Physical, chemical, and biological impact (hazard) of hospital wastewater on environment: presence of pharmaceuticals, pathogens, and antibiotic-resistance genes

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3.1 Introduction

The hospital wastewater (HWW) is the effluents which are generated from all the hospital activities, such as surgery, emergency and first aids, laboratories, diagnosis, and radiology [1]. HWW is produced in a wide range. The quantity and characteristics of the HWW are varied mainly according to the size (big: >500 beds; middle: 100−499 beds; small: <100 beds) and the type (general or special) of the hospital [2]. It was reported that the generation rate of HWW was around 400−1000 L per bed per day worldwide [3−5].

HWW may contain various hazardous materials which can be classified into physical remaining, chemical substances, and biological risks [1,6]. The majority of physical hazards presenting in HWW are the radioactive substances which are utilized in nuclear medicine therapies and diagnostics. The common isotope utilized is the ^{131}I (iodine-131) radio isotope compared to other radionuclides (phosphorus-32, strontium-89, yttrium-90, etc.). The concentration of ^{131}I in the HWW is in the range of 15.0−61.8 Bq/L [7]. It normally poses a much higher physical risk.

The main chemical substances in HWWs are the pharmaceuticals, which are partially metabolized and excreted in the urine [2]. These pharmaceuticals can be antibiotics,

analgesics and antiinflammatories, psychiatric drugs, b-blockers, anesthetics, disinfectants, chemicals from laboratory activities, and developer and fixer solutions from photographic film processing and X-ray contrast media [8]. The hazard chemicals are commonly flushed into the sewer and transported to the wastewater treatment plants (WWTPs) without any pretreatment [9,10].

In general, the biological risk of HWWs is a large variety of pathogen microorganisms (bacteria, protozoa, helminths, and viruses), which are principally from the feces of infected humans. Like partially metabolized pharmaceuticals, the pathogens are also flushed into the sewerage pipeline without pretreatment [11].

Generally, the HWW is required to be treated in situ to reduce the discharge of pharmaceuticals, pathogens, and antibiotic resistance genes (ARGs). However, there are still some places cotreating the HWW along with municipal wastewater. In fact, municipal WWTPs are designed to remove the general contaminants including fats, oils, organic matters, nitrogen, and phosphorus from human wastes [12]. Therefore the traditional wastewater treatment processes are not suitable for the removal of pharmaceuticals, pathogens, and ARGs. It reveals that these substances would discharge to the environment along with wastewater treatment effluent when HWW was treated with municipal wastewater treatment processes. HWW containing all kinds of hazard materials is often transported to the traditional urban WWTPs. Unfortunately, HWW may not be properly treated in the WWTP [13]. It is found that substances, such as antitumor agents, antibiotics, and organ halogen compounds, are barely degraded by the WWTPs and left in the effluents [3]. Nowadays, pharmaceuticals can be detected in surface waters, ground waters, and drinking water due to their inefficient removal in WWTP [14,15]. Pharmaceuticals, which are often water soluble, are generally biologically active compounds and not easily biodegraded [16].

Even though most pharmaceuticals are in low concentrations in the ecosystems and might not induce any harmful impact as single compounds [17], pharmaceuticals may be mixed and interacted in the ecosystem [18]. The mixtures of pharmaceuticals have higher toxicity and more serious environmental impact than they are recognized as single compounds [19]. A good understanding of the pharmaceuticals' impact on the environment and ecosystems is necessary.

In this chapter, the following contents were presented, including the characterization of HWW; the development of ARG; the transportation of pharmaceuticals, pathogens, and ARGs in the environment; and the impact of pharmaceuticals, pathogens, and ARG on human health and environment.

3.2 Pharmaceuticals and pathogens in hospital wastewater

The composition of HWW is very complex. It mainly contains pharmaceuticals and pathogens. Pharmaceuticals are widely prescribed and consumed in the world. It has been reported that the prescription on pharmaceuticals would remain the high level or even elevated [20]. The adverse effect of pharmaceuticals in the environment has been extensively

studied [21]. Among all, the most concern one is the development of antibiotic-resistant bacteria and genes as it would lead to transfer of resistant gene to antibiotic sensitive microbial species. There is the risk of treatment failure when humans or animals are infected with the bacteria which already developed antibiotic-resistant gene. Apart from antibiotics, there are also other compounds such as radiation and X-ray compounds, which can induce reform of DNA and thus cause abnormal diseases. Pathogens are also big problems of HWW. It transforms among the environment and humans.

3.2.1 Pharmaceuticals

It is reported that the pharmaceuticals can be classified into 20 types (Table 3−1). The pharmaceuticals that can expose high threat to the environment and human health are discussed in the following.

3.2.1.1 Antibiotics

Antibiotics are produced by microorganisms (including bacteria, fungi, and actinomycetes) or organism. Antibiotics have been introduced to human since 1940s; thereafter, they became the most important drugs for treating the infectious diseases. Antibiotics derived from natural sources mainly include penicillin, cephalosporins, macrolides, fluoroquinolones, tetracyclines, chloramphenicols, aminoglycosides, carbapenems, rifamycins, glycopeptides, monobactams, polymyxins, penicillin−streptomycin combinations, β-lactams, and carbacephems. Among all the antibiotics, tetracycline, sulfamethoxazole (sulfonamide), streptomycin (aminoglycoside), azithromycin, clarithromycin (macrolide), ciprofloxacin (fluoroquinolone), and amoxicillin (β-lactam) are the most extensively utilized ones as medicine [22,23].

The antibiotic concentration of HWW varies from 20 to 5000 ng/L in summer and from 500 to 800 ng/L in winter [24,25].

Table 3–1   Classification of pharmaceutical.

