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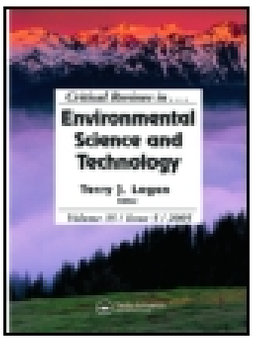

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Controlling factors and toxicokinetic modeling of antibiotics bioaccumulation in aquatic organisms: A review

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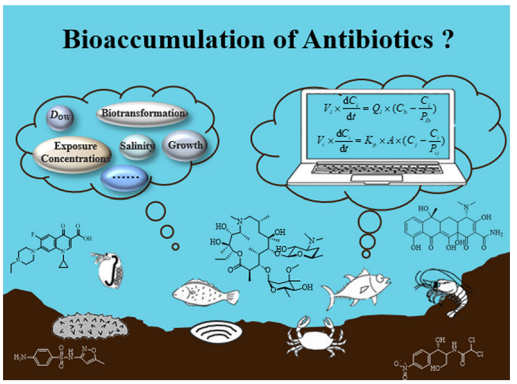
ABSTRACT



Antibiotics are emerging pollutants widely existing in the aquatic environment with adverse effects on both humans and organisms. Understanding bioaccumulation of antibiotics in aquatic organisms is important for their risk assessment. Observations on the bioaccumulation metrics (including bioconcentration factor, biomagnification factor, trophic magnification factor, bioaccumulation factor, and biota-sediment accumulation factor) of antibiotics in aquatic organisms are reviewed in this contribution. It is revealed that close attention should be paid to enrofloxacin, sulfamethiazole, doxycycline, sulfadimidine, clarithromycin, azithromycin, and chloramphenicol, because they have high bioaccumulation potential with the logarithm of bioaccumulation factor values beyond a threshold (3.3 L/kg) stipulated in the REACH regulation. Physicochemical properties of antibiotics (e.g., pH-dependent octanol-water partition coefficient and liposome-water distribution coefficient), biological characteristics of organisms (e.g., lipid content, biotransformation potential, growth stages, and feeding habits) as well as environmental factors (e.g., the presence of sediment, pH, salinity, exposure concentrations, as well as co-existence with dissolved organic matter, heavy metals, and microplastics) can control the bioaccumulation of antibiotics in aquatic organisms. One-compartment and multi-compartment toxicokinetic models on the bioaccumulation of antibiotics in aquatic organisms are summarized. The existing models of antibiotics mainly focused on fish, suggesting more efforts are needed to construct models on other aquatic species. Knowledge gaps and critical research directions on antibiotics bioaccumulation were highlighted.

KEYWORDS Antibiotics; aquatic organisms; bioaccumulation; controlling factors; toxicokinetic models

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1. Introduction

Antibiotics are secondary metabolites produced by microorganisms, or compounds entirely synthesized or semi-synthesized by human beings that can kill microorganisms or inhibit their growth or metabolic activity (Kümmerer, 2009). Since the discovery of penicillin, more than 250 antibiotics have been extensively used in human medicine, animal husbandry, and aquaculture, to treat and prevent bacterial infections or to promote animal growth (Kovalakova et al., 2020). The antibiotics may be divided into different categories by their chemical structures, such as quinolones, sulfonamides, macrolides, tetracyclines, amphenicols, β-lactams, nitrofurans, and others (Liu et al., 2017a; Ribeiro et al., 2018; Van Boeckel et al., 2014; Zhang et al., 2015). Commonly used antibiotics with their CAS numbers, molecular formulas, molecular weights, octanol-water partition coefficients ($\log K_{OW}$), and dissociation constants (pKa), are listed in Table 1.

Due to extensive use and continuous environmental input, approximately 100 antibiotics have been detected in aquatic environment, with concentrations ranging from ng/L to μg/L in water and of μg/kg in sediment (Böger et al., 2021; Du et al., 2017; Huang et al., 2022; Kümmerer, 2009; Wang et al., 2020a; Xie et al., 2020). Antibiotics can be taken up by and be retained in aquatic organisms, increasing their risks to both ecological environment and human health (Chen et al., 2018; Wang et al., 2017; Zhao et al., 2016). Currently, antibiotics have been detected in various aquatic organisms, such as fish, bivalves, gastropods, crustaceans, cephalopods, sea cucumbers, and corals, with concentrations at the ng-μg/kg range (wet weight, WW) except for erythromycin-H_2O (15.1 mg/kg, WW) in shrimp samples collected from farms surrounding the Hailing Island, South China (Chen et al., 2015a; Griboff et al., 2020; Liu et al., 2018a; Świacka et al., 2022; Zhang et al., 2020a; Zhu et al., 2018).

Ecotoxicological studies indicate that antibiotics may cause genotoxicity, phototoxicity, and oxidative stress in aquatic organisms (Kim et al., 2009; Kovalakova et al., 2020; Magdaleno et al., 2015; Zhou et al., 2011). Long-term exposure to antibiotics may pose a public health threat to bacterial resistance. The World Health Organization has recognized the emergence of antibiotic resistance genes as one of the most critical public health concerns in the 21st century. Therefore, concern should be paid to risks of antibiotics.

The risks of antibiotics to organisms depend upon their exposure and hazard profiles, both of which are related to the internal concentrations of antibiotics in organisms. The internal concentrations are determined by the net result of competing uptake and elimination via different exposure routes. Bioaccumulation results from the competing processes and commonly leads to higher internal concentrations. Bioaccumulation potential constitutes an important aspect of identifying and managing environmental chemicals. For instance, chemicals with the logarithm of bioconcentration factor (logBCF) values beyond 3.3 L/kg (bioaccumulative) or 3.7 L/kg (very bioaccumulative) deserve particular concern according to the REACH regulation (European Union, 2006). Consequently, understanding the bioaccumulation behavior of antibiotics in aquatic organisms is of importance.

In the past two decades, studies on the bioaccumulation of antibiotics in aquatic organisms have focused on observations, factors controlling the bioaccumulation, and developing models capable of explaining and predicting the bioaccumulation. Nonetheless, these studies have not yet been fully summarized, necessitating the current review. This review aims to achieve the following objectives: (1) to extensively review the bioaccumulation metrics for antibiotics in aquatic organisms measured both in laboratory and in field conditions; (2) to describe the factors controlling bioaccumulation of antibiotics, including the physicochemical properties of the chemicals, biological characteristics of organisms, as well as environmental factors modifying the uptake; and (3) to summarize toxicokinetic models on the bioaccumulation of antibiotics.

Table 1. Commonly used antibiotics and their categories, CAS, molecular formula, molecular weight (MW), and octanol-water partition coefficient ($logK_{OW}$) and dissociation constant (pKa).

