A review on the ecotoxicological effect of sulphonamides on aquatic organisms

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ABSTRACT

Antibiotics are extensively used to treat human and animal diseases and are especially used in animal production to promote the growth performance of livestock and aquatic animals. Sulphonamides, as important drugs for aquatic animals, are often used in aquaculture to prevent and treat diseases. However, various antibiotics found in the aquatic environment exhibit varying degrees of toxicity to aquatic organisms. Antibiotics in wastewater produced in industrial and agricultural processes are not thoroughly removed by sewage treatment and are released into water, which results in varying degrees of pollution of the surrounding water environment, forcing people to pay attention towards the ecosystem. Several studies have investigated the impact of antibiotics on aquatic organisms in water environment; however, only a few studies have investigated the underlying mechanism. Antibiotics persisting in an aquatic environment for a long time can cause genotoxicity and histopathological changes in various aquatic organisms. Therefore, this paper reviews the sources of antibiotics in aquatic environment, the pollution status of sulphonamides in aquatic environment at home and abroad, and focuses on the research status of ecotoxicological effects of sulphonamides on aquatic organisms. Because there are not only antibiotic pollution, but also many other pollutants, such as heavy metals, micro plastics and other chemicals, it will be a challenge to determine the combined effects of antibiotics or other pollutants on aquatic organisms in future environmental toxicity studies.

1. Introduction

Antibiotics exhibit various biological activities such as inhibition of protein and nucleic acid synthesis [19] and DNA replication and cell division [58], therefore, antibiotics are extensively applied to animal husbandry and aquaculture to prevent and treat bacterial diseases and promote animal growth. However, the residual antibiotics in industrial and agricultural wastewater are not completely eliminated post-treatment at sewage treatment plants, therefore, antibiotic residues often persist in the water environment [50,52]. The discharge of antibiotics into the water environment through different channels carries the risk of development of drug-resistant bacteria and drug-resistant gene transmission [2]. Even at a very low antibiotic concentration (from a nanogram to a microgram per litre), antibiotic-resistant bacterial strains can emerge, which can threaten human health and the environmental ecosystem [26].

The problem of persistence of antibiotic residues in water environment is a hotspot of ecological environment research. Presently, antibiotics, mainly sulphonamides and quinolines [40], can be detected in underground water, surface water, sewage treatment plants, drinking water, and many other water environments. The high detection rate of sulphonamides (SAs) in water environment is because of its wide use and strong hydrophilicity, which means that sulphonamides can easily enter any water environment through drainage and rainwater [10]. The residual sulphonamides in water environment accumulate through biodegradation and nonbiodegradation, and they promote the evolution of drug-resistant strains and affect the growth of animals and plants. Therefore, antibiotics that persist in the water environment inevitably pose a potential risk to ecosystems and humans through the food chain [61]. The effects of residual antibiotics in the aquatic environment on aquatic organisms have reported in many studies; however, limited reports are available on the toxicity mechanism of residual antibiotics in aquatic organisms. Residual antibiotics persisting in an aquatic environment for a long time can cause genotoxicity and negative

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histopathological changes in aquatic organisms. Therefore, this review attempted to summarise the harmful effects of commonly used sulphonamides persisting in the aquatic environment on aquatic organisms.

2. Physicochemical properties and types of sulfa antibiotics

Sulphonamides (SAs) are the derivatives of ammonia benzene sulfonic group, and their molecular structures are composed of a benzene ring, para- amino group, and sulfonphthalalimide group (Fig. 1). SAs have different properties and functions due to their different -R groups, and their polarity will change under different pH [43]. Except for sulfaguanidine (SGM) and sulfasalazine (SSZ), small-molecule SAs are water-soluble and have low Henry constant, which can be slightly adsorbed by soil, so they are easy to diffuse in the environment, but their properties will limit their accumulation in specific biological sites [13]. Sulphonamide antibiotics mainly include sulfaguanidine (SGD), sulfapyridine (SPY), sulfadiazine (SDZ), sulfamethoxazole (SMX), sulfathiazole (STZ), sulfamerazine (SMR), sulfisoxazole (SIZ), sulfamethazine (SMT), sulfamethazine (SMZ), sulfamethoxypyridazine (SMP), sulfachloropyridazine (SCP), and sulfadimethoxine (SDM), which were most commonly used in veterinary medicine.

