Research & Reviews: Journal of Pharmaceutical Analysis

Antibiotic tetracycline in the environments — A review

Po-Hsiang Chang[1], Wei-Teh Jiang[1], Zhaohui Li[2]*, Jiin-Shuh Jean[1], Chung-Yih Kuo[3]

[1]Department of Earth Sciences, National Cheng Kung University, 1 University Road, Tainan 70101, Taiwan

[2]Department of Geosciences, University of Wisconsin – Parkside, 900 Wood Road, Kenosha, WI 53141-2000, USA

[3]Department of Public Health, College of Health Care and Management, Chung Shan Medical University, No. 110,Sec. 1, Chien-kuo N Road, Taichung 40242, Taiwan

Review Article

Received date: 20/05/2015
Accepted date: 27/07/2015
Published date: 03/08/2015

***For Correspondence**

Zhaohui Li, Department of Geosciences, University of Wisconsin – Parkside, 900 Wood Road, Kenosha, WI 53141-2000, USA. Tel.: +1 262 595 2487, Fax: +1 262 595 2056.

E-mail: li@uwp.edu

Keywords: Tetracycline, Adsorption, Residues, Resistance, Ecology toxicity, Detection technology

ABSTRACT

Tetracycline's (TC) are widely used in the treatment of animal diseases, as well as additives in animal feed as a sub-therapeutic dose for animal disease prevention and promotion of animal growth. Due to their extensive use and wide prevalence and persistence in the environment, there might be unforeseeable consequences. The long-term application of livestock excreta can cause the accumulation of antibiotics in the soil, have a negative effect on the ecological environment and result in TC residues. Detection of antibiotics in rivers and lakes has been reported widely. However, a systematic review on discussing the residual conditions in a variety of environmental and behavior of TC, as well as various factors affecting TC adsorption and retention in the environment, is needed and presented here. In the same breadth, the resistance research on animals, plants, and microorganisms and resistant mechanisms and substitutes was also discussed. A holistic overview of the existing detection technologies and the evaluation of environmental impact caused by TC and the latest studies to demonstrate the environmental impact by drug have also been summarized.

INTRODUCTION

Antibiotics

The antibiotics were produced by microorganisms to inhibit or kill other microorganisms at low concentrations. Widely-used antibiotics, according to the chemical structure of sub-categories can be divided into beta-lactam, quinolone, tetracycline (TC), aminoglycosides, macrolides and sulfonamides. For a long time, antibiotics are largely utilized for the cure of diseases of humans and animals. They are also added to animal feeds for animal disease prevention and promoting growth. As most of the antibiotics cannot be absorbed by organisms completely, about 90% of antibiotics as prototype or metabolites were released via the manures or urine of patients and livestock into the environments, such as soil and water, resulting in some degrees of contamination. Currently, the problems of antibiotics pollution have become an important environmental issue in many advanced countries (such as the European Union and the United States) and related researches are rapidly developed.

Because antibiotics are usually used in medical and animal husbandry, antibiotics in the environment are mainly derived from the medicinal and agricultural drugs. Human consumption of animal food which has antibiotic residues, usually manifested chronic poisoning, further cause the deformities, mutations, cancers, and embryo toxicity [1]. Many antibiotics are water-soluble, with about 90% excreted from body via urine and 75% via feces [2]. Therefore, some of the first howls of pain are likely to be heard in contamination of aquatic environment. However, until the late 1990s, there had been no systematic studies to investigate the

residues of antibiotics in the aquatic environment and contamination problems. Recent studies showed that more than eighty kinds of antibiotic drugs, such as macrolide, sulfonamide, and TC were detected in the waters in Austria, Germany, UK, Italy, Spain, Switzerland, the Netherlands, the United States, and Japan [3-5].

Source of TC

Antibiotics in the environment mainly come from the medical and animal husbandry. The medical antibiotics include: (1) discarded expired antibiotics in hospital; (2) antibiotic residues in the vials and equipment's; (3) discharged prescription antibiotics via the feces and urine of patients. Animal husbandry antibiotic may include: (1) loss of the veterinary drug production process or the expired drugs abandon; (2) the residues from used drugs; (3) the residues in urine or feces from animals that had added sub-therapeutic doses over long-term feeding. Untreated animal manures as agricultural organic fertilizer were one of the major pathways of antibiotics into the soil environment. In recent years, with an increase in animal husbandry as well as the development of feed industry, TC, macrolides, penicillin, sulfonamides antibiotics as feed additives were more widely used in livestock farming and aquaculture [6]. According to statistics, the usage of antibiotics in animal farming was about 11,000 tons each year in the United States, accounting for about 70% of the total amount of antibiotics consumption [7]. The same estimation was also made for EU and China [8]. In veterinary antibiotics, oxytetracycline (OTC) and TC are the most widely used ones.

Although antibiotics as veterinary drugs and feed additives to prevent disease and growth promotion played an important role in fighting against livestock and poultry diseases, the antibiotics via oral or intramuscular injection into the animals cannot be absorbed completely; therefore most of them were excreted with urine and feces. It was estimated that amounts of antibiotics as prototype or metabolites form excreted with urine or feces were about 40 - 90% of the dose admitted [2,9-11]. The amount of chlortetracycline (CTC) at the treatment pool of pig's manure could be up to 1.0 mg kg^{-1} [12], while the amount of TC in liquid organic fertilizer could reach to 20 mg kg^{-1} [13]. Thus, when employing manures as organic fertilizers containing untreated antibiotics to farmland, these antibiotics become the major sources of veterinary antibiotics in the soil environment [14].

Why tetracycline

TC antibiotics were made by separation from Streptomyces spp., such as *S. viridifaciens*, or *S. aureofaciens* [15]; CTC by separation from *S. aureofaciens* [16]; and OTC by separation from *S. rimosus* [17]. On medicinal use, TC had inhibitions in leptospirosis, actinomycetes, rickettsial, mycoplasma and large virus, thus, is called broad-spectrum antibiotics [15,18]. TC is by far the most frequently used antibiotics in the animal husbandry with the largest in global production and sales [19]. With agricultural application of livestock manure directly into the soil environment, TC may cause ecological health and safety impact [2], and thus the research on the fate and transport of TC in the environment received special attention.

The use of antibiotics can induce pathogen resistance, especially due to the long-term use of large doses of antibiotics in feeds. In addition, antibiotics can lead to the generation of antibiotic resistance genes that can be passed between different bacteria [20]. Once these resistance genes were transferred to pathogenic bacteria, the potency of threat to human health will be increased. In addition, other effects of TC include superinfection, liver toxicity, TC stained teeth, renal toxicity, gastrointestinal reactions and allergic reactions [20,22-24].

The impact on plant growth and development may be even worse, when antibiotics containing animal manure and municipal sewage were applied to farmlands. There were about 0.009 ~ 0.012 mg L^{-1} TC in animal manure product used for liquid cultures of X'mas flower. The antibiotics effect on plant growth depends on its chemical nature, dose of usage, soil adsorption capacity, and plant species. Therefore, from the above-mentioned health problems, resistance and inhibition of plant growth, the research on how to remove the antibiotics contamination from water, especially drinking water and groundwater, will be a momentous issue.

More details on tetracycline

TC has three pKa values with pKa1, pKa2, and pKa3 at pH 3.3, 7.7, and 9.7, respectively **(Figure 1)** [25,26]. It has a molecular weight of 444.44 g mol^{-1}. The pKa1 is due to the protonation of the oxygen bound in the C3 position, the pKa2 is from the protonation of the dimethyl amine functional group, while the pKa3 originated from the protonation of the oxygen bound in C10 and C12 positions [26]. A later study confirmed that pKa2 was due to the protonation of oxygen bound in C10 and C12 positions and pKa3 was due to the protonation of dimethyl amine functional group bound in the C4 position **(Figure 1)** [27]. At pH < 3.3, TC exists in a cationic form; at pH = 3.3 ~ 7.7, TC exists as a zwitterions. Wherein, almost nearly electrically neutral at pH = 5.5. As the pH increases, the proportion of the negative charge in the TC molecule increases. When pH reaches to 7.0, the TC molecule 25% of the TC is in anionic form [25]. At pH > 7.7, TCs exist as anion (monovalent anion, + — — and divalent anion, 0 — —).

In addition, its log Kow (distribution coefficient between octanol and water) value was -2.2 to -1.3 and its solubility was about 1.7 g L^{-1} [28,29].As the Kow value represents the adsorption of hydrophobic organic matters in the soil, the low Kow value of TC indicates that it is more hydrophilic, which could be confirmed from its high solubility and low adsorption capacity on the activated carbon [30]. In addition, the solid-liquid distribution coefficient kd is 300 ~ 2000 L kg^{-1} [31].

The name of TC originated from its four basic rings (A, B, C, D) **(Figure 1)**. TC has a higher solubility in alcohols such as methanol and ethanol, but its solubility was low in other organic solvents such as ethyl acetate, acetone, and acetonitrile

[32]. The precise distribution of the dissociation constant is still unclear [33]. Under alkaline conditions, hydrogen bonds between N-4 and OH-12a were present in the structure of TC **(Figure 1)** [34]. Under acidic and neutral conditions, due to protonation on N-4, the original bond is broken, the structure is damaged, and the hydrogen-bonding interactions occur in the O-3[35]. TC often contains a small amount of impurities (such as degradation products). The main impurities of TC are epitetracycline (ETC) and anhydro-tetracycline (ATC). At pH = 2~6, the epimerization of TC to formed ETCs will occur, mainly in the C-4 [36,37]. When TC is extracted from environmental samples using McIlvaine buffer solution under pH 4, the formation of ETC can be negligible [38]. Under solution pH 2 extraction using McIlvaine buffer for TC extraction from animal feed, only ETC was found and OTC or TC epimerization did not occur [39]. Under strong acidic conditions, there is a proton transfer at O-11/O-12. The H at C-5a and OH at C-6 on ATC were from dehydration reaction with most of ATCs stable [31,40]. In the case of the unidentified degradation products, it proved that significant degradation (degradation rate > 90%) of TC occurred under strong acidic conditions (1 mol L^{-1} HCl) after 4 days, while the degradation rate was 40% for OTC. For CTC the original structure was still maintained with a degradation rate of 6% [41]. Because TC is very easy to be degraded into its 4-isomers, in order to obtain well reproducibility, under extraction and measurement conditions, the inspection of degradation possibility is very important.

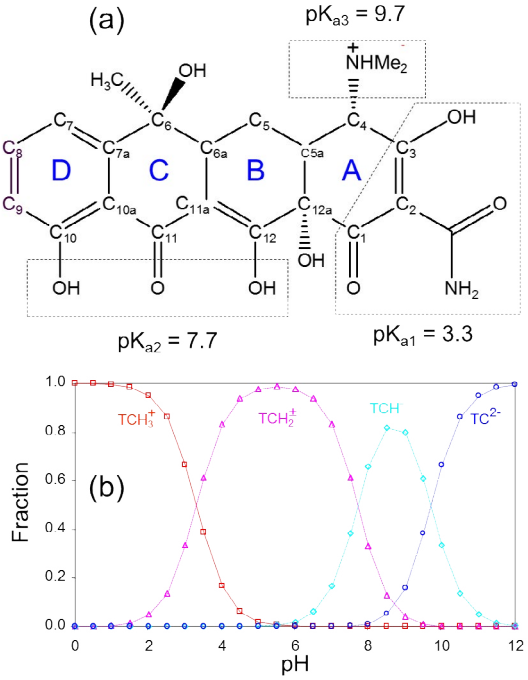

Figure 1. Molecular structure of TC on an planar view (a) and speciation under different pH (b).

TC has 64 different tautomers. However, in general, there are two common structures, one is extended **(Figure 2a)**, wherein the dimethyl amine functional group is below the surface of four rings; compared to the twisted **(Figure 2b)**, in which the functional group is above the surface of four rings. The former is present in the alkaline solution, while the latter present in acidic to neutral solutions [42-44]

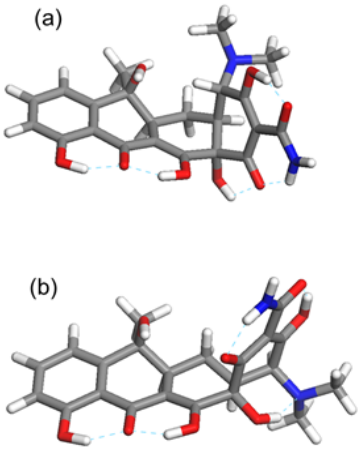

Figure 2. Conformation of TC in twisted (a) and extend form (b).

RESIDUAL OF TETRACYCLINE IN THE ENVIRONMENTS

The antibiotics are frequently detected in surface water, groundwater, and wastewater, and have strong adsorption onto sediments as studied in recent years [44-53]. These studies have confirmed the widespread existence of the antibiotics in soils,

surface waters, ground waters, sediments, urban sewages, and manures. Because of its low price, large-scale and persistence use in many countries resulted in residues in the environment. When TC enter the human or animal body, changes of these drugs made their physiochemical properties and ecological toxicities varied due to oxidation, reduction, hydrolysis, and conjugated bonding (Gibson and Skett, 1986), but after discharge, the metabolized substances may restore its parent compounds [54].

Water

The use of antibiotics and growth hormones on human and animals have a major impact on the surface water and groundwater. Twenty years ago, Wattes first described antibiotic residues in surface water, and their research team detected sulfonamides and TCs content of 1 μg L^{-1} in rivers of the United Kingdom, followed by more antibiotics being found in surface water. Detected in 139 rivers in the United States in 1999 and 2000, The concentrations of TC, macrolides, sulfonamides, and fluoroquinolones ranged between 0.06 and 0.69 μg L^{-1}, and 95 known organic wastewater contaminants (OWCs) were detected in 82 rivers with the concentrations of antibiotics in the range between 0.01 ~ 150 μg L^{-1} [55]. The TC and its decomposition products were examined in the soil and groundwater of long-term application of manure, the concentration of each substance was less than 0.5 mg L^{-1} [56]. In Korea, the antibiotics were detected in over 80% of the surface water, drinking water, and wastewater [57].

In addition, the use of antimicrobial drugs resulted in discharges of them into the domestic sewage and eventually into the wastewater treatment plants. TC was still detected after wastewater treatment process in eight wastewater treatment plants of five cities in Canada with the maximum concentration up to 0.01 μg L^{-1} [58]. Samples from several wastewater treatment plants in Wisconsin showed 80% detection of TC and OTC in the influent waters with concentrations of 48 ± 3 and 47 ± 4 μg L^{-1}, respectively. After wastewater treatment process, their concentrations were still 3.6 ± 0.3 and 4.2 ± 0.4 μg L^{-1}, respectively [59]. In addition to the contamination of the environment, the wide presence of antibiotics in the environment may increase the spread of bacterial resistance [19,47].

The pollution of antibiotics on the environment is global problem; such substances generally possessed high biological activity and persistence, which determines its inevitable potential ecological environmental risks. Especially, with the rapid development of modern animal husbandry, the threat of antibiotics to the ecosystem as well as human health is increasing. Although, the emerging pollutants such as the pharmaceuticals and personal care products (PPCPs) caused more problems of ecological and environmental, and attracted more and more attentions, the study of PPCPs to environmental contamination is still in great need [44,60-62].

Soil

Numerous studies have shown that antibiotic residues in the soil or manure soil reached 11 - 300 μg kg^{-1}, and its content is close to the standard of other pesticides in the soil [14,13,63-67]. There are some discrepancies among researches' results. The contents of CTC, OTC, and TC in animal manures were up to 46, 29 and 23 mg kg^{-1}, respectively [68]. In Italy and Turkey, the contents of OTC and CTC in manure soil were up to 500 μg kg^{-1} [69,70]. In Germany, Denmark and Canada, OTC, CTC and TC contents were lower than 100 μg kg^{-1} [63,70,71]. These results were related to the climatic factors of different geographic areas such as temperature and humidity which affect the environmental behavior of antibiotics in the soil; usually high temperature and high humidity are conducive to the degradation of antibiotics [72]. In addition, there are other important control factors, such as manure species (pig manure, chicken manure, etc.), fertilization methods, and sampling time after fertilization. Soil characteristics and farming conditions both will affect the antibiotics content in manure soil, and these factors may be interact each other. The antibiotic contents in manure soil may have great changes with time [73].

