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Oxidation of antibiotics by ferrate(VI) in water: Evaluation of their removal efficiency and toxicity changes

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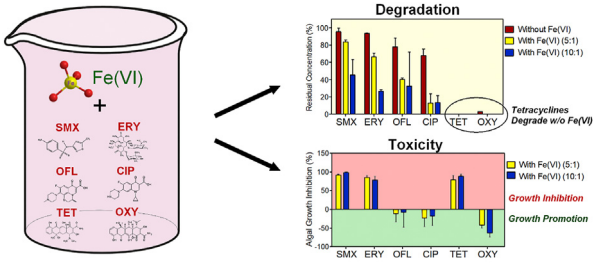
HIGHLIGHTS

- Studied antibiotics have EC_{50} < 1.0 mg/L against *R. subcapitata* and *S. elongatus*.
- Excess Fe(VI) compared to antibiotics has high removal efficiency at pH 8.0
- Excess Fe(VI) treatment of antibiotics gave varied decreases in algal toxicity.
- OFL, CIP, and OXY lose algal toxicity after excess Fe(VI) treatment.
- SMX, ERY, TET, and their degradation byproducts remain toxic after Fe(VI) treatment.

GRAPHICAL ABSTRACT



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ABSTRACT

Antibiotics in water and wastewater have been determined extensively. The treatment of antibiotics in water needs evaluation of possible harmful effects on aquatic ecosystems and human health. This paper presents the toxicity evaluation of antibiotics after their treatment with ferrate (VI) ($Fe^{VI}O_4^{2-}$, Fe(VI)) in water. The antibiotics (sulfamethoxazole (SMX), erythromycin (ERY), ofloxacin (OFL), ciprofloxacin (CIP), tetracycline (TET), oxytetracycline (OXY), and trimethoprim (TMP)) were treated at pH 8.0 by applying two concentrations of Fe(VI) to have molar ratios of 5:1 and 10:1 ([Fe(VI)]:[antibiotic]). Under the studied conditions, incomplete removal of antibiotics was observed, suggesting that the treated solutions contained parent antibiotics and their transformation products. The toxicity of antibiotics without Fe(VI) treatment was tested against freshwater green alga *Raphidocelis subcapitata* and cyanobacterium *Synechococcus elongatus*, which were determined to be generally sensitive to antibiotics, with EC_{50} < 1.0 mg/L. The toxicity of Fe(VI) treated solution was tested against *R. subcapitata*. Results found no toxicity for the treated solutions of OFL, CIP, and OXY. However, SMX, ERY, and TET remained toxic after Fe(VI) treatment (i.e., more than 75% growth inhibition of *R. subcapitata*). Results demonstrated that *R. subcapitata* may be applied to test the toxicity of antibiotics after oxidative treatments.

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1. Introduction

In recent years, the presence of pharmaceuticals and personal care products (PPCPs) in the environment has become the subject of growing concern (Costa et al., 2019; Zainab et al., 2020; Rout et al., 2021). PPCPs include numerous chemical classes such as antibiotics, antimicrobials, anti-inflammatory drugs, β-blockers, lipid regulators, synthetic musks, and preservatives, together with their metabolites and transformation products (Cizmas et al., 2015; Kummerer et al., 2018). Antibiotics are one of the most widely used categories of PPCPs and are employed in both human and veterinary medicine to prevent or treat microbial infections for growth promotion and prophylaxis (Magdaleno et al., 2015; Binh et al., 2018; Kovalakova et al., 2020). After administration, antibiotics may be excreted and discharged to the surface waters and wastewater in their biologically active form (Kummerer, 2009). All classes of antibiotics have been detected in surface waters of many countries. The recorded concentrations of antibiotics in surface waters are usually within the range of ng/L-μg/L (Kovalakova et al., 2020).

Many treatment approaches have been investigated for the removal of antibiotics from water, including filtration (microfiltration, ultrafiltration, activated carbon filtration), chlorination, and advanced oxidation processes such as UV radiation, ozonation, Fenton reaction, and photocatalysis, and their novel combinations and modifications (Wang and Bai, 2017; Hu et al., 2018; Jain et al., 2018; von Gunten, 2018; Xia et al., 2018a; Xia et al., 2018b; Lu et al., 2019; Monteil et al., 2019; Xia et al., 2019; Chen et al. 2021; Lee et al., 2020; Roy and Moholkar, 2020; Rueda-Marquez et al., 2020; Wang and Chen, 2020; Wu et al., 2020a; Wu et al., 2020b; Yang et al., 2020; Zhang et al., 2020b). Recently, ferrate (VI) ($Fe^{VI}O_4^{2-}$, Fe(VI)) has been studied as a green chemical that can perform multi-functional treatments (i.e., disinfection, oxidation, and coagulation) (Goodwill et al., 2019; Liu et al., 2019b; Luo et al., 2019; Manoli et al., 2019; Sun et al., 2019a; Xie and Cheng, 2019; Shao et al., 2020; Zhang et al., 2020a; Zheng et al., 2020). Fe(VI) not only disinfects viruses and bacteria, but also minimizes the formation of disinfection by-products (Sharma, 2007; Liu et al., 2020; Manoli et al., 2020; Dong et al., 2021). Oxidation by Fe(VI) can treat a wide range of contaminants including PPCPs (Yang et al., 2012a; Zhou and Jiang, 2015; Luo et al., 2019; Manoli et al., 2019; Zhang et al., 2020a; Zheng et al., 2020). Many studies have been published in the last few years demonstrating the removal of contaminants by Fe(VI) (Shin et al., 2018; Feng et al., 2019; Liu et al., 2019a; Sun et al., 2019b; Pan et al., 2020). However, scant information is available on the toxicity of the corresponding solutions after Fe(VI) oxidation. Researchers are applying the Ecological Structure-Activity Relationships (ECOSAR) program to predict the toxicity of the transformation products after reaction of Fe(VI) with contaminants and experimental toxicity evaluations are rarely conducted. Fe(VI) has shown success to some extent for removing antibiotics in water (Anquandah et al., 2011; Shao et al., 2019; Sun et al., 2019b; Acosta-Rangel et al., 2020). However, information on the toxicity of oxidized products of antibiotics is largely missing in the literature. The present paper examines the toxicity of a wide range of antibiotics and their corresponding transformation products after oxidation by Fe(VI).