3. Sources of antibiotics in aquatic environments

The discharge of livestock and aquaculture wastewater is one of several main anthropogenic factors resulting in antibiotic pollution in water environment [65], such that the detected concentration of sulfamethoxazole (SMX) was as high as 54.83 μg/L [54]. Fig. 2 shows the sources of sulpha antibiotics in the water environment. Danner et al. [15] summarised different types of antibiotics persisting as residues in surface water or freshwater globally, such as quinolones, sulphonamides, tetracyclines, macrolides, penicillins, cephalosporins, and nitroimidazoles. Among these antibiotics, quinolones, sulphonamides, tetracyclines, and macrolides are most commonly present in the water environment. The aquatic toxicity of these drugs has been extensively studied. A study reported that the main sources of doxycycline, tetracycline, oxytetracycline, and sulfamethoxazole are aquaculture and humans, whereas the main source of sulfadiazine and sulfaphthylipyrimidine is animal husbandry (Li et al., 2016a).

Hospitals discharge a large amount of antibiotics into the aquatic environment and thus are the main source of antibiotics. To test the elimination efficiency of antibiotics, researchers collected samples from the wastewater at a treatment plant (Loganathan et al., 2009). Afsa et al. [1] reported that antibiotics, mainly derived from nearby hospitals and sewage treatment plants, detected off Mahadia (Tunisia) in coastal seawater. The detection frequency of three SAs (SDZ, SMX and SMT) in the Mediterranean Sea is as high as 100% [1]. The release of antibiotics from animal husbandry into the aquatic environment is also a matter of concern. The use of antibiotics is not limited to humans and animal husbandry; they are widely used in aquaculture and orchards. Aquaculture is a key industry to meet human demand for aquatic products. Therefore, the use of antibiotics in aquaculture is increasing (Liu et al., 2017c; Miranda et al., 2018). Simultaneously, high-resolution mass spectrometry screening method has been extensively applied to monitor the residual antibiotics in aquatic products (Turnipseed et al., 2019).

Considering these problems, several analytical techniques have been developed to accurately measure the antibiotic removal efficiency in wastewater treatment plants. However, according to the 2017 United Nations World Water Development Report, wastewater treatment rates vary from country to country. In low-income countries, untreated wastewater accounts for more than 90%, which seriously threatens the human ecosystem. Sato et al. [47] reported that in 2013, only 62 countries and 103 countries in the world reported wastewater reuse. The removal efficiency of antibiotics can be greatly improved by using treatment technologies such as chlorination, ultraviolet and fungal treatment [50]. Many studies have shown that in many cases, the residual concentration of antibiotics detected in the aquatic environment generally does not exceed 1 mg/L. Studies of antibiotic toxicity in fish have revealed the biological activity of exposure to conditions similar to environmental exposure. However, in order to determine the concentration leading to biological toxicity, or to study the mechanism of action of specific antibiotics in fish, the effect should also be determined at a concentration higher than the environment related concentration. In addition, fish were exposed to antibiotics under different conditions according to the purpose of determining the acute or chronic effects. Before analyzing the toxic mechanism of contaminated antibiotics on fish, the antibiotics that fish may be exposed to or may accumulate in fish tissues should be studied.

4. Pollution status of sulpha antibiotics in water environment

After digestion by humans and animals, approximately 30–90% of sulphonamides enter the environment in the form of matrix or metabolites [44,56]. Sulphonamide metabolites will not lose biological activity in water environment, and can further form other compounds under specific conditions [42]. According to estimates, more than 20,000 tons of sulphonamide antibiotics (excluding herbicides) with anti-bacterial properties enter the biosphere every year [44]. Sulphonamides can enter water environment through many routes. Several national and international studies have reported the presence of sulphonamide residues in various water environments (including surface water, groundwater, drinking water, and seawater). Table 1 lists the residual mass concentration of sulphonamides in the water environment reported in literature.