Animal manure as organic fertilizer was applied to the soil to provide nutrients. The residual antibiotic in the fecal will be accumulated in soil during long-term use of manure. In the research of two different soils in German from 2001-2003, it was found that TC was more persistent in the sandy loam which contain manure, and its concentration was maintained at 150 μg kg^{-1} [13]. Meanwhile, there were about 330 grams of TC and 7 grams of CTC derived from the manure per hectare of soil (at the depth of 0 to 30 cm) investigated from 2000 to 2002. The highest average TC concentration was 400 μg kg^{-1} (0 to 10 cm of agricultural surface soil), 86.2 μg kg^{-1} (0 cm to 10 cm), 198.7 μg kg^{-1} (10 cm to 20 cm), 171.7 μg kg^{-1} (20 cm to 30 cm), respectively. On the other hand, the CTC concentration was 4.6 to 7.3 μg kg^{-1} in the three sublayers at the depth of 30 to 90 cm and no CTC was detected in groundwater, which suggested that TC can be strongly adsorbed onto soil with a poor mobility [13] found A TC concentration of 52 μg kg^{-1} was found in soil in Canadian [63]. The research on the migration of TC in the system of animals - feces - soil also suggested that long-term application of antibiotic-containing manure can lead to antibiotic residues in the soil, and that cow's manure applied to the soil had 281.34, 67.25, and 3.60 mg kg^{-1} of TC after 22, 70 and 114 days at the depth of 0-5 cm soil [73]. The above studies illustrate wide use of TC in the world also resulted in slow degradation in the field, and accumulation of TC in the manure soil caused a great deal of potential threat to the soil environment.

Manure

The antibiotics could not be completely absorbed by the organisms. About 30 to 90% TC came out as prototype effluent with urine or feces, and are persistence long-term in the soil. Analyses of 54 samples of chicken's manures and 28 samples of cow's manures collected from eight cities in China, showed the detected OTC concentration of 59060 and 59590 μg kg^{-1} and

CTC concentration of 21060 and 27590 μg kg^{-1} in chicken's and cow's manure, respectively [74]. Analyses of 30 pig manure, 20 chicken, and 30 soil samples collected from Australia reveled the maximum concentrations of CTC, OTC, and TC at 46000, 2900,0 and 23000 μg kg^{-1} [68]. In intensive livestock farms, studies showed that 21% OTC residues in sheep feces, 17 to 75% CTC residues in the bull's feces [75]. In a five-day oral experiments, the additional of 60000 μg kg^{-1} dosage of OTC onto the fifty simmentaler resulted in a half-life of 30 days, and the OTC residues was still detected 5 months later with a content of 820 μg kg^{-1} [13].

Visceral and muscle tissues of animals and the others

There are 100 beef and chicken samples collected from the southern part of Taiwan, which have 41 and 27 valid samples, respectively [76]. Thirty-five out of 41 beef samples have TC residues, 6 of 41 have TC and CTC residues. 27 chicken samples had the CTC residues. In Japan, during an observation from May 1985 to March 1998, among the 424 samples (147 bovine kidney and 277 pig kidney) 131 samples contained TC, CTC, OTC, and doxycline (DC) residues [77]. In an investigation in Belgium in 1998, using the enzyme immunoassay (ELISA) method, 12 and 19 samples were positive out of 19 pork and 21chicken, respectively [78]. Further measurement by high-performance liquid chromatography (HPLC) revealed 10 and 18 samples containing doxycline, respectively. In Belgium in 2001, among the 250 samples (228 broilers and 27 turkey thigh), 16 had doxycline detected [79]. In addition, several reports revealed antibiotic residues in animal bones [37,80,81].

INFLUENCE FACTORS OF TETRACYCLINE ADSORBED IN THE ENVIRONMENT

The adsorption is a critical factor affecting in residues, distribution, migration, transformation, and final destination of antibiotics. So, many studies have focused on the antibiotics adsorption behavior. These studies include OTC adsorption on soils and in combination of clay minerals and organic matters [25], on clay mineral [47], on aluminum and iron oxide [49], on metal oxide-rich soil [48], on many soils [48,53,82,83]. Under natural conditions, many factors influenced antibiotics adsorption behavior from water, including the physical and chemical properties of antibiotics as well as environmental factors such as temperature, pH value, ionic strength, multivalent metal ions, hydrogen bonds, coordination bonds, and cation dipole bond.

Temperature

Normally, the adsorption process of contaminants on soil or clay minerals was either exothermic or endothermic. The research of thermodynamic behavior of norfloxacin adsorption on soil showed that the adsorption process was an exothermic reaction [84]. On the other hand, the results showed that the adsorption on clay minerals such as illite and palygorskite was endothermic [45,46], but exothermic on kaolinite [62].

pH

The pH has significant impact on the adsorption by changing the charge state of the antibiotics and adsorbents. OTC, for example, exist as a cation OTC+ at pH < 3.6; as a neutral species OTC0 at neutral 3.6 < pH < 7.5; and as an anion OTC- at pH > 7.5. When the adsorbents such as clay minerals with a large number of exchangeable cations on the surface, OTC+ adsorption will increase with a decrease in pH due to an increased CEC [47]. When the adsorbent is a metal oxide, because the strong variability of surface charges with pH changes, OTC and metal oxide could be repulsion due to the same charge of their surface in the acidic and alkaline solutions, thus, resulting in a lower amount of adsorption. The maximum amount of adsorption occurs at neutral pH [48,49]. When the adsorbent is organic matter, because it contains several functional groups, especially for deprotonated species (such as:-COOH). The degree of deprotonation of functional groups were small in the low pH condition, OTC could be combined with organic matters by hydrogen bonding. As pH increased, -COO- increased with deprotonated enhancement, the hydrogen bonding weakens, resulting in attractive or repulsive interactions of OTC+ or OTC- with -COO- through electrostatic interaction [50;86].

TC can exist as the form of cationic, zwitterion, and anionic respectively in different pH conditions. Under acidic conditions, TC exists as cationic form and adsorption on soil or clay mineral by cation exchange or electrostatic adsorption with a negatively charged of clay mineral surface. Under alkaline conditions, the TC majority exists in anionic form, which will cause the electrostatic repulsion with negatively charged clay mineral or soil surface, thereby reducing adsorption. Therefore, the amount of adsorption will gradually decrease with pH increase.

Cation exchange capacity (CEC)

Generally, the surface area of swelling clays can be divided into the internal and the external surface area. Usually, adsorbents with high CEC values can enhance the adsorption. The TC adsorption on rectorite [86], illite (IMt-2) [44], palygorskite (PFI^{-1}) [45] and montmorillonite (MMT) [44] suggested that the order of the adsorption capacity was MMT > PFI^{-1} > rectorite > IMt-2, in agreement with their CEC values.

Ionic strength and metal charges

A monovalent metal ion like Na^+ and K^+ can affect the adsorption due to competitive with antibiotic as cationic form on adsorption sites. Therefore, based on cation exchange, the increase of the ion concentration will lead to competitive adsorption, thus reducing the amount of adsorption. The adsorption coefficient Kd value is significantly reduced for OTC adsorption on montmorillonite when the NaCl concentration increased from 10 mM to 510 mM [47]. The same trend happened in TC adsorption

on clay minerals [45,46,62,87]. A high ionic strength could significantly reduce the TC adsorption on the humic acid and hydrated ferric oxide [50,88].

The presence of multivalent metal ions (such as Ca^{2+}, Mg^{2+}, Cu^{2+}, Al^{3+}, and Fe^{3+}) is an important factor to control the adsorption behavior of some antibiotics. At high pH, these cations can play a bridging role, connecting the negatively charged part of the antibiotic and the negative adsorption sites of solid surface by covalent bonds, to form complexes of antibiotics and metal ion, thus contributing to adsorption [86]. Addition of Ca^{2+} or Cu^{2+} under alkaline condition would considerably promote the TC adsorption capacity on montmorillonite [72,89]. Simultaneous adsorption and desorption of cadmium and TC on cinnamon soil showed a concurrent increase in TC adsorption in the presence of Cd and the increase was attributed to bridging the TC and soil surface in the presence of Cd [83]. On the other hand, the presence of Cu(II) in the soil solution suppressed the adsorption of TC on soils at pH less than 4.7, due to the competition of Cu^{2+} against TC, TC–Cu complexes in aqueous phase, and the increased positive surface charge of soil by Cu(II) adsorption [90]. Adsorption of TC on Al_2O_3 was involved in the formation of complexes [40]. Meanwhile, coating of hydrous Al oxide (HAO) with soil humic acid significantly suppressed TC adsorption, attributable to altered HAO surface charge characteristics and/or direct competition between Elliott soil humic acid and TC for potential sorption sites [91].

Organic matter and dissolved organic matter

The presence of soluble organic matter is another important factor to control antibiotic-solid interactions. Many functional groups, such as deprotonated –COO– in organic matter, offer the possibility of adsorption sites for antibiotic [92]. Hydrogen bonding between antibiotics and the polar functional groups of organic matter could contribute further to antibiotic adsorption [50]. Generally, the content of organic matter on soil was very low, and it could be utilized to cover the adsorption sites on clay mineral surfaces [91]. At low concentrations, co-adsorption of dissolved organic matter (DOM) could promote further adsorption of antibiotics on the montmorillonite [25]. On the contrary, the significant solubilization of power of DOM when present in high concentration will facilitate removal of antibiotics from sorbents.

Hydrogen bonding

Hydrogen bond is an important mechanism for the adsorption of organic molecules on the surface of clay minerals. It can be regarded as a dipole-dipole interaction. Since hydrogen atoms as a bridge between two electronegative atoms, one caught by covalent bond, another attracted by electrostatic interaction. The organic molecules may form hydrogen bonds with oxyl group or hydroxyl group on the surface of the soil minerals and could be adsorption by water bridging.

BEHAVIOR OF TETRACYCLINE IN THE ENVIRONMENT

Once the antibiotics are effluent into the environments through a variety of ways, they will present different behaviors like adsorption, migration, degradation, and accumulation in a variety of environmental media like soil, water, sediment, and plants. To grasp the migration, transformation, plant uptake, and cumulative characteristics of TC, analyses of their environmental behavior comprehensively could provide efficacious removal of TC from the environments.

Adsorption and migration

Adsorption has an important influence on the migration, activity, and bioavailability of antibiotics, which depends largely on antibiotics and soil characteristics. Furthermore, the adsorption studies of TC, CTC and OTC on different soil properties, such as different pH, clay contents, soil types, cation exchange, anion exchange and organic carbon contents, showed Their strong adsorption on soil (especially for acidic and high viscosity soils) [7]. The study of TC and CTC adsorption on potassium- and calcium-saturated soil clays, humic substances and clay-humic complexes indicated that strongly adsorption occurred on soil clays, followed by humic substances, and then on clay-humic complexes [53]. In addition, the results suggested that the adsorption mechanism was cation exchange and the adsorption capacity of Ca-saturated soil was greater than that of the K-saturated one. Humic substances could weaken the adsorption of TC on the soil, especially on soil that has high organic matter content [50]. Using the method of rainfall simulation plots to investigate the outflow trend of several antibiotics include the TC, CTC, the sulfathiazole work (STZ), sulfamethazine (SMZ), erythromycin (ERY), tylosin (TYL), and monensin (MNS) by runoff [93] found that the TC and CTC concentrations did not significantly reduce after runoff for 1 hour. As a consequence, further confirmed the TCs have a high adsorption capacity on soil. The study suggests that the minerals and organic matters of soil were the main adsorption sites for antibiotics, while hydrophobic property, cation exchange, cation bridging, surface complexation and hydrogen bonding play an important in the process of adsorption [31]. TC adsorption decreased with the reduction of organic matter on cinnamon soil [82].

TCs may be absorbed by plants and aquatic organisms. Some antibiotics did not combine with solid materials, making them easy to enter the aquatic environments, posing a threat to groundwater. In the soil, when TC is leaching into nearby rivers, it will affect the organisms in the river even in the marine ecosystems ultimately. The migration of TC depended on the nature of the different kinds, different metabolic pathways and different doses in the environments.

As for adsorption, our research team used seven clay minerals to uptake TC [44-46,87] under different environment factors like pH value, temperature, or ionic strength. The objectives of these sequential studies were to look for the adsorption mechanisms. One of the most important results showed that the maximum adsorbed amount was 1053 mmol kg^{-1} at pH 1.5 for SAz^{-1}, which is close

to its CEC **(Table 1)**. The cation exchange was the major adsorption mechanism expect for SYn-1 and SWy-2 at low concentration **(Table 2)**. Besides, the isotherm studies demonstrated that Langmuir model was suitable to express the experiment data of seven **(Table 2 and Figure 3)**. To further understand the mechanism of cation exchange, surface complexation or hydrogen bonding, the other clays should be conducted **(Table 3)**. According to published papers, all of the mechanisms were determined by virtues of ionic analysis under unadjusted pH condition **(Table 3)**, the solution pHs were maintained in the range of cation or zwitterion forms after adsorption [45-47,62,87,94]. Thus, the slope of adsorbed and desorbed cations can be used to decipher the adsorption mechanism. Besides, we cannot acquire the mechanism under alkaline or acidic condition but can obtain it from FTIR data [48;95]. On the other hand, not all of the maximum TC adsortion happened when TC was a cation or zwitterion form under the mechanism of cation exchange. Take palygorskite for instance. The Sm was 223 mmol/kg at pH 8.7 when TC was in an anion form **(Table 3)**. The pH adsorption edge effect showed that H+ strongly competed against TC on adsorption sites on clay surface to reduce the adsorption capacity when TC exists as a cation form **(Figure 1)** [45] It seems that, if adsorption mechanism was cation exchange, the maximum adsorption amount is not necessarily located at the same pH condition, it is still determined by other effects like pH or ionic strength effect. As for surface complexation, if the slope of linear between desorbed and adsorbed cations is very low and the adsorbate have no lone pairs like hydrogen, oxygen or fluorine, the mechanism should be surface complexation instead of hydrogen bonding such as TC adsorption on Syn-1 [94], in which the mechanism was attributed to surface complexation **(Table 3)**.

Table 1. Maximum adsorption capacities and CEC values of clay minerals at four pH values.

Clay minerals	Rectorite	PFl-1	SWy-2	SAz-1	SYn-1	SHCa-1	IMt-2
Highest initial concentration (mg/L)	1000	800	3000	3000	2000	2000	2000
Point of zero charge (pHpzc)[a]	4.2 (100)	4.1 (101)	8.35 (102) 8.45 (103)	8.44 (103) 5.88 (104) 8.0 (105) 10.54 (106)	None	8.3 (107)	2.4 (108) 3.5 (109)
Original CEC (meq/kg)[a]	410 (110)	165 (111) 195[b]	850 (111) 764 (112)	1200 (100) 1230 (111)	700~1400 (100)	66 (111)	140 (112)
Sm at pH 1.5 (mg/g)	131	61	404	468	217	330	—
CEC at Sm (mmol/kg)	295	137	910	1053	489	743	—
Sm at pH 4~6 (mg/g)	140	56	340	422	170	350	32
CEC at Sm (mmol/kg)	315	126	766	950	383	788	72
Sm at pH 8.7 (mg/g)	107	99	210	302	122	375	—
CEC at Sm (mmol/kg)	241	223	473	680	275	845	—
Sm at pH 11 (mg/g)	54	23	140	86	59	227	—
CEC at Sm (mmol/kg)	122	52	315	194	133	511	—

[a]Data from Chen et al. (2012) [275] (100), Alexander and Arieh (2000) [276] (101), Panagiota et al. (2007) [277] (102), Stadler and Schindler (1993) [278] (103), Charlet (1993) [231] (104), Zysset (1992) [279] (105), Goldberg and Glaubig (1986) (106), Tombácz (2004) [97] (107), Xia et al. (2009) [280] (108), Lan et al. (2007) [281] (109), Hong et al. (2008) [282] (110), Borden and Giese (2001) [283] (111) and Kahle and Stamm (2007) [284] (112).

b Data from http://www.clays.org/SOURCE%20CLAYS/SCdata.html.

Sm=Maximum adsorption amount.

Table 2. Adsorption behaviors of tetracycline on clay minerals.

