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**Occurrence, fate and health risk assessment of 10 common antibiotics in two drinking water plants with different treatment processes**

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**Abstract**

The occurrence of antibiotics in drinking water has become a serious problem worldwide as they are a potential and real threat to human health. In this study, the variability of 10 typical antibiotics in two drinking water plants was investigated in two seasons ( $n = 12$ ). The total concentrations of target antibiotics in raw water were significantly higher in winter than in summer, which may be attributed to the more frequent occurrence of colds and respiratory diseases as well as less rainfall in winter. The efficiency in removing the antibiotics varied from -46.5% to 45.1% in water plant A (WP-A) using a conventional process and 40.3% to 70.3% in water plant B (WP-B) with an advanced treatment process. Results indicated that the antibiotics in WP-A were mainly removed via the coagulation process. However in WP-B, the ultraviolet + chlorination process played a key role in antibiotics removal, followed by the pre-ozone + coagulation process. According to the human health risk assessment, it was suggested that the risk of drinking water was significantly higher than that of skin contact. However, the risk of carcinogenesis and non-carcinogenesis caused by antibiotics was at an acceptable level.

Keywords: Distribution characteristic; Seasonal variation; Removal efficiency; Health risk assessment

**1. Introduction**

Safe drinking water is the basic requirement of human survival, which is directly related to human health and life safety (Baken et al., 2018; Li et al., 2018a). Currently, pollution of the water environment caused by pharmaceuticals and personal care

products (PPCPs) is now doing serious damage to drinking water sources in many societies (Lin et al., 2016; Yang et al., 2017). Antibiotics constitute one of the most important drugs that people often use. It is estimated that the number of antibiotics used worldwide ranges from 100,000 to 200,000 tons annually (Li et al. 2014) . Approximately 5460 and 3465 tons of antibiotics are used annually in humans and animals in the European Union and Switzerland, respectively (Hu et al., 2018a). Due to the lack of scientific drug management and guidance as well as public misunderstanding about the use of antibiotics, the abuse of antibiotics has become very serious in China (Bu et al., 2016; Qiao et al., 2018). China consumes 180,000 tons a year, which is approximately 10 times larger than the annual consumption in the United States (Hu et al., 2018a).

The total antibiotic usage was estimated to be approximately 162,000 tons for 2013, and 52% of which was consumed by animals (Zhang et al., 2018). Antibiotics have the characteristics of low concentration, high toxicity and "pseudo-persistence" in the environment (Binh et al., 2018). Human beings, and aquatic and terrestrial organisms can be exposed to antibiotics for a long time. Even if existing in the environment in the level of  $\mu\text{g/L}$  and  $\text{ng/L}$ , they will wield adverse effects on human health and the natural environment (Schafhauser et al., 2018). Therefore, it is important to investigate the occurrence, distribution and human health risk of antibiotics in the aquatic environment.

Different kinds of antibiotics have been detected in the surface waters of Haihe River (Dang et al., 2017), Huangpu River (Chen and Zhou, 2014), Jiulong River

(Zheng et al., 2011), Yangtze River (Sun et al., 2017), Yellow Sea (Na et al., 2014), Bohai Sea (Liu et al., 2016), Pearl Harbor (Li et al., 2018b) and Victoria Harbor (Minh et al., 2009) in China. Urban sewage discharge is an important way for antibiotics to enter the surface water environment. Rainwater, runoff erosion and aquaculture are also factors that cannot be ignored. Similarly, antibiotic residues were also detected in groundwater. Hirsch et al. (1999) studied the infiltration of groundwater by livestock wastewater and agricultural irrigation water in Germany, discovering the existence of 0.47 µg/L sulfamethoxazole and 0.16 µg/L sulfadiazine. Sacher et al. (2001) detected 49 ng/L of erythromycin and 410ng/L sulfamethoxazole in groundwater in Germany. Campagnolo et al. (2002) detected tetracyclines, sulfonamides, beta-lactams and macrolides in groundwater near a pig farm in the United States. It should be noted that antibiotics are also found in drinking water, not just surface and groundwater. Zuccato et al. (2000) detected tylosin with a concentration of 0.6-1.7ng/L in drinking water in the Italian city of Lodi. Boleda et al. (2014) detected azithromycin, clarithromycin, erythromycin and sulfamethoxazole in Spanish drinking water, with maximum concentrations of 9.5, 2.2, 1.5 and 1.4ng/L, respectively. Perret et al. (2006) detected three sulfonamide antibiotics in Italian drinking mineral water at concentrations ranging from 9 to 80 ng/L.

Studies have shown that different concentrations of antibiotics have been found in the freshwater aquaculture water, Haihe River and soil in Tianjin (Chen et al., 2014; Li et al., 2014). Various types of antibiotics were also detected in water sources in a recent analysis (Su et al., 2018). It is therefore clearly evident that the chemical safety

of drinking water caused by these antibiotics is attracting much more research attention. However, the source, distribution and migration of antibiotics in environmental waters are mostly concentrated in surface water, groundwater and sewage treatment plants, and there is little research on the water supply system. The quality of water that is transported along the water supply system has a direct impact on human health (Zhang et al., 2016). Existing water treatment units have not been designed for novel pollutants such as antibiotics, and the migration and removal of antibiotics in the process of drinking water and water supply are still not fully understood. Therefore, it is of great significance for drinking water safety to study the distribution characteristics and transfer regularities of antibiotics in the water supply system and the removal efficiency of existing water treatment units.

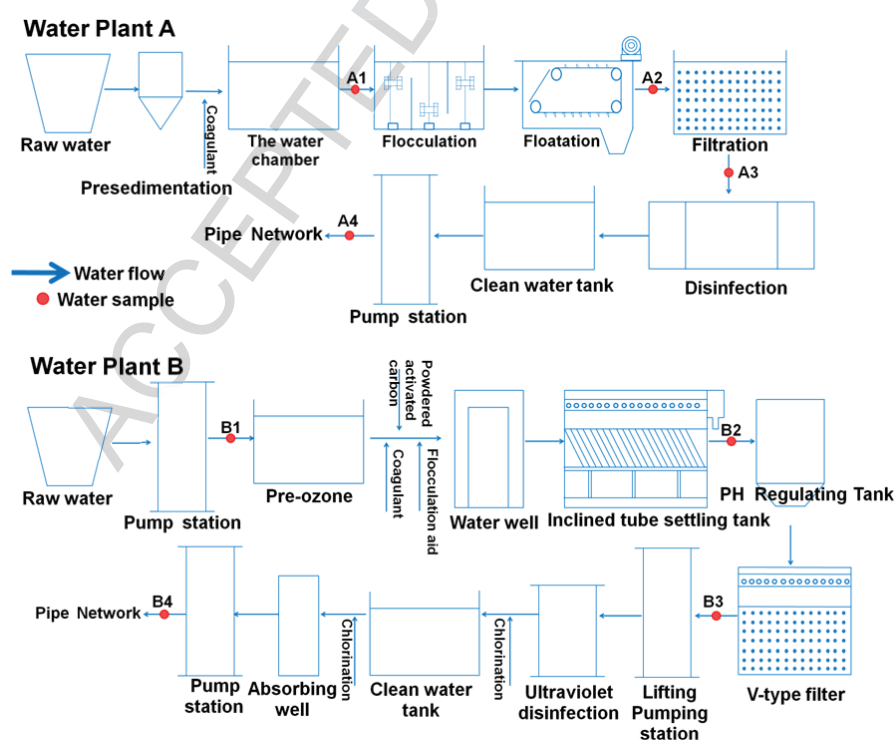
This study focused on 10 typical antibiotics found in Tianjin's water supply system, and analyzed here were the concentration level and distribution characteristics of antibiotics in two different drinking water plants. An evaluation was carried out of the health risks caused by antibiotics in drinking water based on the uncertainty analysis method. It can provide good description of the distribution characteristics, migration and transformation of antibiotics as well as their potential hazards in Tianjin's water supply system, so that the urban drinking water is completely safe to use.