No.	Pharmaceuticals	No.	Pharmaceuticals
1	Infectious diseases treatment drugs	10	Blood and hematopoietic system diseases treatment drugs
2	Cancer treatment drugs	11	Endocrine, nutritional, and metabolic diseases treatment drugs
3	Nervous system disease treatment drugs	12	Affect the immune system drugs
4	Mental and behavioral disorder treatment drug	13	Other treatment drugs for various diseases
5	Connective tissue and rheumatic diseases treatment drugs	14	Adrenocorticoids, sex hormones, gonadotropins, and contraceptives
6	Circulatory diseases treatment drugs	15	Natural medicines and their compound preparations
7	Digestive system diseases treatment drugs	16	Vaccines, biochemical drugs, and biological preparations
8	Respiratory system diseases treatment drugs	17	Other medicine, diagnosis, and medication
9	Urogenital system diseases treatment drugs		

3.2.1.2 Radiation and X-ray compounds

Radioactive materials are unstable naturally occurring or man-made elements. They include α, β, and γ radioisotopes, and are normally used in many physical examinations. Radionuclides (e.g., ^{90}Y, ^{125}I, ^{131}I, ^{89}Sr, ^{192}Ir, ^{60}Co, ^{137}Cs) are also utilized to examine and treat cancer patients by shrinking tumors and killing cancer cells [26].

Radioactive materials could cause many serious negative impacts on both proliferative and nonproliferative tissues of humans and animals. The leakage of radioactive material should be controlled. After utilization of the radionuclides, the radioactive pollutants enter to the environment along with the waste including wastewater. In fact, nowadays along with the development of nuclear medicine, the application of radionuclides in clinical diagnosis, treatment, and medical research has become much more extensive. Apart from the direct discharge to the wastewater, the radionuclides can also go to the environment from patient discharge. After they enter to the WWTP which is not capable of removing radionuclides, they reach to water source and threat on mammalian systems [27].

3.2.1.3 Nonbiodegradable and persistent compounds

Psychoactive drugs are of ubiquitous nature and persistence in the aqueous environment. Among all, carbamazepine is one of the most widely prescribed medicines to treat epilepsy, trigeminal neuralgia, and some other psychiatric diseases (e.g., bipolar affective disorders), which shows important endocrine disrupting effects. Carbamazepine is frequently detected in both WWTP effluents and river water. In fact, carbamazepine can be completely transformed during metabolism. Normally, less than 5% of a dose remains unchanged after being taken by human being. Therefore high concentrations of the metabolites of carbamazepine are detected instead of the parent compound in WWTPs influents and effluents, even reaching few micrograms per liter [28].

3.2.1.4 Hormones

Hormones are commonly found in the environment including water and soil as they are widely applied in livestock breeding, aquaculture, and clinical treatment. They have great impact on human and other organisms (such as birds, mammals, and fish). The major impact of hormones on humans includes endocrine dyscrasia, nervous system disorders, obstruction of the reproductive system, and even causing the malformed fertility. Similar impacts of hormones on other organisms are observed as well. Overall, the threat of hormones on humans and other organisms is on the nervous system, reproductive system, and immune system.

3.2.2 Pathogens

HWW usually contains a variety of bacteria, viruses, protozoa, and parasitic worms [29]. These bacteria, viruses, and parasitic worm eggs have strong resistance in the environment and could survive in sewage for a long time. These pathogens are discharged along with

wastewater to the receiving water bodies. The vegetables could be contaminated when the water recycled from WWTP or river water is used for watering. Through food chain, humans thus could get contacted with pathogens and get sick. It could even lead to the outbreak of infectious diseases [30]. HWW contains various high concentration of antibiotics. Thus it is normal that multidrug-resistant bacteria (MDRB) are found in the HWW. The major MDRB include ESBL-producing *Escherichia coli*, vancomycin-resistant *enterococci*, and *Pseudomonas aeruginosa*. The HWW characteristics and the types of pharmaceuticals and pathogens are summarized in Table 3−2.

Overall, pharmaceutical compounds and pathogens are frequently detected in the environment due to the widely utilization and improper handling. The major problem is that no regulation has been set to control the discharge of pharmaceutical compounds and pathogens to the environment. The concentrations of pharmaceutical compounds and pathogens in wastewater range from nanograms to milligrams and 10^7 to 10^{10}, respectively. It indicates that pharmaceutical compounds and pathogens represent a serious problem in natural ecosystems. The main issue is related to toxicity and DNA damage, as well as oxidative stress caused to living organisms [31].

Table 3–2   The characterization of hospital wastewater.

Composition	Type	Substances	Concentration
Pharmaceuticals	Antibiotics	Azithromycin	Summer: 38.9 ± 3.80 ng/L
			Winter: 3547 ± 1.88 ng/L
		Erythromycin	Summer: 1.37 ± 0.14 ng/L
			Winter: 7.65 ± 1.56 ng/L
		Trimethoprim	Summer: 2.02 ± 1.37 ng/L
			Winter: less than detection line
		Sulfamethoxazole	Summer: 9.51 ± 1.88 ng/L
			Winter: 0.66 ± 0.19 ng/L
	Radiation compounds	Total β radioactivity	0.012−0.33 Bq/L
		Total α radioactivity	0.017−0.7 Bq/L
		^{131}I	15.0−61.8 Bq/L
	Nonbiodegradable compounds	—	ND
	Persistent compounds	—	ND
Pathogens	Total coli-form count	—	$2.38 \times 10^7 - 2.38 \times 10^{10}$ L^{-1}
	Fecal coli-form count	—	$1.60 - 2.30 \times 10^8$ L^{-1}
pH	—	—	6.0−8.5
TOC	—	—	286 mg/L
TN	—	—	90 mg/L
COD	—	—	180−340 mg/L
BOD	—	—	50−200 mg/L
TDS	—	—	0.5 mg/L
SS	—	—	80−160 mg/L
NH$_3$-N	—	—	10−50 mg/L

3.3 The development of antibiotic resistance genes

Antibiotics have been applied in agriculture and medicine for nearly 70 years. It has become very common contaminant in the environment. It is reported that the annual antibiotic consumption is around 0.21 Mt in China [32]. Most of the antibiotics cannot be completely metabolized and go to the environment along with urine and feces. It can be in the form of matrix or metabolites, conjugates, or both. The application of antibiotics has resulted in hundreds of ARGs developed in the environment.

3.3.1 The common antibiotic resistance genes in the environment

ARGs are mainly developed by the following mechanisms: (1) target bypass: antibiotic cannot access their target enzyme due to mutational changes or loss on the enzyme gene; (2) efflux pump: the intracellular concentration of antibiotics is reduced due to the change of cell membrane structure; (3) antibiotic inactivation: antibiotic molecules are directly deactivated; or (4) target modification: the action sites of antibiotic are modified. The development of ARGs may occur through multiple routes [33]. According to the differences of the antibiotics, these are classified into the types as shown in the following sections.