Antibiotic	CAS	Molecular formula	MW	logKow	pKa
Quinolones					
Enoxacin	74011-58-8	$C_{15}H_{17}FN_4O_3$	320.3	−0.2	7.04, 8.19
Ciprofloxacin	85721-33-1	$C_{17}H_{18}FN_3O_3$	331.3	0.28	6.43, 8.7
Norfloxacin	70458-96-7	$C_{16}H_{18}FN_3O_3$	319.3	0.46	6.34, 8.75
Ofloxacin	82419-36-1	$C_{18}H_{20}FN_3O_4$	361.4	−0.39	7.26, 7.81
Enrofloxacin	93106-60-6	$C_{19}H_{22}FN_3O_3$	359.4	0.70	7.59, 8.7
Balofloxacin	127294-70-6	$C_{20}H_{24}FN_3O_4$	389.4	0.99	NA
Fleroxacin	79660-72-3	$C_{17}H_{18}F_3N_3O_3$	369.3	0.24	5.5, 8.2
Lomefloxacin	98079-51-7	$C_{17}H_{19}F_2N_3O_3$	351.4	−0.3	5.7
Moxifloxacin	151096-09-2	$C_{21}H_{24}FN_3O_4$	401.4	0.95	6.3, 9.3
Sparfloxacin	110871-86-8	$C_{19}H_{22}F_2N_4O_3$	392.4	2.5	NA
Pipemidic Acid	51940-44-4	$C_{14}H_{17}N_5O_3$	303.3	−2.15	NA
Sulfonamides					
Sulfapyridine	144-83-2	$C_{11}H_{11}N_3O_2S$	249.3	0.35	2.59, 8.43
Sulfamethoxazole	723-46-6	$C_{10}H_{11}N_3O_3S$	253.3	0.89	1.6, 5.7
Trimethoprim	738-70-5	$C_{14}H_{18}N_4O_3$	290.3	0.91	7.12,
Sulfamethazine	57-68-1	$C_{12}H_{14}N_4O_2S$	278.3	0.89	2.65, 7.65
Sulfathiazole	72-14-0	$C_9H_9N_3O_2S_2$	255.3	0.05	2.2, 7.24
Sulfamonomethoxine	1220-83-3	$C_{11}H_{12}N_4O_3S$	280.3	0.7	NA
Sulfacetamide	144-80-9	$C_8H_{10}N_2O_3S$	214.2	−0.96	NA
Sulfadiazine	68-35-9	$C_{10}H_{10}N_4O_2S$	250.3	−0.09	6.36
Sulfamethiazole	144-82-1	$C_9H_{10}N_4O_2S_2$	270.3	NA	NA
Sulfamethoxypyridazine	80-35-3	$C_{11}H_{12}N_4O_3S$	280.3	0.32	NA
Sulfameter	651-06-9	$C_{11}H_{12}N_4O_3S$	280.3	0.41	NA
Macrolides					
Erythromycin	114-07-8	$C_{37}H_{67}NO_{13}$	733.9	3.06	8.8
Roxithromycin	80214-83-1	$C_{41}H_{76}N_2O_{15}$	837.0	1.7	9.27
Clarithromycin	81103-11-9	$C_{38}H_{69}NO_{13}$	748	3.16	8.99
Azithromycin	83905-01-5	$C_{38}H_{72}N_2O_{12}$	749	4.02	8.74
Tetracyclines					
Chlortetracycline	57-62-5	$C_{22}H_{23}ClN_2O_8$	478.9	−0.62	7.44
Oxytetracycline	79-57-2	$C_{22}H_{24}N_2O_9$	460.4	−0.9	3.27, 9.5
Tetracycline	60-54-8	$C_{22}H_{24}N_2O_8$	444.4	−1.37	3.3, 7.68
Doxycycline	564-25-0	$C_{22}H_{24}N_2O_8$	444.4	0.63	3.09
Amphenicols					
Florfenicol	73231-34-2	$C_{12}H_{14}Cl_2FNO_4S$	358.2	−0.12	NA
Chloramphenicol	56-75-7	$C_{11}H_{12}Cl_2N_2O_5$	323.1	1.14	NA
Thiamphenicol	15318-45-3	$C_{12}H_{15}Cl_2NO_5S$	356.2	−0.27	NA
β-lactam					
Penicillin G	61-33-6	$C_{16}H_{18}N_2O_4S$	334.4	1.83	2.74
Amoxicillin	26787-78-0	$C_{16}H_{19}N_3O_5S$	365.4	−1.99	2.64, 7.39
Cefalexin	15686-71-2	$C_{16}H_{17}N_3O_4S$	347.4	0.65	2.5, 7.1
Cefradine	38821-53-3	$C_{16}H_{19}N_3O_4S$	349.4	−1.5	2.6, 7.6
Cefotaxime	63527-52-6	$C_{16}H_{17}N_5O_7S_2$	455.5	−0.5	NA
Nitrofurans					
Furazolidone	67-45-8	$C_8H_7N_3O_5$	225.2	−0.04	NA
Nitrofurantoin	67-20-9	$C_8H_6N_4O_5$	238.2	−0.47	7.2
Others					
Lincomycin	154-21-2	$C_{18}H_{34}N_2O_6S$	406.5	0.2	7.6
Salinomycin	53003-10-4	$C_{42}H_{70}O_{11}$	751	5.11	4.5, 6.5

MW, molecular weight (g/mol); NA, not available.

Data were obtained from the software QSAR Tool Box and databases including Chemspider (https://www.chemspider.com/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/).

2. Observations on bioaccumulation of antibiotics in aquatic organisms

Bioaccumulation potential is commonly characterized by metrics such as bioconcentration factor (BCF), biomagnification factor (BMF), trophic magnification factor (TMF), bioaccumulation factor (BAF), or biota-sediment accumulation factor (BSAF) (Armitage et al., 2017; Arnot & Gobas, 2004).

2.1. Bioconcentration factor

Bioconcentration in aquatic organisms involves uptake of chemicals from water alone, which may occur through the respiratory surface and/or skin of the organisms (Mackay & Fraser, 2000). BCF (L/kg) is defined as the ratio of the chemical concentration in an organism (C_O, ng/kg) and the concentration of the chemical in water (C_W, ng/L) in equilibrium. However, the equilibrium state is challenging to achieve. Kinetically determined BCF, defined as the ratio of uptake rate constant (k_u) and elimination rate constant (k_e), is usually used instead. The k_u and k_e values are generally estimated by determining time-course internal concentration curves under controlled waterborne exposure conditions in laboratory according to standardized protocols such as OECD TG305 (OECD, 2012):

$$BCF = C_O/C_W = k_u/k_e \quad (1)$$

A total of 115 logBCF counts for antibiotics in different tissues for different species under different exposure concentrations were reported, as listed in Table S1 of the Supporting Information. The measurements focused on 20 antibiotics, including nine quinolones, four sulfonamides, four macrolides, one tetracycline, and two amphenicols. Fish were the most studied taxonomic species, including *Cyprinus carpio*, *Danio rerio*, *Carassius auratus*, *Carassius carassius*, *Acipenser schrenkii*, and *Oryzias melastigma*. Beyond fish, *Daphnia magna*, *Chironomus riparius*, and *Apostichopus japonicus* were also assessed.