4.1. Pollution status of sulpha antibiotics in domestic water environment

China is one of the leaders in the production and use of antibiotics. A large amount of wastewater containing sulphonamides is produced in the livestock and poultry breeding, aquaculture, and medical system, resulting in the discharge of sulphonamides in water environment. Ying [68] detected a high content of sulpha antibiotics in Dishui lake water samples, which accounted for more than 90% of the total detected antibiotics. Ou et al. [41] detected sulphamethazine in multiple samples, with an average concentration of 78.3 ng/L, which was the highest among those of nine sulpha antibiotics detected. Luo et al. [37] studied the source and migration of 12 antibiotics (including tetracyclines, sulphonamides, quinolones, and macrolides) in the 72 km reach of Haihe River, China. Among these antibiotics, sulphonamides had the highest concentration (24–385 ng/L) and frequency (76–100%). Overall, the concentrations of SAs in surface water tended to be higher. For example, enormously high concentrations of SMX could be observed in the Hai River system, China (up to 4.87 μg/L) [11]. In addition, a higher level of SDZ was detected in the Chaobai River at 1.181 μg/L, and SMZ was detected in Erlong Lake of China at 2.231 μg/L [33,53]. Although the types of veterinary antibiotics in animal wastewater and residual level of surface water around the farm are related to animal species and have spatial differences, sulpha antibiotics account for a large proportion. Various sulphonamides are present in the environment, which can potentially harm human health and ecosystem balance. Therefore, an in-depth study on the ecotoxicological effects of sulphonamides is necessary.
4.2. Pollution status of sulpha antibiotics in water environment globally

Because of the extensive use of sulphonamides, water environment is polluted globally in varying degrees by sulphonamides. From 1999–2000, the United States Geological Survey investigated 139 rivers in 30 states and detected 21 antibiotics. Other countries have similar reports on high levels of SAs in surface water, such as in India (up to 4.66 µg/L) [22], Korea [28], Kenya [27], and Vietnam [55]. As for surface water, SMX was found in high levels of 2.42 µg/L and 3.066 µg/L in the Joao Mendes River, Brazil, and Charmoise River, France, respectively [17,45]. The highest concentration of SMX (142.6 µg/L) was detected in Machakos, Kenya [27]. The concentration of SMZ was higher (21.3 µg/L) in the streams near concentrated animal feedlots, as evinced by data from Korea [28]. Sulpha antibiotics have also been detected in groundwater samples. For example, the highest concentration of selected antibiotics was 1.285 µg/L for SMX in Yaoundé, Cameroon [9]. Moreover, sulphamethoxazole, which poses an uncertain threat to human health, was detected in drinking water samples in the United States [7]. Shimizu et al. [48] detected seven sulphonamides in 150 livestock and aquaculture wastewater and river samples from five tropical Asian countries (namely Vietnam, Philippines, Indonesia, Malaysia, and India); the results showed that the concentration of target antibiotics in wastewater was at sub- to low- ppb levels, and the antibiotics, sulphamethoxazole, lincomycin, and sulphathiazole, were present in the highest concentration. The average content of sulphonamides in sewage waters was 1720 ng/L in Vietnam (Hanoi, Ho Chi Minh, Can Tho: n = 15), 802 ng/L in Philippines (Manila: n = 4), 538 ng/L in India (Kolkata: n = 4), 282 ng/L in Indonesia (Jakarta; n = 10), and 76 ng/L in Malaysia (Kuala Lumpur: n = 6). These concentrations were higher than those in the corresponding waters of Japan, China, Europe, the United States, and Canada.

