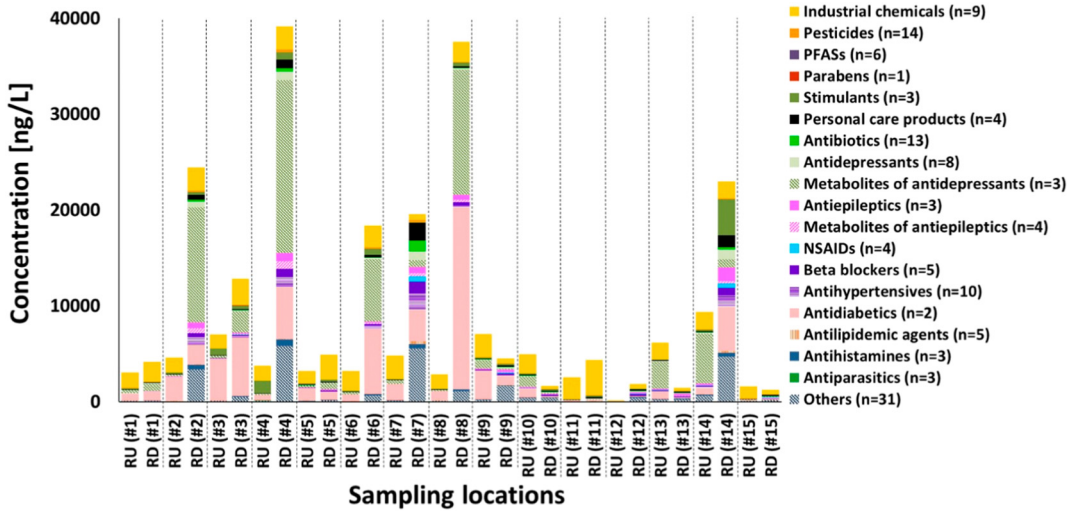

Fig. 6. Combined concentrations of chemicals of emerging concern (CECs) in recipient water samples. RU – recipient upstream, RD – recipient downstream, NSAIDs – nonsteroidal anti-inflammatory drugs, PFASs – per- and polyfluoroalkyl substances.

which was confirmed in the present study. Because of dilution, sorption, biodegradation, and photodegradation, CEC concentrations are typically lower in surface water than in WWTP effluent (Debska et al., 2004; Ferguson et al., 2013; Kasprzyk-Hordern et al., 2009; Vieno et al., 2005).

Our results showed that WWTP effluent could be one of the main sources of CECs in aquatic environments, which is in agreement with previous findings (Gago-Ferrero et al., 2017; Sörengård et al., 2019). In general, the concentrations of CECs in water at the downstream location were, on average, 50% higher than those upstream of the WWTPs. This can be explained by the WWTP effluent most likely being a major point-source input of these compounds to the recipient. These CECs residues may pose a risk to the aquatic environment and/or human health, so further studies are needed to evaluate their effects on ecosystems.