3.3.1.1 Antibiotic resistance genes related to tetracycline

The application of tetracycline has induced the development of ARGs related to tetracycline in the environment. In recent years, tetracycline resistance genes encoding ribosome protective proteins including tetM, O, s, Q, and W have been detected in microbial community of wastewater treatment systems, hospital or animal production wastewater, and even in natural water environments [34].

To date, at least 38 different tetracycline resistance genes (tet) and 3 oxytetracycline resistance genes (otr) have been identified [35]. These genes include 23 genes encoding efflux proteins (efflux pump mechanism), 11 ribosome protective protein genes (targeted modification mechanisms), and 3 inactivated genes. The development of tet is considered due to enzymes and also unknown gene resistance mechanisms.

Tet has a broad host range and is found in many environmental genera, including Gram-negative and Gram-positive species. So far, more than 22 tet or otr genes were isolated from the bacteria of aqueous environment. Many tet genes are located in nonflowing plasmids or incomplete chromosomal transposons, but some genes encode efflux enzymes (tetA, B, C, E, H, Y, Z, and 33) and ribosome protective proteins (tetM and O). TetA, B, C, D, and E efflux genes are frequently found in activated sludge (AS) of WWTPs, fish ponds, and surface waters [36].

In recent years, tetE is often found in a large horizontal transferable plasmid of *Aeromonas* which are isolated from farm pond water. In addition, tetE is found to have good interspecies transfer ability. The environmental microbial antioxidant tetracycline plasmids TetA, D, and M can also be transferred horizontally to chicken, pig, and intestinal bacteria [36]. It indicates that tetrandrine has great potential for harm the environment.

3.3.1.2 Antibiotic resistance genes related to aminoglycoside

The main mechanism of aminoglycoside resistance is revealed to be the direct inactivation of these antibiotics by enzyme modification. Till date, more than 50 modified enzymes have been identified. These enzymes are divided into three groups based on their biochemical effects on aminoglycoside substrates, including acetyltransferases, phosphoryltransferases, and nucleotide transferases (glycosyltransferases). They are encoded by the acetyltransferase (aac), phosphotransferase (aph), and nucleotidyl transferase (ant)genes, respectively [23].

The aph, aac, and ant genes are widely distributed in multiple genera such as *Aeromonas*, *E. coli*, *Vibrio*, *Salmonella*, and *Listeria*, as well as a variety of pests isolated from contaminated or natural water. AacC1 gene C2, C3, C4 encoding aminoglycoside-3-*N*-acetyl-transferase (aminoglycoside-3-*N*-acetyltransferase) is often found in microbial communities or isolated from AS, and two glands. The basal transferase genes aadAI and aadA2 have been detected worldwide in aquaculture isolates of rivers, sewage treatment plants, and urban surface waters. Aminoglycoside ARGs encoding antibiotics (neomycin-resistant and streptomycin phosphorous transferase genes) are found in rivers of Canada.

3.3.1.3 Antibiotic resistance genes related to macrolide−lincosamide−streptogramin, chloramphenicol, and vancomycin

Although macrolide, lincosamide, and streptogramin are structurally unrelated, macrolide-resistance genes and lincosamide-resistance genes (lincosamide and streptogramin) are often simultaneously studied. It is due to that they encode resistance to these two or all three compounds. In total, more than 60 different genes are resistant to one or more macrolide streptomycin (MLS) antibiotics. It includes methylation, excretion, and related genes of ribosomal RNA (rRNA). MLS resistance mainly mediates methylated adenine residues through rRNA methylase (encoded by erm gene), preventing the entry of three antibacterial drugs into ribosomal proteins. The erm gene can be easily transferred from one host to another as they are usually acquired and related to mobile elements such as plasmids and transposons [27].

Several erm genes were detected in *Enterococcus* isolated from poultry wastewater and in environmental DNA extracted from farms. Six types of erm genes (A, B, C, F, T, and X) were detected and quantified from samples of mature animal, lagoon, and biological filtration systems employed to treat swine wastewater. Among the factors determining macrolide resistance, ermB is considered to be the most common gene in environmental microorganisms, especially enterococci and streptococcal SPP strains [37]. The resistance mechanisms of chloramphenicol and fluorophenol include chloramphenicol acetyltransferase (encoded by the cat gene), specific exporters (encoded by the CML gene), and multidrug transporters. Among the currently known antichloramphenicol genes, several types of cat or CML genes have been reported. Vancomycin resistance was first observed in *Enterococcus* and recently in *Staphylococcus aureus*. It indicates that the ARGs' transfer between microorganisms exists.

3.3.1.4 Antibiotic resistance genes related to sulfonamides and trimethoprim

Sulfonamides are the most widely used antibiotics in clinical practice and their target is recombinant human deoxyhypusine synthase (DHPS). Trimethoprim competitively used to

inhibit dihydrofolate reductase (DHFR), which is responsible for the reduction of dihydrofolate to tetrahydrofolate. These two biological enzymes are responsible for the biosynthesis of folic acid to some extent. They could impact on the production of thymine and the growth of microorganisms. Sulfonamides and trimethoprim resistance are generally encoded by mutations located in highly conserved regions of the DHPS and DHFR genes.

Four southern genes were detected in the bacteria derived from environment. Yellowing and Il were also found in areas where bacteria were isolated from dairy farms, water or aquaculture sediments, rivers or seawater, and even in areas without evidence of contamination. As a type of integrator, Sull can be horizontally spread and transferred into bacteria in wastewater, river water, and seawater [37].

3.3.1.5 Antibiotic resistance genes related to β-lactam

The β-lactams are the most widely used antibiotics due to their less toxic and effective to a variety of infections. However, their resistance is a serious threat. The β-lactam resistance mechanisms include the inaccessibility of antibiotics to their target enzymes, modification of target enzymes, and/or direct inactivation of 3-lactamases to antibiotics. The main resistance mechanism of Gram-negative bacteria is the cleavage of the β-lactam ring to inactivate the β-lactamase. More than 400 β-lactamases encoded by ARGs (βla) have been identified. They have showed mediate resistance to various β-lactamases, including penicillin and cephalosporins [27].