5. Research status of the ecotoxicological effect of sulphonamides on aquatic organisms

5.1. Research status of the ecotoxicological effect of sulpha antibiotics on microorganisms in water environment

With the accumulation of sulpha antibiotics in the environment, their ecological impact is becoming increasingly obvious. As a competitive inhibitor of dihydrofolate synthase that catalyses the conversion of para aminobenzoic acid to dihydrofolic acid (a precursor of folate synthesis), sulphonamides can inhibit the synthesis of nucleic acids and alter the permeability of bacterial cell wall to glutamate, an essential component in folate synthesis [57], further inhibiting protein synthesis. Some researchers have investigated the impact of extensive use of sulphonamides on the bacterial community in the aquaculture environment by analysing the water samples and sediments of four fish ponds in Guangdong. A study showed that Acinetobacter exhibits the highest abundance (35%) among the sulphonamide-resistant strains [62]. Similar results were reported in sediment samples from the rivers affected by sewage treatment plants in India and Spain [32,39]. Some resistant pathogens have also emerged, which may pose a health threat to fishermen and aquatic product processing workers. All sulpha antibiotics in marine water do not exhibit strong acute toxicity to marine bacteria because of their low concentrations. However, because these compounds can interfere with biological metabolic pathways, their potential harm should not be underestimated. Kim et al. [30] calculated the concentration of antibiotics for 50% of the maximal effect on marine bacteria through a 15-min luminescence inhibition experiment by using the following antibiotics: sulphamethoxazole (78.1 mg/L); sulphachloropyridazine (26.4 mg/L); sulphathiazole (1000 mg/L); sulphamethazine (344.7 mg/L); and sulphamethazine (500 mg/L).
Table 1
Concentrations of sulphonamides in the water environment.

| Sources                  | Research area | Composition and mass concentration | Literature source |
|-------------------------|---------------|-------------------------------------|-------------------|
| Drinking water          | China         | 14.50 ng/L SMZ, 3.49 μg/L SCP, 20.82 ng/L SDZ | [14]              |
| Groundwater             | America       | 0.0099-1.1100 μg/L SMX                | [4]               |
|                        | Barcelona     | ND – 208 ng/L SDZ                     | [36]              |
|                        | Spain         | ND – 29.2 ng/L SMZ, ND – 65 ng/L SMX | [36]              |
|                        | Cameroon      | 1.285 μg/L for SMX                    | [9]               |
|                        | China         | 25.29 ng/L/SMZ                        | [70]              |
|                        | America       | 0.015-18.000 μg/L SMX                 | [4]               |
| Urban area of China     | Beijing       | 1.82 ng/L/SMX                         | [38]              |
|                        |                |                                    |                   |
| Surface water           | China         | 4.87 μg/L SMX                         | [11]              |
|                        | India         | 4.66 μg/L SMX                         | [22]              |
|                        | Korea         | 21.3 μg/L SMZ                         | [28]              |
|                        | Brazil        | 17.4 μg/L STZ                         |                   |
|                        | Spain         | 49.9 – 149.2 ng/L SMX                 | [55]              |
|                        | China         | 1.181 μg/L/SMX                        | [33]              |
|                        | Southeast China | 2.231 μg/SMZ                        | [53]              |
|                        | China         | 1.605 ng/L/SMZ                        | [67]              |
|                        | Brazil        | 2.42 μg/L SMX                         | [17]              |
|                        | Spain         | 3.7-227.0 ng/L SDP                    | [29]              |
|                        | Spain         | 160-260 ng/L/SMZ                      | [25]              |
|                        | South Korea   | 1.5-3.1 μg/SMX                        |                   |
|                        | Croatia       | 3.066 μg/L SMX                        | [45]              |
|                        | Spain         | 272.5-596.0 ng/L SMZ                  | [17]              |
|                        | Guangdong of China | 4.12–15.4 ng/L SDZ                  | Zheng et al., 2012 |
|                        | China         | 9.3–19.3 ng/L SMZ                     | [24]              |
|                        | Guangxi of China | 19.5–187.0 ng/L SDZ               | Zhou et al., 2012 |
|                        | China         | 9.3–19.3 ng/L SMZ                     | [22]              |
|                        | South Korea   | 10–123 ng/L STZ                       | [29]              |
|                        | China         | 14.8 μg/L SDZ                         | [16]              |
|                        | China         | 4.7 μg/L/SDZ                          | [12]              |
| Lake water              | Beibu gulf of China | 1.81–15.90 ng/L SMX                 | [69]              |
|                        | China         | 0.34–6.57 ng/L SMZ                    |                   |
|                        | River water   | 11.9 ng/L/SMR, 19.5 ng/L/SMX          | [21]              |
|                        | Pearl River   | 11.9 ng/L/SMR, 19.5 ng/L/SMX          | [21]              |
|                        | Estuary       | 3.1 μg/L/SMX                          | [16]              |
|                        | Main river of Hongkong | 3.2 μg/L/SPY                     |                   |
|                        | Beijing-Tianjin region of | 8.8 ng/L/SMZ, 11.6 ng/L/SMX          |                   |
|                        | China         |                                   |                   |