Antibiotics and their mixtures pose a threat to the aquatic environment (Guan et al., 2017; Valitalo et al., 2017; Yao et al., 2017; Hamid et al., 2020; Wang et al., 2020). Freshwater green algae and cyanobacteria have frequently been used to assess antibiotic toxicity (Gonzalez-Pleiter et al., 2013; Kolar et al., 2014; Fu et al., 2017; Chen et al., 2020; Dong et al., 2020; Xu et al., 2021). The studies conducted previously have shown that both green algae and cyanobacteria are sensitive to selected antibiotics and cyanobacteria have the highest sensitivity of all the test organisms studied (Kovalakova et al., 2020) Therefore, in our study, we have used the green algae as a model organism to assess the toxicity of Fe(VI) treated water containing antibiotics.

The objective of the present study was to evaluate the toxicity (measured as growth inhibition) of seven antibiotics commonly found in surface water to freshwater green algae *Raphidocelis subcapitata* and cyanobacteria *Synechococcus elongatus* to determine the baseline toxicity in water only (i.e., without Fe(VI)). This study allowed for the first time the comparison of the toxicity of the antibiotics to both green algae and cyanobacteria. The chosen antibiotics in investigations were sulfamethoxazole (SMX), erythromycin (ERY), ofloxacin (OFL), ciprofloxacin (CIP), tetracycline (TET), oxytetracycline (OXY), and trimethoprim (TMP). Chemical structures are given in Table SM-1. These antibiotics were selected due to their high toxicity and frequent occurrence in the aquatic environment (Kovalakova et al., 2020). This study was followed by toxicity tests of the Fe(VI)-treated solutions, obtained by mixing Fe(VI) with the selected antibiotics at molar ratios of 5:1 and 10:1 ([Fe(VI)]:[antibiotic]) at pH 8.0. The measurements of the toxicity of Fe(VI)-treated antibiotics in literature are restricted to only cell lines and luminescent bacteria and information of ecotoxicity is almost unknown. The present study thus aims to determine the toxicity of Fe(VI)-treated antibiotics in the water against green alga *R. subcapitata*.

2. Materials and methods

2.1. Chemicals and reagents

The salts used for preparing algal growth media and phosphate-borate buffer salts were all of analytical reagent grade and were obtained from Fisher-Scientific (Austin, TX, USA) or Sigma-Aldrich (St. Louis, MO, USA). The 3,5-dichlorophenol (99% purity grade) was purchased from Acros Organics (New Jersey, USA). The following antibiotics (greater than 98% purity) were used: erythromycin (ERY) (CAS No. 114-07-8) and tetracycline hydrochloride (TET) (CAS No. 64-75-5), both from Sigma Aldrich (St. Louis, MO, USA)); oxytetracycline hydrochloride (OXY) (CAS No. 2058-46-0) (Alfa Aesar, Heysham, UK), sulfamethoxazole (SMX) (CAS No. 723-46-6) and trimethoprim (TMP) (CAS No. 738-70-5), all from TCI Chemicals (Tokyo, Japan); ofloxacin (OFL) (CAS No. 82419-36-1) (J&K Scientific, Shanghai, China), and ciprofloxacin (CIP) (CAS No. 85721-33-1) (Fluka, Muskegon, MI, USA). Solid potassium ferrate (K_2FeO_4) of ~98% purity was synthesized by the wet chemical technique (Luo et al., 2011). All solutions were made in demineralized water that was obtained from a purification system (18 MΩ cm Milli-Q Millipore, Waters Alliance, Milford, MA, USA). For the high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis, erythromycin standard and formic acid (98%) were purchased from Sigma Aldrich (Darmstadt, Germany). Methanol and acetonitrile of LC-MS grade (99.95%) were purchased from Biosolve (Dieuze, France).

2.2. Toxicity tests

The freshwater unicellular green alga *Raphidocelis subcapitata* UTEX 1648 (formerly known as *Selenastrum capricornutum* or *Pseudokirchneriella subcapitata*) and cyanobacterium *Synechococcus elongatus* UTEX 625 (also known as *S. leopoliensis* or *Anacystis nidulans*) were obtained from the UTEX culture collection (University of Texas, Austin, TX, USA). Cultures were maintained in the 50% ZBB medium (i.e. a 1:1 mixture of Zehnder medium (Staub, 1961) and Bold's Basal medium (Bold, 1949) and with continuous mixing at 150 rpm using a rotator shaker (New Brunswick Scientific Co., Inc., N.J., USA) for at least 14 d prior to the test.