The βla genes have been widely found in milk farm slurry and salt lake, culture water or sediment, AS, and surface water. They are commonly in animal-derived environmental pathogens, including *Aeromonas*, *Enterobacter serrata*, and *Staphylococcus*. The ampC gene encoding β-lactamase has been detected in microbial isolates of wastewater, surface water, and even drinking water membranes. The MecA gene encoding methicillin-resistant *Staphylococcus* is ubiquitous in HWW biofilms.

The βla gene usually coexists with other antibiotic resistance determinants and may also be associated with mobile genetic elements. It thus increases the possibility of multidrug resistance and environmental transmission. Plasmids containing βla obtained from WWTPs are often associated with transponders and integrons. They could also carry other resistance determinants, including aad (or aac) encoding amino glucoside nucleoside transferase, encoding chloramphenicol CML of the effluent, and cat encoding chloramphenicol acetyltransferase [38].

3.3.2 The impact of antibiotic resistance genes on the environment and humans

Antibiotics are widely used to protect people's health, and most antibiotics are naturally discharged into the environment. Therefore currently the potential impact of antibiotic residues on the environment has received increasing attention. Antibiotics are very common in the surface water except the primitive mountains where rivers or streams did not flow through cities or agricultural areas. As reported, some antibiotics were even found in groundwater

10 m depth. In addition to the chemical contamination caused by the antibiotic itself, the use of antibiotics may accelerate the development of ARGs and bacteria [39]. These bacteria may be transmitted from the environment to human through direct or indirect contact. It thus causes serious problem to the human being.

3.3.2.1 Antibiotic resistance genes impact on environment

Antibiotics enter to the environment through the disposal of solid waste and discharge of wastewater. The common route is presented in Fig. 3−1.

After the antibiotics reach water, it would promote the development of ARGs in the soil and water. The ARGs will be induced in the bacteria of the soil or water. The ARGs could be horizontally transported to the plants or fishes. Then through food chain, the ARGs could reach animals and humans.

3.3.2.2 Antibiotic resistance genes impact on humans

Due to the development of ARGs in bacteria, it could cause death when the humans are infected with the bacteria. The development of ARGs in the bacteria could lead to the treatment failure as the original antibiotic cannot control the bacteria. It requires stronger antibiotic for treating the patient. However, the development of the antibiotic is normally later than the emergence of the bacteria infection. It indicates that the patient may have die before the suitable antibiotic is developed. It is reported that around 2 million persons are infected by bacteria every year, and around 50%−70% belong to antibiotic resistance bacteria. Out of these, around 14,000 death cases are due to the antibiotic treatment failure. In Europe, more than 25,000 persons die each year due to the infection with antibiotic-resistance bacteria [40]. As stronger antibiotics are applied in the patient treatment, more powerful antibiotic resistance bacteria will be created. Then the treatment becomes much difficult thereafter.

The most popular examples are severe acute respiratory syndrome (SARS) occurred in 2002 [41]; 8422 persons were infected in 34 countries and caused 919 deaths and
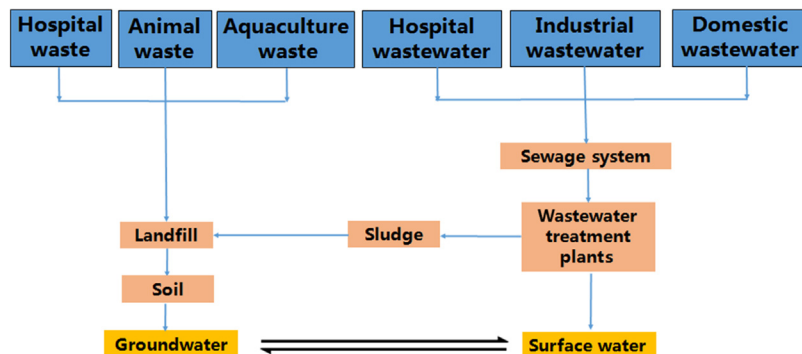

FIGURE 3–1 The transportation of antibiotic in the environment.

enterohemorrhagic *E. coli* occurred in 2011 in Germany; 3000 persons were infected and caused 33 deaths, there were also 470 persons encountering kidney failure [42].

3.4 The transportation of pharmaceuticals and pathogens in the environment

Pharmaceuticals and pathogens are mainly transferred to the environmental through hospital activities. There are a large number of patients in hospitals, which suggests that pharmaceuticals are consumed in large amount with high variations. The transportation of pharmaceuticals and pathogens is shown in Fig. 3–2.

After the antibiotics intake by human body, they would be transferred due to hydroxylation, cracking, and glycosidase acidification and so on a series of metabolic reactions to generate the product of inactive [43,44]. However, most of the antibiotics cannot be fully utilization, and metabolism of pharmaceuticals is not higher than 15% [43]. Most of the antibiotics are water soluble; hence, it would go out of the patient body along with urine. Though some of them will not be dissolved or used, they would be eliminated from patient body to the environment through the patient's feces.
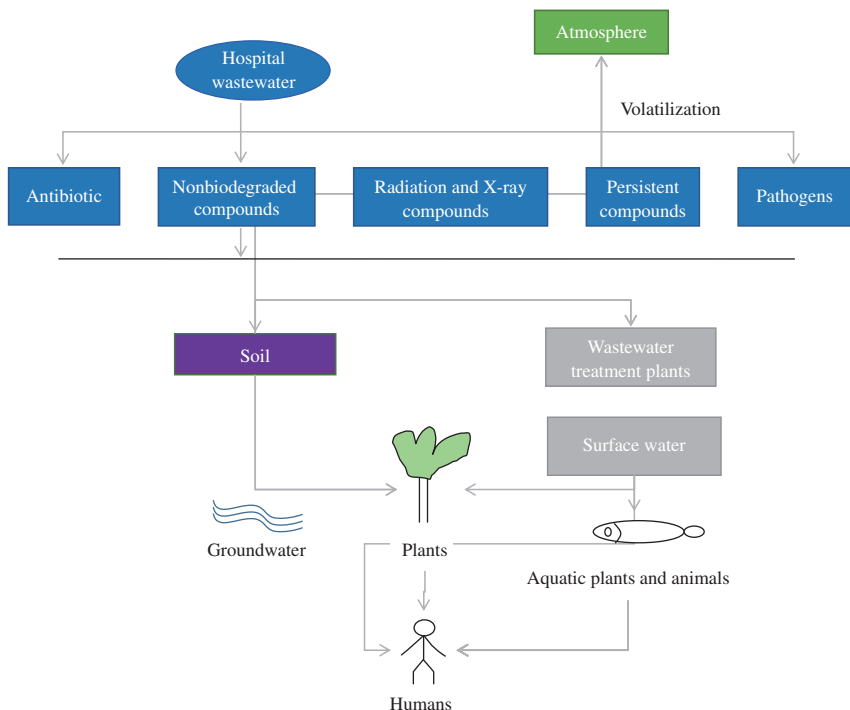

FIGURE 3–2 The transportation pathway of pharmaceuticals and pathogens.