3.4. Zebrafish embryo toxicity of wastewater and recipient water samples

Water samples from 11 different WWTPs in Sweden were evaluated for lethal, sub-lethal, and behavior effects in early developing zebrafish embryos. The number of adversely affected zebrafish embryos after 144 hpf of exposure to the different WWTPs samples was generally low (Table S4 in SI). It is important to note that ecotoxicologically important chemicals might have been missed during the extraction process, compared with toxicological testing of whole water samples. The most commonly recorded adverse effects were side-lying and edema of the pericardial sac and the yolk-sac, but no statistically significant differences in the number of malformations were recorded for any of the treatment groups. However, exposure to some of the WWTP samples resulted in toxicity compared with the respective control group. Exposure to influent samples from both WWTP 9 and WWTP 10 resulted in 100% mortality after only 24 hpf. The survival rate of embryos was high overall in all other samples from the different WWTPs. The influent from WWTP 4 reduced spontaneous movements measured at 24 hpf. Decreases in heart rate at 48 hpf were recorded for embryos exposed to both influent and effluent water, and to upstream and downstream recipient samples, from WWTP 8 (Fig. 7A). As shown in the chemical analysis, WWTP effluent contains a vast amount of CECs, including pharmaceuticals, and many of these (e.g., β-blockers) are known to reduce heart rate in zebrafish (Sun et al., 2014). Longer time to hatching was recorded for embryos exposed to influent samples from WWTP 4 (Fig. 7B), and to both influent and effluent samples from WWTP 8 (Fig. 7C). Effects on hatching time may be due to general physiological stress and reduced health from the total chemical exposure burden. Low concentrations of chemicals might thus stress embryos to hatch earlier, while high concentrations can negatively affect their overall health, resulting in delayed hatching or even failure to hatch. The overall chemical burden might also affect swimming behavior. Exposure to the influent samples from both WWTP 4 and WWTP 15 (Fig. 8) resulted in reduced swimming distances compared with controls. Neuro-active pharmaceuticals in sewage water can also contribute to behavior changes affecting heart rate, hatching, and swimming (Carlsson et al., 2013; Pohl et al., 2019). Overall, the chemical analyses in the present study revealed high occurrences of antidepressants, opioids, and stimulant drugs, which can all be causative agents for the observed effects in zebrafish embryos. However, PLS analysis of relationships between ZFET and individual CEC concentrations did not show significant correlations ($R^2X < 0.3$). Hence, no individual compound or group of compounds could explain the toxicity in ZFET.

4. Conclusions

A total of 119 contaminants were detected in at least one sample, in average concentrations ranging from ng/L to mg/L in water samples and from ng/g dw to μg/g dw in sludge samples. The most commonly detected CECs in WWTP influent and effluent, sludge, and surface water samples were industrial chemicals (tetraethylene glycol, laureth-5 and DEHPA), a personal care product (sulibenzone), pharmaceuticals (diclofenac, losartan, venlafaxine, lamotrigine, carbamazepine, tramadol, fexofenadine, citalopram bicalutamide, metformin), and stimulants (caffeine and nicotine). Removal of CECs in the WWTPs varied widely for individual compounds. In general, CECs can be removed via degradation or sorb onto solids, which can be removed by activated sludge treatment. However, there is a risk of CECs degrading to more persistent and toxic transformation products. There is also a risk of CECs being released into the environment when sludge is applied on agricultural land. The CEC concentrations in recipient waters were generally one order of magnitude lower than those in WWTP effluent. Comparisons of CEC concentrations in upstream and downstream recipient samples showed on average 50% higher concentrations downstream of WWTPs compared with upstream, indicating that WWTP effluent can have a marked impact on recipient waters. Overall, the results in this study indicate that most WWTPs investigated achieve sufficient removal of chemicals, given that zebrafish embryos were non-affected by the effluent and recipient samples. However, observed adverse effects were observed for WWTP 4 and WWTP 8, indicating that potentially toxic CECs were less efficiently removed in these WWTPs. In addition, constant