The growth inhibition assay was performed according to the Organization for Economic Cooperation and Development (OECD) guideline No. 201 (OECD, 2011). The assay was performed in transparent 96-well microplates, with a sample volume of 250 μL per well, with at least six replicates for each concentration and respective controls. The initial concentrations were 50,000 and 200,000 cells per mL of exponentially growing algae and cyanobacterium in 50% ZBB medium, respectively. The positive control used in these experiments was 3,5-dichlorophenol. The pH was measured at the beginning of each test and 96 h. Organisms were exposed to selected antibiotics for 96 h at 25 ± 1 °C under continuous illumination (100 μmol/m^2 s) by a 6500 K growth lamp (Flarescent F54T5/H0, HTG Supply, Commerce City, CO, USA). The growth rate was evaluated after 72 h and 96 h, respectively, by *in vivo* chlorophyll fluorescence measurements with a microplate reader Synergy 4 (BioTek, Winooski, Vermont, USA) using a 485/670 nm excitation/emission filter. Range finding assays were performed prior to the final definitive tests to determine the concentration range, in which effects are likely to occur. Definitive experiments were carried out in three independent replicates using eight concentrations in a two-fold dilution range. The concentration range was 5.0−0.04 mg/L for ERY and SUL, 20.0−0.20 mg/L for TET and OXY, 50.0−0.40 mg/L for OFL and CIP, and 400−3.1 mg/L for TMP.

The growth inhibition was expressed as a decrease in chlorophyll fluorescence compared to control according to the guideline No. 201 (OECD, 2011). The percentage of growth inhibition for each test replicate was calculated using Eq. (1).

$$I\mu_i = \frac{\mu_c - \mu_i}{\mu_c} \times 100\ \% \quad (1)$$

where $I\mu_i$ = growth inhibition of the test concentration I, μ_i = mean measured fluorescence for the test concentration I, and μ_c = mean measured fluorescence for the control.

2.3. Statistical analysis

The statistical analysis was performed using the software GraphPad™ Prism 5 (GraphPad Software, San Diego, California, USA). The concentration of each antibiotic that caused 20% and 50% inhibition of measured parameters compared to control (EC_{20} and EC_{50}, respectively) were derived from the four-parametric logistic curve using nonlinear regression analysis along with the 95% confidence intervals (95% CI). After determining the EC_{20} and the EC_{50}, the data were tested for normality and homogeneity of variance. The No Observed Effect Concentration (NOEC, the highest concentration that causes no significant effect on algal growth) and the Lowest Observed Effect Concentration (LOEC, the lowest concentration that causes a significant effect on algal growth) were estimated using Dunnett's multiple comparison test (one-tailed, $p < 0.05$).

2.4. Degradation of antibiotics by Fe(VI)

Experiments of antibiotic degradation were conducted using a phosphate-borate buffer at pH 8.0 at room temperature (24 ± 1 °C) (working solution of 10 mM KH_2PO_4 and 10 mM Na_2HPO_4 (pH ≈ 7.6), and borate buffer (5 mM Na_2HPO_4 and 1 mM $Na_2B_4O_7$•$10H_2O$) (pH ≈ 9.2). The stock solutions of antibiotics were prepared by adding the selected antibiotics to phosphate buffer to produce an initial concentration of 20.0 mg/L. This studied concentration was imperative to perform the algal tests after treating with Fe(VI).

The stock solution of Fe(VI) was prepared by dissolving solid potassium ferrate in borate buffer at pH ≈ 9.2, in which the stability of Fe(VI) solution could be maintained prior to the experiment (Li et al., 2005; Luo et al., 2014). The concentration of Fe(VI) solution was calculated from the absorbance measurement at a wavelength of 510 nm using a UV−Vis spectrophotometer (DR-5000, Hach Co., Loveland, CO, USA), and by applying an extinction coefficient $\varepsilon_{510\ nm} = 1150\ M^{-1}\ cm^{-1}$ (Sharma, 2011).

The degradation experiments were performed in 50.0 mL beakers. The reaction was initiated by adding 5.0 mL of Fe(VI) stock solution of known concentration to 5.0 mL of the antibiotic solution under rapid mixing on the magnetic stirrer (200 rpm) at [Fe(VI)]:[antibiotic] of 5:1 to 20:1. On the completion of Fe(VI) oxidation, the supernatant was filtered using a 0.45 μm nylon filter (Fisherbrand, Waltham, MA, USA) and subjected to ultra-high performance liquid chromatography (UHPLC) analysis and algal bioassay to determine the residual antibiotic concentration and toxicity, respectively.

2.5. Degradation of antibiotics in the test solution

The decomposition of antibiotics was monitored under the same conditions that were used during the ecotoxicological bioassay. Tests were carried out in the same experimental setting as the tests used to assess antibiotic degradation by Fe(VI), except that no Fe(VI) treatment was used. Briefly, stock solutions of antibiotics prepared in phosphate buffer were mixed 1:1 (v/v) with borate buffer. Subsequently, antibiotics in phosphate-borate buffer were mixed 1:1 (v/v) with 100% ZBB medium, either with or without algal cells, to obtain an initial antibiotic concentration of 10.0 or 20.0 mg/L. Then, samples were kept under the same temperature and light conditions as those during toxicity testing (25 ± 1 °C, 100 μmol/m^2 s). Prior to the analysis, samples were filtered using a 0.45 μm nylon filter (Fisherbrand, Waltham, MA, USA). Samples were then analyzed using UHPLC at 0 h, 72 h, and 96 h, except erythromycin which was analyzed using the LC-MS/MS method. Control samples that were maintained in the dark at 4 °C were also evaluated.