It is very common that antibiotics enter the sewage. According to the statistics reports, there is no HWW without antibiotics, and their contents are at high pollution levels [44,45]. The antibiotics are discharged into the urban sewage treatment plant through the pipe network. Generally, the sealing effect of the pipe is not up to the standard, leading to the leakage of sewage. It would thus contaminant the soil and groundwater.

At present, the general wastewater treatment processes are screening, gritting, primary sedimentation, biological treatment, and secondary sedimentation. The conventional processes are not specially designed for removal of antibiotics; thus, they will not be able to be removed. It was reported that the removal rate of antiepileptic drug carbamazepine was only 8% and the removal rate of cholesterol-lowering drug clofibrate almost zero [46,47]. It suggests that the residual antibiotics after wastewater treatment will be discharged to the receiving water bodies along with the WWTP effluent. As the surface water circulates with the groundwater, the water in the river will enter the groundwater through the soil, which will then not only contaminate the groundwater, but also accumulate antibiotic drugs in the soil. Especially, the antibiotic content in the river sediment will be higher, which will also bring pollution to the farmland soil environment. So far, antibiotics have become a very common pollutant in the environment.

HWW also contains radioactive materials utilized in the diagnosis and treatment of patients taking or injecting radioactive isotopes. It is very common that hospitals do not handle the radioactive waste in proper ways and cause radioactive substances to spread in the air and adversely affecting the surrounding environment and human body. If radioactive substances are discharged from sewage pipes, they will pollute the water environment, and especially pose a serious threat to aquatic life [27].

Most hospitals use liquid chlorine and sodium hypochlorite to disinfect the HWW. Such disinfection method will form chloroform and other chlorine derivatives, which have potential carcinogenic effects and are difficult to biodegraded naturally. In addition, the HWW contains nonbiodegradable compounds such as mercury, which cannot be removed by general biological treatment [48]. After being discharged from the WWTP, it will not only accumulate in the fish and other organisms in the river, but also exist in the sediments. When the river water is utilized for irrigation, nonbiodegradable compounds in the water will be transported to the soil and be absorbed by crops. When poultry, livestock, and humans take these crops, the metals will accumulate in the body, and with the improvement of nutrient level, the accumulation will be much more.

Due to the characteristics of high toxicity, persistence, and accumulation, persistent compounds pose a serious threat to environmental pollution and human health. Moreover, most of the persistent compounds have volatile properties. Even at room temperature, they could volatilize into the air, and thus cause an impact on the quality of the atmosphere. As the air flows, it will have a global impact. After entering the organism, persistent compounds will accumulate in the organism at all levels of nutrition through the food chain. Studies have shown that persistent compounds have been found in Antarctic ice, snow, and sediments. It indicates that persistent compounds could be transported over long distances and can be transferred around the world [49].

Pathogens in HWW flow into the sewage treatment plant along the pipeline. It also transported to the soil and then groundwater along the pipeline leakage. Hence, pathogen pollution is possible in the groundwater. In addition, as mentioned wastewater treatment processes cannot completely remove the pathogens in wastewater, and thus rivers, lakes, and reservoirs would suffer from different degrees of pollution when they are the receiving water bodies of the effluent of WWTPs [4]. Many pathogenic microorganisms accumulate in plants and animals in water. When human gets contact with these plants and animals, they will pose a threat to human health and cause many intestinal diseases. For example, typhoid and paratyphoid could be caused by salmonella typhi or salmonella paratyphoid. Air is also an important route for the spread of pathogens. Some pathogens live in the air for a long time and spread between human and animals as the air moves [50].

3.4.1 The impact of pharmaceuticals and pathogens on microorganisms

3.4.1.1 The impact of pharmaceuticals (antibiotics) on the DNA and gene

Antibiotics are chemical compounds derived from organisms (mainly fungi, actinomycetes, or bacteria). They are used to kill or inhibit the action of other organisms (mainly microorganisms) in its metabolism. Antibiotics are not only extracted from microbial culture fluids, but also obtained by artificial synthesis or semisynthesis. Antibiotics can have antibacterial, sterilization, and bacteriostatic effects at different levels. Its mechanism of action mainly includes: death by inhibiting the formation of bacterial cell walls, causing the loss of bacterial cell wall protection, changing the permeability of the cytoplasmic membrane to hinder the function of the bacterial barrier and the transportation of substances, blocking protein synthesis and causing bacterial growth to be persecuted, affecting DNA and RNA metabolism, and hindering bacterial growth and division [51].

3.4.1.1.1 Antibiotics lead to selective retention of bacterial resistance genes

Certain bacteria are inherent in resistance genes to antibiotics, which are genetically intrinsic to encode antibiotic resistance. These pathogens with intrinsic resistance genes are distributed in the environment, and large-scale use of antibiotics will exert selective pressure on these bacteria. These pathogens carrying ARGs can survive in the environment where antibiotics exist and gradually become dominant bacteria in specific environments, and thus leads to changes in the community structure of pathogens in the environment. The drug-resistant genes are highly transferable [52]. After these strains carrying the resistance genes become dominant bacteria, the spread of ARGs in the same species and between different species of bacteria is accelerated.

