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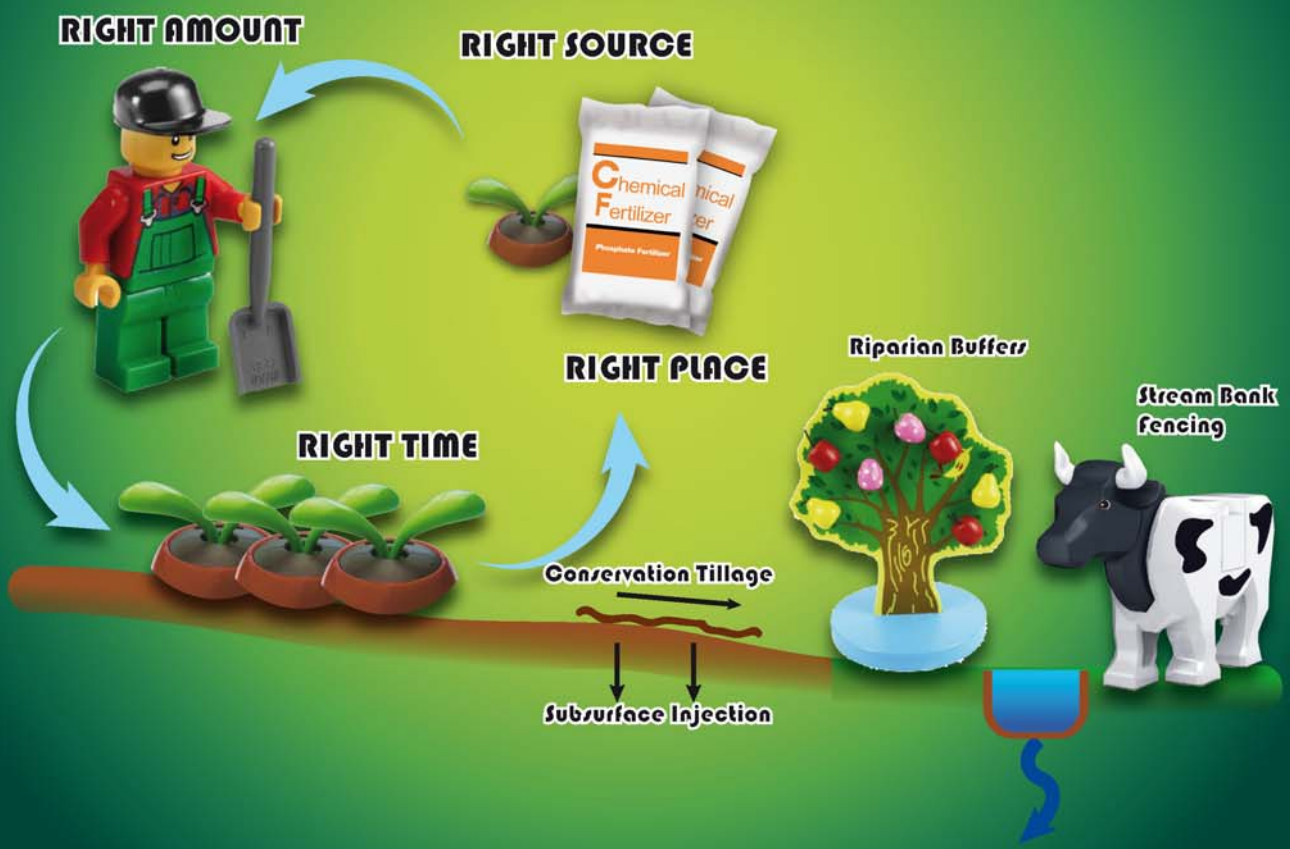

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Acute toxicity evaluation for quinolone antibiotics and their chlorination disinfection processes

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ABSTRACT

Acute toxicity of 21 quinolone antibiotics was monitored using photobacterium *Vibrio fischeri* assay. The minimum IC_{20} (inhibitory concentration for 20% luminescence elimination) was obtained at the least 18.86 μmol/L for the tested quinolones. A quantitative structure–activity relationship model was established to investigate the possible mechanism for the acute toxicity. The critical physicochemical descriptors, describing σ and π atom electronegativity, implied that the electron transfer might occur between the quinolones and photobacterium *V. fischeri*. Although the quinolones exhibited limited acute toxicity to photobacterium, toxicity elevation was detected after their chlorination. Hence, chlorination disinfection treatment of quinolone-containing water should be of concerns.