Clay minerals	Rectorite	PFL-1	IMt-2	SAz-1	SWy-2	SHCa-1	SYn-1
Kinetic model	Pseudo-second-order model		Elovich model	Pseudo-second-order model			
Equilibrium time (h)	24	2	8	2			8
Adsorption model	Langmuir model		Freundlich model	Langmuir model			
Maximum adsorption amount (mg/g)	pH = 4~6	pH = 8.7	pH = 5~6	pH = 1.5	pH = 1.5	pH = 8.7	pH = 1.5
	140	99	32	468	404	375	217
Adsorbed TC / desorbed cations	1 : 2.5	*	1 : 1.5	1 : 0.9	1 : 1.5	1 : 1.7	1 : 0.2
Major desorbed cation	Ca2+	Ca2+	Ca2+	Ca2+	Ca2+, Na+	Ca2+, Na+	Na+
Swelling amount of d-spacing	17.3 Å at pH 11	0 Å		10.3 Å at pH 8.7 & 11		11 Å at pH 5~6	0 Å
Clay crystallinity	Descend	Unchange		Descend			Unchange
Interaction between clays and TC (FTIR band shift in cm-1	Strong interaction				Medium interaction	Strong interaction	Medium interaction
	+ 5~20	+ 10~15	+ 20~50	+ 6	Unchange	+ 16	Unchange
TC decomposition temperature	410 °C	205 °C	—	—	—	—	—
Adsorption mechanism	Cation exchange		Cation exchange		urfacecomplexation (< 800 mg/L); cation exchange (> 800 mg/L)	Cation exchange	Surface complexation

* Non-linear but positive relation; — data not available.

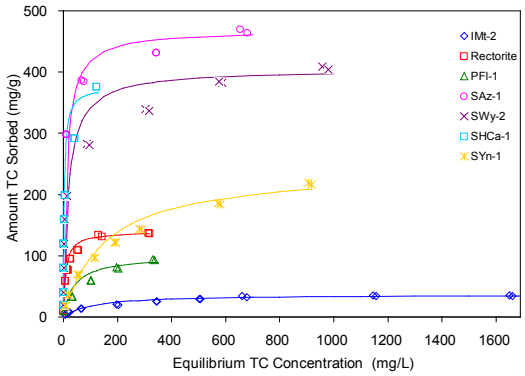

Figure 3. TC adsorption on seven clay minerals. Lines are Langmuir fit to the observed data expect to IMt-2 is Freundlich.

Table 3. The properties of adsorption between clay and iron-oxide minerals and TCs at various pHs.

Adsorbate	Adsorbent	Sm(mmol/kg)	pH	TCform	Isotherm model	Solid/water	Mechanism, TC form	Reference
TC	rectorite	315	4~6	+/-	Langmuir	0.1 g/20 mL	Cation exchange, +/-	[88]
	palygorskite	223	8.7	-				[52]
	illite	72	5~6	+/-	Freundlich	0.1 g/10 mL		[50]
	SAz-1	1053	1.5	+	Langmuir	0.1 g/20 mL		[51,89]
	SAz-2	1010	6	+/-				[95]
	SWy-2	910	1.5	+				[51,89
	SHCa-1	845	8.7	-				[51,89]
	SYn-1	489	1.5	+			surface complexation, +/-	[51,89]
	kaolinite	9	5~6	+/-		1.0 g/10 mL	cation exchange, +/-	[60]
OTC	SWy-2	800	1.5, 5	+, +/-	Freundlich	1.0 g/1 L		[96]
OTC	Na-kaolinite	30	5.5	+/-	Langmuir	4.76×10-3 kg/1 L	Cation exchange & surface complexation, +/-	[97]
OTC	Na-montmorillonite	7				4×10-4 kg/1 L		
TC		112						
CTC		167						
OTC	goethite	2.8×10-4 (mmol/m2)				0.1 g/10 mL	surface complexation, +/-	[98]
	hematite	4.2×10-4 (mmol/m2)						
TC	Na bentonite	108	4.55			—		[99]
	Ca bentonite	280				—		

Sm=maximum adsorption amount ; data not available.

Point of zero charge (PZC) is an important parameter for characterization of surface charge properties of clay minerals. When the solution pH is lower than PZC, the surface of clay mineral is positively due to protonation; when the solution pH > PZC, that is negatively charged; the solution pH = PZC, that is uncharged surface. Therefore, the positively charged of clay mineral surface is by virtues of the adhesion of H+ from the acid solution on clay surfaces. With the pH value increase, the concentration of H+ deceased and the surface returned to neutral. Once the solution pH is alkali, the surface is negatively charged. For SAz^{-1} montmorillonite **(Table 1)**, at pH < pHpzc, both of the surface of clay mineral and TC were positively charged; while pH > pHpzc, that is negatively charged. Under these two conditions, it should be mutually exclusive between clay surface and TC and the adsorption amount should be low. But the experimental results showed moderate adsorption in acid or alkali solution **(Table 1)**. Obviously, the adsorption cannot be simply interpreted as electrostatic adsorption, but may be ascribe to other mechanisms such as hydrogen bonding, Van de Waals, and intermolecular charge distribution, polar functional groups complexation and hydrophobic interaction.

From this investigation, we also confirmed that adsorption ability not only depends on the CEC value of clays **(Table 1)**, [96-98], but also on the function groups of TC or pH values [45,46,87]. For example, the maximum adsorption was 210 mmol kg^{-1} at pH 8.7 under which TC was in its anionic form TCH- [45], the presence of positively charged functional group of dimethyl ammonium played a significant role, thus, enhance the adsorption capacity. In this case, the swelling or unswelling property of clays seems not played an important role. On the other hand, the correlation between adsorbed TC and desorbed metals **(Figure 4)** better illustrated the adsorption mechanism. Furthermore, the extra desorbed amounts **(Table 2)** suggested that other mechanisms like hydrogen bonding; cation bridging or complexes also played a second role on TC adsorption.

Degradation

Different antibiotics in the environment may undertake hydrolysis, photo degradation, and microbial degradation, which are related to their chemical properties such as water-soluble, temperature, light, pH value, and the doses [1]. Hydrolysis is the main

behavior in aquatic environments. The photo degradation processes can affect antibiotic activity in water, and will occur on the surface layer of the soil and manure surface, but the role of influence played by the photo degradation process was relatively weak compared to the others. Microbial degradation is the most important way of degradation in the environments.

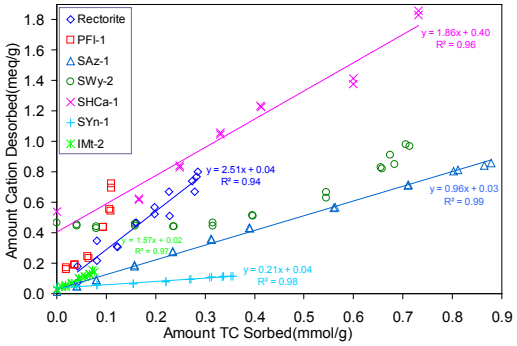

Figure 4. Desorption of exchangeable cations as affected by TC uptake by seven clay minerals. The lines are straight line regression against the total cations desorbed.

The TC has different degradations at different environments with a half-life from a few days to hundreds days [99]. At a lower temperature (4°C), the degraded product was stable, but degrade accelerated at a higher temperature (43°C), the half-life was 0.26 ± 0.11 days. On the other hand, light exposure can cause photochemical degradation of OTC. In addition, OTC was stable at pH 3.0, its half-life was 46 ± 5 days, but rapidly degraded in alkaline conditions with a half-life of 9 ± 4 days. In the presence of an absorbent such as bentonite, a 17% decrease in OTC concentrations within 5 min of contact was observed, and addition of organic matter (fish feed) along with the substrate, decreased the OTC concentration by 41% within 5 min of contact [100]. Under exposure to light, the half-life of TC was 32, 2, and 3 days in non-steriled, distilled, river and wetland water, respectively. While it will be 83, 18 and 13 days with no light exposure. In contrast, the half-life was 9, 1, and 1 day for distilled, river and wetland water respectively in sterile water (exposed to light) and they were 18, 11 and 7 days (no light exposure). In natural sunlight conditions, when ultraviolet radiation (UV) was present, TC half-life was 26, 17, and 18 min, respectively, in comparison to 39, 28, and 32 min in the absence of UV. The experimental study indicated that the matrixes, light, and UV play an important role in catalyzing the removal of TC from waters. The effects of light on TC may be considerably reduced in deep waters and in systems where sunlight is highly attenuated [100]. A study of the degradation of TC in water and liquid manure indicated that TC degradation rate accelerated more markedly under ventilated than unventilated conditions within 8 days and suggested that TC may oxidize during degradation [40]. The temperature substantially influenced the degradation of OTC of compost. In the study of rapid degradation of OTC in the calves manure, it was found that levels of extractable OTC in the compost decreased from 115 μg g^{-1} ± 8 μg g^{-1} dry weights to 6 μg g^{-1} ± 1 μg g^{-1} dry weight within the first 6 days under incubation at 25°C, resulting in a degradation rate of 95% [101]. Besides, the levels of extractable OTC incubated in room temperature and sterilized mixtures decreased only 12–25% after 37 and 35 days, respectively. The metabolites of OTC in pore water in the soil are very stable except for dehydroxytetracycline, for which the half-life could rise to 270 days [102]. In a laboratory simulation test, an increase in moisture content can accelerate the degradation of OTC, but at water-saturated manure, it became very durable and the degradation slowed significantly [72]. On the other hand, the moisture is the important factor in TC degradation in manures; a possible reason was when the moisture increased, conducive to the activities of microorganism's increased [99]. The concentration of the drugs and its activity in the feces may increase with accretion of moisture, while adsorption surface area decreased and conduced to the degradation of the drug in the feces [103].

Influence of plant growth and microorganism activity

Antibiotics that bind strongly to soil usually have long half-lives, and these drugs could be taken by plants and affect the microorganism activities [104,105]. The degree of absorption mainly depends on the type of plant and antibiotic. Crops such as corn, green onion and cabbage could absorb OTC [8]. Among nine antibiotics applied to plants only three were absorbed by lettuce in detectable amounts while four were absorbed by carrots, and the concentrations were much lower than FDA acceptable daily intake levels [104]. Thus, the uptake of antibiotics by plants as a result of spreading livestock manure does not pose an appreciable human health risk [104].

The microorganisms have a certain impact caused by accumulated TC in soil environment. The study indicated that when the residual amount of sulfadiazine in the soil was up to 0.003 mg kg^{-1} the reduction capacity of soil microbes for Fe3+ decreased by 50% [105]. However, the inhibition on soil microbes depends on the species of microbes, too. The study of the influence of antibiotics on the soil and water microorganisms showed that only 7 kinds of antibiotics within 36 typical microorganisms are sensitive, and their growth was significantly inhibited [106]. The activity of the Euphorbia pulcherrima is inhibited when the concentration of TC up to 0.009 ~ 0.012 mg kg^{-1} [107]. The impact of five major categories of commonly used antibiotics interfered with protein, DNA / RNA synthesis of Vibrio fischeri during growth due to strong toxicity of antibiotics to these bacteria [108]. Plants treated with TC at the concentrations of 400 mg L^{-1} restricted in branching for more than 20 weeks [109]. Similarly, the inhibition on the growth of Medicago sativa L. when the OTC concentration in the culture medium is higher than 0.002 mm [110]. The results of investigation on the concentrations of antimicrobials that occur in the final effluents of WWTPs in Canada showed that the concentrations

were unlikely to be high enough to impact the growth and survival of plants or bacteria [58]. Overall, a significant inhibition of TC on microorganisms in the environment and the growth of plants can be absorbed by plants. Thus, the residual antibiotics like TC can enter the plants and cause a threat to human health through the food chain [8,111].

ECOLOGY TOXICITY

The antibiotics generally have high biological activity and are persistent, which make an inevitable outcome for the humans and the organisms in the environments to have potential health threatening [112]. Particularly, with the rapid development of modern animal husbandry, the antibiotics exposed to the environments cause a grave threat to the ecosystem and human health. Although the ecological and environmental problems caused by the drugs and PPCPs pollutants draw more and more attentions, the research on the environmental pollution caused by the pollutants as TCs is still limit, especially its pollution mechanism and Eco toxicity research is still in the beginning phase [19,60]. Therefore, it's necessary to study the ecotoxicology. At present, the researches on the toxic reaction of aquatic organisms caused by antibiotics contamination almost focus on the short-term and acute toxic test and mainly to discuss the growth, death and reproduction conditions caused by antibiotics. The researches on the physiological and biochemical properties of the aquatic organisms caused by antibiotics exposure to the low-dose and long-term pollution are in great need, too. Moreover, many laboratory studies were carried out, but most of them used the higher concentration (mg kg^{-1}) of antibiotics exposure to the organisms, that's very different from the real residual concentration in water environment and difficult to explain the toxic effects and its mechanism on the organisms that exist in the real environments. In addition, it is worth mentioning that the effects of antibiotics on bacteria and algae are generally found 2 to 3 orders of magnitude below the toxic values for higher trophic levels [113]. For instance, one experiment was carried out that antibiotic adsorption on a variety of plants resulted in bioaccumulation at a higher sulfadimethoxine content (13 ~ 2000 mg kg^{-1}) and the cumulative effect on root was significantly higher than on stem [114]. However, no absorption effect of the antibiotics was tested in the field conditions [9]. Although the antibiotic is not TC, it's visibility that the Eco toxicological properties of antibiotic of laboratory works must correlate with practice pollution status in the environments, the conclusions of laboratory studies may throw some new lights on the practical application.

Toxicity in aquatic plants

The studies on the Eco toxicity of plants, in particular the aquatic plants and terrestrial plants, caused by TC were mainly focused on the simulated conditions in the laboratory. The effect of inhibition on plants by TC showed that the peptide elongation activity of the S-30 fraction of pea chloroplasts of a higher plant was inhibited in a dose-dependent manner, the (p)ppGpp synthase activity of pea chloroplast extracts in vitro was also affected [107,115].

Toxicity in aquatic animals

Compared with the aquatic plants, the reports of Eco toxicity on aquatic animals attracted more attention. TC can suppress the activity of a variety of enzymes within aquatic animals. The acute and chronic toxicity study of 9 antibiotics (including TC) to Daphnia magna indicated that toxicities (as 48-h EC50 values) were 1,000 and 44.8 mg L^{-1}, respectively [113]. Besides, the NOECs value was 340 mg L^{-1}, the effect of reproductive output occurred generally at concentrations range of 5-50 mg L^{-1}, which was at least one order of magnitude below the acute toxic levels. One interesting study showed that the OTC could significantly inhibit the antibody levels, so that the decline in the number of lymphocytes, but no significant effect on the survival rate of fish [116]. In a study, 14 antimicrobials in WWTP effluents were detected in samples in Canada with the concentrations less than 0.9 μg L^{-1}, which is unlikely to induce acute toxicity in aquatic animals near sewage discharge [58]. Even though another study suggested that it can't be ruled out that chronic exposure of bacteria and other microorganisms to antimicrobials will contribute to the development of antibiotic resistance in the environment [117].

Toxicity in aquatic microorganism

TC is used to inhibit the growth and development of the bacteria, so the researchers in recent years have done extensive studies into the ecotoxicity of bacteria, fungi and microalgae caused by TC. Generally, the toxicity caused by TC on prokaryotes (such as cyanobacteria) was higher than that on the single-cell eukaryotes (such as microalgae), the sensitivity of single-cell organisms to antibiotics is higher than multi-cellular organisms. For example, the study on the toxicity of Vibrio fischeri showed that EC50 value of TC was 0.025 mg kg^{-1} [108]. The inhibition of the growth of Tetraselmis chuii and Artemia caused by OTC results showed that Artemia was 70 times more sensitive to TC than Tetraselmis chuii [118]. This trend was identified with many similar experiments [119-121]. The toxicity of microalgae caused by TC is mainly reflected in the inhibition of the protein synthesis and chloroplast generation of microalgae, ultimately resulting in the inhibition of the growth of the microalgae. In addition, the protein synthesis of Microcystis aeruginosa and Selenastrum capricornutum were also suppressed by TC [119,120].