The counts covered tissue/organ types like whole body, gill, bile, liver, kidney, digestive tract, mouth, and muscle. As can be seen from Figure S1, which compares the logBCF values of antibiotics in different tissues in fish, the mean logBCF values decrease in the order of bile (0.75) > liver (0.58) > gill (0.19) > muscle (0.04) > kidney (0.02), indicating that the antibiotics tend to accumulate in the bile and liver of the aquatic organisms.

Significant variations were observed for logBCFs among different antibiotics, species, and exposure concentrations. The maximum mean logBCF was observed for ofloxacin (3.2 L/kg) in the respiratory trees of *A. japonicus* at an exposure concentration of 1 μg/L (Zhu et al., 2020). This is below the bioaccumulative criterion (3.3 L/kg) of the REACH, indicating the low bioconcentration potential of the antibiotics in the aquatic organisms. It is common to see orders of magnitude differences in the BCF measurements for a given antibiotic, suggesting that apart from the physicochemical properties of the antibiotics, other factors could also influence their bioaccumulation.

Figure 1 displays the profiles of logBCF values of the antibiotics in the aquatic organisms reported in multiple independent studies. It should be noted that data of erythromycin, florfenicol, thiamphenicol, and pipemidic acid were not presented, because only the minimum and the maximum logBCF values of these chemicals were reported (Liu et al., 2014a; Sun et al., 2020). It can be seen that high median logBCFs across all the studies were observed for ofloxacin (2.30 L/kg), followed by clarithromycin (2.26 L/kg), trimethoprim (2.18 L/kg), and azithromycin (2.11 L/kg).

It deserves mentioning that exposure concentrations significantly impact the bioconcentration of the antibiotics in aquatic organisms. As can be seen from Table 2, high logBCFs were observed for the antibiotics under the low exposure concentrations. Similar phenomena were reported for perfluorinated compounds, and benzotriazole ultraviolet stabilizers (Liu et al., 2011; Zhang et al., 2021a). A possible explanation is that these chemicals can bind to proteins, with the limited number of binding sites limiting the number of chemicals adsorbed to the target sites (Craig & Kunin, 1976; Liu et al., 2011). Thus, the binding affinity of various antibiotics to specific proteins, and its effects on the bioaccumulation of the antibiotics deserve to be clarified. Further studies may also focus on identifying specific proteins and chemicals essential to determine the bioconcentration of chemicals in aquatic organisms.

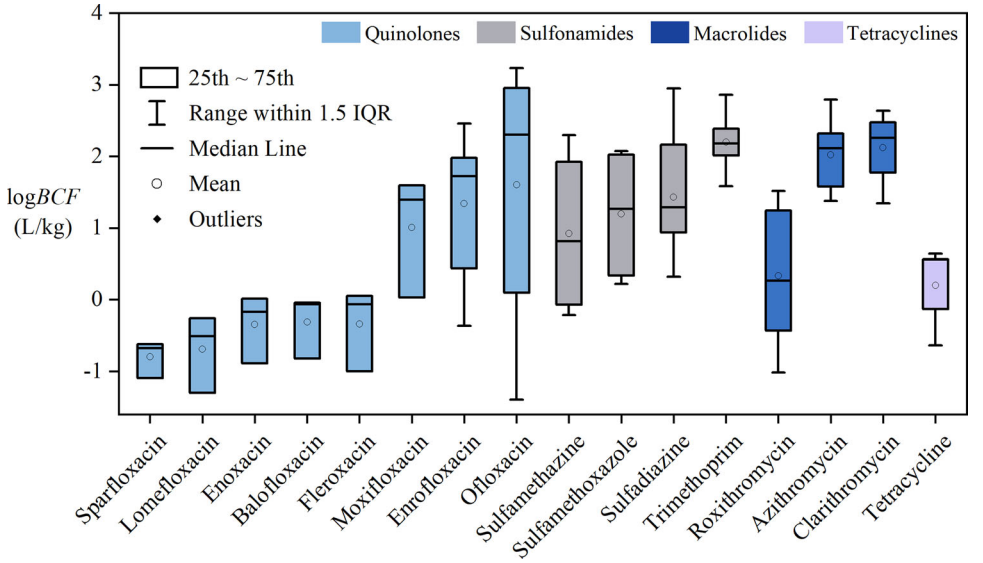

Figure 1. Boxplot of logBCF values of antibiotics in aquatic organisms.

Table 2. Comparison of logBCF values for antibiotics in aquatic organisms under low and high exposure concentrations.

	Low exposure concentration		High exposure concentration		
Antibiotic	Mean	SD	Mean	SD	Reference
Sulfamethazine	0.08	NA	−0.21	NA	Hou et al., 2003
Tetracycline	0.60	0.06	−0.04	0.85	Kim et al., 2014; Xie et al., 2019
Roxithromycin	1.34	0.14	−0.48	0.48	Liu et al., 2014b
Sulfamethoxazole	2.05	0.04	0.28	0.08	Zhao et al., 2015a
Sulfadiazine	2.15	0.65	0.72	0.37	Zhao et al., 2015a; Zhu et al., 2020
Enrofloxacin	2.15	0.38	1.12	0.85	Zhu et al., 2020
Ofloxacin	2.98	0.20	1.00	1.69	Zhu et al., 2020
Trimethoprim	2.39	0.35	2.01	0.33	Zhu et al., 2020
Azithromycin	2.15	0.58	1.90	0.43	Zhu et al., 2020
Clarithromycin	2.23	0.60	2.01	0.37	Zhu et al., 2020

NA, not available.

2.2. Biomagnification factor and trophic magnification factor

Biomagnification in aquatic organisms involves the uptake of chemicals due to dietary absorption (Mackay & Fraser, 2000), which can be characterized by BMF. The BMF can be defined as the ratio of C_O to C_{Food} (i.e., chemical concentration in food, ng/kg) in equilibrium:

$$BMF = C_O/C_{Food} \tag{2}$$

Besides the BMF, the biomagnification potential of a chemical in aquatic food webs can be characterized by the TMF, calculated as the antilog of the slope (b) for the relationship between trophic levels (TLs) and logarithm of internal concentrations (Lavoie et al., 2013). The TLs in food webs were usually derived via stable carbon and nitrogen isotope ratios (Liu et al., 2017b; Wu et al., 2021):

$$\log C_O (\text{or } \ln C_O) = a + b \times TL \tag{3}$$

$$TMF = 10^b (\text{or } e^b) \tag{4}$$

where a stands for the intercept.

