Human and veterinary antibiotics during composting of sludge or manure: Global perspectives on persistence, degradation, and resistance genes

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Clean Version

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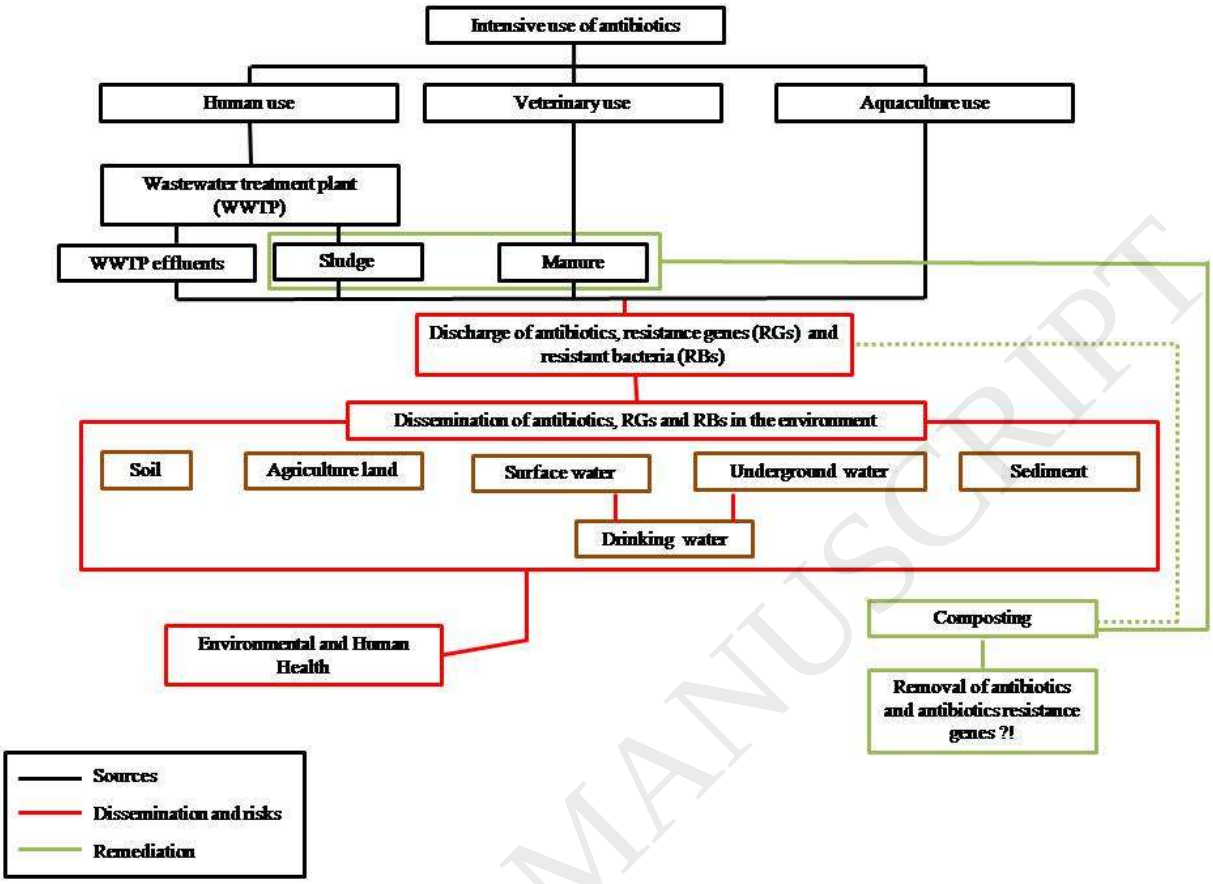
Graphical abstract



Highlights

- Sludge and manure present high range and level of antibiotics.
- Composting is a solution to partially remove some antibiotics.
- The transformation pathways are barely known.
- The fate of antibiotic resistance genes during composting still remains inconsistent.
- Authorized levels of antibiotics in sludge, manure and compost should be considered.

Abstract

Wastewater treatment plant effluent, sludge and manure are the main sources of contamination by antibiotics in the whole environment compartments (soil, sediment, surface and underground water). One of the major consequences of the antibiotics discharge into the environment could be the prevalence of a bacterial resistance to antibiotic. In this review, four groups of antibiotics (Tetracyclines, Fluoroquinolones, Macrolides and Sulfonamides) were focused for the background on their wide spread occurrence in sludge and manure and for their effects on several target and non-target species. The antibiotics concentrations range between 1 and 136,000 μg kg^{-1} of dry matter in sludge and manure, representing a potential risk for the human health and the environment. Composting of sludge or manure is a well-known and used organic matter stabilization technology, which could be effective in reducing the antibiotics levels as well as the antibiotic resistance genes. During sludge or manure composting, the antibiotics removals range between 17-100%. The deduced calculated half-lives range between 1 to 105 days for most of the studied antibiotics. Nevertheless, these removals are often based on the measurement of concentration without considering the matter removal (lack of matter balance) and very few studies are emphasized on the removal mechanisms (biotic/abiotic, bound residues formation) and the potential presence of more or less hazardous transformation products.