3.4.1.1.2 Antibiotics promote the development of resistance genes

The widespread of antibiotics in nature leads to a general change in the community structure of the bacteria, and the ARGs of the bacteria continue to increase. It is speculated that the cause may be the rapid proliferation of pathogens with ARGs present at low basal levels in the pathogen community and the horizontal gene transfer of ARGs mediated by mobile genetic elements such as phage and plasmid. For example, phage particles have recently

been found in *S. aureus* to capture genomic DNA at low frequency, including ARGs and transduce these resistance genes to other bacterial cells [52]. At the same time, phage can also indirectly lead to bacterial resistance, for example, by altering the cell surface structure of the host bacteria and the structure of the cell envelope to render the antibiotics ineffective. A wide range of host-wide plasmids can rapidly transfer multiple ARGs by ligation or movement to produce antibiotic genes in bacteria in their surrounding environment. In the process of antibiotic transmission, the bacteria can also enhance the expression level of the resistance gene through mutations in the p-endosaminotransferase promoter, thereby increasing their resistance to antibiotics.

3.4.1.1.3 Antibiotics cause disorders in microorganisms

Antibiotics mainly kill bacteria by blocking or interfering with the key life processes of the bacteria. The targets of these antibiotics are usually highly genetically and structurally conserved in the pathogens [53]. Hence, the antibiotics kill the pathogens. It also causes collateral damage to human microbial flora that live in the same environment. The destruction of the structure of human microbial flora is likely to cause some pathogenic bacteria to play a pathogenic role. The genes, metabolites, and interactions between the human microbial flora and the host form a normal ecosystem of the human body. When the microbial flora is disturbed, the whole organism's genes will be disordered.

3.4.1.2 The development of super virus

The abuse of antibiotics and their widespread in nature will enhance the resistance of certain viruses. Certain viruses with resistant genes will continue to evolve into super virus, which is in a broad sense refer to incurable viruses that can kill humans [54]. For example, NDM-1 is a typical representative of super viral disease. NDM-1 is in fact a super virus resistance gene, and SARS virus carries NDM-1. In fact, the super virus has been existed for a very long time, which means it is not a new virus. The reason why the super virus is now entering the public view is due to that its strong drug resistance problem is now highlighted. Since the advent of antibiotics, the global use of viruses has increased resistance to traditional antibiotics. If the virus is multidrug resistant, once it spreads, it will be very difficult to be controlled.

3.4.1.2.1 Spread of super virus

One of the major threats of a super virus is that it is very easy to spread. Super viruses can spread from person to person by simply touching or sharing private items. Also they are able to enter the body through the rupture of the skin and the nasal passages.

The spread of super virus mainly includes horizontal and vertical transmission. Horizontal transmission refers to the spread of viruses between different individuals in the population, including the spread of viruses from animals to humans. Common levels of horizontal transmission are as follows: through the respiratory tract, the digestive tract, the genitourinary tract, the skin wound, and the blood. The way that the virus passes through the placenta, the birth canal, and breastfeeding from the mother to the fetus or newborn is called vertical transmission.

The characteristics of super virus easy to spread will make the super virus spread rapidly on a global scale. In addition, the global transportation mode is more developed and the flow is faster. The super virus can be carried around the world with the carrier, which accelerates the spread of the super virus. Global organisms bring fatal disasters.

3.4.1.2.2 Rapidly copying nature of super viruses

After the virus invades the body, it relies on hemagglutinin to adsorb to the surface of the host cell and enters the cytosol after swallowing. With entering the cytosol, the viral envelope fuses with the cell membrane to release the contained ss-RNA. The eight segments of ss-RNA encode RNA polymerase, nuclear protein, matrix protein, membrane protein, hemagglutinin, neuraminidase, nonstructural protein, and other components in the cytoplasm. Matrix protein, membrane protein, hemagglutinin, neuraminidase, and other encoded proteins assemble M protein and envelope on endoplasmic reticulum or Golgi apparatus. In the nucleus, the genetic material of the virus continuously replicates and forms a viral core with nuclear proteins, RNA polymerases, etc. The final viral core binds to the M protein and envelope on the membrane and is released outside the cell by budding. The replication cycle is within 8 h.

Due to the characteristics of rapid replication, super virus will cause infected organisms to develop pathogenic characteristics in a short period of time. The patient is dying before the disease could be diagnosed or the antibody could be developed. It indicates that the super virus has great risk to treat on human health.

3.4.1.2.3 High mortality rate

In the case of the super virus, Ebola virus is a bleeding disorder that causes death on human. In the 1976 epidemic in Sudan, the case fatality rate was 53.2% but in Zaire, it was as high as 88.8% [55]. Some patients died after 48 h of Ebola infection. The incubation period of Ebola virus infection is around 2−21 days. All infected people have sudden high fever, headache, sore throat, weakness, and muscle pain, followed by vomiting, abdominal pain, and diarrhea. Within 2 weeks after the onset of the disease, the virus overflows, causing blood in the body and outside the body, blood coagulation, and necrosis to quickly spread to various organs of the body. The patient eventually develops symptoms such as oral, nasal, and anal bleeding, and the patient can die within 24 h. In approximately 1500 confirmed cases of Ebola virus.

Super viruses have a high mortality rate, and if a super virus breaks out, it will be a severe test for humans around the world. If antiviral agents are not invented in time, it may lead to a sharp decline in the number of population worldwide, and even a devastating disaster for global creatures.

3.4.2 The impact of pharmaceuticals and pathogens on organisms

3.4.2.1 Sea creatures and worms

As HWW contains a large number of pathogens and drugs, it must be treated before it is discharged. Otherwise, pathogens and drugs in the wastewater will pollute the water and cause diseases. The pathogens in medical wastewater are pathogenic pollutants in water.

Pathogenic pollutants are pathogenic microorganisms and bacteria that can cause diseases in humans and animals. Hospitals often need to disinfect and treat patients. Therefore the hospital's wastewater usually contains a certain amount of toxic substances such as antibiotics, mercury, and phenols [56]. The HWW is discharged to the surface runoff, and the pollutants in the wastewater enter the sea along the river. These pollutants can adversely affect marine life.

Marine life refers to various organisms in the ocean, including marine animals, marine plants, microorganisms, and viruses. The marine animals include invertebrates and vertebrates. The primary contact pathways of marine organisms with pollutants are ingestion, including both adsorption and assimilation [57]. Adsorption is the process by which a substance binds to the cell wall of a body surface. There are both reversible physical adsorption and less reversible chemical adsorption. Assimilation is the passage of contaminants through the body surface (through the wall of the digestive tract) into the body, actively or passively transferring (via the blood, circulation of the hemolymph) to other tissues and organs. The second important biological process of pollutants in the ocean is accumulation, which depends on factors such as the assimilation efficiency, concentration, and acute or chronic pollution of the pollutants [57].