## **2. Materials and methods**

### **2.1 Study sites and sampling**

The water plants designated as A and B in Tianjin were selected for this research.

WP-A and WP-B used the same source of water (mainly Changjiang river water, while Luanhe river water has served as the standby water source). The water supply capacity of WP-A and WP-B is 500 thousands  $\text{m}^3/\text{d}$  and 300 thousands  $\text{m}^3/\text{d}$ , respectively. Raw water, unfiltered water, filtered water and effluent water which are treated by these waterworks were all collected. A water sample (5L) was collected with a water sample collector after each continuous water discharge which lasted for 10 minutes. The collected water samples were then quickly transported in brown bottles to the laboratory and kept in a refrigerator at  $4^\circ\text{C}$ . The process units and sampling points (n=12) of each water plant are shown in Fig. 1, of which S1-S6 were collected in summer and W1-W6 were collected in winter. Antibiotics were analyzed within 24h. In order to ensure the accuracy of the data, three parallel samples were established in each water sample and the average value was finalized.



**Fig. 1** Sampling flow diagram in WP-A and WP-B.

## 2.2 Chemicals and standards

According to the full scanning analysis of the species of antibiotics in tap water and the study of the distribution of antibiotics in Tianjin's main source of water, 10 antibiotics were determined, including the following: tetracyclines: tetracycline (TC, 98%) and doxycycline (DXC, 98.7%); quinolones: ofloxacin (OFC, 99%), enrofloxacin (ERC, 98.5%) and trimethoprim (TMP, 98.7%);  $\beta$ -lactams: penicillin G (PEN, 99.5%); macrolides: roxithromycin (ROX, 97%); lincosamides: lincomycin (LIN, 99.2%); and sulfonamides: sulfamerazine (SMR, 99.2%) and sulfamethoxazole (STX, 99.0%). The physicochemical properties of the target antibiotic compounds are summarized in Table 1. All the standard samples were powder samples purchased from Dr. Ehrenstorfer GmbH, Germany; Acetone solution of  $^{13}\text{C}_3$ -Atrazine at a concentration of 100ng/ $\mu\text{L}$  purchased from Bailingwei, China; and Methanol solution of  $^{13}\text{C}_3$ -Caffeine at a concentration of 1.0mg/mL purchased from Cambridge Isotope Laboratories, USA. Other solvents include methanol (HPLC, Fisher, USA), formic acid (85%, HPLC, Duksan), acetonitrile (HPLC, Fisher, USA) and ammonium formate (HPLC, CNW, Germany).

Table 1

The physicochemical properties of the target antibiotic compounds.

Antibiotic compounds	Acronym	CAS number	Molecular weight	LogK <sub>ow</sub>	pK <sub>a</sub>	Molecular formula
Tetracycline	TC	60-54-8	444.43	-1.30	3.3	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>8</sub>
Doxycycline	DXC	564-25-0	444.44	-0.02	n/a	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>8</sub>



Ofloxacin	OFC	82419-36-1	361.37	-0.39	n/a	$C_{18}H_{20}FN_3O_4$
Enrofloxacin	ERC	93106-60-6	359.40	0.7	n/a	$C_{19}H_{22}FN_3O_3$
Trimethoprim	TMP	738-70-5	290.32	0.91	7.12	$C_{14}H_{18}N_4O_3$
Penicilline	PEN	113-98-4	373.48	-0.301	n/a	$C_{16}H_{18}N_2O_4SK$
Roxithromycin	ROX	80214-83-1	837.1	2.75	9.17	$C_{41}H_{76}N_2O_{15}$
Lincomycin	LIN	154-21-2	406.5	0.56	8.78	$C_{18}H_{34}N_2O_6S$
Sulfamerazine	SMR	127-79-7	264.3	0.14	n/a	$C_{11}H_{12}N_4O_2S$
Sulfamethoxazole	STX	723-46-6	253.3	0.89	5.6	$C_{10}H_{11}N_3O_3S$

### 2.3 Sample pretreatment

A water sample of 1L was filtered by a 0.22  $\mu\text{m}$  glass fiber filter (50mm i.d., Pall, USA) to remove suspended particulate matter. When 0.5 g ethylenediamine tetraacetic acid disodium ( $\text{Na}_2\text{EDTA}$ ) was added, the solution was shaken up and the pH was adjusted to 2-3 with concentrated hydrochloric acid. Then 150ng  $^{13}\text{C}_3$ - caffeine was added to the water sample and mixed well. The samples were extracted and enriched using Oasis HLB SPE cartridges (6 mL/500 mg, USA). Before loading the pretreated water samples, cartridges were activated with 6 mL of methanol, 6mL of 2.5g/L  $\text{Na}_2\text{EDTA}$  solution and 6 mL of ultra-pure water. The flow rate was 3-5ml /min. After the water samples were filtered, the cartridges were leached with 6mL ultra-pure water immediately and dried under negative pressure for 30 minutes. Using 6mL methanol and 6mL acetonitrile as the elution solvents, the target analytes were eluted under gravity conditions and the eluent was collected. The collected eluent was blown off to less than 1 mL by nitrogen gas in a water bath at 40°C. The samples were re-dissolved by methanol repeatedly eluting the side wall. The final volume was determined to 1 mL. The eluent was transferred to the injection bottles after adding 10

$\mu\text{L}$  50ppm  $^{13}\text{C}_3$ -atrazine for instrumental analysis .

#### 2.4 Antibiotics analysis

1200 high performance liquid chromatography (HPLC) (Agilent, USA) coupled with a 6410B triple quadrupole mass spectrometer (MS) (Agilent, USA) was utilized for the quantitative analysis of antibiotics. A Zorbax Eclipse Plus C18 (with diameter, length and pore size of 2.1 mm, 100 mm, 1.8  $\mu\text{m}$ , respectively) chromatographic column was used for chromatographic analysis. The column temperature was set to 40°C, the sample injection volume was 10  $\mu\text{L}$ , and the mobile phase flow rate was 0.3 mL/min. The aqueous phase (phase A) consisted of 3% formic acid and 0.1% ammonium formate aqueous solution. The organic phase (phase B) was methanol and acetonitrile with a volume ratio of 1: 1. The gradient programs of the UPLC were set up as shown in Table A1. All antibiotics were well separated and chromatographic peaks were well formed. The whole instrumental analysis process was completed in 19 minutes. The correlation coefficients  $R^2$  were all greater than 0.9990, the detection limit was 0.001-0.26 ng/L, the recovery was 77.12% - 126.37%, and the relative standard deviation was less than 9.34%. The specific values of each antibiotic were shown in Table A2.