Note: 1) ND means not detected.

5.2. Research status of the ecotoxicological effect of sulpha antibiotics on algae and aquatic plants

Algae and cyanobacteria, as primary producers, play an important role as the base of the food chain in aquatic ecosystems [66]. Among all aquatic organisms, algae are more susceptible than fish and crustaceans to the selected antibiotics, including SMX [31]. Because the algae form the basis of aquatic food chain, the reduction in the algal population will directly affect the balance of the whole aquatic ecosystem [46]. Studies have shown that nearly all sulphonamides can have toxic effects on algae, and their EC50 value ranges from 1.54 to 32.25 μg/L (6.1–113.55 mmol/L). The three most toxic drugs to green algae are sulphamethoxazole (EC50 = 6.2 μmol/L), sulphadiazine (EC50 = 4.9 μmol/L), and sulphamethoxypyridazine (EC50 = 13.64 μmol/L). Differences in the toxicity level of sulphonamides may be related to their molecular structure; the higher: the number of CH₃ groups in the side R group, the lower is the toxicity.

The toxicity mechanism of sulpha antibiotics in plants is similar to that of bacterial activity inhibition, which affects plant growth by inhibiting the activity of dihydrofolate synthase. A few studies have reported the toxicity of sulpha antibiotics in aquatic plants. Additionally, studies have shown that sulphamethoxazole has the strongest toxic effect on duckweed (EC50 = 0.081 μg/L, followed by sulphamethazine (EC50 = 0.248 mg/L), sulphasartazine (EC50 = 1.277 mg/L), and sulphathiazole (EC50 = 3.552 mg/L) [8].

5.3. Research status of the ecotoxicological effect of sulphonamides on aquatic animals

Sulpha antibiotics can induce toxicity in aquatic animals. Fishes produce some electrophilic intermediates in the metabolic process of antibiotics, which may induce changes in the antioxidant enzyme activity in organisms, leading to oxidative stress [59]. Most of the existing studies have used lower aquatic organisms as the research object, and the number of available studies is extremely low. Some researchers have used isolated acetylcholinesterase and glutathione reductase to verify the toxic effect of sulphonamides on the activities of key enzymes present in the antioxidant system of fish. Although no obvious activity inhibition due to sulphonamides has been observed, the possibility of their influence on the whole redox state of cells cannot be ruled out [3]. When fishes are cultured in a laboratory with sulphonamides at a concentration much higher than that in the environment, obvious teratogenic and lethal effects could be found [35]. For example, researchers in our research team exposed zebrafish to different concentrations (3, 6, 12, 24 mg/L) of SMX and SD. The results showed that low concentration (3 mg/L) of SMX inhibited the growth of zebrafish, while high concentration (24 mg/L) of SD inhibited the growth of zebrafish (unpublished). Our results show that there are significant differences in the negative effects of different kinds of sulfa antibiotics on aquatic animals.

Sulpha antibiotics exert a cumulative effect on fishes. For example, Xu et al. [63] studied the enrichment of sulphamethazine and sulphamethoxazole in zebrafish and found that the maximum bioconcentration factor (BCF) value of fishes for sulphamethazine and sulphamethoxazole was 1.11 and 1.15, respectively. The BCF value represents the ratio of drug content in fishes (mg/kg) to the drug content in water (mg/L), which reflects the enrichment degree of drugs in fishes. Some researchers have found the residues of sulpha antibiotics in cultured fish samples in China [51]. Although the residue level in seawater fish is lower than that in freshwater fish [23], sulphonamides have been detected in marine fish. For example, they have been detected in wild fish samples in Mediterranean coastal waters and seafood samples [60] in South Korea. Sulphonamides can easily accumulate in other organisms, in addition to fishes. Hiba et al. [24] analysed 304 meat samples and found residues of sulphonamides in 46 samples; the mass concentration detected in chicken and beef samples was 151.4 mg/kg, respectively, which seriously exceeds the concentration limit specified in Europe.