There were a few studies concerning the biomagnification of antibiotics in aquatic organisms. The BMF of tetracycline in *D. magna* through dietary exposure was 0.19 ± 0.04, indicating that

the magnification of tetracycline through the food chain did not occur (Kim et al., 2014). The TMFs were in the range of 1.2–3.9 for sulfonamides in marine food webs in Laizhou Bay, North China, but were below 1.0 for fluoroquinolones and macrolides. Therefore, the sulfonamides have the potential to biomagnify, while the fluoroquinolones and macrolides can be diluted across the food chain (Liu et al., 2017b).

Zhang et al. (2020b) observed TMF values approaching 1.0 for enrofloxacin, norfloxacin, ofloxacin, and flumequine (with TMFs of 1.08–1.10, 1.05–1.06, 0.90–0.97, and 0.84–0.88, respectively) in a benthic food web from a macrophyte-dominated shallow lake in North China. A recent study observed trophic magnification of sulfadiazine (TMF = 1.32) and enoxacin (TMF = 1.58), and trophic dilution (TMF < 1.0) of enrofloxacin, ofloxacin, ciprofloxacin, and erythromycin-H_2O in a marine food web from Beibu Gulf in South China (Wu et al., 2021). Thus, it can be concluded that antibiotics tend to have low levels of biomagnification potential based on the limited data available. This is likely due to their weak hydrophobicity and high biotransformation potential (Zhang et al., 2021b; Zhu et al., 2020).

2.3. Bioaccumulation factor

BAF is also defined as the ratio of C_O to C_W in equilibrium, but considering uptake by all exposure pathways, including diet, respiration, and dermal contact (Mackay & Fraser, 2000). BAFs are generally obtained under field conditions assuming the equilibrium is achieved.

Table S2 lists logBAF values for antibiotics obtained from previous studies. A total of 188 unique measurements have been reported for 29 antibiotics in fish, arthropods, mollusca, echinodermata, coelenterata, or reptilia. It can be seen that the BAF values were determined on aquatic organisms collected from China. Further studies are needed to investigate antibiotics bioaccumulation on a larger spatial scale since environmental conditions can influence the bioaccumulation of the chemicals.

The logBAF values varied with antibiotics, species, tissues, and sampling locations. It should be noted that the BAFs were mostly calculated using a one-time sampling concentration, which might lead to errors in the BAF values. By contrast, the time-weighted average concentrations obtained by passive sampling techniques, such as diffusive gradients in thin-films, may be applied instead (Xie et al., 2018, 2021). Besides, higher values are usually observed for logBAF than for logBCF of a given antibiotic, indicating that long-term low-concentration exposure to the antibiotics for aquatic organisms deserves great concern.

As shown in Figure 2, macrolides, sulfonamides, and quinolones generally have higher measured logBAFs than tetracyclines and amphenicols. According to the REACH regulation, enrofloxacin (logBAF = 3.5), sulfamethiazole (logBAF = 3.4), and doxycycline (logBAF = 3.6) can be classified as bioaccumulative compounds based on their median logBAF values, while sulfadimidine (logBAF = 3.8), clarithromycin (logBAF = 4.0), azithromycin (logBAF = 4.8), and chloramphenicol (logBAF = 3.7) can be regarded as very bioaccumulative compounds, indicating that close attention should be paid to the occurrence of these seven antibiotics due to their bioaccumulative potential.

2.4. Biota-sediment accumulation factor

Sediment-ingesting benthic organisms may be exposed to sediment-associated chemicals via direct contact with porewater and overlying water, and via ingestion of contaminated sediment particles. As a result, benthic organisms usually have a more considerable body burden of pollutants than pelagic biota (Liu et al., 2017b). Therefore, it is necessary to characterize the bioaccumulation potential of chemicals in benthic organisms due to sediment exposure. The most widely used metric is the BSAF.

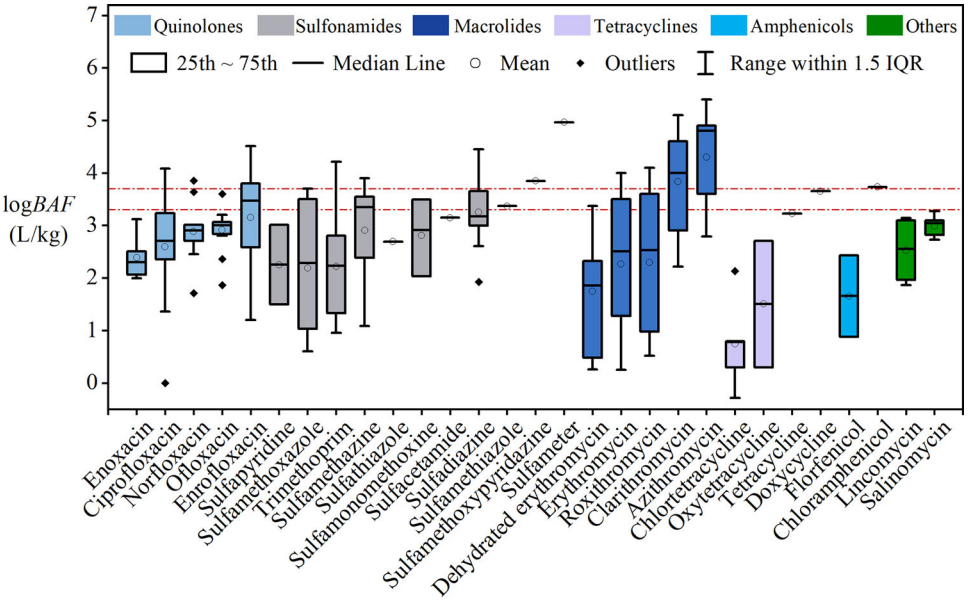

Figure 2. Boxplot of logBAF values of antibiotics in aquatic organisms.

The BSAF can be obtained either under laboratory conditions or in field, which is calculated as the ratio of the lipid-normalized concentration of chemicals in an organism, to the carbon-normalized concentration in sediment (OECD, 2008):

$$BSAF = \left(C_O/f_{lip}\right)/\left(C_S/f_{OC}\right) \tag{5}$$

where C_S is the chemical concentration in sediment (ng/kg), f_{lip} is the fraction of lipids in organisms, and f_{OC} is the fraction of sediment organic carbon.

Although antibiotics have been widely detected in sediment (Bayen et al., 2016; He et al., 2019; Luo et al., 2011), only two studies examined the sediment-associated accumulation of antibiotics in aquatic organisms. As listed in Table 3, the BSAF values were far below 1.0 for four antibiotics (chlortetracycline, roxithromycin, erythromycin, and trimethoprim) in freshwater organisms sampled from Eastern China (Li et al., 2021). Wu et al. (2021) investigated the bioaccumulation of sulfonamides, fluoroquinolones, and macrolides in benthic marine aquatic organisms from the Beibu Gulf in South China, also finding that most antibiotics had low BSAF values (< 3.09) except for enoxacin (BASF $= 7.41$) and sulfadiazine (BASF $= 77.62$).