Marine worms include polychaete worms, ribbon worms, tube worms, and flatworms [58]. These marine caterpillars belong to the annelid gate. The most important feature of an annelid is the body that is divided into similar links from beginning to end. The new link of the worm will come out from the tail, and there is a sensory organ on the head to sense the environment. There are many caterpillars in the ocean. They are mainly benthic animals. In general, plankton in the ocean or other floating foods are the main food source of marine worms. Marine worms are an important source of food for many fish and wading birds, and this can have an impact on the entire food chain.

When HWW enters the ocean from rivers and sludge, the pathogens and drugs directly poison marine organisms. Through the food chain, it can cause much more marine organisms to be poisoned.

3.4.2.2 The impact of pharmaceuticals on organisms

Studies have shown that pharmaceuticals enter environment mainly through three pathways [16,22,27,32]: (1)the cleaning of unused pharmaceuticals in the containers, (2)the dumping of the unused pharmaceuticals, and (3)the unabsorbed fraction of the patient's metabolites. Usually, these unused pharmaceuticals have little or no change in their chemical structure when discharged from HWW. They are easy to form conjugated compounds with polar molecules, and these conjugated bonds are very easy to be broken in municipal wastewater treatment. Therefore the original pharmaceuticals are released into the water environment through the effluent from the WWTP.

3.4.2.2.1 Antibiotics

Antibiotics are mainly used to treat various bacterial infections or pathogenic microbial infections, and generally do not cause serious side effects to their hosts. It is believed that

antibiotics commonly used in medicine such as ciprofloxacin, ofloxacin, and metronidazole are almost impossible to be biodegraded in water, and their reproductive toxicity does not only harm human health, but also affects biological organisms in the water environment [59]. Excessive exposure of antibiotics into the water environment can lead to increased resistance of bacteria to antibiotics. Studies have shown that *Vibrio parahemolyticus*, *Vibrio alginolyticus*, and *Aeromonas hydrophila*, which are associated with aquatic animal infections, have developed resistance to commonly used antibiotics [60].

3.4.2.2.2 Radioactive compounds

Due to the patient's treatment needs, HWW often contains trace amounts of radioactive elements and heavy metals (such as mercury, nickel, lead, arsenic, zinc, chromium, cadmium, and copper). If these elements are not removed, they will enter the water environment and may even migrate and transform [48]. Marine organisms have an enrichment effect on radioactive materials. They can absorb and accumulate nuclides directly from seawater or through feeding. Nuclide can be transferred along the marine food chain (food web), and some can be expanded along the food chain. In addition, in a polluted environment, marine organisms are exposed to radiation from inside and outside the body, and genes are prone to mutations that affect the growth and reproduction of offspring.

3.4.2.2.3 Nonbiodegradable and persistent compounds

General HWW contains nonbiodegradable and persistent drugs. Persistent organic pollutants are characterized by toxicity, bioaccumulation, semivolatility, and stable in nature, and can remain in seawater for a long time. The persistent compound normally has hydrophobic and lipophilic properties, large molecular weight, complex structure, easy to be enriched in the organism, and not easily biodegradable. The persistent compound is easy to accumulate in the environment, and thus can lead to damage the ecosystem, weaken the immunity of the ecosystem, and increase the biological diseases [61].

3.4.2.3 The impact of pathogens on organisms

Pathogens derived from HWW can enter the ocean and contaminate seawater, adversely affecting marine life and marine worms. After host cells are infected by pathogens (such as bacteria, viruses, and parasites), it may directly or indirectly cause problem on the host cell such as genotoxic agents, tumor proteins, pathogen replication, and inflammatory reactions, and thus affecting the activation of the DDR pathway. This puts tremendous pressure on the stability and integrity of the cell genome [62]. In addition, due to the presence of pathogens, marine organisms often carry pathogenic bacteria. For example, the contaminated parts of fish are mainly oral cavity, sputum, stomach, intestines, and excretory cavities. Moreover, oysters, which are closely related to pathogens in shellfish, can spread typhoid fever. Besides, marine worms also carry pathogens due to predation, thereby expanding the spread of pathogenic bacteria.

3.4.3 The impact of pharmaceuticals and pathogens on humans

HWW contains a large number of unique and highly toxic pharmaceuticals, pathogens, etc., which can accumulate in drinking water and aquatic foods. As mentioned earlier, most of the HWWs are not completely treated before discharging into the water body. There are many ways in which humans come into contact with the contaminants of HWW: directly drinking contaminated source water; taking aquatic animals and plants grown in contaminated water; and inhaling these toxic and harmful substances after volatile poisons entering the air.

Once humans get contacted with the harmful substances, many problems could occur. For example, the immune system could be destroyed. It was also found the pharmaceuticals could induce problem of the reproduction on humans, and the impact was much bigger in the aquatic organisms such as fish [63]. The presence of cyclophosphamide and ifosfamide in water could induce cancer risk to humans. In the cancer and tumor treatment, large amount of the antitumor agents are prescribed. Most of the unused agents and their metabolites would end up in the HWW, municipal wastewater treatment processes cannot eliminate pharmaceuticals; they would remain in the effluent and finally go to receiving water bodies, and then causes genotoxic and carcinogenic effects on humans. Due to the lack of specific risk assessment mechanisms, carcinogens in the water environment cannot be accurately quantified, but existing studies have been able to determine that they have a greater impact on newborns and children than adults [64]. In addition to this, there is a great possibility of synergism between various trace amounts of toxic and harmful substances present in water bodies, which cannot be ignored.

The impact of HWW on humans, in addition to direct exposure to intake, its toxicity can also be affected by the bioconcentration of the food chain and the flow of substances through the biological chain, which is considered as bioaccumulation. It is another important pathway of pharmaceuticals transported to humans. For example, antibiotics are a major class of drugs. Antibiotics discharged into the water with the hospital's wastewater are accumulated in drinking water and aquatic foods. Humans can accumulate antibiotics in the body by taking water which are contaminated by antibiotics or taking the aquatic products obtained from the antibiotic contaminated waste. It then can cause biomagnifications to increase their concentration, and then lead to chronic toxicity, allergic reactions, and "three-in-one." It will also break the balance of normal flora in the human body; thereby impact on various physiological functions of human beings to threaten human health. In addition, antibiotics can produce drug resistance genes in migration and transformation, and drug resistance genes transmit mutations in different bacteria [65]. When these drug resistance genes are transferred to pathogenic bacteria, they increase the threat to human health.