Sulphamethoxazole is one of the antibiotics with the lowest removal efficiency in wastewater treatment plants [50]. Sulphamethazine (0.2–2000 μg/L) can cause physiological changes in the whole life cycle of organisms, in which the embryonic stage is more sensitive than for adults [64]. Zebrafish were exposed to the lowest treatment concentration of sulphamethazine (0.2 μg/L), the results showed that the contents of SOD and MDA in zebrafish embryos increased, indicating that sulphamethazine caused redox imbalance in fish [64]. The results of our
enzyme activity. Exposure of zebrafish to sulfamethoxazole at a concentration of 260 ng/L increased the mortality of zebrafish and increased intestinal inflammatory cytokines such as TNF-α And IL-1 gene expression, and reduced the number of intestinal goblet cells [71]. However, our results showed that exposure of zebrafish to low concentrations (3 mg/L) SMX did not affect IFN, IL-6 and TNF-α mRNA expression, while exposure of zebrafish to 6–9 mg/L SMX decreased the expression of the above genes in liver. (unpublished). Under standard culture conditions, tilapia were exposed to sulfamethoxazole at a concentration of 260 ng/L, the results showed that exposure to sulfamethoxazole changed nutritional metabolism and inhibited the innate immune system [34]. In addition, sulfamethoxazole increased the transcription of SOD in the intestine and liver of tilapia, and increased cytokines such as IL-1β and TNF-α mRNA expression [34]. These results suggest that sulfamethoxazole may cause genotoxicity to fish tissues. Thus, some sulfon antibiotics will cause physiological and genetic changes of fish even at low concentration, and even if they will not affect the survival of fish. Therefore, long-term exposure of fish to sulfon antibiotics should be avoided; further research is needed to understand the clear provisions for the use of sulphonamides near the aquatic environment.

6. Conclusion

Sulpham antibiotics are widely used globally as veterinary drugs and feed additives, as well as for the treatment of human diseases. Although the half-life of sulpham antibiotics is short, it causes a ‘false persistence’ phenomenon owing to their frequent use and continuous entry into the environment. Sulpham antibiotics entering the natural environment are adsorbed and degraded; however, the drugs that do not undergo decomposition pollute the natural environment and pose a threat to the ecological environment and human health. Sulphonamides remaining in water and sediments directly or indirectly exert ecotoxicological effects on microorganisms, algae, plants, and fishes in water. Although the low concentration of sulpham antibiotics in the environment does not cause obvious acute toxicity to aquatic animals and plants, their cumulative effect poses a potential threat to human health. To reduce the environmental harm of sulphonamides, countries throughout the world should focus on managing the sulphonamide pollution and reducing sulphonamide discharge from the source. This review covers a comprehensive knowledge of the toxicity of antibiotics that can be exposed to aquatic microorganisms. Among many aquatic organisms, it is well known that fish are not as sensitive as aquatic microorganisms. However, recent studies have shown that antibiotics may affect fish health even at acute or chronic environmental exposure levels. Therefore, this review suggests that fish raised in water that may contain some antibiotics should be eaten carefully. In addition, there are not only antibiotic pollution, but also many other pollutants, such as heavy metals, micro plastics and other chemicals in the water environment. Therefore, in the future environmental toxicity research, we should pay attention to the comprehensive impact of antibiotics and other pollutants on aquatic organisms.