Previous studies indicated that sediment-uptake was a vital exposure route for chemicals such as polychlorinated dibenzo-*p*-dioxins and furans, polybrominated diphenyl ethers (PBDEs), and polycyclic aromatic hydrocarbons (PAHs) (Fan et al., 2017; Lyytikäinen et al., 2003; Tian et al., 2012). However, data covering sediment-associated antibiotics bioaccumulation in aquatic organisms are limited. Since sediment may also be a sink for antibiotics, more studies are needed to investigate the uptake of different antibiotics from sediment in aquatic organisms, and the sediment-associated bioavailability of the antibiotics.

Overall, the BCF assesses the bioaccumulation potential of chemicals in aquatic organisms under only waterborne exposure conditions, while the BAF applies to multi-route exposure scenarios (including water and food). Both the BMF and the TMF are metrics characterizing biomagnification potential. The BMF is suitable for dietary exposure scenarios, while the TMF is usually used to evaluate whether a chemical can be accumulated in organisms at high trophic levels. The BSAF is a critical metric to assess the bioaccumulation potential of chemicals related to sediment-associated exposure in benthic organisms.

Table 3. Overview of BSAF values for antibiotics.

Chemical	Species	Tissue	Region	BSAF	Reference
Chlortetracycline	Fish, Crab, Turtle, Prawn, Clam,	Muscle	Jiangsu, China	0.01	Li et al., 2021
			Anhui, China	0.01	
			Zhejiang, China	0.08	
			Shanghai, China	0.01	
Roxithromycin	Fish, Crab, Turtle, Prawn, Clam,	Muscle	Jiangsu, China	0.01	Li et al., 2021
			Anhui, China	0.01	
			Zhejiang, China	0.05	
			Shanghai, China	0.005	
Erythromycin	Fish, Crab, Turtle, Prawn, Clam,	Muscle	Jiangsu, China	0.02	Li et al., 2021
			Anhui, China	0.003	
			Zhejiang, China	0.6	
			Shanghai, China	0.01	
Trimethoprim	Fish, Crab, Turtle, Prawn, Clam,	Muscle	Jiangsu, China	0.02	Li et al., 2021
			Anhui, China	0.01	
			Zhejiang, China	0.08	
			Shanghai, China	0.004	
Sulfadiazine	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	77.62	Wu et al., 2021
Sulfamethazine	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	1.78	Wu et al., 2021
Erythromycin-H_2O	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	3.09	Wu et al., 2021
Enoxacin	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	7.41	Wu et al., 2021
Norfloxacin	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	1.51	Wu et al., 2021
Ofloxacin	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	1.66	Wu et al., 2021
Ciprofloxacin	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	2.95	Wu et al., 2021
Enrofloxacin	Fish, Cephalopod, Crustacean	Soft Tissue or Muscle	Beibu Gulf, China	2.29	Wu et al., 2021

3. Factors controlling bioaccumulation of antibiotics in aquatic organisms

Bioaccumulation depends on the absorption, distribution, metabolism (biotransformation), and excretion (ADME) processes of chemicals in organisms. These processes are controlled by the physicochemical properties of the chemicals, biological characteristics of the organisms, and environmental factors. Understanding the factors controlling the bioaccumulation of antibiotics and underlying mechanisms of action is important to explain apparent observations, and to predict the bioaccumulation potential.

3.1. Physicochemical properties of antibiotics

3.1.1. pH-dependent octanol-water partition coefficient (D_{OW})

It is generally considered that the bioaccumulation potential of organic chemicals is related to their hydrophobicity, with their logBCF values positively correlating with their $\log K_{OW}$ values (Arnot & Gobas, 2006; Mackay & Fraser, 2000). Nevertheless, many antibiotics are ionizable organic chemicals (IOCs), which can ionize under environmental and physiological pH conditions.

The fraction of neutral and ionized forms (chemical speciation) depends on the pKa of chemicals, and the pH of exposure medium. The chemical speciation of antibiotics should be considered when assessing their bioaccumulation. Hence, D_{OW}, which can characterize the apparent partition coefficients of neutral and charged forms of chemicals, is more suitable than K_{OW} when considering the bioaccumulation of IOCs (Chen et al., 2017a; Fu et al., 2009). A previous study depicted that the antibiotics with high $\log D_{OW}$ values had high bioaccumulation potential (Liu et al., 2017b). However, negative correlations were observed between $\log D_{OW}$ of detected antibiotics and their logBAF values in corals from the South China Sea, and in a subtropical marine food web from the Beibu Gulf in South China (Wu et al., 2021; Zhang et al., 2019a).

3.1.2. Liposome-water distribution coefficient (D_{lipw})

Since many antibiotics are predominantly charged at physiological pH, they may interact with phospholipids via electrostatic forces (Armitage et al., 2012). This is because the phospholipids

are zwitterionic with positively charged groups (e.g., choline, ethanolamine, and serine) and negatively charged groups such as phosphate groups. Liu et al. (2018b) found that logBAF values significantly increased with increasing $logD_{lipw}$ values in the gill, kidney, and liver tissues in fish. This indicates that D_{lipw} may be a good descriptor to predict antibiotics bioaccumulation in phospholipid-rich tissues.

3.1.3. Fluorine substituent

The introduction of fluorine substituents may increase lipophilicity, decrease metabolic susceptibility, reduce binding capacity with plasma proteins, and accordingly influence the bioaccumulation of chemicals (Conder et al., 2008; Sun et al., 2020). Sun et al. (2020) confirmed that antibiotics containing a fluorine substituent were more likely to be accumulated in crucian carp (*C. carassius*) compared to nonfluorinated analogues. It deserves mentioning that chlorine and methoxy substituents can increase the bioaccumulation potential of chlorinated paraffins, and polychlorinated diphenyl ethers in organisms (Castro et al., 2019; Koistinen et al., 2007). However, it remains unknown whether the substituents influence the bioaccumulation of antibiotics in aquatic organisms.

In addition to the aforementioned physicochemical properties, a previous study observed positive linear relationships between logBCFs and membrane-water distribution coefficients ($logD_{MW}$), albumin-water distribution coefficients ($logD_{BSAW}$), and muscle protein-water distribution coefficients ($logD_{MPW}$) for pharmaceuticals and personal care products (PPCPs) in zebrafish (*D. rerio*). Hence, it deserves further investigation whether these properties control the bioaccumulation of antibiotics in aquatic organisms.

3.2. Biological characteristics of aquatic organisms

3.2.1. Lipid content

It is well known that many organic compounds preferentially accumulate in lipids of aquatic organisms, and the extent of accumulation is more significant in those organisms or tissues with a higher lipid content (Deribe et al., 2011; Mackay & Fraser, 2000). Previous studies indicated that antibiotics were more likely to be concentrated in lipid-rich tissues such as liver (Liu et al., 2018b; Yan et al., 2017; Zhang et al., 2021b).