Introduction

Antibiotics are one of the most widely used groups of pharmaceuticals due to their potency against diseases in human, veterinary and industrial farming (Cruz Moreno-Bondi et al., 2009; Kummerer, 2009; Pan et al., 2011). Quinolones are among the five classes of antibiotics (β-lactam, macrolides, quinolones, sulfonamides, and tetracyclines) used to treat a broad variety of Gram (+) and Gram (–) bacterial infections. They kill target bacteria by inhibiting the activity of bacterial DNA gyrases, which are required for replication and transcription in prokaryotes (Bryan et al., 1989; Hooper, 2001). Owing to the advantages of broad-spectrum antibacterial activity, high potency, non-cross resistance and low price, quinolones have been extensively used in recently years. However, due to the incomplete assimilation and metabolism in organism, a considerable fraction of those drugs has been discharged into the environment. The removal of quinolones in municipal sewage treatment plants plays a crucial rule in their pollution control (Jia et al., 2012), while low removal efficiency and a high discharge from secondary effluents lead to a serious pollution to the aquatic environment. Consequently, quinolones have been frequently detected in various environmental matrices. For example, eight quinolones were the prominent contaminants in sediments and aquatic plants of the Baiyangdian Lake, China, with the concentrations of 65.5–1166 and 8.37–6532 μg/kg, respectively (Li et al., 2012). Ciprofloxacin, one of the most commercial quinolones, was found in Switzerland hospital effluents as high as 89 μg/L (Hartmann et al., 1998). It was reported that ciprofloxacin and enrofloxacin were not readily biodegradable by sewage sludge organism (Ebert et al., 2011). The hazard quotients (HQs) for the aquatic environment of ciprofloxacin and ofloxacin were 3.5 and 1.5 to algae in Baiyangdian Lake, indicating that those two compounds were harmful to algae in the lake water (HQ > 1 means that the harmful ecological impact is significant for the selected antibiotic) (Hernando et al., 2006; Li et al., 2012). Hu et al. (2007) investigated genotoxicity potential of 20 quinolones by umuC bioassay; the result indicated that all the tested compounds showed high toxicity with 10% of the maximum response concentration (EC_{10}) ranged from 0.61 to 2917 nmol/L. In

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addition, it was reported that genotoxicity in the wastewater of the hospital was mainly caused by quinolone antibiotics (Hartmann et al., 1998). The removal of those compounds in sewage treatment plants is a complex issue, and their toxicity patterns are flexible under various treatment processes, such as ozonation, UV photolysis and chlorination disinfection. Report regarding acute toxicity elevation has been disclosed in levofloxacin chlorination process (El Najjar et al., 2013). Therefore, it is necessary to consider the toxic effects for not only quinolone precursors but also their transformation products. Biological test, which can reflect the toxicity formation during the treatment process as a whole, would be an efficient way to evaluate those toxicity risks to the environment.

Limited research has been conducted on the aquatic ecotoxicity of quinolone antibiotics. Therefore, the main aim of this study is to provide basic toxicity data for quinolone antibiotics towards the photobacterium *Vibrio fischeri*, which is a standard aquatic toxicity model species representing decomposer trophic level. The 21 quinolones examined in this study were chosen on the basis of their wide usage in human and veterinary, as well as their detection levels in the environment. As all the compounds share the same quinolone skeleton, the quantitative structure–activity relationship (QSAR) method was used to investigate the relationship between toxicity and molecular structure. Finally, the acute toxicities of those quinolones after chlorination were measured to evaluate their toxicity changes during chlorination disinfection treatment. This study could provide useful information on evaluating the potential risks of quinolones towards the aquatic environment.