Toxicity in soil microorganism

The microbe is an important parts of the soil ecosystem, ecological balance disorders may be caused by the selective pressure of TC ultimately affect the quality and fertility of the soil. The study on the toxicity effects of OTC on microorganisms was conducted in in two different soil surfaces, with the soil microbial and fungal biomass determined by the fumigation extraction

and ergosterol methods [122]. In addition, there are some measurement methods of microbial biomass like basal respiration (BR), the dehydrogenase activity (DHA), the substrate-induced respiratory (SIR), and Fe (III) reduction. The results show that at the OTC content up to 1000 μg g^{-1}, the BR and DHA were not affected. In addition, the effect on microorganisms by OTC was related to contact time; the determination of a short period of time may give inaccurate results. OTC reduced the biomass in the soil significantly, leading to increase of fungi / bacteria ratio of the soil. At actual environmental concentrations, OTC can also produce selective pressure on microorganisms in the soil. At the OTC concentrations of 0.01, 1, and 100 mg kg^{-1}, no significant mortality of Eisenia foetida S. was observed after 7 h and 21 h, although a decrease in seed germination rate was observed, but sporadically [123]. Obviously, there were no significantly dose/response effects. At the OTC concentrations of OTC of 100 and 1,000 mg kg^{-1}, the respiration rate of soil microbial was inhibited about 16 - 25% and 28 – 38%. Manure can greatly change the ecotoxic effects of OTC in a multi-species-soil system [123].

The lack of research on the ecological toxicity of TC attributes to the research conducted mainly on the cells and individuals such as soil animals and aquatic microorganisms in acute toxic research. Although reports of chronic toxic have been published, little was focused on the influence of microorganism's community even in the ecology system. In addition, the environmental factors like heavy metals or nutrients may affect the TC ecological toxicity. Differences in the culture medium may lead to large differences of the measurement results with the divalent and trivalent metal ions complexation with antibiotic may occur to increase IC50 values, and these factors are less considered [118].

TC RESISTANCE

Most of the drugs within the livestock excreta always have long-term half-life and very easy to be accumulated in the waters. If these drugs do not easily adsorb on the adsorbents, they will have high concentrations in waters and will be accumulated in aquatic animals which causes the chronic toxicity to organisms. Under this selective pressure of drugs, microbes exposed to the drugs over a long term may inhibit the activity of microorganisms and stimulate the pathogens' resistance. The resistant bacteria may infect animals and humans, resistance genes may spread between bacteria, animal and humans [124-126]. There is a true case that one patient in China was riddled with multiple strains of drug-resistant bacteria [127].

In recent years, many antibiotics pollution on the marine environment and marine microbial resistance had been also reported [128,129]. A study showed the transfer of OTC-resistant isolates of *Aeromonas salmonicida* to *Escherichia coli* [130], but also transferred between *Aeromonas spp.* and *Escherichia coli*. [131]. In 2005, the first isolated resistant bacteria as C. jejuni was discovered. This bacterium has resistance in ciprofloxacin, erythromycin, and ceftriaxone [132]. Therefore, how to ward off calamitous outbreaks of drug-resistant has become a momentous issue.

Resistance on bacteria

Unreasonable application of antibacterial drugs may cause some pathogenic bacteria resistant enhanced, the production of diversity and to form the resistant strains. This resistance will be obtained by bacteria and passed on to the next generation [133], and may result in the production of strong viability bacteria [134]. The related studies of bacteria resistant to TC [135-138] were focused on the use of medicine and animal husbandry. Lower concentration of antibiotics in the environment and co-existence in a variety of antibiotics, created favorable conditions of resistance bacteria especially for cross-resistance strain and have a certain impact on microbial communities [139]. Furthermore, the impact may occur through the food chain for advanced biological, thereby undermining the balance of the ecosystem [140].

Symbiotic bacteria within animals, such as *Salmonella*, Urea plasma Urealyticum, *Streptococcus suis* and *Escherichia coli* as a repository of resistant indicator and resistance genes to understand their resistant properties and mechanisms have significant implications for the prevention and control of the disease. Salmonella in Enterobacteriaceae is a common important pathogenic spp. Salmonellas caused about 16 million infections worldwide each year, of which 0.6 million deaths [141]. The strains of antibiotics resistance increased with the rate of Salmonella resistance increased [142,143]. According to the reports of the U.S. centers for Disease Control and Prevention (CDC), Salmonella to TC resistance rates rose from less than 1% in 1979 to 34% in 1996 [144]. The mechanism of bacterial resistance has related to many factors such as plasmids. It can transmit between bacteria through conjugation, transformation, and transduction, so these plasmids transmit can cause resistance and even the spread of multi-resistant [145]. Urea plasma Urealyticum (Uu) is one of the main pathogens infections of the genitourinary system. Understanding the infection of Uu and its sensitivity changes to drugs can better guide the clinical reasonable drugs used [146]. TC resistance of Uu and to the tetM plasmid genes were successively confirmed by the strong correlation between them [147]. *Streptococcus suis* (Su) is a zoonosis, not only cause the pig's disease [148], but arise the humans death [149]. Therefore, understanding the sensitivity and resistance of Su to TCs and their relationship with resistance genes will have important implication for effective treatment of diseases and to prevent resistance. For healthy pigs in Canada and the United Kingdom, their TC-resistant rates of *E. coli* were 83% and 78.7%, respectively [150; 151]. Although the TC resistance of E. coli from different countries and regions may be different, but the TC resistance of *E. coli* is the most serious for most of the antibiotics. While the resistance, the extensive use of growth-promoting drugs in treatment and prevention are very closely linked and inseparable [152]. In addition, the TC resistance of *E. coli* within unhealthy pigs was substantially higher than that within healthy pig [151]. Studies showed that 78% of the *E. coli* within healthy pigs has resistance, but only 47% within chickens [153]. In addition, the resistance rates of the E. coli within healthy pigs and

chickens in Switzerland were 10.3% and 6.5%, respectively [154]. While the resistance rate of the E. coli within pork and chicken meat were 76% and 63%, respectively [155]. Bacterial resistance is not unique. Over the years, there are indications that the anti-viral drug amantadine accused extensive appearance of drug-resistant H5N1 [156].

Antibiotics resistance genes

The application of manure as organic fertilizer containing TC-residues into the farms generate a selection pressure on the resistance of the microorganisms in the soil environment, inducible TC resistance gene (ARGs) generator [157]. It was first proposed ARGs as a new type of environmental pollutant by Pruden [158]. Because ARGs possess persistence in the environment and can be migrating, translating and disseminating between bacteria, thus, the damages will be greater than antibiotic itself [159-161]. The current methods are to cure ARGs having plasmid-curing [162-164]. Due to the peculiarity of the structure and physiology, the differences in cure mechanisms of ARGs of different strains are not universally applicable in resistant elimination. The newest research showed that copper was supposed to prevent horizontal dissemination [165]. They point out that rapid death of both antibiotic-resistant strains and destruction of plasmid and genomic DNA were observed on copper and copper alloy surfaces, which could be useful in the prevention of infection spread and gene transfer.

The ARGs can be detected by PCR-DGGE, but can't be quantitative [166]. Therefore, more researched using real-time quantitative PCR technology to explore the change of ARGs in the environments and these quantitative results get more comprehensive and credible [158,167]. Other reports have also proven correlation between the use of antibiotics and ARGs [166-169].

The use of veterinary antibiotics caused the failure of clinical cure of Salmonella infection and resulted in human death [170]. DT104 vicious strain derived from pork was present inside of 5 patients through tracking of farms, slaughterhouses, and patients in Danish [170]. This finding supported that the livestock body strains could transfer ARGs to human. Other studies showed that resistant bacteria in the farm have been a way to enter the human body [171- 173].

China is the largest antibiotic manufacturing and consumption country in the world [127]. One group investigated the use of TCs of three large-scale pig farms in China [174]. A large number of TCs-resistant pathogens were found in the environment surrounding the farms due to large use of TCs without supervision. In all collected samples, a total of 149 types of high-resistance gene were identified, that can withstand all major antibiotics. The concentration of transposable enzyme in the sample increased, which promoted the spreading of ARGs. It means that the risk of the spread of TC-resistant bacteria in humans will increase. Meanwhile, the presence of arsenic, copper, and other heavy metals in the environment will also strengthen the resistance of microorganisms [174].

Resistance mechanism

There were four current resistance mechanisms. They are efflux, ribosomal protection, enzymatic and an unknown mechanism [152]. Except the fourth mechanism that was only found in a gene tet(U), the others have already sequenced multiple resistance genes, with the total number up to 40, and these genes are located in conjugative plasmid or bonding transposing [175,176,]. Generally, it's believed that efflux and ribosomal protection are the main mechanism of TC resistance, while the mainly mechanism of Gram-negative bacteria was efflux with the genes such as tet(A), tet(B) and tet(C). On the contrary, the mainly mechanism of Gram-positive bacteria was ribosomal protection with the genes such as tet(W), tet(K), tet(L), tet(M), and tet(O) [177- 179].

The newest study found a new "riboswitches" regulated by aminoglycoside antibiotic and the "switch" on the control of such antibiotics resistance for the first time in the antibiotic-resistant pathogens [180]. With the wide application of antibiotics, pathogens resistance was enhanced. Therefore, to find out how to form the new mechanism of resistance becomes the difficult problem. But the newly discovered riboswitches are expected to overcome this problem. The study proved that riboswitch was an aptameric which had regulation whereby small-molecule binding leading to the induction of antibiotic resistance and existed within nature bacteria or higher plants. It was located in specific noncoding genes [180]. This regulatory mechanism has been discovered, resulting in the immediate concern of scientists from scientists of various countries.

Substitute for antibiotics

Although some scientists committed to the research and development of new antibiotics [85], the research team found that a critical antibiotic-resistant protein as TcaR, which was previously only restricted to the binding ability of double-strand DNA (dsDNA), could interact strongly with single-strand DNA (ss DNA), rewriting the former cognition. It also provides a new direction for antibiotic research and development. The result showed that as the concentration of ssDNA increased within bacteria, TcaR will combine with ssDNA not dsDNA through the analysis by electron microscopy, electrophoretic mobility shift assay and circular dichroism technologies [181].

The current researches are struggling to find and develop new additive or green feed additives to replace antibiotics, like probiotics [181,182]. These include the Chinese herbal medicine [183,184], the enzyme preparations [185,186], prebiotics [187,188], acidulant [189,190], garlic [191,192], and oregano essential oil [193-195]. In particular, probiotics can promote the growth of beneficial bacteria in the digestive system and inhibit the reproduction of harmful bacteria to ensure that the balance of intestinal flora with no residue, non-polluting, low-price, high efficiency characteristics.

The latest research showed an antibiotic from peptides in human sweat that can fence off superbugs in the hospital and fatal strains of tuberculosis bacteria [196]. The chemical substance is called dermcidin that can be activated in a salty, slightly acidic perspiration and pierces the cell membrane of harmful microbes, eventually killing them. The scientists hope to use peptides to research and develop new drugs for the suppression of a series of bacteria. Antibacterial function of protein commonly found in the surface of the body, when bacteria attempt to invade the body, these natural antibiotics play a role of innating immune response, in order to prevent the bacteria intrude. However, the mechanism of how to kill bacteria of dermcidin remains a mystery [197].

THE DETECTION TECHNOLOGY OF TC IN ENVIRONMENTAL SAMPLES

The residual and cumulative of antibiotic in the environment can induce drug-resistant bacteria, which pose a potential threat to the ecosystem and human health [198,199]. The urban WWTPS are an important source of antibiotic contamination in the environment. In recent years, there has been the detection of antibiotics in municipal WWTPs [200-203]. Antibiotics in the WWTPs may be due to adsorption on activated sludge [204]. The remaining sludge applied to farmland may lead to migration of residues of antibiotics to the soil or groundwater, causing secondary contamination through the food chain and ultimately harm human health [205]. TC is one of them frequently detected in the final effluent of the WWTPs [206,207].

When studying the environmental behavior of the antibiotics, the first question is the detection limit. The concentrations were usually in ng L^{-1} [208-211]. But it may be up to several hundred μg kg^{-1} in soils or sediments [212].

Pre-treatment

During the pre-treatment process of HPLC detection, the extraction is an important step. Weakly acidic EDTA-McIlvaine and citric acid buffer solution is often used to extract TC in the environment solid samples [73,205], and in the food [213]. However, when the pH < 2, the decomposition of TC will occur [18].

Solvent extraction includes liquid-liquid extraction, solid-liquid extraction and accelerated solvent extraction [13,209,214,215], lyophilization method [3,216] and solid-phase extraction (SPE) [216,217]. These are the common methods of separation and enrichment of antibiotics used in environmental samples. Because SPE possess the advantages of enriching the target to analyze and remove the interfering impurities [55,218], it is often used as the pre-treatment method of trace contaminants of environmental samples, but the NOMs (mainly humic acid) are usually high in waters, soils and sediments, and single column of SPE can't remove them completely [219]. Therefore, it must eliminate the interference of organic matters when environmental samples were enriched [213,219]. Molecular imprinting solid phase extraction (MISP) was used to improve the selectivity of the SPE [220-222]. In addition, TC was easy to form complexes with metal ions [213], to avoid the complexation between metal ions in the matrix, care must be taken during extracting.

Detection methods

The mainly methods were microbiological method, thin-layer chromatography (TLC) [223], ELISA [73,224], HPLC [45,46,87,225] and liquid chromatography - mass spectrometry (LCMS) [226-228]. In addition, the research was also conducted on related detection technologies of TC residues or metabolites [229-231]. With the development of the detection method, the detection limit has been reached to 3-7 ng L^{-1} [211,233] and can detect TC higher than 0.01 μg L^{-1} in water. But in water within aquaculture field, antibiotics concentration could be up to 1~ 6 mg L^{-1} [210]. Both of the microbiological methods and immunoassays usually lack specificity. Compared to TLC, it has similar sensitivity but is much higher specificity and easily discriminate one TC antibiotic from another [233].

Microbial detection method

Microbial detection method is widely used in the TCs determination of biological samples, but is less reported for environmental samples such as soil, sediment or sludge because of its limited sensitivity and specificity [234,235]. The detection of the microbiological method takes a long time. It has poor sensitivity and specificity due to the interference from other antibiotics. However, the use of HPLC may cause miscarriage of justice due to similar peaks, thus, microbiological method is still worth considering [236,237]. Because TC-sensitive bacteria can't distinguish between TC derivatives and various types, further supplements by TLC, HPLC, and ELISA to analyze the types of antibiotic residues are needed [238].

Thin layer chromatography

Thin layer chromatography (TLC) can be divided into two methods of a silica gel high performance thin layer chromatography (HPTLC) and reverse phase thin layer chromatography (RP-TLC) [239]. HPTLC usually uses silica gel, aluminum oxide and cellulose as adsorption layer with added Na2EDTA in order to eliminate the effect of metal ions in the solid/liquid system. For RP-TLC, oxalic acid was added in order to eliminate the complexation between TC and metal ions [239]. The TLC has the advantages of simple, fast and no complex fittings but can't be quantitative. Therefore, the method is suitable for the rapid qualitative identification of TC antibiotics mixture.

Immunoassay

Researches were also conducted on the analysis of the radioimmunoassay (RIA) [66], ELISA [73,240], fluore immunoassay (FIA)

and immunoaffinity chromatography, etc... TCs residues in milk were detected by RIA and further confirmed by LC/MS technology with a detection limit of 1 μg L^{-1} [66]. The technology is the effective for antibiotics preliminary detection in water. TCs and sulfonamide in water and wastewater was monitored routinely by SPE-RIA technology [241]. The detection limits of TC and tylosin in surface water and groundwater by ELISA, were 0.05 and 0.10 μg L^{-1}, respectively [240]. The low cost, the fast detection can be used to the preliminary detection of TC, CTC, and tylosin in water.