To evaluate the removal efficiency of target antibiotics in each treatment unit and the entire process in the water treatment plants, the calculation formula of the removal rate of antibiotics was as follows:

$$\eta_{j,i} = \frac{c_{j,i} - c_{j+1,i}}{c_{j,i}} \times 100\% \quad (1)$$

$$\eta_{t,i} = \frac{c_{r,i} - c_{e,i}}{c_{r,i}} \times 100\% \quad (2)$$

where  $\eta_{j,i}$  is the removal rate of antibiotic  $i$  by  $j$  process,  $c_{j,i}$  is the concentration of antibiotic  $i$  in  $j$  process (ng/L),  $c_{j+1,i}$  is the concentration of antibiotic  $i$  in the subsequent process of  $j$  process (ng/L),  $\eta_{t,i}$  is the total removal rate of antibiotic  $i$  in various processes of waterworks,  $c_{r,i}$  is the concentration of antibiotic  $i$  in raw water (ng/L), and  $c_{e,i}$  is the concentration of antibiotic  $i$  in effluent (ng/L).

## 2.5 Human health risk assessment

Health risk assessment mainly evaluates the risk of exposure and the impact of harmful factors on individual people's health by estimating the probability of adverse effects on the human body. Based on the health risk assessment theory of EPA (USEPA, 2001), the carcinogenic and non-carcinogenic risks of antibiotics that can arise in drinking water and bathing were assessed with the Monte Carlo method.

Quantitatively estimating the population's intake of pollutants through diet (mainly drinking water) (Streng et al., 1995) is:

$$CDI_{dw} = C_{dw} \times TF \times U \times ABS \times \frac{EF \times ED}{BW \times AT} \quad (3)$$

where  $CDI_{dw}$  is the daily exposure dose of pollutants in drinking water [mg/(kg×d)],  $C_{dw}$  is the concentration of pollutants in water (mg/L),  $TF$  is the purification coefficient of waterworks,  $U$  is the daily average water intake (L/d),  $ABS$  is the gastrointestinal absorption factor,  $EF$  is exposure frequency (d/a, at 360),  $ED$  is the exposure period (a, at 75),  $BW$  is the average body weight (kg), and  $AT$  is the average exposure time and should be the average of  $EF$  and  $ED$  product for the

population studied.

In the process of bathing, the human body absorbs pollutants in the water through the skin. The exposure models are as follows (Streng et al., 1995):

$$CDI_{sc} = C_{dw} \times SA \times K_p \times FE \times FT \times CF \times \frac{EF \times ED}{BW \times AT} \quad (4)$$

where  $C_{dw}$  is the concentration of pollutants in water (mg/L), SA is the accessible skin surface area ( $\text{cm}^2$ ),  $K_p$  is the osmotic constant of chemical contaminants on skin surface (cm/h), FE is the bath frequency (d), FT is bath time (h), CF is the unit transformation factor ( $1\text{L}/1000\text{cm}^3$ ), EF is exposure frequency (d/a, at 360), ED is the exposure period (a, at 75), BW is the average body weight (kg), and AT is the average exposure time and should be the average of EF and ED product for the population studied. By means of questionnaire survey and taking families as units, a sample survey was conducted among residents in Tianjin to determine the values of exposure parameters of population behavior characteristics. The specific data refer to Table A3.

The model established by Barratt (1995) was used to calculate the skin permeability coefficient. The fitting degree of the model was 0.904, and the formula was as follows.

$$\log PC = -0.00933 \times MV + 0.82 \times \log P - 0.00387 \times mpt - 2.355 \quad (5)$$

where PC is the skin permeability coefficient (m/h), MV is the molecular weight of each antibiotic, logP is the octanol ratio, mpt is the melting point ( $^{\circ}\text{C}$ ).

The risk assessment of antibiotics is based on the risk value (risk, R)(Crouch and

Wilson, 2010):

$$R = CDI \times \beta \quad R < 0.01 \quad (6)$$

where CDI is the exposure dose per unit weight [mg/(kg×d)], while  $\beta$  is the exposure to carcinogenic intensity coefficient (kg×d/mg).

Carcinogenic risk of multiple antibiotics:

$$R^C = \sum_{i=1}^n R_i \quad (7)$$

where  $R_i$  is the carcinogenic risk of chemicals i.

The carcinogenic effect was calculated using models established by Zeise et al (2010):

$$\beta = \frac{D}{LD_{50}^c} \quad (8)$$

where  $LD_{50}$  (Zheng, 2005) is the median lethal dose of animals (mg/kg), and C and D are the regression coefficients.

Human carcinogenic potency:

$$\beta_h = K_{ah} \times \beta_a \quad (9)$$

where  $\beta_h$  is the human carcinogenic intensity coefficient (kg×d/mg),  $K_{ah}$  is the intermediate conversion coefficient (US EPA recommended value is 4.7), and  $\beta_a$  represents the animal carcinogenic intensity coefficient (kg×d/mg).

Non-carcinogenic risk of antibiotics:

$$HQ = \frac{CDI}{RfD} \quad (10)$$

where HQ is the risk hazard quotient, and RfD is the non-carcinogenic reference

dose of pollutants [mg/(kg×d)].

The non-carcinogenic reference dose was estimated by the model proposed by Streng et al (1995):

$$RfD = LD_{50} \times 4 \times 10^{-5} \quad (11)$$

where  $4 \times 10^{-5}$  is the empirical transformation coefficient ( $d^{-1}$ ).

Comprehensive evaluation of non-carcinogenic risk of multiple compounds and multiple exposure routes:

$$HI = \sum_{j=1}^n \sum_{i=1}^n \frac{CDI_{ij}}{RfD_{ij}} \quad (12)$$

where  $CDI_{ij}$  is the exposure dose per unit body weight for the  $j$  exposure pathway of the  $i$  pollutant [mg/(kg×d)], and  $RfD_{ij}$  is the non-carcinogenic reference dose for the  $j$  exposure pathway of the  $i$  pollutant [mg/(kg×d)].

Crystal Ball 11.1.2.2 helped to to implement Monte Carlo sampling analysis and uncertainty analysis concerning health risk assessment. The objective here was to: firstly, improve the reliability of risk assessment results; and secondly, reduce the risk associated with decision-making.

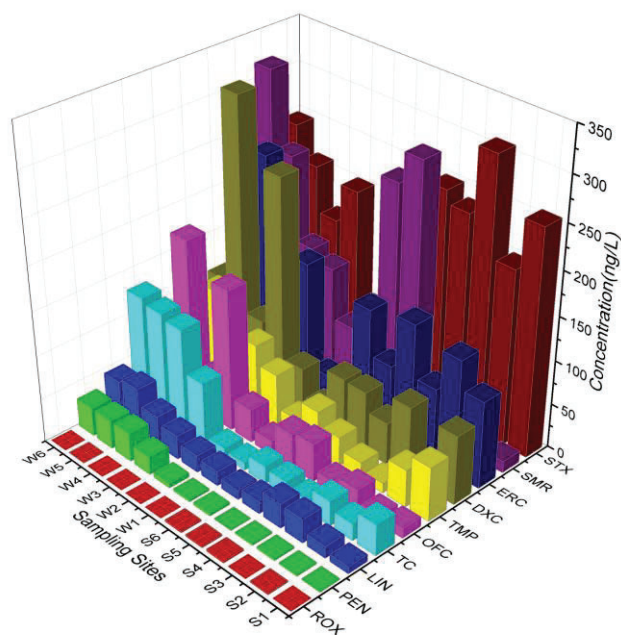
### 3. Results and discussion

#### 3.1 Seasonal variation of antibiotics concentration in raw water

The changes in antibiotic concentration in raw water over time are shown in Fig. 2. The dotted line indicates the division between winter and summer. Except for sulfonamide antibiotics (SAs), the detected concentrations of other antibiotics were significantly higher in winter than in summer ( $p < 0.05$ ). This was mainly due to the