1. Materials and methods

1.1. Reagents and chemicals

Based on their usage in human and veterinary as well as their availability from the manufactory, 21 quinolone antibiotics were chosen in this study. Cinoxacin (CIN), ciprofloxacin (CIP), danofloxacin (DAN), difloxacin hydrochloride (DIF), enoxacin (ENO), enrofloxacin (ENR), fleroxacin (FLE), levofloxacin (LEV), lomefloxacin hydrochloride (LOM), moxifloxacin hydrochloride (MOX), norfloxacin (NOR), ofloxacin (OFL), pazufloxacin (PAZ), pipemidic acid (PIP), sarafloxacin hydrochloride (SAR) and sparfloxacin (SPA) were purchased from Sigma-Aldrich as HPLC or analytical reagent (>98% purity, MO, USA). Balofloxacin (BAL), gatifloxacin (GAT), nadifloxacin (NAD) and pefloxacin (PEF) were obtained from the National Institutes for Food and Drug Control of China (at least 97% purity, Beijing, China). Rufloxacin hydrochloride (RUF) with 99% purity was obtained from International Laboratory (USA). The NaClO (8%) aqueous solution was obtained from Wako Co. (Tokyo, Japan). All reagents were used directly without further purification. The stock solutions of all studied compounds were prepared in ultrapure water produced by a Milli-Q ultrapure water system (Millipore MA, USA).

1.2. Chlorination disinfection

The chlorination experiments were performed in borosilicate glass bottles. Water bath and magnetic stirring apparatus were used to maintain the reaction temperature at 25 °C. In order to investigate the formation characteristics of disinfection byproducts in chlorination disinfection treatment of quinolones, the conception and significance of disinfection byproducts formation potential recommended by APHA (1998) were referenced. In addition, it was reported that OFL, CIP and NOR were labile during chlorination treatment within pH 6.0–8.0 (Li and Zhang, 2012). Therefore, in this study, the chlorination treatment on the target compound was performed with 10 molar equivalents of free available chlorine at pH 7. The 0.02 mol/L phosphate buffer solution was used to maintain the pH at 7 during the reaction period. After 60 min, sodium sulfite solution (1.5 equivalents to free available chlorine) was added to quench reaction. The quenched reaction solution was freeze-dried; 10 mL of mixed solvent methanol/acetone (1/1, *V*/*V*) was added to extract organic components. Supernatants were collected and dried with gentle N_2 flow, dissolved with dimethyl sulfoxide for toxicity test. The chlorination experiment for each quinolone compound was conducted in triplicate. A blank control without adding free available chlorine was set as well.

1.3. Toxicity test

The photobacterium acute toxicity test quantifies the effects of pollutants by measuring the decrease of luminescence intensity of the test bacteria. The test bacteria strain (*V. fischeri*, freeze-dried powder) was provided by the Institute of Soil Science, Chinese Academy of Sciences (Nanjing, China). The quinolone samples (both before and after chlorination) were diluted into a series of exposure solutions, and 20% inhibition concentration (IC_{20}) was calculated after the 15 min exposure. For each test, a dose–response curve of Hg^{2+} ($HgCl_2$) as positive control was conducted as well.

1.4. QSAR method

The ADRIANA.Code program (Ver 2.2.4) was applied to calculate physicochemical parameters of the target molecules. In total, 8 shape descriptors, 29 global molecular descriptors and 88 2D property-weighted autocorrelation (or topological) descriptors were calculated. All calculated descriptors were selected as independent variables and pIC_{20} ($-\log IC_{20}$) values were selected as dependent variables. Stepwise multiple linear regression method was used to establish QSAR model.

2. Results and discussion

2.1. Acute toxicities of 21 quinolones

The toxicity values for 21 quinolone compounds are listed in Table 1. The IC_{20} values for all the tested compounds ranged from 18.86 to >700 μmol/L. Among those compounds, DIF and MOX exhibited a notable higher toxic effect than the others, with IC_{20} values of 18.86 and 22.85 μmol/L, respectively. It is interesting to note that DIF and MOX are the third generation of quinolones with wider antimicrobial activity and stronger potency than those of the first and second generation ones. However, CIN, one of the first generation quinolones with limited antimicrobial activity, is the second toxic compound (with IC_{20} value of 35.02 μmol/L) among all the tested ones. This may attribute to more O atoms contained in CIN structure (a substituent of 1,3-dioxolane at 6- and 7-positions), and this will be explained later (Section 2.2). Hu et al. (2007) have found that the genotoxic potential of the earliest quinolones

Table 1 – Acute toxicity values of tested compounds and molecular structure descriptors involved in QSAR model.