HPLC-UV/HPLC-FD/HPLC-MS/MS

HPLC is the most commonly used method of detecting TC residues. It is efficient, fast, high sensitivity, but the pre-treatment was more complex and instruments were expensive. HPLC-ESI-MS-MS technology was used to detect the TC in the river samples with a detection limit at ng L^{-1} [242]. HPLC-MS was used to detect the TCs and quinolones residues in the inlet and outlet water of WWTPs with a detection limit of 4.0 ~ 6.0 ng L^{-1} [243]. The same technology was used to detect TC residues in groundwater and sewage from livestock farms with a detection limit of 0.3-3.8 μg L^{-1} [244]. Solid-Phase Extraction (SPE)-HPLC-DAD (photodiode array detector) was used to analyze variety of antibiotics in wastewater with a detection limit of 0.1~ 40 μg L^{-1} [200]. This result also suggested that this method can be a useful tool to determine the amount of pharmaceuticals discharged from WWTPs to the aquatic environment and to evaluate the effect of conventional WWTPs in the elimination of pharmaceutical compounds in wastewater [200]. Compared to HPLC-MS, HPLC-UV and HPLC-FD detection technologies were less used in recent years for the TC detection in environmental samples [204,245], mainly because these two methods need derivatization reagent [246]. The conventional photoelectric diode array detector (PDA) needs to be completely separated, and it has relatively low sensitivity of determination, the requirement of sample pre-treatment. Under the ESI model, the sensitivity of TC could be affected by matrix. On the contrary, there was no effect under APCI model. ESI was more suitable to polar, nonpolar and thermally unstable compounds than APCI model, so ESI applied to detect the TC residues in the environments was more commonly and widely used [247,248]. Even if this, the study indicated that OTC had splendid detection result and sensitivity under ESI and APCI models, in particular ESI [132].

LC-MS/LC-UV/LC-FD

The analysis of HPLC-MS was widely effective in reducing background interference, high sensitivity and the results are accurate and reliable; therefore, it's very widely used [73]. Likely, reversed-phase liquid chromatography (RP-LC) [249,250] with different detection modes, such as spectrophotometry [251], fluorescence [252], fast-atom-bombardment mass spectrometry (FAB-MS) [253] and MS–MS [254,255] was also prevailed. LC/MS-ESI(+)(-)/-APCI(+)(-) was used to detect TC and sulfonamides residues in groundwater and surface water with a detection limit of 0.05-5.0 ng L^{-1} [133]. LC-MS has good sensitivity and selectivity, and the analyte can be qualitative and quantitative without complete separation. However, for very complex matrix such as wastewater and sludge, matrix effects are very large, so that the intensity of the analyte ionization became weak or strong affecting the reproducibility and accuracy. In order to improve the sensitivity, some of the mobile phase was modified to contain ethyl acetate [206], formic acid [13], citric acid [13], oxalic acid [206] or formic acid [13,71,244]. But, the non-volatility compounds like oxalic acid or citric acid in the mobile phase could be blocked in the interface or precipitation within the column [206]. The liquid chromatography-fluorescence detection (LC-FD) and liquid chromatography ultraviolet detection (LC-UV) are usually only used for the detection of several antibiotics, thus limiting their application and the sensitivity is relatively low. With the development of MS and LC-MS technologies, especially electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), the areas of application of LC-MS were widened, not only in the detection range, high sensitivity, but also with strong anti-interference ability.

HILIC

The hydrophilic interaction chromatography (HILIC) [256] was the chromatographic patterns of a separation of strongly polar and hydrophilic compounds developed rapidly in recent years [257- 260]. Since the low viscosity of mobile phase, The separation performance of polar compounds in HILIC is better than RPLC [261]. Another reason was the compatibility of the mobile phase of HILIC and MS [262]. Some polar organic pollutants have a characteristic absorption spectrum in the ultraviolet region. Therefore, HILIC-UV could be quantitatively used to analyze the TC in wastewater [263]. The experiments confirmed that unbounded silica gel column can be used for determination of TC compounds; overthrowing the existing literature that silicone column can't be used in the determination of these compounds [264].

Aptamer biosensor and others

A novel aptameric biosensor was investigated for the rapid determination of TC [265,266]. Aptamers are oligo-nucleotides that are discovered by systematic evolution of ligands by exponential enrichment (SELEX) in vitro. It can bind protein or other small molecules with high specificity and affinity [267,268]. Aptamer biosensor, compared with the conventional biosensor, has the following advantages [269]: 1) a very high affinity for their targets by incorporating small molecules into their nucleic acid structure or integrating into the structure of larger molecules such as proteins [270]; 2) a high binding specificity; 3) aptamers are isolated by in vitro methods that are independent of animals; 4) aptamers are produced by chemical synthesis and purified to a very high degree by eliminating the batch-to-batch variation; 5) aptameric structure is simple, and sensor layers based on aptamers can be regenerated more easily than antibody-based layers; 6) more resistant to denaturation and have a much longer shelf life; 7) aptamers can be amplified during their selection procedure; 8) their nuclease sensitivity which is very critical for their use in ex vivo and in vivo applications [271], and can be improved by chemical modification [272]. Capillary electrophoresis was also used for the analysis of TC residues in milk, serum, and urine samples [273]

ENVIRONMENTAL IMPACTS

The humans may touch the drug-resistant microorganisms through food, drinking water or contact with farm employees, causing a potential threat to human health [172]. In addition, the feces or soils containing drug-resistant bacteria may penetrate into the water bodies, or spread through the air as dust and the farm composting could be sold as green organic fertilizer. The drug-resistant microorganisms in the farm environment should be regarded as hazardous substances [173]. Using PCR technology provides strong evidence that OTC within septic tank caused the contamination of groundwater [165].

The latest research showed that consumption of anxiolytic drug (oxazepam) could make natural shy perch (Perca fluviatilis) become more bold [274]. All sewers in the world can find different drugs residues, since wastewater into the ecological cycle systems of water resources, at the long-term, may affect the ecological environment. This study aimed at the ecological effects by wastewater containing pharmaceuticals from sewers. The results indicated that the behavior of perch changed, not only leave the fish group, but the eating became gobble (increased feeding rate). This change of behavior and eating habits caused ecological impacts such as aquatic community compositions, consequently, the functioning of aquatic systems. Anyway, this research suggested that fish fitness and food-web structures are altered in oxazepam-contaminated waters [274]. Although this study only focused on oxazepam, it could be possible that different drug residues in sewer worldwide could become an urgent issue.

REFERENCES

1. Kümmerer K. Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources--a review. Chemosphere. 2001; 45: 957-969.
2. Halling-Sørensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, Holten Lützhøft HC, et al. Occurrence, fate and effects of pharmaceutical substances in the environment--a review. Chemosphere. 1988; 36: 357-393.
3. Hirsch R, Ternes T, Haberer K, Kratz KL. Occurrence of antibiotics in the aquatic environment. Sci Total Environ. 1999; 225: 109-118.
4. Person JL, McHutchison JG, Fong TL, Redeker AG. A case of cyclosporine-sensitive, steroid-resistant, autoimmune chronic active hepatitis. J Clin Gastroenterol. 1993; 17: 317-320.
5. Ternes TA. Occurrence of drugs in German sewage treatment plants and rivers. Water Res. 1998; 32 (11): 3245-3260.
6. Haller MY, Müller SR, McArdell CS, Alder AC, Suter MJ. Quantification of veterinary antibiotics (sulfonamides and trimethoprim) in animal manure by liquid chromatography-mass spectrometry. J Chromatogr A. 2002; 952: 111-120.
7. Sassman SA, Lee LS. Sorption of three tetracyclines by several soils: assessing the role of pH and cation exchange. Environ Sci Technol. 2005; 39: 7452-7459.
8. Kumar K, Gupta SC, Baidoo SK, Chander Y, Rosen CJ. Antibiotic uptake by plants from soil fertilized with animal manure. J Environ Qual. 2005; 34: 2082-2085.
9. Jjemba P K. The potential impact of veterinary and human therapeutic agents in manure and biosolids on plants grown on arable land: a review. Agric. Ecosyst. Environ. 2002; 93 (1-3): 267-278.
10. Kumar K, Gupta SC, Chander Y, Singh AK. Antibiotic use in agriculture and its impact on the terrestrial environment. Adv. In Agron. 2005; 8: 1-54.
11. Phillips I, Casewell M, Cox T, De Groot B, Friis C, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. J Antimicrob Chemother. 2004; 53: 28-52.
12. Campagnolo E R, Johnson K R, Karpati A, Rubin C S, Kolpin D W, et.al. Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. Sci Total Environ. 2002; 299 (1-3): 89-95.
13. Hamscher G, Sczesny S, Höper H, Nau H. Determination of persistent tetracycline residues in soil fertilized with liquid manure by high-performance liquid chromatography with electrospray ionization tandem mass spectrometry. Anal Chem.2002; 74: 1509-1518.
14. Baguer AJ, Jensen J, Krogh PH. Effects of the antibiotics oxytetracycline and tylosin on soil fauna. Chemosphere. 2000; 40: 751-757.
15. Moellering RC. Special consideration of the use of antimicrobial agents during pregnancy, post-partum, and in the newborn. Clin Obstet Gynecol. 1979; 22: 373-378.
16. Duggar B M. Aureomycin: a product of the continuing search for new antibiotics. Ann N Y Acad Sci. 1948; 51 (2): 177.
17. Finlay A C, Hobby G L, P'an S Y, Regna P P, Routien J B, et.al. Terramycin, a new antibiotic. Sci. 1950; 111 (2874): 85-85.
18. Oka H, Ito Y, Matsumoto H. Chromatographic analysis of tetracycline antibiotics in foods. J Chromatogr A. 2000; 882: 109-133.
19. Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects

of veterinary antibiotics (VAs) in the environment. Chemosphere. 2006; 65: 725-759.

20. Picó Y, Andreu V. Fluoroquinolones in soil--risks and challenges. Anal Bioanal Chem. 2007; 387: 1287-1299.
21. Gorbach SL, Bartlett JG. Pseudomembranous enterocolitis: a review of its diverse forms. J Infect Dis 135 Suppl. 1977; S89-94.
22. Kasik JE, Thompson JS. Allergic reactions to antibiotics. Med Clin North Am. 1970; 54: 59-73.
23. WHO.WHO Drug information. 1995; 9 (1): 14
24. WHO. Public health in Europe. National drug policies. Denmark. 1979; 12.
25. Kulshrestha P, Giese RF Jr, Aga DS. Investigating the molecular interactions of oxytetracycline in clay and organic matter: insights on factors affecting its mobility in soil. Environ Sci Technol. 2004; 38: 4097-4105.
26. Stephens CR, Murai K, Brunings KJ, Woodward RB. Acidity constants of the tetracycline antibiotics. J Am Chem Soc. 1956; 78 (16): 4155-4158.
27. Leeson LJ, Krueger JE, Nash RA. Concerning the structural assignment of the second and third acidity constants of the tetracycline antibiotics. Tetrahedron Lett. 1963; 4 (18): 1155-1160.
28. Colaizzi JL, Klink PR. pH-Partition behavior of tetracyclines. J Pharm Sci. 1969; 58: 1184-1189.
29. Miller GH, Smith HL, Rock WL, Hedberg S. Antibacterial structure-activity relationship obtained with resistant microorganisms. 1 Inhibition of R-factor resistant Echerichia coli by tetracyclines. J Pharm Sci. 1977; 66 (1): 88-92.
30. Polubesova T, Zadaka D, Groisman L, Nir S. Water remediation by micelle-clay system: case study for tetracycline and sulfonamide antibiotics. Water Res. 2006; 40: 2369-2374.
31. Tolls J. Sorption of veterinary pharmaceuticals in soils: a review. Environ Sci Technol. 2001; 35: 3397-3406.
32. Mitscher LA. The chemistry of the tetracycline antibiotics. Marcel. Dekker. Inc. 1978; 352.
33. Qiang Z, Adams C. Potentiometric determination of acid dissociation constants (pKa) for human and veterinary antibiotics. Water Res. 2004; 38: 2874-2890.
34. Terada H, Inagi T. Proposed partition mechanism of tetracycline. Chem Pharm Bull (Tokyo). 1975; 23: 1960-1968.
35. Wessels JM, Ford WE, Szymczak W, Schneider S. The complexation of tetracycline and anhydrotetracycline with Mg2+ and Ca2+: A spectroscopic study. J Phy Chem B. 1998; 102 (46): 9323-9331.
36. Chen WR, Huang CH. Adsorption and transformation of tetracycline antibiotics with aluminum oxide. Chemosphere 2010; 79: 779-785.
37. Küehne M, Wegmann S, Kobe A, Fries R. Tetracycline residues in bones of slaughtered animals. Food Control. 2000; 11 (3): 175-180.
38. Pena AL, Lino CM, Silveira IN. Determination of oxytetracycline, tetracycline, and chlortetracycline in milk by liquid chromatography with postcolumn derivatization and fluorescence detection. J AOAC Int. 1999; 82: 55-60.
39. Martinez EE, Shimoda W. Liquid chromatographic determination of epimerization of chlortetracycline residue to 4-epi-chlortetracycline residue in animal feed, using McIlvain's buffer as extractant. J Assoc Off Anal Chem. 1989; 72: 848-850.
40. Kühne M, Ihnen D, Möller G, Agthe O. Stability of tetracycline in water and liquid manure. J Vet Med A Physiol Pathol Clin Med. 2000; 47: 379-384.
41. Onji Y, Uno M, Tanigawa K. Liquid chromatographic determination of tetracycline residues in meat and fish. J Assoc off Anal Chem. 1984; 67: 1135-1137.
42. Duarte HA, Carvalho S, Paniago EB, Simas AM. Importance of tautomers in the chemical behavior of tetracyclinesdagger. J Pharm Sci. 1999; 88: 111-120.
43. Othersen OG, Beierlein F, Lanig H, Clark T. Conformations and tautomers of tetracycline. J Phy Chem B. 2003; 107 (49): 13743-13749.
44. Chang P.H, Li Z, Jiang W-T, Jean J-S. Adsorption and intercalation of tetracycline by swelling clay minerals. Appl Clay Sci. 2009; 46 (1): 27-36.
45. Chang PH, Li Z, Yu TL, Munkhbayer S, Kuo TH, et al. Sorptive removal of tetracycline from water by palygorskite. J Hazard Mater.2009; 165: 148-155.
46. Chang P-H, Li Z, Jean J-S, Jiang W-T, Wang CJ, Lin K-H. Adsorption of tetracycline on 2:1 layered non-swelling clay mineral illite. Appl. Clay Sci. 2012; 67-68: 158- 163.
47. Figueroa RA, Leonard A, MacKay AA. Modeling tetracycline antibiotic sorption to clays. Environ Sci Technol. 2004; 38: 476-483.
48. Figueroa RA, MacKay AA. Sorption of oxytetracycline to iron oxides and iron oxide-rich soils. Environ Sci Technol. 2005; 39:

6664-6671.

49. Gu C, Karthikeyan KG. Sorption of the antimicrobial ciprofloxacin to aluminum and iron hydrous oxides. Environ Sci Technol. 2005; 39: 9166-9173.

50. Gu C, Karthikeyan KG, Sibley SD, Pedersen JA. Complexation of the antibiotic tetracycline with humic acid. Chemosphere. 2007; 66: 1494-1501.

51. Kulshrestha P, Giese RF Jr, Aga DS. Investigating the molecular interactions of oxytetracycline in clay and organic matter: insights on factors affecting its mobility in soil. Environ Sci Technol. 2004; 38: 4097-4105.

52. Parolo ME, Savini MC, Vallés JM, Baschini MT, Avena MJ. Tetracycline adsorption on montmorillonite: pH and ionic strength effects. Appl. Clay Sci. 2008; 40 (1-4): 179-186.

53. Pils JR, Laird DA. Sorption of tetracycline and chlortetracycline on K- and Ca-saturated soil clays, humic substances, and clay-humic complexes. Environ Sci Technol. 2007; 41: 1928-1933.

54. Berger K. Petersen B. Buningpfaue H. Persistence of drugs occurring in liquid manure in the food chain. Archiv Lebensmittelhygiene. 1986; 37 (4): 99-102.

55. Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, et al. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ Sci Technol. 2002; 36: 1202-1211.

56. Mackie RI, Koike S, Krapac I, Chee-Sanford J, Maxwell S, et al. Tetracycline residues and tetracycline resistance genes in groundwater impacted by swine production facilities. Anim Biotechnol. 2006; 17: 157-176.

57. Kim SD, Cho J, Kim IS, Vanderford BJ, Snyder SA. Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. Water Res. 2007; 41: 1013-1021.

58. Miao XS, Bishay F, Chen M, Metcalfe CD. Occurrence of antimicrobials in the final effluents of wastewater treatment plants in Canada. Environ Sci Technol. 2004; 38: 3533-3541.