low rainfall in winter, as well as the frequent occurrence of colds and respiratory diseases which triggered the large use of antibiotics. A large amount of rainfall runoff in summer will wash antibiotics from the surface into the bodies of water and increase the antibiotic content in the water source, but because of dilution brought about by a large amount of rainfall, the concentration of antibiotics will be reduced. The seasonal distribution of DXC, OFC and ERC revealed a consecutive increase. The highest value (253.2 ng/L) of DXC was about 36 times larger than the lowest value (9.1 ng/L), the highest value (150.7 ng/L) of OFC was about 15.7 times larger than the lowest value (9.6 ng/L), and the results for ERC (the highest value: 245.9 ng/L; the lowest value: 20.8 ng/L) were 11.8 times. This may explain why the sources of these antibiotics were intermittent and their use increased significantly during winter. The content of PEN was very small in summer but the detected concentration in winter rose significantly and remained at a certain level (>30 ng/L), which resulted in a great difference between the average and the median concentration (Table 2). Considering the easy hydrolysis of PEN, it indicated that the use of PEN in winter not only increased, but did so frequently, resulting in a high concentration of PEN continuously being deposited in the raw water. Due to the small detection frequency of ROX, the annual seasonal variation was significant. LIN had a small peak from June to July, which may be due to the concentrated use of LIN during this period. The concentration level of STX was higher in both winter and summer, and the peak value of SMR appeared in both winter and summer, while the content was low for the rest of the time. This may suggest that the pollution emission of SMR was relatively

concentrated.



**Fig. 2** Seasonal distribution of antibiotics in raw water

### 3.2 Occurrence and distribution of antibiotics in two water plants

#### 3.2.1 Antibiotics concentrations in WP-A

The concentration of antibiotics in each stage of WP-A are documented in Table 2. Ten antibiotics were detected in raw water, and the content of antibiotics ranged from 337.4-1531 ng/L. Except for the detection frequencies of ROX and PEN were 41.7% and 91.7%, respectively, the detection rates of other antibiotics reached 100%. The average concentration of STX (206.8 ng/L) was the highest, followed by SMR (136.8 ng/L). The high detection rate and high concentration of sulfonamide antibiotics are not only related to the large use of sulfonamide antibiotics, but also because of the high stability and hydrophilicity of them in water, which are easy to enter the water environment through runoff and rainwater erosion, resulting in the



pollution of sulfonamide antibiotics in water (Hu et al., 2018b). PEN is one of the world's most abundant antibiotics, but the detected concentration in raw water was not high, with an average concentration of 12.5 ng/L. The main reason is that  $\beta$ -lactam antibiotics are easily hydrolyzed in a water environment and not easily detected (Kim et al., 2018).

The raw water was collected at A2, after the coagulation-air flotation process and before entering the filter. The total antibiotic level in pre-filtration water ranged from 134.5 to 1032 ng/L, and the concentration of single antibiotic varied from 1.4 to 241.3 ng/L. Except for ROX (the detection frequency was 41.7%), 100% of all the other antibiotics were detected in the 12 samples. Similar to the distribution of antibiotics in raw water, the average concentration of STX (104.7 ng/L) was the highest, followed by SMR (93.0 ng/L).

The filter in WP-A was a double-valve filter. After passing through the filter, the total concentration of antibiotics ranged from 172.9 ng/L to 966.6 ng/L. The average concentration of STX (111.6 ng/L) was the highest, followed by DXC (100.2 ng/L). Compared with DXC, the average concentration of TC was only 27.1 ng/L, indicating that DXC was more widely and abundantly used than TC. The average concentration of LIN was 13.3 ng/L, which was only higher than that of PEN (10.8 ng/L) and ROX (0.7 ng/L). ERC was the highest quinolone antibiotic with an average concentration of 80.13ng/L, higher than OFC (51.9 ng/L) and TMP (20.9 ng/L).

The chloramine contact disinfection tank was the final treatment unit, and only then after disinfection would tap water be delivered to the user. The total

concentration of antibiotics in the effluent ranged from 197.9 to 1138 ng /L. The content of DXC in tetracycline was higher than that in TC, and its concentrations were 41.0-256.5 ng/L and 2.1-90.6 ng/L, respectively. The content of STX in sulfonamides was larger, with an average concentration of 122.3 ng/L, and the average concentration of SMR was 74.2 ng/L. The highest concentration of ERC was 234.5 ng/L, which was much higher than Macau's 5.2 ng/L and Guangzhou's 8.3 ng/L (Yiruhan et al., 2010), indicating that the pollution of ERC in Tianjin's waterworks had reached very serious levels. Meanwhile, the average concentration of OFC was 62.0 ng/L, which was similar to or more serious than the concentration of OFC in surface water (Hu et al., 2018c). The concentration of ROX was the lowest and the average concentration was only 1.0 ng/L.

Table 2

The concentration of antibiotics in each stage of WP-A (ng/L).

Testing items	Antibiotic compounds										
	TC	DXC	OFC	ERC	TMP	PEN	ROX	LIN	SMR	STX	
Raw water (n=12)	Max <sup>a</sup>	134.1	320.1	189.9	243.4	122.3	33.2	1.7	53.1	317.8	307.4
	Min <sup>b</sup>	4.5	8.8	12.1	20.6	12.0	nd <sup>e</sup>	nd	8.3	13.4	76.6
	Med <sup>c</sup>	49.0	98.2	55.8	105.4	56.1	12.5	1.1	24.9	136.8	206.8
	Mean	23.0	72.4	39.6	92.1	54.2	3.2	1.0	23.0	112.5	212.3
	Fre <sup>d</sup> (%)	100.0	100.0	100.0	100.0	100.0	91.7	41.7	100.0	100.0	100.0
Unfiltered water (n=12)	Max	82.7	241.3	146.9	161.8	61.8	36.6	2.4	23.2	229.8	215.1
	Min	1.4	2.8	5.8	9.8	3.3	1.7	nd	7.7	13.6	3.6
	Med	27.9	87.6	48.2	74.5	22.6	9.7	1.0	14.1	93.0	104.7
	Mean	8.8	43.0	14.7	71.1	12.4	4.9	0.7	11.3	39.2	103.0
	Fre(%)	100.0	100.0	100.0	100.0	100.0	100.0	41.7	100.0	100.0	100.0
Filtered water (n=12)	Max	86.6	236.6	154.0	169.6	63.3	31.6	2.1	23.4	210.5	211.1
	Min	1.8	<41.6	1.7	13.7	3.4	1.0	nd	3.7	2.4	12.8
	Med	27.1	100.20	51.9	80.1	20.9	10.8	0.7	13.7	60.7	111.6
	Mean	8.6	56.4	26.5	78.7	12.3	5.7	0.4	13.9	35.8	98.8
	Fre(%)	100.0	100.0	100.0	100.0	100.0	100.0	41.7	100.0	100.0	100.0

Effluent water (n=12)	Max	90.6	256.5	157.2	234.5	112.7	38.2	2.0	27.7	246.7	232.0
	Min	2.1	41.0	14.4	13.9	7.9	0.6	nd	3.3	5.7	47.4
	Med	34.3	121.1	62.0	126.4	45.5	10.9	1.0	14.2	74.2	122.3
	Mean	17.0	83.5	38.3	122.6	27.6	4.7	0.7	12.1	33.4	115.2
	Fre(%)	100.0	100.0	100.0	100.0	100.0	100.0	41.7	100.0	100.0	100.0

a: Maximum, b: Minimum, c: Median, d: Frequency e: Not Detected

### 3.2.2 Antibiotics concentrations in WP-B

The concentration of antibiotics in each treatment stage of WP-B are shown in Table 3. The total content of antibiotics in raw water ranged from 444.2 ng/L to 941.9 ng/L. Except for ROX, the detection frequency of other antibiotics was 100%. SMR concentrations were the highest with an average of 231.5 ng/L. STX was the next largest, and its average concentration was 105.4 ng/L. The concentrations of SMR and STX in raw water of WP-B were smaller than those of WP-A. The average concentrations of PEN and LIN were 26.0 ng/L and 26.2 ng/L respectively, which were slightly higher than those in WP-A.