Comp.	Acute toxicity values		QSAR				
	IC_{20} (μmol/L)	pIC_{20} (mol/L)	3DACorr_PiEN_3 ($\times10^{-2}$)	3DACorr_SigEN_3 ($\times10^{3}$)	3DACorr_PiChg_3 ($\times10^{2}$)	pIC_{20} (Pred.)	Residual
CIN	35.02	4.40	−1.95	2.41	7.04	4.33	0.07
CIP	281.87	3.55	−5.34	2.58	5.60	3.38	0.17
DAN	212.51	3.25	−5.33	2.81	5.67	3.55	−0.29
DIF	18.86	4.70	−5.82	3.30	9.65	4.67	0.02
ENO	590.41	3.23	−7.11	2.59	6.14	3.14	0.09
ENR	289.91	3.54	−5.34	2.78	5.60	3.51	0.03
LEV	564.08	3.68	−5.49	2.94	6.26	3.73	−0.05
LOM	229.70	3.64	−5.45	2.92	6.21	3.72	−0.08
MOX	22.85	4.70	−5.44	4.03	6.34	4.44	0.26
NAD	487.67	3.31	−5.32	2.75	5.58	3.48	−0.17
NOR	583.44	3.24	−5.41	2.52	5.57	3.32	−0.09
OFL	478.64	3.32	−5.49	2.94	6.26	3.73	−0.41
PAZ	116.22	3.92	−4.49	3.03	6.37	4.03	−0.11
PEF	263.74	3.59	−5.41	2.65	5.57	3.41	0.18
PIP	334.14	3.48	−5.42	2.29	5.66	3.20	0.28

Compounds BAL, FLE, GAT, RUF, SAR and SPA showed low inhibition effect at 700 μmol/L and were removed from QSAR model.

were lower than that of the new generation ones, while this trend was not obvious for the acute toxicity data. Six compounds BAL, FLE, GAT, RUF, SAR and SPA exhibited weak acute toxicity, and their luminescence elimination was less than 10% even at 700 μmol/L of exposure concentration. Therefore, there were no satisfactory dose–response curves and exact IC_{20} values for these six compounds.

Previous studies demonstrated that cyanobacterium *Microcystis aeruginosa* and *Anabaena flosaquae* are the most sensitive species to quinolones, the EC_{50} ranged from 0.02 to 7.50 μmol/L (for 7 tested quinolones) and 0.03 to 0.48 μmol/L (for CIP and ENR), respectively. Duckweed (*Lemna minor*) was also confirmed to be the sensitive species with EC_{50} values of 0.14, 0.17 and 0.30 μmol/L to LEV, CLI (Clinafloxacin) and LOM, respectively. In addition, the green alga *Pseudokirchneriella subcapitata*, dicotyledonous macrophyte *Myriophyllum spicatum*, crustacean *Daphnia magna* and *Artemia salina*, and fathead minnow *Pimephales promelas* showed limited toxicity to quinolones, with several μmol/L EC_{50} or no observed effect to the tested compounds (Ebert et al., 2011; Migliore et al., 1997; Robinson et al., 2005; Yang et al., 2008). Compared with the organisms involved above, the short term test of bioluminescence inhibition assay with *V. fischeri* is not sensitive to quinolone antibiotics. On the viewpoint of the trophic level of test species, the sensitivity order for quinolone test was producers (cyanobacterium, green alga, and duckweed) > primary consumers (crustacean) > advanced consumers (fathead minnow) ≈ decomposers (photobacterium).

2.2. Possible toxicity mechanism

The studied quinolones contain the same skeleton (basic structure shows in Fig. 1). The spectrum and potency of antibacterial activities are mainly dominated by the type of substituent and the substituted positions on quinolone skeleton. Therefore, QSAR technique can exert its advantages on discovering the relationship between the quinolone molecular structures and their acute toxicities (Wang et al., 2010). Involving 15 compounds (excluding the six compounds BAL, FLE, GAT, RUF, SAR and SPA), a statistical model (Eq. (1)) between the acute toxicities (pIC_{20} values) and physicochemical descriptors was developed by stepwise multiple linear regression analysis. The plot of observed *vs.* predicted pIC_{20} values is shown in Fig. 2.

$$pIC_{20} = 1.587(\pm0.540) + 0.002(\pm0.001) \times 3DACorr\_PiEN\_3 + 0.001(\pm0.0002) \times 3DACorr\_SigEN\_3 + 21.215(\pm5.893) \times 3DACorr\_PiChg\_3$$
$$N = 15, R^2 = 0.851, R^2_{adj} = 0.810, SE = 0.22, F = 20.87, p < 0.001 \quad (1)$$

where, N represents the number of compounds, R^2 is multiple correlation coefficient, R^2_{adj} is multiple correlation coefficient adjusted by the degree of freedom, SE is standard error, F is the F-test value for analysis of variable, and p is the significance.