3.2.2. Biotransformation potential

Biotransformation is a vital process that decreases concentrations of parent compounds in an organism (Fu et al., 2020). It was observed that biotransformation greatly reduced the bioaccumulation potential of enrofloxacin in *Scophthalmus maximus*, *Penaeus vannamei*, *Penaeus japonicus*, and *A. japonicus* (Zhang et al., 2021b; Zhu et al., 2020). Many previous studies also identified the metabolites of antibiotics in aquatic organisms (Liu et al., 2014a, 2014b; Zhao et al., 2016).

It deserves mentioning that some metabolites of antibiotics are more toxic than their parent compounds. García-Galán et al. (2012) indicated that the 50% effective concentration (EC_{50}) of acetylated sulfapyridine was lower than the EC_{50} of sulfapyridine for *Vibrio fischeri*. Lower EC_{50} values were also observed for ciprofloxacin than those of its parent compound enrofloxacin regarding the growth inhibition effect on aquatic organisms (Ebert et al., 2011). In addition, some transformation products have higher bioaccumulation potential than their parent compounds (Gao et al., 2016). Consequently, attention should be paid to ecological risks posed by the metabolites of antibiotics.

3.2.3. Growth stages

Organisms at different growth stages may exhibit distinct bioaccumulation characteristics on chemicals due to differences in growth rates, lipid content, biotransformation enzyme content, ingestion rates as well as assimilation efficiency (Li et al., 2018; Zhang & Wang, 2007). A recent study revealed that fish accumulated more antibiotics was significantly higher at their youth stages than at the growth and adult stages, which may be due to lower amounts of biotransformation enzymes, higher percentages of lipids, and stronger ingesting ability of fish during the youth stages (Zhang et al., 2021b). A previous study also observed that the distribution of antibiotics in fish tissues related to fish size, including weight and length (Chen et al., 2018). Therefore, growth dilution may play a role in the bioaccumulation of chemicals (Gobas & Lee, 2019).

3.2.4. Others

Wu et al. (2021) observed that there was a negative correlation between the total internal concentrations of antibiotics and the relative carbon source values that were normally applied to assess whether an organism was more pelagic or benthic feeding, for marine organisms sampled from the Beibu Gulf in South China. This indicates that feeding habits are crucial factors for the bioaccumulation of antibiotics. Zhang et al. (2019a) investigated antibiotics bioaccumulation in corals from the South China Sea and discovered that higher BAF values were obtained for the corals than those in the crabs, shrimps as well as oysters from the same area, which may be due to their large surface area and the existence of mucus with high content of particulate organic matter.

3.3. Environmental factors

3.3.1. Presence of sediment and its physicochemical properties

The presence of sediment can influence the bioaccumulation of antibiotics in aquatic organisms. Chen et al. (2017b) reported that the existence of sediment reduced the bioaccumulation of sulfamethoxazole in zebrafish (*D. rerio*) by 13%–28% due to the competition between the sediment and the antibiotic. This decrease could be influenced by the physicochemical properties of sediment, such as particle size, specific surface area, and organic carbon content, by affecting the distribution of sulfamethoxazole between sediment and water (Chen et al., 2017b).

Nevertheless, some previous studies also reported that the presence of sediment may accelerate the bioaccumulation of pollutants in aquatic organisms (Fan et al., 2017; Liu et al., 2017a; Tan et al., 2018; Tian et al., 2010, 2012). For instance, uptake of PBDEs in carp (*C. carpio*) was significantly higher in the presence of sediment than in the absence of sediment, which could be attributed to direct contact with spiked sediment, and ingestion of contaminated suspended particulate matter (Tian et al., 2012). Previous studies ascertained that benthic fish accumulated more pollutants (e.g., antibiotics, PBDEs, and PAHs) than pelagic fish (Fan et al., 2017; Liu et al., 2017a; Tian et al., 2010). A possible explanation is that the benthic organisms have more opportunities to be exposed to pollutants through ingesting and direct contact with contaminated sediment than the pelagic ones. Hence, it depends on the exposure routes, the bioavailability of the chemicals, and the living habits of organisms, whether the presence of sediment increases or decreases the bioaccumulation.

3.3.2. Physicochemical properties of water

Low temperatures could inhibit biological activities, including the absorption and excretion processes of organisms, and therefore could influence the bioaccumulation of organic pollutants (Maulvault et al., 2018; Tarja et al., 2003). Sun et al. (2020) observed that less time was needed to reach the maximum concentration for florfenicol, thiamphenicol, ofloxacin, and pipemidic acid in crucian carp (*C. carassius*) at higher temperatures. Nevertheless, temperature variations generally

have no significant effect on antibiotics bioaccumulation. The rationale for this is that the dynamics of absorption and excretion changes simultaneously, eventually leading to a similar equilibrium in the organisms upon changes in temperatures. Thus, the effect of temperatures on the bioaccumulation depends on whether the temperatures have a more significant effect on absorption or on excretion.

Salinity can influence the bioaccumulation of compounds in aquatic organisms by affecting the physiology of the organisms, such as osmotic regulation, metabolism, and digestive enzyme activity (Boeuf & Payan, 2001; Chen et al., 2017b). For instance, the bioaccumulation of sulfamethoxazole in zebrafish (*D. rerio*) was inhibited under high salinity of 20‰, and the extent of inhibition was more significant when sediment was present (Chen et al., 2017b). This observation may be caused by the fact that high salinity not only affects the physiology of the organisms but also decreases the bioavailability of sulfamethoxazole due to the salting effect (Chen et al., 2017b). Thus, high salinity may inhibit the bioaccumulation potential. However, it remains unclear whether variation in osmotic, metabolism, or digestive enzyme activity of the aquatic organisms is responsible for the inhibition.

Although there is no study regarding the effects of pH on antibiotics bioaccumulation in aquatic organisms, it can be speculated that pH may influence the bioaccumulation by modifying the chemical speciation of the antibiotics since many antibiotics are IOCs. Previous studies reported that the uptake rate constants of IOCs were more than three orders of magnitude lower for their ionized forms than for their corresponding neutral forms (Karlsson et al., 2017). Scott et al. (2019) observed that the BCFs of weak base pharmaceuticals (diltiazem and diphenhydramine) were significantly elevated upon increasing pH. Liu et al. (2017b) reported that the $\log D_{OW}$ rather than $\log K_{OW}$ of sulfonamides and fluoroquinolones significantly correlated with their TMFs in marine food webs in the Laizhou Bay, North China. More laboratory experiments or field observations are needed to understand the promotion or inhibition effects of pH on antibiotics bioaccumulation since many antibiotics are zwitterionic (Kümmerer, 2009).