Water samples were collected at B2 once the pre-ozone contact tank, mechanical coagulation tank and inclined tube sedimentation tank had been completed. Consistent with the original water, 9 antibiotics excluding ROX were detected in the pre-filtration water with a concentration range of 395.2-695.2 ng/L. SMR was still the dominant compound with an average concentration of 182.2 ng/L. Meanwhile the LIN concentration was the lowest at 16.6 ng/L. The concentrations of TC and DXC were 25.1 ng/L and 68.6 ng/L, respectively, which were lower than those in WP-A. The concentrations of three QNs were similar and the average concentrations of OFC, ERC and TMP were 45.3, 42.2 and 48.5ng/L, respectively. The concentration of PEN

ranged from 8.8 ng/L to 35.8 ng/L, which was about twice the average concentration of that in raw water of WP-A.

The WP-B adopted a v-type filter with an integral filter plate. The concentration range of antibiotics in water was 332.3-670.9 ng/L after filtration. SAs constituted the most abundant antibiotic, accounting for 45.3% of total antibiotics. The average concentrations of SMR and STX were 135.5 ng/L and 70.5 ng/L, respectively. PEN and LIN were the two smallest concentrations of antibiotics, with an average concentration of 17.6 ng/L and 17.1 ng/L, respectively. OFC, ERC and TMP accounted for 29.34% of the total antibiotics, and the highest concentrations were 45.2, 40.8 and 47.5 ng/L, respectively.

The total concentration range of antibiotics in the effluent water was 199.4-320.1 ng/L. The concentration of TC was the lowest, with an average concentration of 10.9 ng/L. The contents of LIN and PEN were slightly higher than those of TC, with an average concentration of 12.7 and 13.5 ng/L, respectively. The average concentration of STX was 51.7 ng/L, much lower than that of 115.2 ng/L in the effluent of WP-A.

Table 3

The concentration of antibiotics in each stage of WP-B (ng/L).

Testing items	Antibiotic compounds										
	TC	DXC	OFC	ERC	TMP	PEN	ROX	LIN	SMR	STX	
Raw water (n=12)	Max <sup>a</sup>	57.3	129.0	86.4	95.2	101.7	59.6	nd	38.7	332.3	156.9
	Min <sup>b</sup>	8.4	40.7	31.8	26.0	47.2	9.2	nd	16.6	149.3	41.2
	Med <sup>c</sup>	30.1	88.3	59.5	56.4	76.7	26.0	nd	26.3	231.5	105.4
	Mean	32.1	93.8	63.0	56.9	85.5	14.3	nd	25.6	227.2	103.4
	Fre <sup>d</sup> (%)	100.0	100.0	100.0	100.0	100.0	100.0	nd	100.0	100.0	100.0
Unfiltered	Max	36.4	95.6	57.4	66.7	86.9	35.8	nd	24.2	282.0	116.1

water (n=12)	Min	5.7	45.1	32.2	26.8	19.9	8.8	nd	11.8	65.3	47.8
	Med	25.1	68.6	45.3	42.2	48.5	20.2	nd	16.6	182.2	83.0
	Mean	31.5	67.4	47.7	36.5	36.6	15.0	nd	16.1	170.6	85.3
	Fre(%)	100.0	100.0	100.0	100.0	100.0	100.0	nd	100.0	100.0	100.0
Filtered water (n=12)	Max	34.6	83.6	59.4	74.1	98.0	37.8	nd	27.8	276.0	101.3
	Min	4.1	38.7	30.8	11.1	14.8	5.6	nd	8.8	62.4	15.8
	Med	20.4	60.5	45.2	40.8	47.5	17.6	nd	17.1	135.5	70.5
	Mean	22.0	59.0	47.1	35.8	32.2	12.4	nd	14.8	120.3	78.5
Effluent water (n=12)	Max	18.1	62.0	38.1	41.6	41.2	25.3	nd	19.7	120.3	78.3
	Min	4.0	24.1	22.9	9.4	5.7	5.7	nd	8.3	45.1	12.6
	Med	10.9	42.4	29.5	21.0	21.8	13.5	nd	12.7	72.3	51.7
	Mean	10.0	38.4	27.9	11.9	16.6	9.8	nd	10.7	65.4	57.8
	Fre(%)	100.0	100.0	100.0	100.0	100.0	100.0	nd	100.0	100.0	100.0

a: Maximum, b: Minimum, c: Median, d: Frequency e: Not detected

### 3.3 Removal of antibiotics in the two waterworks

#### 3.3.1 Removal of antibiotics utilizing each treatment unit in WP-A

The total removal efficiency of antibiotics in WP-A ranged from -46.5%-45.1%.

The mechanical flocculation tank of WP-A was two-stage flocculation, with 16 flocculation units in two groups. The flocculation time was 10min, and the velocity gradient was  $100\text{s}^{-1}$ . There were 2 groups of 8 air flotation tanks, with a hydraulic retention time of 16 minutes and a dissolved gas ratio of  $6 \times 10^5$ - $7.5 \times 10^5$  Pa. It can be seen from Fig.3(a) that the coagulation air flotation process exhibited a certain removal effect on all antibiotics except PEN. The antibiotics were bonded on the surface of the flocculus by adsorption and removed with the air flotation process. The average removal efficiencies of TC and DXC were 49.4% and 2.7%, respectively. According to the structure characteristics (bis-tetraphenylbenzene skeleton) of TC and DXC, they belong to hydrophobic organisms, which are easy to interact with the

surface of solid particles. Therefore, it is likely that TC and DXC were removed from water phase to solid phase through adsorption. For PEN, hydrolysis is easy to occur in the water phase, so the detection rate and detection concentration were relatively low. However, due to the hydraulic shear and friction, PEN attached to the particulate matter was transferred from the solid phase to the water phase, resulting in a rising PEN concentration in the water before filtration. The acid dissociation coefficient (pKa) of LIN is 8.78 (Table 1). Under the pH of a neutral environment, LIN exists mainly in the form of cations ( $\text{pH} < \text{pKa}$ ), and furthermore it can be electrostatically adsorbed on the surface of particulate matter (Chen et al., 2010). The average removal rate of LIN in the coagulation process was 42.8%.