CRediT authorship contribution statement

Jie Zhou: Conceptualization, Investigation, Writing – original draft. Writing – review & editing. Xiao Yun: Conceptualization, Writing – original draft, Writing – review & editing. Jiting Wang: Conceptualization, Methodology, Writing – review & editing. Project administration, Supervision. Qi Li: Resources, Writing – review & editing. Yanli Wang: Resources, Writing – review & editing. Declaration of Competing Interest

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

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References

[1] S. Afsa, K. Hamden, P.A.L. Martin, H.B. Mansour, Occurrence of 40 pharmaceutically active compounds in hospital and urban wastewater and their contribution to Multimedia coastal seawater contamination, Environ. Sci. Pollut. Res. 27 (2) (2020) 1941–1955.
[2] M. Akiba, T. Sekizuka, A. Yamashita, M. Kuroda, Y. Fujii, M. Murata, K. Lee, D. I. Joshua, K. Balakrishna, I. Bairy, K. Subramanian, P. Krishnan, N. Munuswamy, R. K. Sinha, T. Iwata, M. Kumamoto, K.S. Garge, Distribution and relationships of antimicrobial resistance determinants among extended-spectrum-cephalosporin-resistant or carbapenem-resistant Escherichia coli isolates from rivers and sewage treatment plants in India, Antimicrob. Agents Chemother. 60 (2016) 2972–2980, https://doi.org/10.1128/AAC.01950-15.
[3] B.B. Anna, S. Stolte, J. Aming, U. Uebers, A. Boschen, P. Stepnowski, M. Matzke, Ecotoxicity evaluation of selected sulphonamides, Chemosphere 85 (2011) 928–933, https://doi.org/10.1016/j.chemosphere.2011.06.058.
[4] W. Baran, E. Adamek, Z. Ziemianska, A. Sobczak, Effects of the presence of sulphonamides in the environment and their influence on human health, J. Hazard. Mater. 196 (2011) 1–5, https://doi.org/10.1016/j.jhazmat.2011.08.082.
[5] A. Bezerra, S. Simatovic, I. Konje-Vukovic, I. Senta, M. Ahel, S. Babic, T. Saric, J. J. Gonzalez Plaza, M. Milatovic, N. Udovic-Kolic, Negative environmental impacts of antibiotic-contaminated e-waste from pharmaceutical industries, Wat. Res. 126 (2017) 79–87.
[6] M.J. Benotti, R.A. Trenholm, B.J. Vanderford, J.C. Holaday, S.A. Snyder, Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water, Environ. Sci. Technol. 43 (3) (2009) 579–603, https://doi.org/10.1021/es9014479.
[7] R.A. Brain, A.J. Ramirez, B.A. Fulton, C.K. Chamblish, B.W. Brooks, Herbicidal effects of sulfamethoxazole in Lemna gibba: using p-aminobenzoic acid as a biomarker of effect, Environ. Sci. Technol. 42 (23) (2008) 8965–8970, https://doi.org/10.1021/es801611a.
[8] P. Branca, N.A. Castro, H. Fenet, E. Gomez, F. Courant, D. Sebag, J. Grondon, C. Jourdan, B.N. Ngatcha, I. Kengne, E. Cadot, C. Gonzalez, Anthropic impacts on sub-Saharan urban water resources through their pharmaceutical contamination (Yaoundé, center region, Cameroon), Sci. Total Environ. 660 (2019) 868–898, https://doi.org/10.1016/j.scitotenv.2018.11.078.
[9] W.W. Buchberger, Novel analytical procedures for screening of drug residues in water, waste water, sediment and sludge, Anal. Chem. Acta 593 (2007) 129–139, https://doi.org/10.1016/j.aca.2007.05.006.
[10] H. Chen, L. Jing, Y. Teng, J. Wang, Characterization of antibiotics in a large-scale river system of China: occurrence pattern, spatiotemporal distribution and environmental risks, Sci. Total Environ. 618 (2018) 409–418.
[11] J. Cheng, L. Jiang, T. Sun, Z. Du, L. Lee, Q. Zhao, Occurence, seasonal variation and risk assessment of antibiotics in the surface water of North China, Arch. Environ. Contam. Toxicol. 77 (2019) 88–97, https://doi.org/10.1007/s00244-019-00410-x.
[12] M. Conde-Cid, G. Ferreira-Coelho, A. Fernandez-Calvino, M.J. Nunez-Delgado, M. Fernandez-Sanjurjo, E. Arias-Estevé, E. Alvarez-Rodriguez, Single and simultaneous adsorption of three sulphonamides in agricultural soils: effects of pH and organic matter content, Sci. Total Environ. (2020), 140872.
[13] C. Cui, Q. Han, L. Jiang, L. Ma, L. Jin, D. Zhang, K. Lin, T. Zhang, Occurrence, distribution, and seasonal variation of antibiotics in an artificial water source reservoir in the Yangtze River delta, East China, Environ. Sci. Pollut. Res. 25 (2018) 19393–19402.
[14] M.C. Dannier, A. Robertson, V. Behrends, J. Reiss, Antibiotic pollution in surface fresh waters: occurrence and effects, Sci. Total Environ. 664 (2019) 793–804, https://doi.org/10.1016/j.scitotenv.2018.10.040.
[15] D. Deng, N. Li, H. Zheng, H. Lin, Occurrence and risk assessment of antibiotics in river water in Hong Kong, Ecotoxicol. Environ. Safety 125 (2016) 121–127.
[16] Q.T. Dinh, E. Moreau-Guignon, P. Labadie, F. Alliot, M.J. Teil, M. Blanchard, M. Chevreuil, Occurrence of antibiotics in rural catchments, Chemosphere 168 (2017) 483–490.
[17] O. Fahimi, Z. Zhang, R.M. Ranade, J.R. Gillespie, S.A. Creason, W. Huang, S. Shihata, X. Barros-Alvarez, C. Verlinde, W.G.J. Hol, E. Fan, F.S. Buckner, Development of methionyl-tRNA synthetase inhibitors as antibiotics for gram-
[65] L. Yang, Y. Zhou, B. Shi, J. Meng, B. He, H. Yang, S.J. Yoon, T. Kim, B. Kwon, J. S. Khim, T. Wang, Anthropogenic impacts on the contamination of pharmaceuticals and personal care products (PPCPs) in the coastal environments of the yellow and bohai seas, Environ. Int. 135 (2020), 105306.