59. Karthikeyan KG, Meyer MT. Occurrence of antibiotics in wastewater treatment facilities in Wisconsin, USA. Sci Total Environ. 2006; 361: 196-207.

60. Batt AL, Bruce IB, Aga DS. Evaluating the vulnerability of surface waters to antibiotic contamination from varying wastewater treatment plant discharges. Environ Pollut. 2006; 142: 295-302.

61. Li Z, Chang PH, Jean JS, Jiang WT, Wang CJ. Interaction between tetracycline and smectite in aqueous solution. J Colloid Interface Sci. 2010; 341: 311-319.

62. Li Z, Schulz L, Ackley C, Fenske N. Adsorption of tetracycline on kaolinite with pH-dependent surface charges. J Colloid Interface Sci. 2010; 351: 254-260.

63. Aust MO, Godlinski F, Travis GR, Hao X, McAllister TA, et al. Distribution of sulfamethazine, chlortetracycline and tylosin in manure and soil of Canadian feedlots after subtherapeutic use in cattle. Environ Pollut. 2008; 156: 1243-1251.

64. Karci A, BalcioÄŸlu IA. Investigation of the tetracycline, sulfonamide, and fluoroquinolone antimicrobial compounds in animal manure and agricultural soils in Turkey. Sci Total Environ. 2009; 407: 4652-4664.

65. Kay P, Blackwell PA, Boxall AB. A lysimeter experiment to investigate the leaching of veterinary antibiotics through a clay soil and comparison with field data. Environ Pollut. 2005; 134: 333-341.

66. Meyer MT, Bumgarner JE, Varns JL, Daughtridge JV, Thurman EM, Hostetler K. Use of radioimmunoassay as a screen for antibiotics in confined animal feeding operations and confirmation by liquid chromatography. Sci. Total Environ. 2000; 248 (2-3): 181 -188.

67. Thiele-Bruhn S. Pharmaceutical antibiotic compounds in soils - a review. J Plant Nutr Soil. 2003; 166 (4): 546-546.

68. Martínez-Carballo E, González-Barreiro C, Scharf S, Gans O. Environmental monitoring study of selected veterinary antibiotics in animal manure and soils in Austria. Environ Pollut. 2007; 148: 570-579.

69. Brambilla G, Patrizii M, De Filippis SP, Bonazzi G, Mantovi P, et al. Oxytetracycline as environmental contaminant in arable lands. Anal Chim Acta. 2007; 586: 326-329.

70. De Liguoro M, Cibin V, Capolongo F, Halling-Sørensen B, Montesissa C. Use of oxytetracycline and tylosin in intensive calf farming: evaluation of transfer to manure and soil. Chemosphere. 2003; 52: 203-212.

71. Jacobsen A M, Halling-Sørensen B, Ingerslev F, Hansen S H. Simultaneous extraction of tetracycline, macrolide and sulfonamide antibiotics from agricultural soils using pressurised liquid extraction, followed by solid-phase extraction and liquid chromatography-tandem mass spectrometry. J. Chromato. A. 2004; 1038 (1-2): 157-170.

72. Wang Q, Yates SR. Laboratory study of oxytetracycline degradation kinetics in animal manure and soil. J Agric Food Chem. 2008; 56: 1683-1688.

73. Aga DS, O'Connor S, Ensley S, Payero JO, Snow D, et al. Determination of the persistence of tetracycline antibiotics and their degradates in manure-amended soil using enzyme-linked immunosorbent assay and liquid chromatography-mass spectrometry. J Agric Food Chem. 2005; 53: 7165-7171.

74. Zhao L, Dong YH, Wang H. Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. Sci Total Environ. 2010; 408: 1069-1075.

75. Montforts MH, Kalf DF, van Vlaardingen PL, Linders JB. The exposure assessment for veterinary medicinal products. Sci Total Environ. 1999; 225: 119-133.

76. Ali Abdullah A. S. Detection of Tetracycline's and Sulfonamides Residues in Chicken and Beef in Southern Taiwan, National Pingtung University of Science and Technology, Taiwan 2003.

77. Oka H, Ito Y, Ikai Y, Matsumoto H, Kato K, et al. Survey of residual tetracyclines in kidneys of diseased animals in Aichi Prefecture, Japan (1985-1997). J AOAC Int. 2001; 84: 350-353.

78. Missana T, Garcia-Gutierrez M, Alonso U. Sorption of strontium onto illite/smectite mixed clays. Phy and Chem Earth. 2008; 33: S156-S162.

79. De Wasch K, Okerman L, Croubels S, De Brabander H, Van Hoof J, et al. Detection of residues of tetracycline antibiotics in pork and chicken meat: correlation between results of screening and confirmatory tests. Analyst. 1998; 123: 2737-2741.

80. Körner U, Kühne M, Wenzel S. Tetracycline residues in meat and bone meals. Part 1: methodology and examination of field samples. Food Addit Contam. 2001; 18: 293-302.

81. Kühne M, Körner U, Wenzel S. Tetracycline residues in meat and bone meals. Part 2: the effect of heat treatments on bound tetracycline residues. Food Addit Contam. 2001; 18: 593-600.

82. Bao Y, Zhou Q, Wan Y. Adsorption characteristics of tetracycline by two soils: assessing role of soil organic matter. Soil Res. 2009; 47 (3): 286-295.

83. Wan Y, Bao Y, Zhou Q. Simultaneous adsorption and desorption of cadmium and tetracycline on cinnamon soil. Chemosphere. 2010; 80: 807-812.

84. Mary LA, Senthilram T, Suganya S, Nagarajan L, Venugopal J, Ramakrishna S, Ramakrishna S. Centrifugal spun ultrafine fibrous web as a potential drug delivery vehicle. Express Polym Lett. 2013; 7 (3): 238-248.

85. Chang YM, Chen CK, Chang YC, Jeng WY, Hou MH, et al. Functional studies of ssDNA binding ability of MarR family protein TcaR from Staphylococcus epidermidis. PLoS One. 2012; 7: e45665.

86. MacKay AA, Canterbury B. Oxytetracycline sorption to organic matter by metal-bridging. J Environ Qual. 2005; 34: 1964-1971.

87. Chang P-H, Jean J-S, Jiang W-T, Li Z. Mechanism of tetracycline sorption on rectorite. Colloids Surf A Physicochem Eng Asp. 2009; 339 (1-3): 94-99.

88. Gu C, Karthikeyan KG. Interaction of tetracycline with aluminum and iron hydrous oxides. Environ Sci Technol, 2005; 39: 2660-2667.

89. Loke ML, Tjørnelund J, Halling-Sørensen B. Determination of the distribution coefficient (log Kd) of oxytetracycline, tylosin A, olaquindox and metronidazole in manure. Chemosphere. 2002; 48: 351-361.

90. Jia DA, Zhou DM, Wang YJ, Zhu HW, Chen JL. Adsorption and cosorption of Cu (II) and tetracycline on two soils with different characteristics. Geoderm. 2008; 146 (1-2): 224-230.

91. Gu C, Karthikeyan KG. Sorption of the antibiotic tetracycline to humic-mineral complexes. J Environ Qual. 2008; 37: 704-711.

92. Sibley SD, Pedersen JA. Interaction of the macrolide antimicrobial clarithromycin with dissolved humic acid. Environ Sci Technol. 2008; 42: 422-428.

93. Davis JG, Truman CC, Kim SC, Ascough JC 2nd, Carlson K. Antibiotic Transport via Runoff and Soil Loss. J Environ Qual. 2006; 35: 2250-2260.

94. Li B, Zhang T. Biodegradation and adsorption of antibiotics in the activated sludge process. Environ Sci Technol. 2010; 44: 3468-3473.

95. Sithole BB, Guy RD. Models for tetracycline in aquatic environments. Water, Air, and Soil Pollution. 1987; 32: 303-321.

96. Goldberg S, Glaubig RA. Boron adsorption and silicon release by the clay minerals kaolinite, montmorillonite, and illite. Soil Sci Soc Am J. 1986; 50: 1442-1448.

97. Tombácz E. Surface charging and particle interactions in aqueous dispersions of metal oxides and clay minerals. 12th Ostwald-Kolloquium, March 25-26, Kiel, German. 2004.

98. Charlet L, Schindler PW, Spadini L, Furrer G, Zysset M. Cation adsorption on oxides and clays: The aluminum case. Aquatic Sci. 1992; 55: 291-303.

99. Doi A M, Stoskopf M K. The kinetics of oxytetracyline degradation in deionised water under varying temperature, pH, light, substrate and organic matter. J Aquat Anim Health. 2000; 12 (3): 246-253.

100. Verma B, Headley JV, Robarts RD. Behaviour and fate of tetracycline in river and wetland waters on the Canadian Northern Great Plains. J Environ Sci Health A Tox Hazard Subst Environ Eng .2007; 42: 109-117.

101. Arikan OA, Sikora LJ, Mulbry W, Khan SU, Foster GD. Composting rapidly reduces levels of extractable oxytetracycline in manure from therapeutically treated beef calves. Bioresour Technol. 2007; 98: 169-176.

102. Halling-Sørensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, Holten Lützhøft HC, et al. Occurrence, fate and effects of pharmaceutical substances in the environment--a review. Chemosphere. 1998; 36: 357-393.

103. Muangsiri W, Kirsch LE. The kinetics of the alkaline degradation of daptomycin. J Pharm Sci. 2001; 90: 1066-1075.

104. Boxall AB, Johnson P, Smith EJ, Sinclair CJ, Stutt E, et al. Uptake of veterinary medicines from soils into plants. J Agric Food Chem. 2006; 54: 2288-2297.

105. Thiele-Bruhn S. Microbial inhibition by pharmaceutical antibiotics in different soils--dose-response relations determined with the iron (III) reduction test. Environ Toxicol Chem. 2005; 24: 869-876.

106. Van Dijck P, van de Voorde H. Sensitivity of environmental microorganisms to antimicrobial agents. Appl Environ Microbiol.1976; 31: 332-336.

107. Bradel BG, Preil W, Jeske H. Remission of the free-branching pattern of Euphorbia pulcherrima by tetracycline treatment. J PhytopatholPhytopathologi Z. 2000; 148 (11-12): 587-590.

108. Backhaus T, Grimme LH. The toxicity of antibiotic agents to the luminescent bacterium Vibrio fischeri. Chemosphere. 1999; 38: 3291-3301.

109. Migliore L, Cozzolino S, Fiori M. Phytotoxicity to and uptake of flumequine used in intensive aquaculture on the aquatic weed, Lythrum salicaria L. Chemosphere. 2000; 40: 741-750.

110. Kong WD, Zhu YG. A review on ecotoxicology of veterinary pharmaceuticals to plants and soil microbes. Asian J Ecotoxicol. 2007; 2 (1): 1-9.

111. Migliore L, Civitareale C, Cozzolino S, Casoria P, Brambilla G, Gaudio L. Laboratory models to evaluate phytotoxicity of Sulphadimethoxine on terrestrial plants. Chemosphere. 1998; 37 (14-15): 2957-2961.

112. Warman PR, Thomas RL. Chlortetracycline in soil amended with poultry manure. Canadian J Soil Sci. 1981; 61 (1): 161-163.

113. Wollenberger L, Halling-Sørensen B, Kusk KO. Acute and chronic toxicity of veterinary antibiotics to Daphnia magna. Chemosphere. 2000; 40: 723-730.

114. Migliore L, Brambilla G, Cozzolino S, Gaudio L. Effect on plants of sulphadimethoxine used in intensive farming (Panicum miliaceum, Pisum sativum and Zea mays). Agric. Ecosyst. Environ. 1995; 52 (2-3): 103-110.

115. Kasai K, Kanno T, Endo Y, Wakasa K, Tozawa Y. Guanosine tetra- and pentaphosphate synthase activity in chloroplasts of a higher plant: association with 70S ribosomes and inhibition by tetracycline. Nucleic Acids Res. 2004; 32: 5732-5741.

116. Lunden T, Miettinen S, LÖnnstrÖm LG, Lilius EM, Bylund G. Influence of oxytetracycline and oxolinic acid on the immune response of rainbow trout (Oncorhynchus mykiss). Fish Shellfish Immunol. 1998; 8 (3): 217-230.

117. Goñi-Urriza M, Pineau L, Capdepuy M, Roques C, Caumette P, et al. Antimicrobial resistance of mesophilic Aeromonas spp. isolated from two European rivers. J Antimicrob Chemother. 2000; 46: 297-301.

118. Ferreira CS, Nunes BA, Henriques-Almeida JM, Guilhermino L. Acute toxicity of oxytetracycline and florfenicol to the microalgae Tetraselmis chuii and to the crustacean Artemia parthenogenetica. Ecotoxicol Environ Saf. 2007; 67: 452-458.

119. Halling-Sørensen B. Algal toxicity of antibacterial agents used in intensive farming. Chemosphere. 2000; 40: 731-739.

120. Lützhøft HH, Halling-Sørensen B, Jørgensen SE. Algal toxicity of antibacterial agents applied in Danish fish farming. Arch Environ Contam Toxicol. 1999; 36: 1-6.

121. Migliore L, Civitareale C, Brambilla G, Di Delupis GD. Toxicity of several important agricultural antibiotics to Artemia. Water Res. 1997; 31 (7): 1801-1806.

122. Thiele-Bruhn S, Beck IC. Effects of sulfonamide and tetracycline antibiotics on soil microbial activity and microbial biomass. Chemosphere. 2005; 59: 457-465.

123. Boleas S, Alonso C, Pro J, Fernández C, Carbonell G, et al. Toxicity of the antimicrobial oxytetracycline to soil organisms in a multi-species-soil system (MS.3) and influence of manure co-addition. J Hazard Mater 2005; 122: 233-241.

124. Acar JF, Moulin G. Antimicrobial resistance at farm level. Sci Tech. 2006; 25: 775-792.

125. Sengelov G, Halling-Sørensen B, Aarestrup FM. Susceptibility of Escherichia coli and Enterococcus faecium isolated from

pigs and broiler chickens to tetracycline degradation products and distribution of tetracycline resistance determinants in E. coli from food animals. Vet. Microbiol. 2003; 95 (1-2): 91-101.

126. Teuber M. Veterinary use and antibiotic resistance. Curr Opin Microbiol. 2001; 4: 493-499.

127. Hvistendahl M. Public health. China takes aim at rampant antibiotic resistance. Science. 2012; 336: 795.

128. Bjorklund H, Bondestam J, Bylund G. Residues of oxytetracycline in wild fish and sediments from fish farms. Aquaculture. 1990; 86 (4): 359-367.

129. Krumperman PH. Multiple antibiotic resistance indexing of Escherichia coli to identify high-risk sources of fecal contamination of foods. Appl Environ Microbiol. 1983; 46: 165-170.

130. Adams CA, Austin B, Meaden PG, McIntosh D. Molecular characterization of plasmid-mediated oxytetracycline resistance in Aeromonas salmonicida. Appl Environ Microbiol. 1998; 64: 4194-4201.

131. Rhodes G, Huys G, Swings J, Mcgann P, Hiney M, Smith P, Pickup RW. Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: implication of Tn1721 in dissemination of the tetracycline resistance determinant tet A. Appl. Environ. Microbiol. 2000; 66 (9): 3883-3890.

132. Moore JE, Barton MD, Blair IS, Corcoran D, Dooley JS, et al. The epidemiology of antibiotic resistance in Campylobacter. Microbes Infect. 2006; 8: 1955-1966.

133. Lindsey ME, Meyer M, Thurman EM. Analysis of trace levels of sulfonamide and tetracycline antimicrobials in groundwater and surface water using solid-phase extraction and liquid chromatography/mass spectrometry. Analyt Chem. 2001; 73 (19): 4640 -4646.

134. Stepanauskas R, Glenn TC, Jagoe CH, Tuckfield RC, Lindell AH, et al. Elevated microbial tolerance to metals and antibiotics in metal-contaminated industrial environments. Environ Sci Technol. 2005; 39: 3671-3678.

135. Hawkins WA, Dale JW. High and low level tetracycline resistance in Shigella sonnei. J Hyg (Lond). 1978; 81: 131-138.

136. Henwood CJ, Gatward T, Warner M, James D, Stockdale MW, et al. Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936). J Antimicrob Chemother. 2002; 49: 479-487.