Three physicochemical descriptors were involved in Eq. (1). 3DACorr_PiEN_3, 3DACorr_SigEN_3 and 3DACorr_PiChg_3 are the 3D autocorrelation weighted by π atom electronegativity, σ atom electronegativity and π atom charges, respectively. The detailed calculation methods for those parameters are provided in the reference (Wang et al., 2012).

As shown in Eq. (1), the acute toxicity of quinolones was heavily dependent on the atom charge and electronegativity.

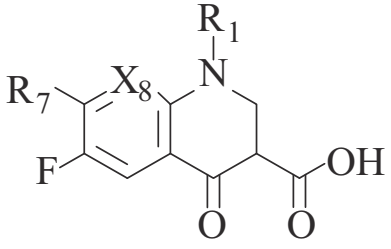

Fig. 1 – Basic structure of quinolones.

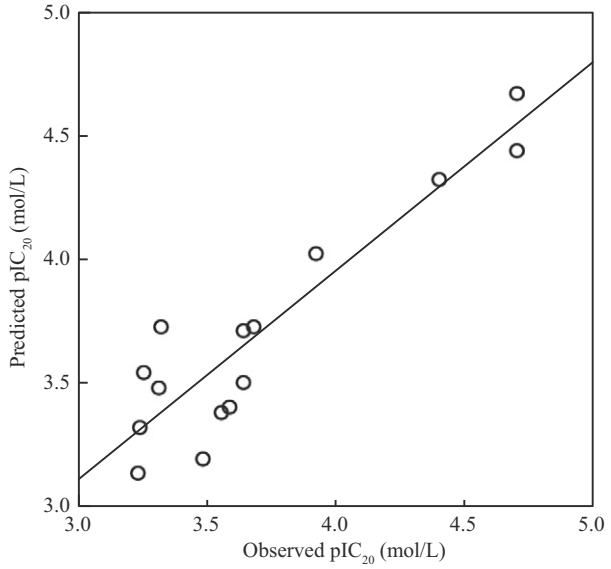

Fig. 2 – Plot of observed *vs.* predicted pIC_{20} values in QSAR model.

In quinolone molecule, π atom charge and electronegativity derived from the structure analog of 2-benzoylacrylic, which is composed of a big conjugation system containing 12 π electrons; σ atom electronegativity derived from C, O, S, N, and F atoms, and so on. All structure descriptors involved in Eq. (1) are concerning atom charge and electronegativity, indicating that electron transfer may happen when the test bacteria are expose to quinolone antibiotics. This conclusion can be further evidenced by the luminance mechanism of *V. fischeri*, which is described as follows:

$$FMNH_2 + RCHO + O_2 \xrightarrow{\text{Bacterial fluroenzyme}} FMN + RCOOH + H_2O + \text{Light.} \quad (2)$$

$FMNH_2$ is flavin mononucleotide with reduced phase; it can transfer hydrogen and be oxidized to FMN. The $-NH_2$ is an active group in $FMNH_2$ molecule, it can easily form a hydrogen bond with some functional groups which contained high electronegativity atoms, such as O and N; then the hydrogen transfer in the luminance process mentioned in Eq. (2) is hindered and the light emission of *V. fischeri* is inhibited (Wei et al., 2002). In present study, all three parameters describing σ and π atom electronegativity in Eq. (1) take positive contribution to pIC_{20}. This can be explained by the fact that some atoms with high electronegativity in quinolone molecules, such as N, O, and F, donate electron and accept proton H from $FMNH_2$, resulting in the luminance inhibition. A similar electron transfer mechanism was previously reported in the genotoxicity test of quinolones using umuC bioassay (Hu et al., 2007). They pointed out that DNA accepted electron from quinolone antibiotics when quinolones interact with DNA or protein.

Although all the chemical structures of tested compounds based on the same quinolone skeleton, the substituent on the quinolone ring could affect their toxicity quite a bit. Overall, compounds like DIF, CIN and MOX exhibited high acute toxicity at μmol/L level, while compounds BAL, FLE, GAT, RUF, SAR and SPA could not reach 10% inhibition ratio even at 700 μmol/L. In order to get a reliable QSAR model, the six compounds without exact IC_{20} were excluded. As to the toxicity mechanism of those compounds, further research is needed.