2.6. Analytical procedures

Aqueous concentrations of antibiotics before and after Fe(VI) treatment were measured using an Ultimate 3000 UHPLC (Thermo Scientific, Waltham, MA, USA). Chromatographic analysis was performed at a flow rate of 1.0 mL/min on an Atlantics dC_{18} analytical column (Waters, Dublin, Ireland) (4.6 mm × 150 mm, particle size 5 μm) at 30 °C. The mobile phase was 0.05% phosphoric acid in water (A) and methanol (B). The injection volume was 10.0 μL, and the elution conditions that were used for each antibiotic are listed in Table SM-2.

The concentration of ERY was evaluated using an Agilent 1260 Infinity chromatographic system (Agilent Technologies, Inc., CA, USA), equipped with a vacuum degasser, quaternary pump, autosampler, and column thermostat was connected online to an ESI/QqQ mass spectrometer Agilent TripleQuad 6460 (Agilent Technologies, Inc., CA, USA). The chromatographic/mass spectrometric system was controlled by Mass Hunter Workstation software version B.06.00 (Agilent Technologies, Inc., CA, USA). For analytical separation of ERY, an analytical column Poroshell 120 EC-C18 (2.1 mm × 100 mm, 2.7 μm particle size, Agilent Technologies, Inc., CA, USA), and guard column Poroshell 120 EC-C18 (2.1 mm × 5 mm, 2.7 μm particle size, Agilent Technologies, Inc., CA, USA) were used. The mobile phase consisted of 0.1% formic acid in water (solvent A) and acetonitrile (solvent B). The mobile phase gradient was as follows: 0−8 min from 20% B to 70% B, 8.01 min. 100% B held to 11 min, with a subsequent equilibration step 20% B to 15 min. The

flow rate was 0.3 mL/min; 10 μL of the sample was injected. The parameters of the ion source were set as follows: gas temperature 300 °C, gas flow 5 L/min, nebulizer 45 psi, sheath gas temperature 400 °C, sheath gas flow 11 L/min, capillary voltage 4000 V, nozzle voltage 0 V. The precursor ion, two product ions, collision energy, and fragment voltage used for multiple reaction monitoring (MRM) in positive ionization mode are presented in Table SM-3.

3. Results and discussion

3.1. Ecotoxicological evaluation

3.1.1. Validity requirements

In the toxicity test, algae and cyanobacteria were exposed to the test substances for 96 h. Presented data fulfilled validation and acceptability criteria recommended by the OECD No.201 (OECD, 2011). The average cell counts increased by approximately 100-fold within 72 h meeting the criteria of at least a 16-fold increase in cell numbers over three days. The pH in the control medium did not increase more than 0.5 units during the exposure period of 72 h. To verify the conditions of the test and to prove the quality of obtained data, the toxicity of the standard reference compound (i.e., 3,5-dichlorophenol) was determined. The results showed the comparable sensitivity of both organisms with EC_{50} of 2.4 mg/L (95% CI 2.1−2.7) and 2.6 mg/L (95% CI 2.2−3.0) in 72 h for algae and cyanobacteria, respectively. This is in agreement with literature data, in which inter-laboratory test results from nine laboratories obtained the mean value of 3.4 ± 1.3 mg/L for algae *Raphidocelis subcapitata* (ISO, 1989).

3.1.2. Antibiotic toxicity to algae and cyanobacteria

The possible toxic effects of exposure to antibiotics were investigated using freshwater green alga *Raphidocelis subcapitata* and cyanobacterium *Synechococcus elongatus*. The dose-response curves showing growth inhibition of these two species after 72 h of treatment with antibiotics are presented in Fig. 1. The determined EC_{50}, EC_{20}, NOEC, LOEC, and hillslope values for both organisms at 72 h and 96 h are given in Tables SM-4 and SM-5. There was no statistically significant difference between the calculated values at 72 h and 96 h exposure time.

Based on the EC_{50} values, the toxicity of test antibiotics to green algae decreased in the order: TMP > CIP > OFL > OXY > ERY > TET > SMX, and toxicity to cyanobacteria decreased in the order: TMP > OXY > ERY > TET > OFL > SMX > CIP. Three of the tested antibiotics showed EC_{50} value towards green algae was lower than 1.0 mg/L, so these substances would be categorized as very toxic to the aquatic environment according to EU Directive 93/67/EEC (TGD, 2003). SMX was the most toxic antibiotic with an EC_{50} value of 0.49 mg/L, followed by TET and ERY with the EC_{50} values of 0.58 and 0.62 mg/L, respectively. OXY, OFL, and CIP were classified as toxic according to EU Directive 93/67/EEC (TGD, 2003), with EC_{50} values of 2.0 mg/L, 4.2 mg/L, and 4.4 mg/L, respectively.

When toxicity was tested using cyanobacteria, CIP was the most toxic, with an EC_{50} of 0.07 mg/L, followed by SMX and OFL. The results indicate that fluoroquinolones (OFL and CIP) are more effective against prokaryotic organisms than eukaryotes. The antibiotic, CIP is much more toxic (≈60 times) against cyanobacteria (i.e., Gram-negative bacteria) than green algae. Fluoroquinolones, whose mechanism of action is inhibition of type II and type IV topoisomerase, enzymes which prevent the excessive supercoiling of DNA during replication, have 100 times higher affinity for bacterial type II topoisomerase than for mammalian (Isidori et al., 2005; Barisci et al., 2016). The affinity is expected to be lower in all eukaryotic cells, consistent with the observed results.