3.3.3. Co-existing components

Dissolved organic matter (DOM) is a common constituent of water bodies, which plays an essential role in the distribution, transport, and bioavailability of organic pollutants. The DOM may affect the bioaccumulation of antibiotics (Chen et al., 2015b; Delgado-Moreno et al., 2010; Lu et al., 2017). For instance, Liu et al. (2019) mentioned that the uptake of erythromycin (ERY) in aquatic organisms was significantly inhibited by DOM at 20 mg/L, since the DOM could decrease the ERY bioavailability by forming DOM-ERY complexes via ionic bonding between $-COO^-$ and ERY^+, hydrogen bonding, and hydrophobic partitioning. However, no significant difference was observed in the distribution and accumulation of roxithromycin in crucian carp (*C. auratus*) with co-exposed DOM (1 mg/L) when compared with exposure in the absence of DOM (Yan et al., 2017).

The co-existence of antibiotics and other frequently detected pollutants also affects the bioaccumulation of antibiotics. For instance, the bioconcentration of fluoroquinolones in zebrafish (*D. rerio*) was inhibited by co-existent copper since the fluoroquinolones could be complexed with the copper (Zhao et al., 2018). Nevertheless, a previous study focusing on the bioaccumulation of ciprofloxacin and cadmium in organisms from pore water demonstrated that bioaccumulation kinetics and subcellular distribution of ciprofloxacin were not affected by the cadmium addition (Wen et al., 2011). Thus, the effect of complexation between antibiotics and metals on antibiotics bioaccumulation may depend on their interactions, which deserves further investigations.

A recent study indicated that co-exposure to antibiotics and microplastics aggravated the bioaccumulation of oxytetracycline and florfenicol in blood clam (*Tegillarca granosa*) (Zhou et al., 2020). This aggravation was explained by the disruption of detoxification through suppressing

glutathione-S-transferase activity and the expression of detoxification genes by the microplastics (Zhou et al., 2020). However, it remains unknown whether the aggravation can also be observed in different organisms, and whether the mechanisms can be applicable to other antibiotics and microplastics of diverse characteristics.

Yan et al. (2017) observed that the presence of multi-walled carbon nanotubes (CNTs) promoted roxithromycin accumulation in crucian carp (*C. auratus*) with 2–4.9 times, and attributed the promotion to the release of the CNT-bound antibiotics in the organisms. Garcia-Galan et al. (2017) observed that co-existing surfactants decreased the accumulation rates of sulfamethoxazole in crustacean *Gammarus fossarum*, which could be ascribed to the adverse effects of the surfactants on the physiology of the organisms. Co-existence with lactic acid, a widely used feed additive, decreased the bioaccumulation of enrofloxacin in Chinese mitten crab (*Eriocheir sinensis*). This decrease may arise from enhanced biotransformation of enrofloxacin in *E. sinensis* through up-regulating metabolic enzyme activity in the organisms by the lactic acid (Su et al., 2019).

In conclusion, although some scattered laboratory studies have been performed to investigate the effects of co-exposure to other pollutants on bioaccumulation of antibiotics in aquatic organisms, results from the studies are too limited to obtain a clear and comprehensive understanding. Further studies are needed to verify the co-existence of antibiotics with other pollutants in natural environment, and to explore whether the effects can be disparate regarding different antibiotics, organisms, co-existing pollutants, and aquatic environmental factors (e.g., DOM at different concentrations, different metals, microplastics with different types and sizes).

In addition, exposure concentrations also affect the BCF values of antibiotics in aquatic organisms. In general, higher exposure concentrations resulted in lower BCF values of the antibiotics, as discussed in the Section 2.1. Figure 3 gives a comprehensive overview of main factors controlling the bioaccumulation of antibiotics in aquatic organisms. Overall, the bioaccumulation can be influenced by various factors, which can explain the significant variations in the observed logBCF or logBAF values for a given antibiotic.

4. Toxicokinetic models on bioaccumulation of antibiotics in aquatic organisms

Toxicokinetic (TK) models that describe the ADME processes of xenobiotics can be employed to relate environmental exposure concentrations with the internal distribution of the chemicals, which are useful for predicting BCF values and the tissue-specific accumulation of chemicals, and for quantitative *in vitro–in vivo* toxicity extrapolation (Brinkmann et al., 2014; Péry et al., 2014; Zhang et al., 2021a). Therefore, TK models are powerful tools for characterizing the bioaccumulation of chemicals. Generally, two groups of TK models can be distinguished: one-compartment and multi-compartment toxicokinetic (MCTK) models.

4.1. One-compartment toxicokinetic model

The one-compartment TK models regard an organism as one homogenous compartment, in which the bioconcentration of a chemical is usually described by the exchange of the chemical from water to the organisms, and is assumed to obey first-order kinetics (Mackay & Fraser, 2000):

$$dC_O/dt = k_u \times C_W - k_e \times C_O \quad (6)$$

When an organism is continuously exposed to a chemical (C_W = constant), the above equation is integrated to:

$$C_O = (C_W \times k_u)/k_e \times (1 - e^{-k_e t}) \quad (7)$$

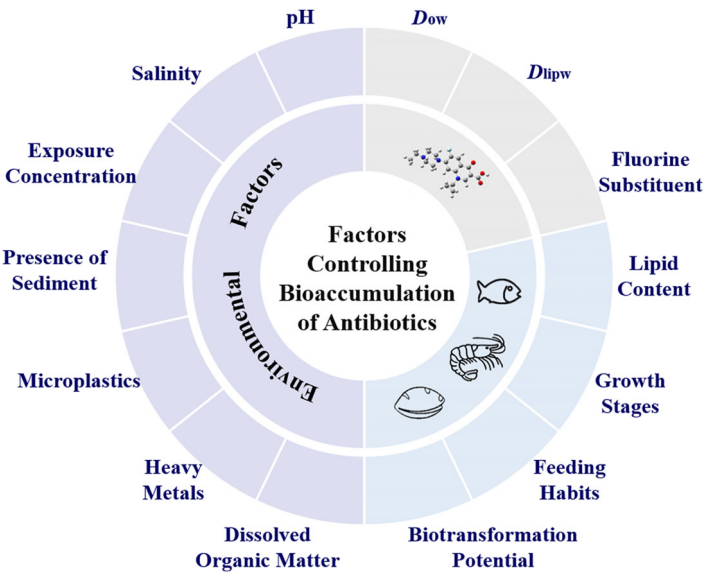

Figure 3. Overview of main factors controlling the bioaccumulation of antibiotics in aquatic organisms.

After long exposure times ($t \rightarrow \infty$), $e^{-k_e t}$ approaches zero, and the BCF can be calculated as $BCF = C_O/C_W = k_u/k_e$.

The one-compartment TK models were successfully applied to derive the BCFs of antibiotics in *A. schrenkii*, *C. auratus*, *C. carpio*, and *D. rerio*, based on k_u and k_e values measured under controlled conditions in laboratories (Hou et al., 2003; Liu et al., 2014b; Zhao et al., 2015a, 2018).