2.3. Potential risk analysis

2.3.1. Toxicity of quinolones in aquatic environment

The environmental concentrations of quinolones are up to 120 ng/L, 500 ng/L and 125 μg/L in surface waters, secondary wastewater effluents of sewage treatment plants and untreated hospital wastewater (Golet et al., 2002, 2003; Hartmann et al., 1998, 1999; Kolpin et al., 2002; Miao et al., 2004; Renew and Huang, 2004). From the current study, it is reasonable to infer that quinolones, which at residual level of environment, cannot lead to short-term acute toxicity to photobacterium *V. fischeri*. However, multiple quinolones coexisted in the environmental matrices in many cases, and their joint biological effects should be of concerns. Backhaus et al. (2000) measured the single and mixture toxicity of 10 quinolones by a long term (with an exposure duration of 24 hr) bioluminescence inhibition assay with *V. fischeri*. It was found that the concentration addition was feasible to predict the mixture toxicity of quinolones. Therefore, it is reasonable to assume that even low concentrations of single compounds may lead to a significant overall toxicity effect when they act simultaneously.

2.3.2. Toxicity of quinolones after chlorination treatment

Although quinolones exhibited limited acute toxicity to *V. fischeri*, an acute toxicity (using photobacterium assay) elevation was observed after chlorination treatment on LEV (El Najjar et al., 2013), which was attributed to the formation of toxic transformation products. Chlorine, as a strong oxidant, is widely used in the disinfection processes of drinking water treatment, wastewater reclamation treatment and hospital wastewater treatment to prevent the spread of harmful pathogens. Considering the wide presence and high concentration of quinolone antibiotics in sewage and hospital wastewater bodies, the toxicity feature of quinolones after chlorination disinfection process should be of concerns.

In this study, a typical chlorination treatment on each quinolone was conducted to simulate the disinfection process in the practical wastewater treatment plants. The photobacterium acute toxicity of the 21 quinolones after chlorination was also tested. In order to easily compare the toxicity before and after chlorination treatment on quinolones, the toxicity value of each compound after chlorination was standardized to equivalence of its precursor, and the results are listed in Table 2. Among all the tested quinolones, 15 compounds exhibited an acute toxicity increase after chlorination treatment, especially compounds PAZ and SPA. The possible reactions of decarboxylation at 3-position (carboxy group), dealkylation at 7-position (piperazine ring) and electrophilic halogenation have been reported in LEV, CIP and ENR chlorination processes (Dodd et al., 2005; El Najjar et al., 2013; Zhou et al., 2011). Indeed, oxidation and Cl atom electrophilic substitution are the typical reactions occurring in chlorination disinfection treatment, which can

Table 2 – Acute toxicity values of tested compounds after chlorination disinfection.

Comp.	IC_{20} [a]	Comp.	IC_{20}	Comp.	IC_{20}	Comp.	IC_{20}
BAL	250.25	ENO	431.57	LOM	139.40	PEF	166.03
CIN	155.20	ENR	200.70	MOX	124.15	RUF	364.83
CIP	344.74	FLE	148.21	NAD	269.50	SAR	181.49
DAN	124.43	GAT	512.67	OFL	192.99	SPA	23.49
DIF	146.15	LEV	284.12	PAZ	16.37	NOR/PIP	ND [b]

[a] IC_{20} in μmol/L unit.
[b] ND means not-detected.

significantly change the atom electronegativity distribution of target molecules. This may be responsible for the acute toxicity elevation. Therefore, attention should be paid to the potential risk of quinolone chlorination disinfection.

3. Conclusions

The acute toxicity of 21 quinolone antibiotics was measured using photobacterium assay. The result suggested that DIF, MOX and CIN showed relatively high acute toxicity among all tested compounds, with IC_{20} values of 18.86, 22.85 and 35.02 μmol/L respectively. Additionally, the action mode of quinolones to *V. fischeri* was investigated with the established QSAR model. The electronegative atoms contained in quinolone molecules, such as F, N, and O atoms, donated electrons to photobacterium and thus inhibited the luminance emission. Although the quinolones showed limited acute toxicity, the coexistence of multiple quinolones in environmental matrices may lead to severe overall toxicity. Furthermore, the toxicity elevation during quinolone chlorination process poses potential ecological risk to chlorination disinfection treatment on quinolone-containing (waste) water. This should be of great concerns and need further investigation.

Acknowledgments

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