All tested antibiotics, except TMP, showed high toxicity to cyanobacteria with EC_{50} lower than 1.0 mg/L. This is in agreement with literature, indicating that cyanobacteria are the most sensitive organisms for antibiotics (Halling-Sorensen, 2000; Robinson et al., 2005; Guo et al., 2015). Additionally, these results also matched well with the literature, in which EC_{50} values of test antibiotics were 1−2 orders of magnitude lower for cyanobacteria than green algae (Ferrari et al., 2004; Isidori et al., 2005; Robinson et al., 2005; Brain et al., 2008; Yang et al., 2008; Brausch et al., 2012; Minguez et al., 2016). The highest EC_{50} values were calculated to be 196 mg/L and >200 mg/L for TMP, using green algae and cyanobacteria, respectively. This indicated that it was relatively non-toxic to both species. Therefore, this compound was omitted from further experiments.

3.2. Degradation of antibiotics in the test solution

3.2.1. Degradation of antibiotics without Fe(VI)

Some of the tested antibiotics are known for their instability (Halling-Sorensen et al., 2002; Werner et al., 2006), and as such, there may be measurable spontaneous degradation under the bioassay conditions. To assess whether all decreases in antibiotic concentration and toxicity were caused by Fe(VI) treatment, the stability of antibiotics under the experimental conditions without Fe(VI) treatment was tested. The differences in antibiotic concentrations in the growth media, with and without algae cells, were determined using UHPLC over 72 h and 96 h. The results of these auto-degradation experiments are presented in Fig. 2. The results showed relatively small losses of SMX and ERY under the test conditions, both with and without cells. OFL and CIP showed a slightly higher concentration decrease in the presence of algae cells compared to the concentration decrease in the medium. This may be attributed to fluoroquinolone's tendency to sorption (Robinson et al., 2005; Janecko et al., 2016; Tiwari et al., 2017). In contrast, TET and OXY underwent essentially complete auto-degradation over 72 h as their concentration decreased by 99% and 95%, respectively. From all tested antibiotics, only SMX and ERY met OECD acceptability criteria of less than 20% variation from the initial concentration during the test period. For the rest of the tested antibiotics, following the OECD guideline TG 201 (OECD, 2011), the geometrical mean concentration during the exposure was used. For readily photodegradable tetracyclines, whose concentration decreased by more than 95%, the value of ECx was calculated using nominal concentrations (OECD, 2011).

3.2.2. Degradation of antibiotics with Fe(VI)

Degradation of antibiotics was studied at different molar ratios of Fe(VI) to antibiotics ([Fe(VI):[antibiotics] = 5:1 and 10:1) at pH 8.0. The results of antibiotic degradation with and without Fe(VI) are shown in Fig. 3. In general, an increasing molar ratio (i.e., [Fe(VI)]:[antibiotic]) resulted in increased degradation of antibiotics. At a molar ratio of 10:1, the maximum removal was for CIP (≈90%) while SMX had the lowest removal percentage (≈55%). Incomplete oxidation of antibiotics suggests additional reactions consuming Fe(VI) during the reaction of Fe(VI) with the target molecule, such as (i) reaction with water and (ii) reactions with oxidized products (OPs) of the antibiotics. The commutative reaction rates of Fe(VI) with the antibiotic, water, and OPs would determine the removal efficiency of Fe(VI) to oxidize a particular antibiotic (Yngard et al., 2008; Lee et al., 2009; Zhou and Jiang, 2015; Sharma et al., 2016; Siskova et al., 2016). Phosphate ions in the buffer used in the study also inhibited the oxidation of contaminants by Fe(VI) (Huang et al., 2018; Kolarik et al., 2018; Luo et al., 2019). Overall, the results of Fig. 3 indicate that the resulting solution after the reaction with Fe(VI) contains the parent antibiotic and its OPs. The toxicity of the solution would be from the