[66] W.W. Yang, Z.P. Tang, F.Q. Zhou, W.H. Zhang, L.R. Song, Toxicity studies of tetracycline on Microcystis aeruginosa and Selenastrum capricornutum, Environ. Toxicol. Pharmacol. 35 (2013) 320–324.

[67] C. Ye, J. Shi, X. Zhang, L. Qin, Z. Jiang, J. Wang, Y. Li, B. Liu, Occurrence and bioaccumulation of sulfonamide antibiotics in different fish species from Hangbu-Fengle River, Southeast China, Environ. Sci. Pollut. Res. 28 (2021) 44111–44123.

[68] Ying, Y.H. Investigation of water quality and contamination characteristics of sulfonamides tetracyclines antibiotics in the surface sediments of Dishui Lake and its flowing rivers[D]. Shanghai, Shanghai Ocean University, 2016.

[69] Q. Zhang, R. Zhang, Y. Wang, X. Pan, J. Tang, G. Zhang, Occurrence and distribution of antibiotics in the Beibu Gulf. China: impacts of river discharge and aquaculture activities, Mar. Environ. Res. 78 (2012) 26–33, https://doi.org/10.1016/j.marenvres.2012.03.007.

[70] A.X. Zhou, X.S. Su, S. Gao, Y.L. Zhang, X.Y. Lin, Y.Y. Zhang, Y.L. An, Determination of four sulfa antibiotics in groundwater, soil and excreta samples using high performance liquid chromatography, Chin. J. Anal. Chem 42 (3) (2014) 397–402, https://doi.org/10.3724/SP.J.1096.2014.30676.

[71] L.J. Zhou, Q.L. Wu, B.B. Zhang, Y.G. Zhao, B.Y. Zhao, Occurrence, spatiotemporal distribution, mass balance and ecological risks of antibiotics in subtropical shallow Lake Taihu, China, Environ. Sci. Process Impacts 18 (2016) 500–513, https://doi.org/10.1039/c6em00062b.