Three certain amounts of quinolone antibiotics (QNs: OFC, ERC and TMP) were removed by coagulation air flotation, with the resultant removal efficiencies being 14.0%, 18.0% and 60.0%, respectively. The removal efficiencies of SMR and STX were -43.4%-87.1% and 11.0%-97.3%, respectively. Consequently, the efficiency in removing antibiotics in the coagulation process is related to three things: the characteristics of flocs; the pKa of antibiotics; and the sediment-water distribution coefficient  $K_{oc}$ . The higher the pKa, the more easily it is to be adsorbed by the positively charged flocs (Qiao et al., 2011).

The double-layer filter tank utilized by WP-A was made of anthracite and quartz sand with a filtration rate of 9.7m/h. The backflush was made of air flush firstly, then steam-water combined flushing, and finally high speed water flush. Once the water passed through the filter, the concentrations of other antibiotics increased except those

for TMP, LIN and SMR, and the average removal efficiencies were negative, which indicated there were antibiotic residues in the filter. The removal ranges of TC and DXC were -166.2%-52.6% and -96.1%-98.9%, respectively, and these figures were related to the enrichment residues of antibiotics in the filter material as well as the frequency and effect of backflush. The average removal rate of TMP was 4.4%, indicating that the filter could reduce the TMP content in the in water, which was consistent with the results of Göbel et al. (2007). The average removal rate of STX was -2.4%, which meant that STX retained a certain amount of residue in the filter media.

The effective volume of the disinfection contact pool was 12188m<sup>3</sup> and the hydraulic residence time (HRT) was 35min. Sequential chlorination disinfection with short-term free chlorine followed by chloramine. The residual chlorine concentration of effluent was 1.2mg/L. According to what is shown in Fig. 3(a), the removal rates of all antibiotics in the chlorination process were negative. The antibiotics content in effluent increased significantly compared with that in filtered water, and the increases of different antibiotics ranged from 19.2% to 245.0%. Qiang et al. (2006) found that the removal rates of most antibiotics could reach 90% when the concentration of Cl<sub>2</sub> was 1 mg/L and the contact time was more than 30 minutes . However, because of the low free chlorine content and long residence time in the contact pool, the chloramine disinfection can not reduce the content of antibiotics, the concentrations of SMR and STX increased by 12.2% and 15.4%, respectively. Research showed that when free chlorine concentration was insufficient to promote sulfonamide breakdown,

N-chlorinated sulfamerazine and N-chlorinated sulfamethoxazole can regenerate SMR and STX, resulting in an increase in sulfonamide antibiotic content (Huang et al., 2004; Huber et al., 2003).

The effect of the whole process on the removal efficiency of antibiotics varied greatly (see the error line in Fig. 3(a)), which was mainly related to the fluctuation of the concentration of antibiotics in raw water and the operating conditions. Generally speaking, the conventional water treatment process adopted by WP-A was greatly restricted to removing antibiotic residues. When the water source is seriously polluted by antibiotics, it is difficult to ensure the right quality of water is maintained when employing the conventional treatment process. This was consistent with the results of other studies (Boyd et al., 2003; Niina M. Vieno et al., 2007).

### 3.3.2 Removal of antibiotics via each treatment unit in WP-B

The removal efficiency of antibiotics in the WP-B is shown in Fig. 3(b). It can be seen that each treatment unit had a certain removal effect on antibiotics. The removal efficiency of antibiotics varied from 0.4% to 53.5%, and the total amount of antibiotics decreased from 700.1 ng/L to 275.8 ng/L. Meanwhile the contact time of pre-ozone process in WP-B was 3 minutes, the contact depth was 6.0 m, and the dosage of ozone was 2 mg/L. The removal efficiencies of TC and DXC by the pre-ozonation and coagulation sedimentation processes were 16.3% and 15.6%, respectively. Studies have shown that ozone oxidation is a promising technical measure for the removal of tetracycline antibiotics in water. The removal efficiencies of OFC, ERC and TMP by the pre-ozone and coagulation precipitation processes were



17.2%, 14.0% and 33.6%, respectively, while those for the flocculated air flotation process in WP-A were 14.0%, 18.0% and 60.0%. This indicates that the pre-ozone process could not significantly remove the quinolone antibiotics in water. LIN is mainly excreted from bodies in its original structure combined with bile and feces. This kind of drug is usually easily adsorbed on solid suspensions and subsequently removed (Göbel et al., 2007).

The removal efficiencies of LIN in WP-A and WP-B were both about 30%, and this was mainly due to the coagulation - air flotation process rather than the pre-ozonation process. Andreozzi et al. (2006) also confirmed that ozone decomposition of lincomycin required an hour of contact time. Huber et al. (2005) used ozone countercurrent aeration to treat antibiotics in water, and they reported that 90% -99% of sulfonamides in water could be removed when ozone dosage ( $> 2 \text{ mg / L}$ ) was used for 10-20 minutes. Meanwhile in this study the removal efficiency of sulfanilamide was about 16%. This is because WP-B was located in a typical low plain landform, and the soil consisted of seashore immersed saline soil. Consequently, the salinity of the soil was high as was the level of mineralization, and the specific geological conditions made the concentration of bromide ions in the water source high. In order to prevent bromate from exceeding the standard, the ozone dosage and contact time of the pre-ozone process in WP-B should not be high.

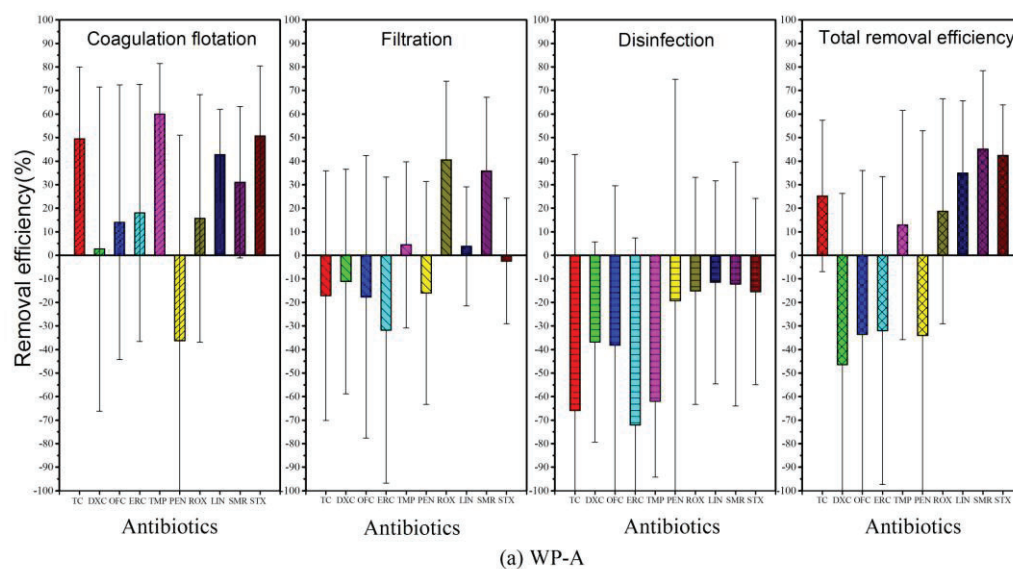
The v-type filter in WP-B was divided into eight groups, and each had a filtration area of  $113.2 \text{ m}^2$  and a filtration rate of  $7.30 \text{ m/s}$ . The filter media was a single layer of homogeneous quartz sand with gas-water backwashing. The removal efficiencies of