It could also inherit from generation to generation. HWW contains a variety of chemical, physical, or biological compositions, which may cause permanent damage to cell structure or function, prevent growth, cause embryo, and even cause embryo death. Reflected on the macrolevel, the harm caused by HWW mainly affects in microcephaly, cardiac and facial edema, and axials. Most importantly, it can cause teratogenesis, which means that if a mother was deformed, the probability of child malformation will be particularly large [48].

The close contact of human with pathogens could cause many diseases. It has been reported that the physicochemical and bacterial pollution caused by the discharge of improper treated HWW has become serious problem to the environment, and it is getting worse. Pathogens such as *Salmonella* and *Vibrio*, which are significantly harmful to the human body, have been considered the main media for the transportation of epidemics.

3.5 The prevention of pharmaceuticals and pathogens into environment

When micropollutants accumulate to a certain amount, the quantitative change will cause a qualitative change, which will have a huge impact on the environment. The impact of this latent pollution is enormous.

In summary, how to effectively treat HWW and prevent pharmaceuticals, pathogens, etc. from entering the environment is actually a problem. In fact, it can be controlled from different points including the source control, process control, and final control.

3.5.1 Source supervision

HWW refers to the sewage discharged by hospitals to the natural environment or urban pipelines. The water quality varies with the nature, scale, and location of the hospitals. The substances contained are mainly various pharmaceuticals and pathogens. Essentially, the most direct way to prevent all types of pharmaceuticals and pathogens in HWW from entering the environment is to control their emissions from the source.

Taking example of the current wastewater discharge regulations, the government should set policies and regulations for HWW discharge, improve and strengthen the relevant regulations of HWW, and strictly limit the limits of pharmaceuticals and pathogens in HWW. The government should be actively attending to the carrying out of the regulations and strictly supervise the hospital to follow the regulations. The hospitals should strictly implement the regulation for reduce the content of pharmaceuticals and pathogens in HWW before discharged.

3.5.2 Process management

HWW can go into surface water, groundwater, soil, etc. One of the most important factors causing the widespread distribution of HWW is the disorderly discharge. HWW itself has more pharmaceuticals such as pathogens and antibiotics, which are discharged into the environment and enter the organism through various cycles, posing a threat to humans (Fig. 3−1). Therefore the hospital's wastewater discharge process is strictly regulated to monitor the occurrence of disorderly discharge, which can make the HWW centralized treatment and reduce its threat to humans and the environment.

3.5.3 Terminal control

At present, the main treatment processes for removal of pharmaceuticals and pathogens from HWW are membrane bioreactors (MBRs) and various advanced oxidation technologies, but there are some emerging technologies with great potential. Mousaab et al. [66] have employed an upgraded MBR system for treating HWW. The aim of this study is to improve the pharmaceuticals removal efficiency with membrane function. Ultrafiltration membrane module was used to couple with an activated sludge basin. The sludge retention time and hydraulic retention time were 20 days and 22 h, respectively. The study revealed that the removal of soluble chemical oxygen demand, total suspended solids, and volatile suspended solids reached 91.8%, 100%, and 93.2%, respectively. The removal efficiencies of codeine, pravastatin, ketoprofen, diclofenac, roxithromycin, gemfibrozil, and iohexol were greater than 95%, which almost remained the same concentration before and after treatment with activated sludge process. The presence of biofilm supports also enhanced particle sorption and improved effluent quality, thus offering better protection of the membranes against fouling and reducing cleaning operations.

It is revealed that nanofiltration (NF) and reverse osmosis (RO) processes are potential technology for further removal of pharmaceuticals and pathogens from HWW after being treated with MBR. Residues of pharmaceuticals in the effluent of MBR can be further separated from water by NF or by RO being retained due to molecular weight and size, sorption, and charge attraction. Among all, sorption is considered as the primary removal mechanism for poorly soluble nonpolar compounds [67,68].

It has been widely reported that advanced oxidation processes (AOPs) are able to completely oxidize and/or destroy organic pollutants in water and wastewater into H_2O, CO_2, and mineral salts. AOPs have also been applied on the HWW treatment for the removal of pharmaceuticals and pathogens. Fenton oxidation and ozone oxidation are commonly used. During advanced oxidation, a variety of radical reactions such as hydroxyl radical (HO•), superoxide radical anion ($O_2^{-•}$), and hydroperoxyl radicals (HO$_2$•, ROO$-$) are generated on site. The formations of these radicals are generally induced due to the combinations of chemical agents and auxiliary energy sources [69,70]. The commonly employed chemical agents are ozone, hydrogen peroxide, transition metals, and metal oxides. The energy can be provided with UV irradiation, electronic current, y-radiation, and ultrasound. Among all, HO• is the most frequently applied oxidant in AOPs. It is mainly attributed to that unlike many other radicals HO• is nonselective, and could readily react with many organic pollutants by converting them into more hydrophilic compounds than the original ones.

For the treatment of HWW, the effective way is to start from the control of source of HWW, control the transportation process of HWW, and continuously strengthen the treatment process of the final HWW.

3.6 Conclusions and perspectives

HWW contains variety of harmful materials including pharmaceuticals and pathogens. HWW is normally treated with sewage wastewater together, although it is not allowed. However,

WWTPs are not designed for treating HWW. Pharmaceuticals and pathogens will be then discharged to the receiving water bodies. Antibiotic as one of the most common pollutant in the HWW can cause the development of ARGs. Therefore pharmaceuticals, pathogens, and ARGs have become the three most important contaminants in the HWW. These pollutants can cause server problems to the environment, microorganism, organism, and humans.

Many studies have revealed the harmful impact of pharmaceuticals on the organisms and humans. The most concerned ones are hormones, antibiotics, radiation, and X-ray compounds. Many others could cause problems to the environment, ecosystem, and humans as well. However, there are not reported due to that the effect is chronic. The strategy for controlling the harmful materials in the HWW can be performed by source control, process control, and terminal control.

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