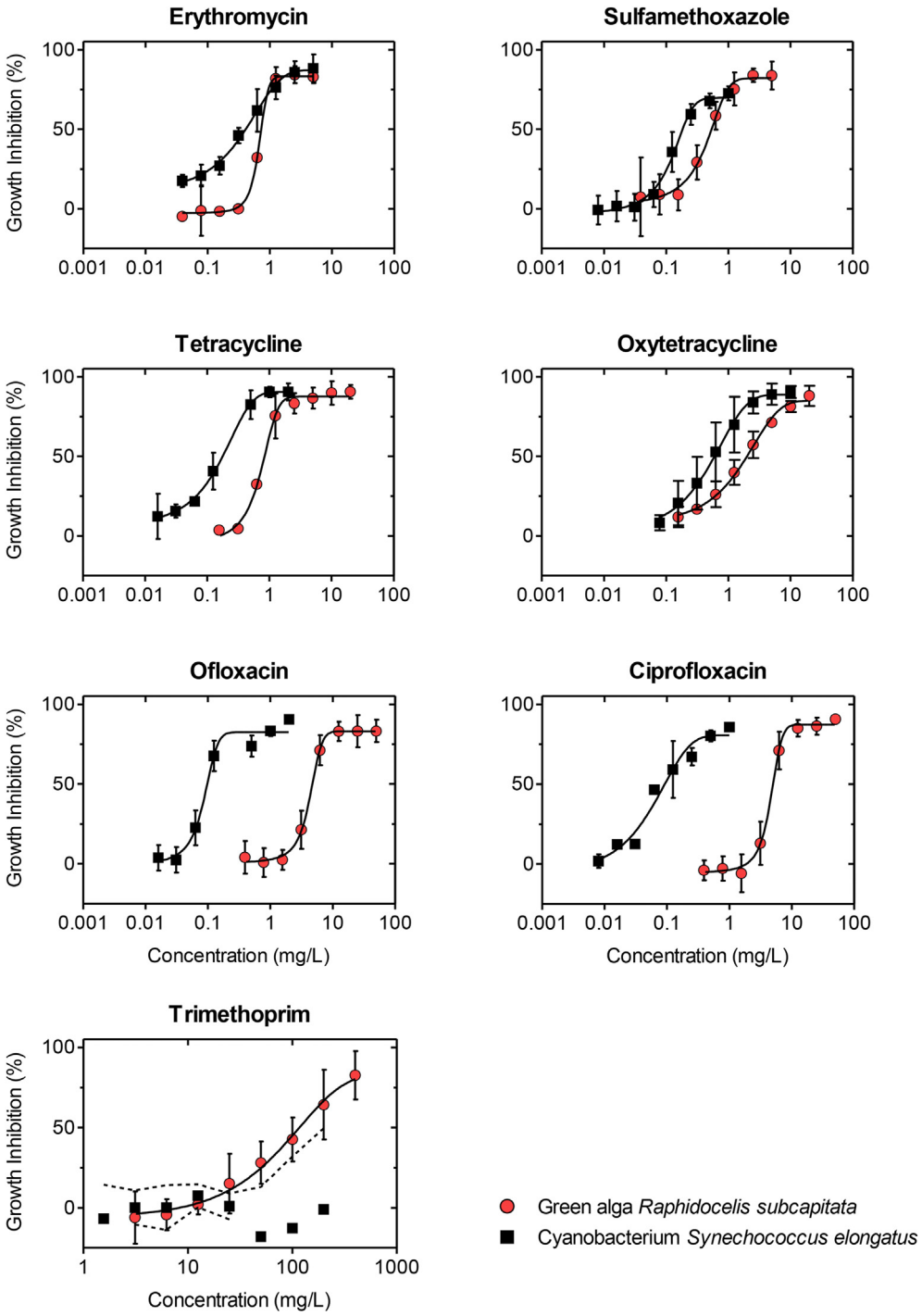

Fig. 1. Growth inhibition of green alga *R. subcapitata* (orange circles) and cyanobacterium *S. elongatus* (black squares) exposed to selected antibiotics for 72 h.

antibiotic and its products. This will be discussed in the next section. It has been shown previously that inorganic ions and natural organic matters (NOM) commonly found in natural water may interfere with antibiotic removal by Fe(VI) oxidation (Anquandah et al., 2011; Feng et al., 2016; Zeng et al., 2016). Reaction of Fe(VI) with components of NOM usually results in a lower amount of the oxidant available to react with contaminants (Deng et al., 2018; Manoli et al., 2019). Future studies may include toxicity evaluation of antibiotics in the presence of NOM with and without Fe(VI) treatment.

3.2.3. Algae toxicity studies

To assess whether the proposed Fe(VI) treatment is an effective way to remove antibiotics from water, the toxicity of the treated antibiotic samples was examined. As can be seen from Fig. 4, the toxicity of OFL, CIP, and OXY completely disappeared after Fe(VI) oxidation. On the other hand, SMX, TET, and ERY remained toxic, causing more than 75% algae growth inhibition (Fig. 4). The EC_{50} values of OFL, CIP, and OXY are lower than 4.5 mg/L, indicating that these compounds are quite toxic. As a result, partial oxidation of Fe(VI) under the studied conditions may not be sufficient to

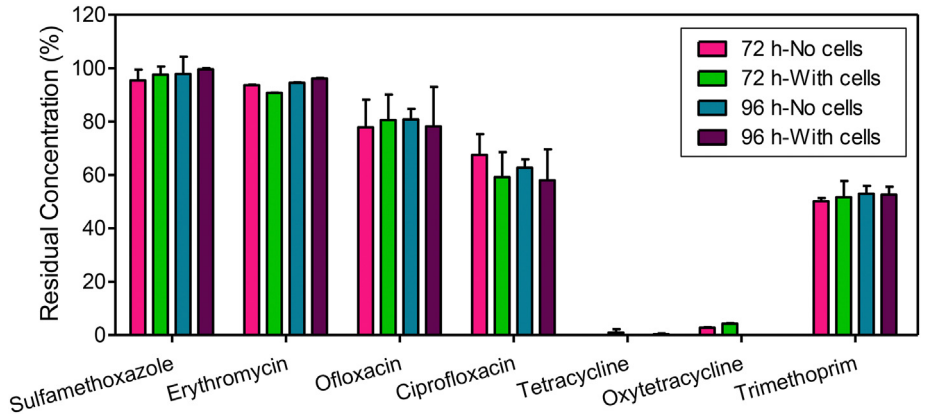

Fig. 2. Degradation of the tested antibiotics (10 mg/L) under the conditions of the ecotoxicological bioassays (continuous lighting, 25 ± 1 °C, in testing medium). Auto-degradation was tested with and without algal cells, and after both 72 h and 96 h.