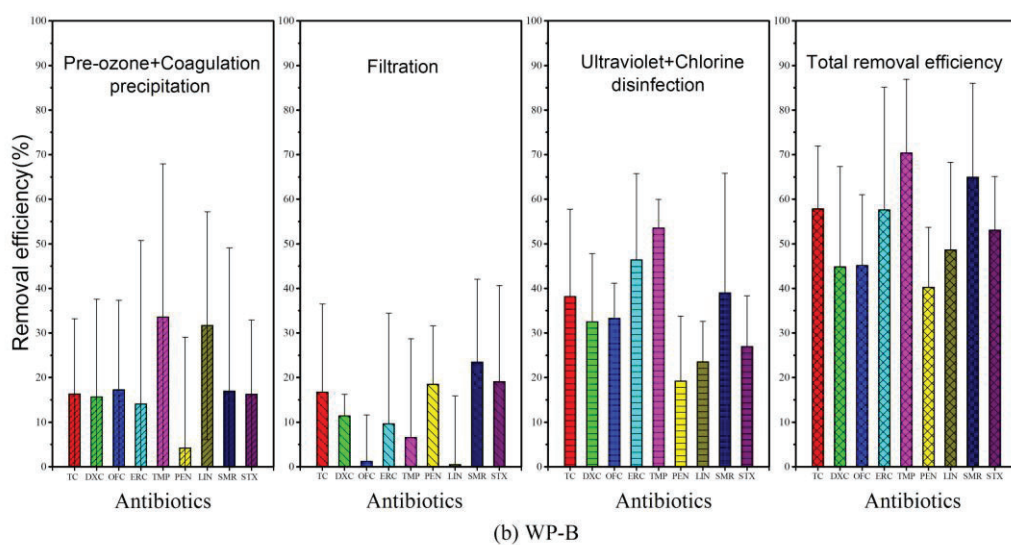
all antibiotics in the v-type filter were 0.4%-23.5%, while the content of all antibiotics in the filtration process in WP-A increased except that for TMP, LIN and SMR. The differences in antibiotic removal outcomes between the two filtration processes may have two reasons. One is that the adsorption performance of filter material (homogeneous quartz sand) in WP-B was better than that of filter material (anthracite and quartz sand) in WP-A. The other is that the backwashing effect of the v-type filter was better than that of an ordinary filter. Therefore, the filter material in WP-B was relatively clean, so there was no antibiotics accumulation or small accumulation.

WP-B was disinfected by the combination of ultraviolet ray and chlorine, with the ultraviolet transmission rate of @235.7nm 90% and the lowest ultraviolet dose of 40mJ/cm<sup>2</sup>. Liquid chlorine was used for chlorine disinfection. The residual chlorine concentration in the effluent was 0.5-1.2 mg/L. Compared with the removal efficiency (-245.0%-11.4% ) of the chlorine disinfection process in WP-A, the efficiency in removing of antibiotics utilizing the ultraviolet-chlorine combined disinfection process in WP-B was superior. In fact the removal efficiency was 19.2%-53.5%. On the one hand, this may be due to the role of ultraviolet disinfection process while on the other, it may be due to there being fewer precursors of antibiotics in water. Ultraviolet disinfection had a better effect on the removal of antibiotics which were easily degraded by light such as quinolone antibiotics, and the removal efficiencies of OFC, ERC and TMP were 33.3%, 46.7% and 53.5%, respectively. The removal efficiency of SMR and STX by ultraviolet-chlorine combined disinfection process in WP-B was 39.0% and 27.0%, respectively. Results were in contrast for

sulfamethoxazole, with easy UV degradability reported by Kim and Tanaka (2009). In this context, adjustments in the UV dose or contact time may be investigated to get higher removal (Collado et al., 2014).

The total removal efficiency of antibiotics was 40.3%-70.3% in WP-B, which was better than that in WP-A's conventional treatment process. It demonstrated that the total removal of antibiotics in water can be improved via the deep treatment process such as pre-ozone, enhanced coagulation and ultraviolet disinfection. The removal of antibiotics mainly occurred during ultraviolet-chlorine disinfection, and the filtration process exhibited the lowest removal outcome. The removal of TMP throughout the entire process was the best (70.3%), followed by SMR (64.9%). Although the treatment process in WP-B proved to be better in the removal of antibiotics, it did not completely remove antibiotics in water.





**Fig. 3** Removal efficiencies of antibiotics in WP-A and WP-B

### 3.4 Human health risk assessment

Previous studies have shown that dysbacteriosis is associated with multiple cancers, and repeated use of specific antibiotics can significantly increase the risk of certain cancers (Boursi et al., 2015). The health risk assessment model recommended by the USEPA (USEPA, 2001) was adopted in this study. Based on the analysis of the water quality of WP-A and WP-B, it showed that the removal efficiency of antibiotics in WP-A was poor and in a more disadvantageous state (see Fig.3). Therefore, considering the most disadvantageous situation, the concentration of antibiotics in the main pipe of WP-A were chose to evaluate the health risk. Konz et al. (1989) pointed out in the Exposure Factor Manual that direct or indirect daily water consumption of people's different age groups showed a logarithmic normal distribution. The daily water consumption of adults older than 21 years of age was 2.985L in the 95%

confidence interval. Skin permeability coefficients, non-carcinogenic reference doses and human carcinogenic intensity coefficients of the 10 antibiotics are given in Table 4.

Based on the distribution and migration data of 10 antibiotics in the water supply network, the exposure dose of antibiotics in water through drinking water and skin contact was simulated by the Monte Carlo method (see Table 5). It is shown that the exposure dose through skin contact was much less than that through drinking water, while the exposure dose from drinking water in adult males was slightly higher than that of adult females, and the exposure dose from skin contact was lower than that of adult females. EPA stipulates that when the carcinogenic risk index of pollutants is less than or equal to  $1 \times 10^{-6}$ , the carcinogenic risk is considered acceptable. When the carcinogenic risk index of pollutants added is higher than  $1 \times 10^{-4}$ , the risk is considered unacceptable. Fig. 4 depicts the level of carcinogenic and non-carcinogenic risk associated with exposure to drinking water. TC, DXC and STX had the highest levels of carcinogenic risk, which was in the order of  $10^{-7}$ , only one order of magnitude different from the warning value (dashed horizontal line), and the other antibiotics were in the order of  $10^{-8}$ . Health risk assessment results showed that the risk of carcinogenesis and non-carcinogenesis caused by multiple antibiotics in drinking water were acceptable (red line).

The level of risk associated with exposure to antibiotics through skin contact is shown in Table 6. As shown in this particular table the non-carcinogenic risk of antibiotic skin contact ranged from  $10^{-12}$  to  $10^{-7}$  magnitude, and the carcinogenic risk

ranged from  $10^{-13}$  to  $10^{-10}$  magnitude, which was below the alert value and therefore deemed acceptable. The risk posed by unsafe drinking water was much higher than that of skin contact, and this the risk was higher for adult males than adult females, while the skin contact route presented the opposite rule. The total carcinogenic risk and non-carcinogenic risk of 10 antibiotics in drinking water were simulated and calculated. Results showed that the total carcinogenic risk (male  $5.64 \times 10^{-7}$ , female  $5.45 \times 10^{-7}$ ) and total non-carcinogenic risk (male  $5.78 \times 10^{-4}$ , female  $5.59 \times 10^{-4}$ ) were at acceptable risk levels.