137. Richmond MH, Linton KB. The use of tetracycline in the community and its possible relation to the excretion of tetracycline-resistant bacteria. J Antimicrob Chemother. 1980; 6: 33-41.

138. Robertson MH. Beta-haemolytic streptococci in South-west Essex, with particular reference to tetracycline resistance. Br Med J. 1965; 2: 569-571.

139. Jones OAH, Voulvoulis N, Lester JN. Human Pharmaceuticals in Wastewater Treatment Processes. Crit. Rev. Environ. Sci. Technol. 2005; 35 (4): 401-427.

140. Richardson BJ, Lam PK, Martin M. Emerging chemicals of concern: pharmaceuticals and personal care products (PPCPs) in Asia, with particular reference to Southern China. Mar Pollut Bull. 2005; 50: 913-920.

141. Trevejo RT, Courtney JG, Starr M, Vugia DJ. Epidemiology of salmonellosis in California, 1990-1999: morbidity, mortality, and hospitalization costs. Am J Epidemiol. 2004; 157: 48-57.

142. Threlfall EJ, Rowe B, Ward LR. A comparison of multiple drug resistance in salmonellas from humans and food animals in England and Wales, 1981 and 1990. Epidemiol Infect. 1993; 111: 189-197.

143. Ramos JM, Alés JM, Cuenca-Estrella M, Fernández-Roblas R, Soriano F. Changes in susceptibility of Salmonella enteritidis, Salmonella typhimurium, and Salmonella virchow to six antimicrobial agents in a Spanish hospital, 1980-1994. Eur J Clin Microbiol Infect Dis. 1996; 15: 85-88.

144. Glynn MK, Bopp C, Dewitt W, Dabney P, Mokhtar M, et al. Emergence of multidrug-resistant Salmonella enterica serotype typhimurium DT104 infections in the United States. N Engl J Med. 1998; 338: 1333-1338.

145. Busch U, Nitschko H. Methods for the differentiation of microorganisms. J Chromatogr B Biomed Sci Appl. 1999; 722: 263-278.

146. Blanchard A, Crabb DM, Dybvig K, Duffy LB, Cassell GH. Rapid detection of tetM in Mycoplasma hominis and Ureaplasma urealyticum by PCR: tetM confers resistance to tetracycline but not necessarily to doxycycline. FEMS Microbiol Lett. 1992; 74: 277-281.

147. Martinez MA, Ovalle A, Santa-Cruz A, Barrera B, Vidal R, Aguirre R. Occurrence and antimicrobial susceptibility of Ureaplasma parvum (Ureaplasma urealyticum biovar 1) and Ureaplasma urealyticum (Ureaplasma urealyticum biovar 2) from patients with adverse pregnancy outcomes and normal pregnant women. Scand. J Infect Dis. 2001; 33 (8): 604-610.

148. Gottschalk M, Segura M. The pathogenesis of the meningitis caused by Streptococcus suis: the unresolved questions. Vet Microbiol. 2000; 76: 259-272.

149. Arends JP, Zanen HC. Meningitis caused by Streptococcus suis in humans. Infect Dis. 1998; 10: 131-137.

150. Enne VI, Cassar C, Sprigings K, Woodward MJ, Bennett PM. A high prevalence of antimicrobial resistant Escherichia coli isolated from pigs and a low prevalence of antimicrobial resistant E. coli from cattle and sheep in Great Britain at slaughter. FEMS Microbiol Lett. 2008; 278: 193-199.

151. Kozak GK, Boerlin P, Janecko N, Reid-Smith RJ, Jardine C. Antimicrobial resistance in Escherichia coli isolates from swine and wild small mammals in the proximity of swine farms and in natural environments in Ontario, Canada. Appl Environ Microbiol. 2009; 75: 559-566.

152. Roberts MC. Update on acquired tetracycline resistance genes. FEMS Microbiol Lett. 2005; 245: 195-203.

153. Bryan A, Shapir N, Sadowsky M J. Frequency and distribution of tetracycline resistance genes in genetically diverse, nonselected, and nonclinical Escherichia coli strains isolated from diverse human and animal sources. Appl. Environ. Microbiol. 2004; 70 (4): 2503-2507.

154. Bywater R, Deluyker, H, Deroover E, Jong A D, Marion H, et.al. A European survey of antimicrobial susceptibility among zoonotic and commensal bacteria isolated from food-producing animals. J. Antimicrob. Chemother. 2004; 54 (4): 744-754.

155. Mayrhofer S, Paulsen P, Smulders FJ, Hilbert F. Antimicrobial resistance in commensal Escherichia coli isolated from muscle foods as related to the veterinary use of antimicrobial agents in food-producing animals in Austria. Microb Drug Resist. 2006; 12: 278-283.

156. Webster RG, Kawaoka Y, Bean WJ, Beard CW, Brugh M. Chemotherapy and vaccination: a possible strategy for the control of highly virulent influenza virus. J Virol. 1985; 55: 173-176.

157. Schmitt H, Stoob K, Hamscher G, Smit E, Seinen W. Tetracyclines and tetracycline resistance in agricultural soils: microcosm and field studies. Microb Ecol. 2006; 51: 267-276.

158. Pruden A, Pei R, Storteboom H, Carlson KH. Antibiotic resistance genes as emerging contaminants: studies in northern Colorado. Environ Sci Technol. 2006; 40: 7445-7450.

159. Bertolla F, Kay E, Simonet P. Potential dissemination of antibiotic resistance genes from transgenic plants to microorganisms. Infect Control Hosp Epidemiol. 2000; 21: 390-393.

160. Dantas G, Sommer MO, Oluwasegun RD, Church GM. Bacteria subsisting on antibiotics. Science. 2008; 320: 100-103.

161. Davison J. Genetic exchange between bacteria in the environment. Plasmid. 1999; 42: 73-91.

162. Herry A, Diouris M, Le pennec M, Chemoautrotrophic symbionts and translocation of fixed carbon from bacteria to host tissues in the littoral bivalve Loripes lucinalis (Lucinidae). Mar Bio. 1989; 101 (3): 305-312.

163. Jahagirdar S, Patwardhan R, Dhakephalkar PK. Curing plasmid-mediated vancomycin resistance in Staphylococcus aureus using herbal naphthoquinones. J Hosp Infect. 2008; 70: 289-291.

164. Ni B, Du Z, Guo Z, Zhang Y, Yang R. Curing of four different plasmids in Yersinia pestis using plasmid incompatibility. Lett Appl Microbiol. 2008; 47: 235-240.

165. Warnes SL, Highmore CJ, Keevil CW. Horizontal transfer of antibiotic resistance genes on abiotic touch surfaces: implications for public health. MBio 3. (2012).

166. Chee-Sanford JC, Aminov RI, Krapac IJ, Garrigues-Jeanjean N, Mackie RI. Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities. Appl Environ Microbiol 2001; 67: 1494-1502.

167. Smith MS, Yang RK, Knapp CW, Niu Y, Peak N, et al. Quantification of tetracycline resistance genes in feedlot lagoons by real-time PCR. Appl Environ Microbiol. 2004; 70: 7372-7377.

168. Peak N, Knapp CW, Yang RK, Hanfelt MM, Smith MS, et al. Abundance of six tetracycline resistance genes in wastewater lagoons at cattle feedlots with different antibiotic use strategies. Environ Microbiol. 2007; 9: 143-151.

169. Seveno NA, Kallifidas D, Smalla K, van Elsas JD, Collard JM, Karagouni AD, Wellington EMH. Occurrence and reservoirs of antibiotic resistance genes in the environment. Rev. Med. Microbiol. 2002; 13 (1): 15-27.

170. Mølbak K, Baggesen DL, Aarestrup FM, Ebbesen JM, Engberg J, et al. An outbreak of multidrug-resistant, quinolone-resistant Salmonella enterica serotype typhimurium DT104. N Engl J Med. 1999; 341: 1420-1425.

171. McDonald LC, Rossiter S, Mackinson C, Wang YY, Johnson S, et al. Quinupristin-dalfopristin-resistant Enterococcus faecium on chicken and in human stool specimens. N Engl J Med. 2001; 345: 1155-1160.

172. Sørensen TL, Blom M, Monnet DL, Frimodt-Møller N, Poulsen RL, et al. Transient intestinal carriage after ingestion of antibiotic-resistant Enterococcus faecium from chicken and pork. N Engl J Med. 2001; 345: 1161-1166.

173. White DG, Zhao S, Sudler R, Ayers S, Friedman S, et al. The isolation of antibiotic-resistant salmonella from retail ground meats. N Engl J Med. 2001; 345: 1147-1154.

174. Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, et al. Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proc Natl Acad Sci U S A. 2013; 110: 3435-3440.

175. Brown MG, Mitchell EH, Balkwill DL. Tet 42, a novel tetracycline resistance determinant isolated from deep terrestrial subsurface bacteria. Antimicrob Agents Chemother 2008; 52: 4518-4521.

176. Kazimierczak KA, Rincon MT, Patterson AJ, Martin JC, Young P, et al. A new tetracycline efflux gene, tet(40), is located in tandem with tet(O/32/O) in a human gut firmicute bacterium and in metagenomic library clones. Antimicrob Agents Chemother. 2008; 52: 4001-4009.

177. Lee C, Langlois BE, Dawson KA. Detection of tetracycline resistance determinants in pig isolates from three herds with different histories of antimicrobial agent exposure. Appl Environ Microbiol. 1993; 59: 1467-1472.

178. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 2001; 65: 232-260.

179. Dolejská M, Senk D, Cízek A, Rybaríková J, Sychra O, et al. Antimicrobial resistant Escherichia coli isolates in cattle and house sparrows on two Czech dairy farms. Res Vet Sci. 2008; 85: 491-494.

180. Jia X, Zhang J, Sun W, He W, Jiang H, et al. Riboswitch control of aminoglycoside antibiotic resistance. Cell. 2013; 152: 68-81.

181. Collado MC, GrzeÅ›kowiak Å, Salminen S. Probiotic strains and their combination inhibit in vitro adhesion of pathogens to pig intestinal mucosa. Curr Microbiol.2007; 55: 260-265.

182. Pascual M, Hugas M, Badiola JI, Monfort JM, Garriga M. Lactobacillus salivarius CTC2197 prevents Salmonella enteritidis colonization in chickens. Appl Environ Microbiol. 1999; 65: 4981-4986.

183. Liu FX, Sun S, Cui ZZ. Analysis of immunological enhancement of immunosuppressed chickens by Chinese herbal extracts. J Ethnopharmacol. 2010; 127: 251-256.

184. Yeh HS, Weng BC, Lien TF. Effects of Chinese traditional herbal medicine complex supplementation on the growth performance, immunity and serum traits of pigs. Anim Sci J. 2011; 82: 747-752.

185. Kiarie E, Owusu-Asiedu A, Peron A, Simmins PH, Nyachoti CM. Efficacy of xylanase and beta-glucanase blend in mixed grains and grain co-products-based diets for fattening pigs. Livestock Sci. 2012; 148 (1-2): 129-133.

186. Thacker P A. Effect of xylanase and protease on the performance of growing-finishing pigs fed corn-based diets. J.Appl. Anim. Res. 2005; 28 (1): 17-23.

187. Callaway T R, Edrington TS, Harvey R B, Anderson R C, Nisbet DJ. Prebiotics in food animals, a potential to reduce foodborne pathogens and disease. Roma Biotechnol Lett. 2012; 17 (6): 7808-7816.

188. Hayhoe M, Archbold T, Wang Q, Yang X, Fan MZ. Efficacy of prebiotics on growth performance in replacing antibiotics in weanling pigs. Can. J Anim Sci. 2011; 91 (3): 481-482.

189. Braz DB, Costa LB, Berenchtei B, Tse M L P, Almeida V V, Miyada VS. Acidifiers as alternatives to antimicrobial growth promoter of weanling pigs. Archivos de Zootecnia. 2011; 60: 745-756.

190. Willamil J, Creus E, Pérez JF, Mateu E, Martín-Orúe SM. Effect of a microencapsulated feed additive of lactic and formic acid on the prevalence of Salmonella in pigs arriving at the abattoir. Arch Anim Nutr. 2011; 65: 431-444.

191. Fonseca M J, Tavares F. Natural Antibiotics: A Hands-on Activity on Garlic's Antibiotic Properties. Am Biol Teach. 2011; 73 (6): 342-346.

192. Mansoub NH, Nezhady MAM. Effect of garlic, thyme and yogurt compared to antibiotics on performance, immunity and some blood parameters of broiler chickens. Indian J Anim Sci. 2011; 81 (12):1197-1200.

193. Bozkurt M. Küçükyilmaz K, Çatli A U, Çinar MS, Afr J. Effect of dietary mannan oligosaccharide with or without oregano essential oil and hop extract supplementation on the performance and slaughter characteristics of male broilers. Anim Sci. 2009; 39 (3): 223-232.

194. Branco PAC, Soares R, Vieites F, Cabral N, Tavares E. Efects of essential oils as growth promoters on performance of weaned pigs. Archivos de Zootecnia. 2011; 60 (231): 699-706.

195. Ozkalp B, Sevgi F, Özcan M, Özcan MM. The antibacterial activity of essential oil of oregano (Origanum vulgare L.). J Food Agric Environ. 2010; 8 (2): 272-274.

196. Song C, Weichbrodt C, Salnikov ES, Dynowski M, Forsberg BO, et al. Crystal structure and functional mechanism of a human antimicrobial membrane channel. Proc Natl Acad Sci U S A. 2013; 110: 4586-4591.

197. Schittek B, Hipfel R, Sauer B, Bauer J, Kalbacher H, et al. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol. 2001; 2: 1133-1137.

198. Boxall AB, Kolpin DW, Halling-Sørensen B, Tolls J. Are veterinary medicines causing environmental risks? Environ Sci

Technol. 2003; 37: 286A-294A.

199. Martínez JL. Antibiotics and antibiotic resistance genes in natural environments. Science. 2008; 321: 365-367.

200. BabiÄ‡ S, Asperger D, MutavdziÄ D, Horvat AJ, Kastelan-Macan M. Solid phase extraction and HPLC determination of veterinary pharmaceuticals in wastewater. Talanta. 2006; 70: 732-738.

201. Carballa M, Omil F, Lema JM, Llompart M, García-Jares C, et al. Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. Water Res. 2004; 38: 2918-2926.

202. Castiglioni S, Bagnati R, Fanelli R, Pomati F, Calamari D, et al. Removal of pharmaceuticals in sewage treatment plants in Italy. Environ Sci Technol. 2006; 40: 357-363.

203. Xu W, Zhang G, Li X, Zou S, Li P, et al. Occurrence and elimination of antibiotics at four sewage treatment plants in the Pearl River Delta (PRD), South China. Water Res. 2007; 41: 4526-4534.

204. Kim S, Eichhorn P, Jensen JN, Weber AS, Aga DS. Removal of antibiotics in wastewater: Effect of hydraulic and solid retention times on the fate of tetracycline in the activated sludge process. Environ Sci Technol. 2005; 39: 5816-5823.

205. Kim SC, Carlson K. Quantification of human and veterinary antibiotics in water and sediment using SPE/LC/MS/MS. Anal Bioanal Chem. 2007; 387: 1301-1315.

206. Göbel A, McArdell CS, Joss A, Siegrist H, Giger W. Fate of sulfonamides, macrolides, and trimethoprim in different wastewater treatment technologies. Sci Total Environ. 2007; 372: 361-371.

207. Yang, SW, Cha JM, Carlson K. Simultaneous extraction and analysis of 11 tetracycline and sulfonamide antibiotics in influent and effluent domestic wastewater by solid-phase extraction and liquid chromatography-electro spray ionization tandem mass spectrometry. J Chromatogr A. 2005; 1097 (1-2): 40-53.

208. Cha JM, Yang S, Carlson KH. Rapid analysis of trace levels of antibiotic polyether ionophores in surface water by solid-phase extraction and liquid chromatography with ion trap tandem mass spectrometric detection. J Chromatogr A. 2005; 1065: 187-198.

209. Hirsch R, Ternes TA, Haberer K, Mehlich A, Ballwanz F, et al. Determination of antibiotics in different water compartments via liquid chromatography-electrospray tandem mass spectrometry. J Chromatogr A. 1998; 815: 213-223.