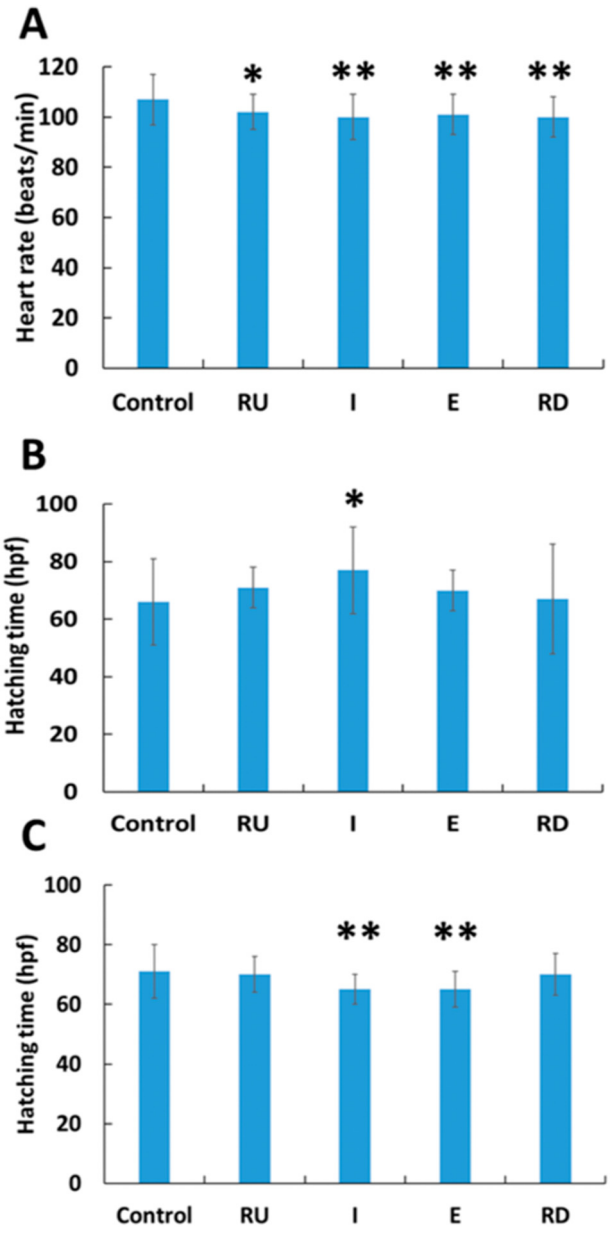

Fig. 7. Zebrafish embryo toxicity of wastewater and recipient water samples. (A) Heart rate (beats per minute) at 48 hpf in zebrafish embryos exposed to water samples from WWTP 8. Mean hatching time of zebrafish embryos exposed to (B) WWTP 4 and (C) WWTP 8. RU – recipient upstream, I – wastewater influent, E – wastewater effluent, RD – recipient downstream.

release of potentially persistent and bioaccumulative chemicals from WWTPs warrants attention in terms of effects on aquatic organisms. Future studies should therefore focus on long-term investigations of lifelong effects of low-dose exposure to pollutants, which is a more likely situation for aquatic organisms in recipient waters. Ultimately, advanced technologies for removal of CECs from wastewater are needed to protect recipient waters.

CRediT authorship contribution statement

Oksana Golovko: Conceptualization, Methodology, Formal analysis, Validation, Data Curation, Writing- Original draft preparation

Stefan Örn: Conceptualization, Methodology, Formal analysis, Resources, Writing- Reviewing and Editing

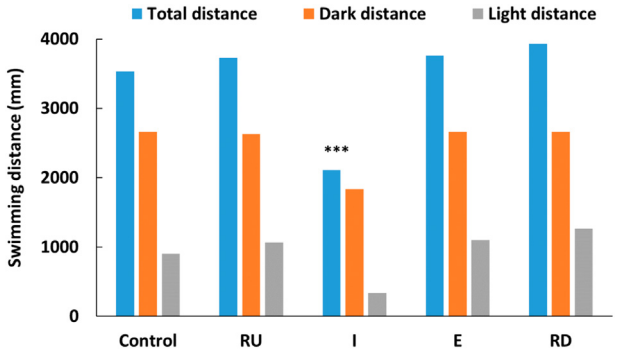

Fig. 8. Swimming distance of zebrafish embryos exposed to water samples from WWTP 4 in alternating dark and light periods at 144 h. Data showing total swimming distance (mm/30 min), swimming distance during dark (mm/15 min), and swimming distance during light (mm/15 min). RU – recipient upstream, I – wastewater influent, E – wastewater effluent, RD – recipient downstream.

Mattias Sörengård: Formal analysis, Data Curation, Writing-Reviewing and Editing

Kim Frieberg: Methodology, Formal analysis

Winnie Nassazzi Methodology, Writing- Reviewing and Editing

Foon Yin Lai Methodology, Writing- Reviewing and Editing

Lutz Ahrens: Project administration, Conceptualization, Methodology, Funding acquisition, Writing- Reviewing and Editing

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.142122.

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