Table 4

Selected values of antibiotic related indexes.

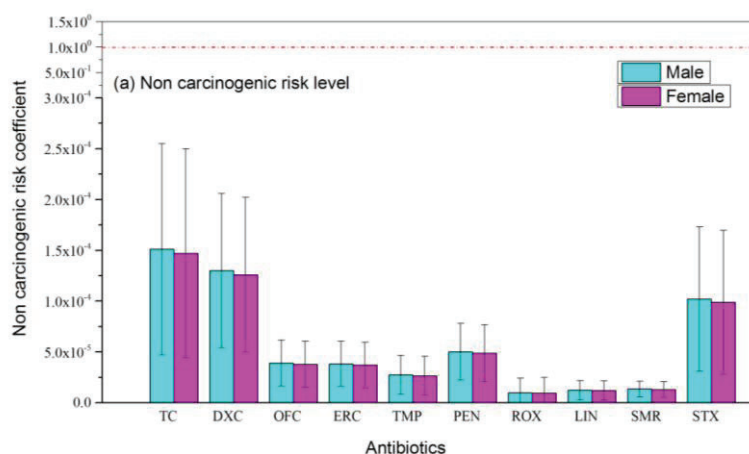
Antibiotics	Skin permeability coefficient (cm/h)	LD <sub>50</sub> (mg/kg)	Non carcinogenic reference dose (mg/kg/d)	Human carcinogenic intensity coefficient (kg·d/mg)
TC	5.82E-07	678	0.02712	3.05E-02
DXC	4.84E-06	1870	0.0748	1.30E-02
OFC	9.35E-06	3590	0.1436	7.51E-03
ERC	1.03E-04	5000	0.2	5.69E-03
TMP	8.17E-04	5300	0.212	5.42E-03
PEN	7.47E-08	2000	0.08	1.23E-02
ROX	4.58E-07	665	0.0266	3.10E-02
LIN	5.10E-05	4000	0.16	6.86E-03
SMR	2.40E-04	25000	1	1.47E-03
STX	2.32E-03	2300	0.092	1.09E-02

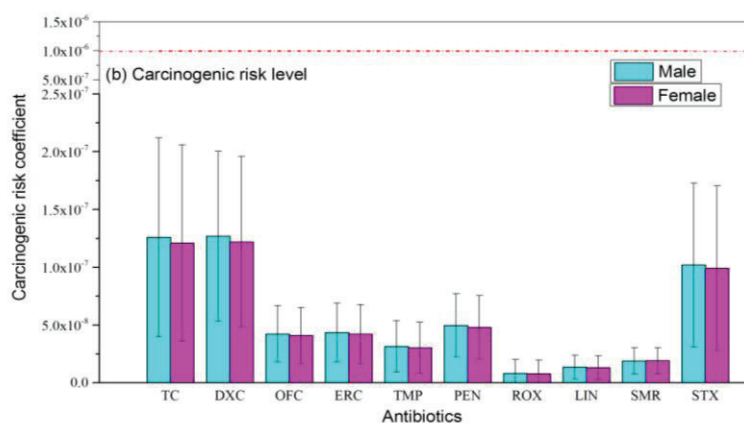
Table 5

Exposure rates of antibiotics to humans through drinking water route and skin contact route.

Antibiotics	Drinking water route				Skin contact route			
	Adult males		Adult females		Adult males		Adult females	
	Mean	Stan <sup>a</sup>	Mean	Stan	Mean	Stan	Mean	Stan
TC	4.12	2.77	3.95	2.77	3.66E-6	4.21E-6	7.01E-6	9.27E-6
DXC	9.69	5.57	9.4	5.57	7.17E-5	7.48E-5	8.64E-4	1.70E-4
OFC	6.53	3.23	5.43	3.20	8.04E-5	8.37E-5	1.55E-4	1.92E-4
ERC	7.68	4.43	7.41	4.41	1.20E-3	1.25E-3	2.32E-3	2.86E-2
TMP	5.84	4.04	5.63	3.99	7.26E-3	8.30E-3	1.40E-2	1.83E-2
PEN	4.04	2.21	3.9	2.21	4.60E-7	4.71E-7	8.87E-7	1.09E-6
ROX	0.26	0.40	0.25	0.38	1.82E-7	3.55E-7	1.41E-7	7.68E-7
LIN	2.00	1.51	1.92	1.48	1.55E-4	1.87E-4	1.72E-4	4.10E-2
SMR	13.51	7.63	13.04	7.67	4.97E-3	5.10E-3	9.54E-3	1.18E-2
STX	9.41	6.48	9.05	6.41	3.33E-2	3.83E-2	3.81E-2	8.69E-2

a: Standard deviation





**Fig. 4** Risk levels of antibiotics in drinking water for different populations: (a) Non-carcinogenic risk level; (b) Carcinogenic risk level

Table 6

Health risk caused by skin contact of different groups.

Antibiotics	Non carcinogenic risk				Carcinogenic risk			
	Adult males		Adult females		Adult males		Adult females	
	Mean	Stan <sup>a</sup>	Mean	Stan	Mean	Stan	Mean	Stan
TC	1.35E-10	1.60E-10	2.57E-10	3.36E-10	1.11E-13	1.28E-13	2.15E-13	2.91E-13
DXC	9.59E-10	1.03E-09	1.85E-09	2.30E-09	9.31E-13	9.87E-13	1.81E-12	2.26E-12
OFC	5.58E-10	5.97E-10	1.08E-09	1.32E-09	6.00E-13	6.32E-13	1.17E-12	1.49E-12
ERC	6.03E-09	6.49E-09	1.16E-08	1.43E-08	6.83E-12	7.31E-12	1.33E-11	1.71E-11
TMP	3.42E-08	3.97E-08	6.54E-08	8.67E-08	3.91E-11	4.55E-11	7.62E-11	1.03E-10
PEN	5.74E-12	5.98E-12	1.10E-11	1.33E-11	5.63E-15	5.81E-15	1.10E-14	1.35E-14
ROX	6.82E-12	1.41E-11	1.31E-11	3.02E-11	5.62E-15	1.18E-14	1.09E-14	2.41E-14
LIN	9.69E-10	1.24E-09	1.86E-09	2.57E-09	1.06E-12	1.31E-12	2.06E-12	2.89E-12
SMR	4.94E-09	5.22E-09	9.53E-09	1.16E-08	7.23E-12	7.59E-12	1.41E-11	1.75E-11
STX	3.61E-07	4.22E-07	6.97E-07	9.47E-07	3.60E-10	4.23E-10	7.01E-10	9.39E-10

a: Standard deviation



#### 4. Conclusions

The total antibiotics content in WP-A ranged from 134.5 ng/L to 1531 ng/L and in WP-B it ranged from 199.4 ng/L to 941.9 ng/L. The seasonal distribution of antibiotics in raw water was significant, and most antibiotics existed in larger concentrations in winter than in summer. The most efficient method for removing antibiotics was the ultraviolet + chlorine disinfection stage, followed by pre-ozone + coagulation precipitation process. In both drinking water plants it was evident that the filtration technology was not very efficient. The risk level of TC, DXC and STX in drinking water was significantly higher than that of other antibiotics, while the risk level of STX in skin contact was the highest. The risk posed by unsafe drinking water was significantly higher than the dangers of skin contact, but the risk of carcinogenesis and non-carcinogenesis caused by antibiotics was at an acceptable level.

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