210. Le TX, Munekage Y. Residues of selected antibiotics in water and mud from shrimp ponds in mangrove areas in Viet Nam. Mar Pollut Bull. 2004; 49: 922-929.

211. Yang S, Carlson K. Evolution of antibiotic occurrence in a river through pristine, urban and agricultural landscapes. Water Res. 2003; 37: 4645-4656.

212. Lalumera GM, Calamari D, Galli P, Castiglioni S, Crosa G, et al. Preliminary investigation on the environmental occurrence and effects of antibiotics used in aquaculture in Italy. Chemosphere. 2004; 54: 661-668.

213. Blackwell PA, Holten Lützhøft HC, Ma HP, Halling-Sørensen B, Boxall AB, et al. Ultrasonic extraction of veterinary antibiotics from soils and pig slurry with SPE clean-up and LC-UV and fluorescence detection. Talanta. 2004; 64: 1058-1064.

214. Christian T, Schneider R J, Farber H A, Skutlarek D, Meyer M T, Goldbach HE. Determination of antibiotic residues in manure, soil, and surface waters. Acta Hydrochimica Et Hydrobiologica. 2003; 31 (1): 36-44.

215. Schlüsener MP, Spiteller M, Bester K. Determination of antibiotics from soil by pressurized liquid extraction and liquid chromatography-tandem mass spectrometry. J Chromatogr A. 2003; 1003: 21-28.

216. Weigel S, Berger U, Jensen E, Kallenborn R, Thoresen H, et al. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. Chemosphere. 2004; 56: 583-592.

217. Xiong, Y, Zhou, HJ, Zhang, ZJ, He, DY, He, C. Molecularly imprinted on-line solid-phase extraction combined with flow-injection chemiluminescence for the determination of tetracycline. Analyst. 2006; 131 (7): 829-834.

218. Yang, SW, Cha, J, Carlson, K. Quantitative determination of trace concentrations of tetracycline and sulfonamide antibiotics in surface water using solid-phase extraction and liquid chromatography/ion trap tandem mass spectrometry. Rapid Commun. Mass Spectrom. 2004; 18 (18): 2131-2145.

219. Blackwell P A, Lutzhoft HCH, Ma H P, Halling-Sørense, B, Boxall ABA, Kay P. Fast and robust simultaneous determination of three veterinary antibiotics in groundwater and surface water using a tandem solid-phase extraction with high-performance liquid chromatography-UV detection. J Chromatogr A. 2004; 1045 (1-2): 111 -117.

220. Guerreiro JRL, Freitas V, Sales MGF. New sensing materials of molecularly-imprinted polymers for the selective recognition of Chlortetracycline. Microchem J. 2011; 97 (2): 173-181.

221. Jing T, Niu J, Xia H, Dai Q, Zheng H, et al. Online coupling of molecularly imprinted solid-phase extraction to HPLC for determination of trace tetracycline antibiotic residues in egg samples. J Sep Sci. 2011; 34: 1469-1476.

222. Kong J, Wang YZ, Nie C, Ran D, Jia XP. Preparation of magnetic mixed-templates molecularly imprinted polymer for the separation of tetracycline antibiotics from egg and honey samples. Anal. Methods. 2012; 4 (4): 1005-1011.

223. Oka H, Ikai Y, Kawamura N, Uno K, Yamada M, et al. Improvement of chemical analysis of antibiotics. X. Determination of eight tetracyclines using thin-layer and high-performance liquid chromatography. J Chromatogr. 1987; 393: 285-296.

224. Korsrud GO, Naylor JM, Salisbury CD, Macneil JD. A comparison of 3 bioassay techniques for the detection of chloramphenicol residues in animal-tissues. J Agric Food Chem. 1987; 35 (4): 556-559.

225. Schneider MJ, Darwish AM, Freeman DW. Simultaneous multiresidue determination of tetracyclines and fluoroquinolones in catfish muscle using high performance liquid chromatography with fluorescence detection. Anal. Chim. Acta. 2007; 586 (1-2): 269-274.

226. Li H, Kijak PJ, Turnipseed SB, Cui W. Analysis of veterinary drug residues in shrimp: a multi-class method by liquid chromatography-quadrupole ion trap mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2006; 836: 22-38.

227. Koesukwiwat U, Jayanta S, Leepipatpiboon N. Solid-phase extraction for multiresidue determination of sulfonamides, tetracyclines, and pyrimethamine in Bovine's milk. J Chromatogr A. 2007; 1149: 102-111.

228. Kaufmann A, Butcher P, Maden K, Widmer M. Quantitative multiresidue method for about 100 veterinary drugs in different meat matrices by sub 2-mu m particulate high-performance liquid chromatography coupled to time of flight mass spectrometry. J Chromatogr A. 2008; 1194 (1): 66-79.

229. Croubels S, Baert K, De Busser J, De Backer P. Residue study of doxycycline and 4-epidoxycycline in pigs medicated via-drinking water. Analyst. 1988; 123: 2733-2736.

230. Croubels S, Vermeersch H, De Backer P, Santos MD, Remon JP, et al. Liquid chromatographic separation of doxycycline and 4-epidoxycycline in a tissue depletion study of doxycycline in turkeys. J Chromatogr B Biomed Sci Appl. 1998; 708: 145-152.

231. Cherlet, M, Schelkens, M, Croubels, S, De Backer, P. Quantitative multi-residue analysis of tetracyclines and their 4-epimers in pig tissues by high-performance liquid chromatography combined with positive-ion electrospray ionization mass spectrometry. Anal. Chim Acta. 2003; 492 (1-2): 199-213.

232. Yang S, Carlson KH. Solid-phase extraction-high-performance liquid chromatography-ion trap mass spectrometry for analysis of trace concentrations of macrolide antibiotics in natural and waste water matrices. J Chromatogr A. 2004; 1038: 141-155.

233. Choma I M. Separation of tetracyclines by thin-layer chromatography. Chem. Analityczna. 2001; 46 (1): 1-9.

234. Delépée R, Maume D, Le Bizec B, Pouliquen H. Preliminary assays to elucidate the structure of oxytetracycline's degradation products in sediments. Determination of natural tetracyclines by high-performance liquid chromatography-fast atom bombardment mass spectrometry. J Chromatogr B Biomed Sci Appl. 2000; 748: 369-381.

235. Sczesny S, Nau H, Hamscher G. Residue analysis of tetracyclines and their metabolites in eggs and in the environment by HPLC coupled with a microbiological assay and tandem mass spectrometry. J Agric Food Chem. 2003; 51: 697-703.

236. Barnes C J. Drug Residues in Animal-Tissues. J.AOAC. 1986; 69 (2): 278-278.

237. Neidert E, Saschenbrecker PW, Tittiger F. Thin layer chromatographic/bioautographic method for identification of antibiotic residues in animal tissues. J Assoc Off Anal Chem. 1987; 70: 197-200.

238. Ashworth RB. Liquid chromatographic assay of tetracyclines in tissues of food-producing animals. J Assoc off Anal Chem. 1985; 68: 1013-1018.

239. Oka H, Uno K, Harada KI, Hayashi M, Suzuki M. Improvement of Chemical-Analysis Of Antibiotics .6. Detection Reagents for Tetracyclines In Thin-Layer Chromatography. J Chromatogr. 1984; 295 (1): 129-139.

240. Kumar K, Thompson A, Singh AK, Chander Y, Gupta SC. Enzyme-linked immunosorbent assay for ultratrace determination of antibiotics in aqueous samples. J Environ Qual. 2004; 33: 250-256.

241. Yang S, Carlson K. Routine monitoring of antibiotics in water and wastewater with a radioimmunoassay technique. Water Res. 2004; 38: 3155-3166.

242. Hirsch R, Ternes T, Haberer K, Kratz KL. Occurrence of antibiotics in the aquatic environment. Sci Total Environ. 1999; 225: 109-118.

243. Reverté S, Borrull F, Pocurull E, Marcé RM. Determination of antibiotic compounds in water by solid-phase extraction-high-performance liquid chromatography-(electrospray) mass spectrometry. J Chromatogr A. 2003; 1010: 225-232.

244. Zhu J, Snow DD, Cassada DA, Monson SJ, Spalding RF. Analysis of oxytetracycline, tetracycline, and chlortetracycline in water using solid-phase extraction and liquid chromatography-tandem mass spectrometry. J Chromatogr A. 2001; 928: 177-186.

245. Rabølle M, Spliid NH. Sorption and mobility of metronidazole, olaquindox, oxytetracycline and tylosin in soil. Chemosphere. 2000; 40: 715-722.

246. Furusawa N. Isolation of tetracyclines in milk using a solid-phase extracting column and water eluent. Talanta. 2003; 59: 155-159.

247. Hilton M J, Thomas K V. Determination of selected human pharmaceutical compounds in effluent and surface water samples by high-performance liquid chromatography-electrospray tandem mass spectrometry. J Chromatogr A. 2003; 1015 (1-2): 129-141.

248. Sørensen LK, Elbaek TH. Simultaneous determination of trimethoprim, sulfadiazine, florfenicol and oxolinic acid in surface water by liquid chromatography tandem mass spectrometry. Chromatographia. 2004; 60 (5-6): 287-291.

249. Cinquina AL, Longo F, Anastasi G, Giannetti L, Cozzani R. Validation of a high-performance liquid chromatography method for the determination of oxytetracycline, tetracycline, chlortetracycline and doxycycline in bovine milk and muscle. J Chromatogr A. 2003; 987: 227-233.

250. Shaikh B, Moats WA. Liquid chromatographic analysis of antibacterial drug residues in food products of animal origin. J Chromatogr. 1993; 643: 369-378.

251. Sporns P, Kwan SR, L A. Hplc analysis of oxytetracycline residues in honey. J. Food Prot. 1986; 49 (5): 383-388.

252. Argauer RJ, Moats W A. Degradation of oxytetracycline in honey as measured by fluorescence and liquid-chromatographic assays. Apidologie. 1991; 22 (2): 109-115.

253. Oka H, Ikai Y, Hayakawa J, Harada K, Asukabe H, Suzuki M , Himei R, Horie M, Nakazawa H, Macneil JD. Improvement of chemical-analysis of antibiotics .22. Identification of residual tetracyclines in honey by frit fab/lc/ms using a volatile mobile-phase. J Agric Food Chem. 1994; 42 (10): 2215-2219.

254. Kaufmann A, Roth S, Ryser B, Widmer M, Guggisberg D. Quantitative LC/MS-MS determination of sulfonamides and some other antibiotics in honey. J AOAC Int. 2002; 85: 853-860.

255. Nakazawa, H, Ino, S, Kato, K, Watanabe, T, Ito, Y, Oka, H. Simultaneous determination of residual tetracyclines in foods by high-performance liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry. J Chromatogr B Analyt. Technol Biomed Life Sci. 1999; 732 (1): 55-64.

256. Alpert AJ. Hydrophilic-interaction chromatography for the separation of peptides, nucleic acids and other polar compounds. J Chromatogr. 1990; 499: 177-196.

257. Dejaegher B, Vander Heyden Y. HILIC methods in pharmaceutical analysis. J Sep Sci. 2010 33: 698-715.

258. Hemström P, Irgum K. Hydrophilic interaction chromatography. J Sep Sci. 2006; 29: 1784-1821.

259. Ikegami T, Tomomatsu K, Takubo H, Horie K, Tanaka N. Separation efficiencies in hydrophilic interaction chromatography. J Chromatogr A. 2008; 1184: 474-503.

260. Valette JC, Demesmay C, Rocca JL, VerdonE. Separation of tetracycline antibiotics by hydrophilic interaction chromatography using an amino-propyl stationary phase. Chromatographia. 2004; 59 (1-2): 55-60.

261. Gritti F, Dos Santos Pereira A, Sandra P, Guiochon G. Efficiency of the same neat silica column in hydrophilic interaction chromatography and per aqueous liquid chromatography. J Chromatogr A. 2010; 1217: 683-688.

262. Nguyen HP, Schug KA. The advantages of ESI-MS detection in conjunction with HILIC mode separations: Fundamentals and applications. J Sep Sci. 2008; 31: 1465-1480.

263. Li R, Yuan Q, Zhang Y, Ling J, Han TT. Hydrophilic interaction chromatographic determination of oxytetracycline in the environmental water using silica column. J Liq Chromatogr Relat Technol. 2011; 34 (7): 511-520.

264. Woods JH, Katz JL, Winger G. Abuse liability of benzodiazepines. Pharmacol. 1987; 39: 251-413.

265. Jeong S, Rhee Paeng I. Sensitivity and selectivity on aptamer-based assay: the determination of tetracycline residue in bovine milk. Scientific World Journal 2012: 159-456.

266. Zhang J, Wu Y, Zhang BB, Li M, Jia SR, Jiang SH, et.al. Label-free electrochemical detection of tetracycline by an aptamer nano-biosensor. Analyt. Lett. 2012; 45 (9): 986-992.

267. Ellington A D, Szostak J W. Invitro selection of rna molecules that bind specific ligands. Nature. 1990; 346 (6287): 818-822.

268. Torres-Chavolla E, Alocilja EC. Aptasensors for detection of microbial and viral pathogens. Biosens Bioelectron. 2009; 24: 3175-3182.

269. Tombelli S, Minunni M, Mascini M. Analytical applications of aptamers. Biosens Bio electron. 2005; 20: 2424-2434.

270. Hermann T, Patel DJ. Adaptive recognition by nucleic acid aptamers. Science. 2000; 287: 820-825.

271. Famulok M, Mayer G, Blind M. Nucleic acid aptamers-from selection in vitro to applications in vivo. Acc Chem Res. 2000; 33: 591-599.

272. Pieken WA, Olsen DB, Benseler F, Aurup H, Eckstein F. Kinetic characterization of ribonuclease-resistant 2'-modified hammerhead ribozymes. Science. 1991; 253: 314-317.

273. Nozal L, Arce L, Simonet BM, Rios A, Valcarcel M. Rapid determination of trace levels of tetracyclines in surface water using a continuous flow manifold coupled to a capillary electrophoresis system. Anal Chim Acta. 2004; 517 (1-2): 89-94.

274. Brodin T, Fick J, Jonsson M, Klaminder J. Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. Science. 2013; 339: 814-815.

275. Chen C, Yang X, Wei J, Tan X, Wang X. Eu(III) uptake on rectorite in the presence of humic acid: a macroscopic and spectroscopic study. J Colloid Interface Sci. 2013; 393: 249-256.

276. Alexander N. and Arieh S. Rheological Properties of Aqueous Suspensions of Palygorskite. Soil Sci Soc Am J. 2000; 64: 427-436.

277. Stathi P, Litina K, Gournis D, Giannopoulos TS, Deligiannakis Y. Physicochemical study of novel organoclays as heavy metal ion adsorbents for environmental remediation. J Colloid Interface Sci. 2007; 316: 298-309.

278. Stadler M, Schindler RW. Modeling of H+ and Cu2+ adsorption on calcium montmorillonite. Clay Clay Miner. 1993; 41: 288-296.

279. Zysset M. Thesis Die protoneninduzierte auflösung von K-montmorillonite. Bern University, Bern, Switzerland. 1992.

280. Xia, LY, Zhong, H, Liu, GY, Huang, ZQ, Chang, QW, Li, X-.G. Comparative studies on flotation of illite, pyrophyllite and kaolinite with Gemini and conventional cationic surfactants. Trans. Nonferrous Met. Soc. China. 2009; 19: 446-453.

281. Lan Y, Deng B, Kim C, Thornton EC. Influence of soil minerals on chromium (VI) reduction by sulfide under anoxic conditions. Geochem Trans. 2007; 8: 4.

282. Hong HL, Jiang, WT, Zhang X, Tie L, Li Z. Adsorption of Cr(VI) on STAC-modified rectorite. Appl. Clay Sci. 2008; 44: 292-299.

283. Borden D, Giese RF. Baseline studies of the clay minerals society source clays: Cation exchange capacity measurements by the ammonia-electrode method. Clay Clay Miner. 2001; 49: 444-445.

284. Kahle M, Stamm C. Time and pH-dependent sorption of the veterinary antimicrobial sulfathiazole to clay minerals and ferrihydrite. Chemosphere. 2007; 68: 1224-1231.