The results from the few studies on the fate of the antibiotic resistance genes during sludge or manure composting are still inconsistent showing either decrease or increase of their concentration in the final product.

Whether for antibiotic or antibiotic resistance genes, additional researches are needed, gathering chemical, microbiological and toxicological data to better understand the implied removal mechanisms (chemical, physical and biological), the interactions between both components and the environmental matrices (organic, inorganic bearing phases) and how composting process could be optimized to reduce the discharge of antibiotics and antibiotic resistance genes into the environment.

Keywords: Sludge, Manure, Composting, Antibiotics, Antibiotic resistance genes.

Contents

1. Introduction

Prior to the beginning of the 20^{th} Century, infectious diseases (cholera, typhoid fever, etc) were expanded worldwide. Thereby, the average life expectancy was 47 years [1]. Since the discovery of penicillin in 1928, the increase of antibiotic use reduced significantly the mortality rate. Today, antibiotics are widely used in human and veterinary medicine [2] (Table 1). The annual use of antibiotics was estimated to be between 100,000 and 200,000 t worldwide [3]. In Europe, 2/3 of antibiotics are used in human medicine and 1/3 for veterinary use [4]. In the United States, 16,000 t of antimicrobial compounds are used annually, 70% are used for non-therapeutic purposes [5]. The intensive use of antibiotics for human purposes leads to their continuous release into wastewater treatment plants. Moreover, most of the wastewater treatment plants, based on biological aerated systems for example [6], were not designed to treat such compounds and present limited performances regarding their elimination [7, 8]. So, a part of these molecules is discharged by the wastewater treatment plant effluent toward the aquatic environment and the other part, adsorbed on sludge, could reach the soil according to the sludge use state rules [9, 10]. Hence, wastewater treatment plants are considered as an anthropogenic source for the environmental contamination by antibiotics [11]. Another hotspot of antibiotic dissemination in the environment is the veterinary use [12, 13]. Very high antibiotic concentrations varying from 91 to 136 mg kg^{-1} of dry matter of sulfonamides [14] and tetracyclines [15], and other molecules were found in manure. As a consequence of these massive discharges into the environment, antibiotics were found in each environmental compartment, in soil [16], sediment [17], surface and groundwater [18]. Such presence is one of the factors contributing to the spread of antibiotic resistance [19]. Thus, it is necessary to propose strategies to manage and reduce the dissemination of antibiotics [20].

Composting is a bioremediation technology able to reduce or eliminate the residual concentrations of antibiotics present in sludge or manure before their application to agricultural fields. The presence of antibiotics and consequently antibiotics resistance genes in sludge and manure and their fate during composting are up to date research topics, particularly since 2009 (Fig. 1). After 2009, the number of publications increased up to 100 publications between 2016 and 2017. The assessment of composting efficiency toward the elimination of antibiotics and their antibiotic resistance genes is still in progress, and needs more knowledge. In the light of the recent researches, providing a global vision and perspectives about the fate of antibiotics and antibiotic resistance genes during composting is highly valuable. In this context, the authors have been worked during 2 years in this review to explore the sources, the dissemination routes and the impacts of antibiotics and their associated antibiotic resistance genes. In addition, the fate of antibiotics and antibiotic resistance genes during composting of sludge or manure was reviewed to assess the potentiality of composting as a strategy to mitigate the dissemination of antibiotics and antibiotic resistance genes.

2. The occurrence of antibiotics in raw and composted sludge or manure and their impact on the environment after soil application

In the European Union, 53% of the sludge produced by wastewater treatment plants is used in agriculture [21]. Many antibiotics end up in sewage sludge as shown on the Figure-1a with concentration varying between few nano-grams and 100 mg kg^{-1} dry matter. The four main families (tetracyclines, sulfonamides, macrolides and fluoroquinolones) have been quantified in raw sludge, including primary, secondary, mixed and dehydrated sludge (Figure. 2a).