4.2. Multi-compartment toxicokinetic model

The MCTK models assume that chemical concentrations may differ among various tissues or organs. The MCTK models that are developed based on the anatomy, physiology, and biochemistry of organisms, are referred to as physiologically based toxicokinetic (PBTK) or physiologically based pharmacokinetic (PBPK) models in the fields of toxicology and pharmacology, respectively (Mackay & Fraser, 2000).

Studies on MCTK models of chemicals date back to the 1980s (McDougal et al., 1986). Most MCTK models were constructed for mammals and humans (Bouchene et al., 2018; Dong et al., 2020; Lin et al., 2015; Reisfeld et al., 2012; Thompson et al., 2019), with the purpose of studying pharmaceutical toxicokinetics. However, models on chemicals in aquatic organisms are generally scarce. Existing studies on MCTK models for aquatic organisms were mainly for fish, and these models simulated the toxicokinetics of neutral chemicals and metals (Péry et al., 2014; Stadnicka et al., 2012; Wang et al., 2016, 2020b; Wang & Wang, 2020; Zhang et al., 2021a).

The MCTK models consist of a set of ordinary differential equations, which describe the concentration change rates of chemicals in fish tissues/organs (i.e., compartments). If the accumulation rate in compartment i is assumed to be controlled by blood flow rate, the following equation is applied (Péry et al., 2014):

$$V_i \times \frac{dC_i}{dt} = Q_i \times \left(C_b - \frac{C_i}{P_{ib}}\right) \quad (8)$$

where V_i (L), C_i (μg/L), Q_i (L/min), and C_b (μg/L) represent the volume of compartment i, the concentration of the chemical in compartment i, the blood flux into compartment i, and the

concentration of the chemical in the blood, respectively. P_{ib} represents the partition coefficient between the compartment i and the blood, calculated as $P_{ib} = C_i/C_b$ in equilibrium.

For compartments such as liver, metabolism or enzyme-catalyzed reaction kinetics should be considered. The Michaelis-Menten equations can be applied to describe a metabolism process:

$$V_i \times \frac{dC_i}{dt} = \frac{V_{max} \times C_i}{K_m \times P_{ib} + C_i} \tag{9}$$

where V_{max} (μg/min) and K_m (μg/L) represent the maximum enzymatic reaction rate, and the Michaelis constant, respectively. If the enzymatic reaction kinetics is related to first-order kinetics, the following equation should be used instead of the Michaelis-Menten equation:

$$\frac{dC_i}{dt} = \frac{k_f \times C_i}{P_{ib}} \tag{10}$$

where k_f (min^{-1}) represents the first-order metabolic rate constant. For compartment i where chemical flux is assumed to be dominated by passive diffusion (such as skin), the following equation can be used:

$$V_i \times \frac{dC_i}{dt} = K_p \times A \times \left(C_j - \frac{C_i}{P_{ij}}\right) \tag{11}$$

where the subscripts "i" and "j" stand for the receptor and the source compartment, respectively; K_p ($cm{\cdot}h^{-1}$) is the permeability coefficient; A (cm^2) is the exposure area; P_{ij} is the partition coefficient calculated as $P_{ij} = C_i/C_j$ in equilibrium.

Some MCTK models have been constructed for organic or inorganic pollutants such as benzotriazole ultraviolet stabilizers, PAHs, PPCPs, mercury, copper, and zinc in aquatic organisms (Tan et al., 2018; Wang et al., 2020a; Wang & Wang, 2020; Zhang et al., 2019b, 2021b). Nevertheless, to date, only two studies have been published concerning MCTK models on antibiotics in aquatic organisms. A PBTK model coupled with Monte Carlo simulation has been successfully employed to predict the withdrawal period (defined as the post-dosing time when the chemical residue is at or below 0.1 ppm with 95% certainty for the 99th percentile population) of oxytetracycline in cultured chinook salmon (*Oncorhynchus tshawytscha*) (Law, 1998).

Zhu et al. (2020) developed an MCTK model on antibiotics in sea cucumber (*A. japonicus*) based on the principles of passive diffusion. This model can successfully predict the time-course concentrations of the antibiotics in different compartments (body wall, digestive tract, respiratory trees, and mouth) of the sea cucumbers. The model was able to predict 88% of the model predictions with a deviation of less than 5-fold from the measured concentrations.

Overall, more studies are needed to develop MCTK or PBTK models on antibiotics in aquatic organisms. Further models should be constructed for different classes, such as Lamellibranchia, Cephalopoda, Gastropoda, and Crustacea. In addition, there is a big data gap in physiological parameters (V_i, Q_i, and body weight), tissue-blood (or celomic fluid) partition coefficients (P_{ib} or P_{ij}), and biochemical parameters (V_{max} and K_m) for antibiotics in aquatic organisms. Therefore, experimental measurement or prediction models on the parameters in MCTK models are urgently required.

5. Summary

In general, observations on the bioaccumulation metrics, including BCF, BMF, TMF, BAF, and BSAF, were reported for around 30 antibiotics, revealing a clear data gap considering that *de facto* more than 250 antibiotics are commonly used. Experimental determination of the bioaccumulation metrics of all the antibiotics shall not be an easy task, and *in silico* methods such as quantitative structure-activity relationship (QSAR) model may serve as alternative methods. Despite the

fact that some QSAR models have been developed for predicting the bioaccumulation metrics of organic chemicals (Bekele et al., 2018; Bertato et al., 2022; Gissi et al., 2013), the applicability domains of these models may barely cover antibiotics. Therefore, it is necessary to extend the applicability domains of the QSAR models on bioaccumulation metrics by including antibiotics to train the models.

Enrofloxacin, sulfamethiazole, doxycycline, sulfadimidine, clarithromycin, azithromycin, and chloramphenicol can be classified as bioaccumulative or very bioaccumulative chemicals based on their logBAF values reported in multiple independent studies. Notably, more studies are needed to assess the biomagnification of antibiotics in food webs. The bioavailability and bioaccumulation of sediment-associated antibiotics in aquatic organisms should be given more attention, because sediment may act as a sink of antibiotics. Furthermore, more investigations are required to clarify the bioaccumulation of antibiotics in exposure scenarios approaching field conditions such as microcosms, rather than ideal laboratorial waterborne exposure conditions.

The controlling factors on the bioaccumulation of antibiotics in aquatic organisms were comprehensively discussed in the review. However, some underlying mechanisms for controlling the bioaccumulation remain to be revealed. For instance, the mechanisms on the interactions between specific proteins and antibiotics, and the effects of the interactions on the bioaccumulation of the antibiotics remain elusive. It still needs clarification whether gut microbiota or the hosts themselves are responsible for the biotransformation of antibiotics.

The MCTK models on the bioaccumulation of antibiotics have been developed for *O. tshawytscha* and *A. japonicus*. However, more MCTK models are needed for other species considering pertinent anatomy, and parameters regarding the models such as the tissue/blood distribution coefficients and metabolic rates of antibiotics are also demanded.

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