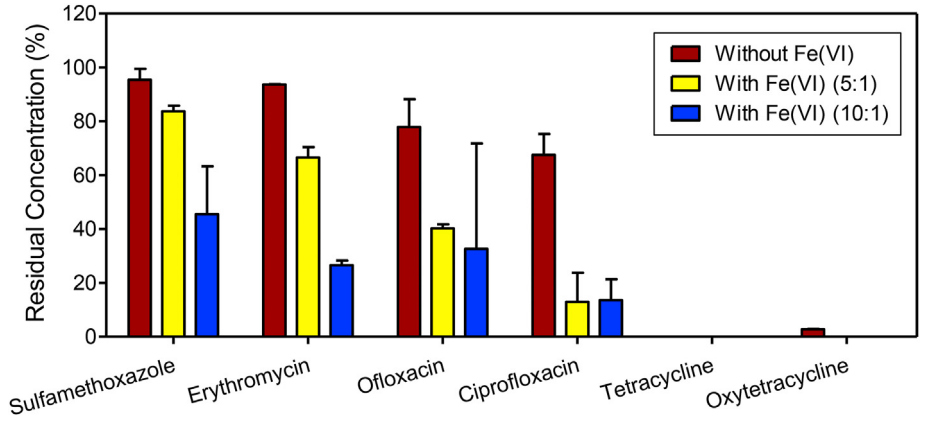

Fig. 3. Percentage of residual antibiotic concentration (20 mg/L) without Fe(VI) and with Fe(VI) treatment and molar ratios of 5:1 and 10:1 ([Fe(VI)]:[antibiotic]) in phosphate-borate buffer at pH 8.0 after 72 h.

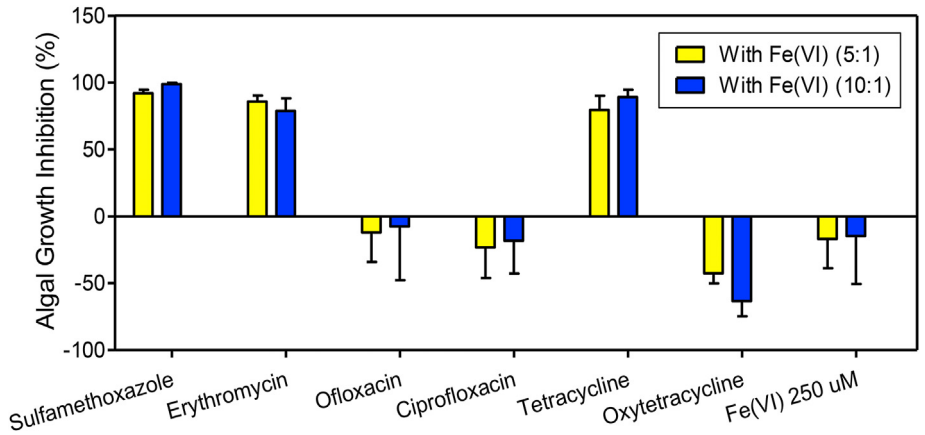

Fig. 4. The residual toxicity of antibiotics (10 mg/L) following Fe(VI) treatment, as measured by the 72 h algal growth inhibition bioassay using the green alga *R. subcapitata*. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

decrease the toxicity to algae, especially in case of SMX and ERY whose EC50 values are lower than 1.0 mg/L. Therefore, the remaining theoretical concentrations of treated solutions were calculated based on the measured toxicity values. In addition, the toxicity of treated antibiotics with initial concentrations of 5.0 mg/L and 2.5 mg/L were measured as well.

Based on the data extrapolated from the growth curves in ecotoxicological bioassays, the residual toxicity, expressed as EC_{50} values, of SMX, TET, and ERY corresponded to 1.4 mg/L, 1.5 mg/L, and 0.8 mg/L of initial antibiotic concentration, respectively. Compared to the residual concentrations of SMX, TET, and ERY after Fe(VI) treatment, which individually corresponded to 4.2 mg/L,

Table 1
Growth inhibition (%) of green alga *R. subcapitata* following 72 h of exposure to antibiotics that had been pre-treated with Fe(VI) at a 5:1 M ratio (Fe(VI)]:[antibiotic]).

Antibiotic	Concentration (mg/L)		
	2.5	5.0	10.0
Erythromycin	87.5%	87.8%	86.1%
Sulfamethoxazole	57.0%	86.6%	94.2%
Tetracycline	−10.6%	37.0%	87.2%

0 mg/L, and 5.2 mg/L, it is obvious that the remaining toxicity did not correlate with the residual concentrations of antibiotics. Furthermore, when compared to the toxicity of diluted antibiotic samples, the toxicity of SMX and TET samples decreased with decreasing initial concentration of antibiotics, but the toxicity of ERY remained unchanged (Table 1).

Our experiments showed good removal efficiency of ERY, where more than 30% and 70% of ERY were degraded in 72 h using 5:1 and 10:1 of [Fe(VI)]:[antibiotic], respectively (Fig. 3). However, the toxicity of ERY solution after Fe(VI) treatment decreased only slightly, from 86% to 79%, suggesting that the degradation products remain toxic (Fig. 4). To the best of our knowledge, little is known regarding the efficiency or mechanisms of degradation of ERY by Fe(VI). However, degradation experiments regarding the removal of mixtures of micropollutants from wastewater effluents showed poor ERY removal (less than 20%) at pH 6.0 using up to 5.0 mg/L Fe(VI) (Jiang and Zhou, 2013), or no reaction at all when 100 μg/L ERY was spiked in wastewater and mixed with 10 mg/L Fe(VI) at pH 7.0 (Yang et al., 2012b).