In raw sludge, ciprofloxacin, norfloxacin, and tylosine are present at the highest concentration with a median value superior to 1000 µg kg^{-1} dry matter. Tetracyclines present a high range of concentrations, particularly tetracycline and oxytetracycline, with medians above 10 µg kg^{-1} dry matter. Macrolides present also medians above 10 µg kg^{-1} dry matter but with a lower range of concentrations. Sulfonamides present medians around 10 µg kg^{-1} dry matter. In composted sludge (Fig. 2b), ciprofloxacin and norfloxacin present lower medians than in raw sludge (near 100 µg kg^{-1} dry matter). For the other compounds, reported values are quite similar between raw and composted sludge. It emphasizes that some compounds are recalcitrant to the biological and physico-chemical transformations occurring during composting. The comparison between Fig. 2a and Fig. 2b revealed that sludge produced on wastewater treatment plants is more studied than the sludge compost, underlying the need to investigate the fate of such compounds during this sludge treatment process and to quantify their presence in the produced organic waste often used as fertilizers on agricultural soil. In the United States, 130 million tons of pig, bovine and chicken manure are produced annually. In Canada, 177.5 million tons are produced per year [22], in France in 2012, over 274 million tons of livestock wastes were generated and applied on soil [23]. Considering the high use of antibiotics in veterinary medicine and depending on pharmacokinetics and specific transformation processes in the animals, large proportions of antibiotics are usually excreted (30-90%) by urine or faeces [24]. Therefore, antibiotics could be released into the environment when urine [25] and manure (Fig. 2c) were used directly as fertilizers. A very high range of concentrations was found from µg to g kg^{-1} dry matter due to the various practices in livestock industries, e.g. use of antibiotics as growth promoters in many developing countries [26]. As it was observed in the Fig. 2a, the Fig. 2c showed that the four main families have been quantified in raw manure. Medians are around 100 and 1000 µg kg^{-1} dry matter. Nevertheless, the Fig. 2d showed that only one paper reported tetracyclines value on composted manure with also a wide range of concentrations [27]. The fluoroquinolones were not studied after manure composting although they may persist. As previously mentioned for sludge composting, the fate of antibiotics in different composted manures must be studied.

A high proportion of antibiotics and potentially bioactive transformation products reach agriculture fields or soil throughout the direct discharge or application of sludge and manure [23, 28-31]. Concentrations in soil compartment vary according to the history of the field. In soils amended with raw or composted sludge, Bourdat-Deschamps et al. [23] have measured 4-10 µg kg^{-1} dry matter of fluoroquinolones. Hu et al. [32] mentioned 2.5-105 µg kg^{-1} dry matter for tetracylines and 33.1-1079 µg kg^{-1} dry matter for chortetracycline in soils amended with organic pig manure. Karci and Balcioglu [33] have quantified sulfonamides (40-400 µg kg^{-1} dry matter) in soils amended with cattle or chicken manure. Very few papers studied the long-term impact of several spreading on soil concentration. One recent paper emphasized that even if high concentration of antibiotics were found in amended fertilizers, no accumulation in soil and few transfer to soil leachates were observed [23]. These results may be explained by the various dissipation mechanisms occurring in soils according to the physical and chemical proprieties of antibiotics (Table 1). Indeed, the majority of antibiotics have low to moderate persistency in the soil with half-lives comprised between days and months (Table 3). In addition, low (sulfamethoxazole, sulfamethazine log K_{oc}<3) [34, 35] or high sorption (fluoroquinolones, log K_{oc}>3) [23] contributes in rendering antibiotics more or less available for water and plant transfer. Indeed, under specific conditions plant uptake have been reported but under field conditions the concentration level of antibiotics in crops has been found to be very low [30, 36]. Prosser and Sibley [37] assessing the human health risk of antibiotics in plant tissues due to sludge or manure amendment concluded to a *de minimis* risk to human health for individual compound, but consider the existence of a risk in the presence of mixtures. [36, 37]. Whatever their behavior (persistence, mobility, transfert), their presence in the soil may impact organisms and biodiversity. Batchelder et al. [38] tested the effect of chortetracycline and oxytetracycline on the apricot plants growth in aerated medium. They showed that a low antibiotic concentration can influence the plant growth. Khadra et al. [39] showed an important genotoxic effect of the quinolones and fluoroquinolones on *Vicia faba* root tip, even at low concentrations of antibiotic mixtures. Antibiotics release was also shown to contribute to the dissemination of the antimicrobial resistance thanks to a concomitant release of antibiotic resistant bacteria and antibiotic resistance genes implying an enrichment of the environmental resistome [40].