After Fe(VI) treatment, the toxicity of 10 mg/L SMX was 94.2%, whereas an initial concentration of 2.5 mg/L of SMX showed 57% toxicity expressed as algal growth inhibition (Table 1). This indicates that the decrease was not proportional to the transformation of the parent compound. SMX was proved to be poorly degradable by Fe(VI) when the used molar ratio of [Fe(VI)]:[antibiotic] was 5:1. The removal of SMX required a higher molar ratio of Fe(VI) to SMX; however, transformation products after reaction with Fe(VI) may also contribute to the toxicity of the mixture of parent antibiotics and its oxidized products (Zhou and Jiang, 2015).

There are only limited data available for the SMX toxicity after oxidation with Fe(VI). Some transformation products have been identified and those that modify *para* amino group exhibited a strong antibacterial effect, or even greater than the parent compound (Majewsky et al., 2014). Byproducts generated during oxidation of sulfonamides by Fe(VI) had similar toxicity as the parent sulfonamide to HEK293 and J774 cell lines than the original antibiotics (Acosta-Rangel et al., 2020). The mixtures of PPCPs, including SMX, inhibited proliferation of HEK293 cells by 30% (Pomati et al., 2006; Cizmas et al., 2015). The toxicity of the photolyzed degraded mixture of SMX towards *Vibrio fisheri* was higher than the toxicity prior to photodegradation, whereas in another study, the toxicity of the mixture formed after one week of exposure of SMX solution to artificial sunlight remained unchanged. This indicated that the formed transformation products still exhibited luminescence inhibiting properties (Trovo et al., 2009; Gmurek et al., 2015).

Tetracycline and oxytetracycline are known to have limited stability in water, particularly upon exposure to light (Halling-Sorensen et al., 2002). For example, average half-life of tetracycline at the surface of sunlit water body is 16 min at pH 8.2 (Werner et al., 2006). In our analysis, tetracycline and oxytetracycline almost completely disappeared after 72 h of continuous illumination (see Figs. 2 and 3), suggesting up to 100% removal of these compounds in the growth medium both with and without Fe(VI) treatment. However, degradation products of TET are toxic (Jiao et al., 2008; Wei et al., 2019), and further investigation is needed to identify and assess the half-lives of the degradation products and evaluate their toxicity. When the TET concentration in water was lower than 2.5 mg/L, Fe(VI) oxidation was capable of completely decreasing the remaining toxicity. Increased toxicity may be seen at the end of various types of water treatment (UV (Gomez-Pacheco et al., 2012), UV/H_2O_2 (Lopez-Penalver et al., 2010), and Fenton-like degradation (Hou et al., 2016)). This may be due to the transformation of tetracyclines into more toxic and highly stable by-products (Halling-Sorensen et al., 2002) and the possibility that longer exposure times are needed to degrade these by-products (Lopez-Penalver et al., 2010). The variability of possible degradation products complicates risk assessment of the tetracyclines present in natural waters, and some photoproducts have shown significant toxicity. For example, enhanced toxicity of tetracycline solution to *Vibrio fisheri* was observed after photolysis, suggesting that the increase in toxicity is caused by degradation products (Jiao et al., 2008; Lopez-Penalver et al., 2010; Wang et al., 2015; Wei et al., 2019). The degradation product 5a,6-anhydrotetracycline hydrochloride showed 2.7 times higher toxicity to aerobic sludge bacteria than the parent tetracycline (Halling-Sorensen et al., 2002). On the other hand, another study did not find any photoproducts with measurable antibacterial activity in natural water samples regardless of the pH and water hardness (Wammer et al., 2011).

In some cases, the ecotoxicity experiments produced negative values of growth inhibition, indicating that the treatment produced algal growth stimulation rather than growth inhibition, as occurred with CIP and OXY (Fig. 4) and TET (Table 1). This may occur due to a net positive effect of the surplus of nutrients, in particular, the presence of ferric ions produced by Fe(VI) decomposition as well as phosphate from the buffer.

4. Conclusions

The toxicity tests of antibiotics, prior to treatment with Fe(VI), against cyanobacteria and green algal species showed varied toxicity. All tested antibiotics, except for TMP, were classified as very toxic to cyanobacteria (EC50 < 1.0 mg/L). SMX, ERY, and TET were classified as very toxic, and OFL, CIP, and OXY were classified as toxic (EC_{50} < 10.0 mg/L) to green algae, respectively. Treatment of antibiotics at level of 20.0 mg/L with Fe(VI) had removal efficiency of at least 50% for all antibiotic tested at a 10:1 M ratio ([Fe(VI)]:[antibiotic]), indicating the tested treated solution consisted of the parent antibiotic and its oxidized products. Fe(VI) treatment of OFL and CIP resulted in their partial removal and the resulting mix with transformation products had no measurable algal toxicity. However, removal of SMX and ERY by Fe(VI) were incomplete and solutions were toxic to *R. subcapitata*, indicating that both parent antibiotic and its oxidized products possessed toxicity to the green algal species. Overall, the strategy used herein is appropriate to evaluate the ecotoxicity of antibiotics and their oxidized products in water.

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.chemosphere.2021.130365.

Credit author statement

Pavla Kovalakova and Mingbao Feng contributed to methodology, validation, formal analysis, investigation, and original draft preparation. Leslie Cizmas, Thomas J. McDonald, Blahoslav Marsalek, and Virender K. Sharma contributed in supervision, review, and editing of the manuscript.

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