The development of antibiotic resistance still remains a very complex process, and even more with antibiotic concentrations below the inhibitory threshold. Bacteria can be intrinsically resistant to certain antibiotics but can also acquire resistance to antibiotics via horizontal gene transfer [41]. Many researchers have demonstrated that sewage sludge contained large amounts of resistant genes [42, 43] to tetracyclines [44-49], sulfonamides [49], macrolides [48] and antibiotic resistant bacteria that are usually multi-resistant (*Escherichia coli* or *Enterobacteriaceae* [50-53], *Enterococcus* [54], *Peudomonas* sp [55], *Staphylococcus aureus* [56] and *Salmonella* sp [57]). Antibiotic resistance genes and antibiotic resistant bacteria are also present in livestock manure [58-62]. Antibiotic resistance genes can be readily disseminated via bacterial division and horizontal gene transfer among bacteria in the environment [63]. Therefore, a transfer of antibiotics resistance determinant toward bacteria of human beings including pathogens is established [63]. It has been estimated that antibiotic resistance is responsible for more than 25,000 and 23,000 deaths every year in the European Union and the United States respectively [64]. Infections by antibiotic resistant bacteria have an annual cost of 1.5 billion dollars in the European Union [41]. Antibiotics and antibiotic resistance genes are considered as new contaminants and may pose a potential worldwide human health risk [20, 65, 66]. Therefore, improving the removal of antibiotics and antibiotic resistance genes from sewage sludge or manure before their application to soil is necessary.

3. The fate of antibiotics during composting

Several processes used to treat sludge or manure may impact the fate of antibiotics. Incineration was used to dispose of sludge [67]. However, a large quantity of energy is required. In addition, high amounts of nutrients are transformed into nitrogen oxides, and even dioxins are produced during the process. Pasteurization, thermal hydrolysis, advanced oxidation processes and ammonia treatment can also be used [68]. But the elevated costs of these processes limit their application. To investigate the fate of antibiotics during sludge or manure management, anaerobic digestion was also tested in several researches [69, 70]. On one hand, a significant inhibition of anaerobic digestion was shown at very high antibiotic concentrations (up to 100 mg L^{-1}), for example, by affecting the methane production [71-73], and on the other hand, a lower antibiotic degrading ability was also observed [74].

Since aerobic system like composting is one of the promising options to manage contaminated sludge and manure, an overview of the fate of antibiotics and antibiotic resistance genes during this process is presented below.

a. Composting

Composting is an aerobic biological decomposition process where pH, C/N ratio, and moisture are controlled in the initial mixture to be composted. These key factors determine the microbial development and the organic matter stabilization. Microorganisms growing during composting reflect the evolution and the performance of the process. The different communities occurring during composting are: bacteria, *Actinobacteria*, fungi, protozoa or algae [75]. Composting consists of two main stages. During the thermophilic stage, the organic matter undergoes firstly a microbial decomposition which liberates CO_2 and ammonia. The organic matter degradation is accompanied by a heat release involved in the elimination of pathogens [76]. At the end of the thermophilic stage, the easily biodegradable part (sugars, amino acids) is completely mineralized. During the maturation stage, another part of the less biodegradable organic matter such as lignin serves as a new material to build molecules leading to humic substances [77, 78]. Regarding the agronomical value of the final product, composting has been widely used for producing soil amendments [79, 80].

b. The efficiency of antibiotics removal during composting

Composting is an effective approach for stabilizing sludge and manure via the biological degradation of organic matter. It has also been shown to be effective in reducing the levels of persistent organic pollutants [81, 82] and certain antibiotics [83-88]. Indeed, the fate of antibiotics during composting was followed in several studies as summarized in the Table 2. The main findings on recent studies are summarized hereafter:

- The tetracyclines family is the most studied one followed by sulfonamides, macrolides and fluoroquinolones;
- 82% of these studies were conducted at laboratory scale using a reactor and only 18% were carried out by windrowing the compost mixture;

- Only 3 studies were conducted without spiking sludge or manure and the rest was conducted by spiking sludge before composting at high concentrations varying between 1 and 150 mg kg^{-1} dry matter;
- The removal rates were calculated by referring to the initial and final concentrations (expressed in mg or µg per kg of dry matter) without taking into account the compost mass or ash content evolution during composting;
- Composting showed very high removal for the molecules belonging to the tetracyclines, sulfonamides and macrolides families with an elimination rate of 70-99%. For the fluoroquinolone family, some studies reported an elimination rates up to 99% for the enrofloxacin and norfloxacin. In contrast, other studies showed the persistence of norfloxacin, ciprofloxacin and ofloxacin in the final compost product;
- The half-lives in days, are calculated on the basis of first order kinetic model and they varied according to each antibiotic family from 1-105, 2-105, 1-17 and 200-2500 respectively for tetracyclines, macrolides, sulfonamides and fluoroquinolones;

High antibiotics concentrations are often used during these experiments, showing no inhibition on the organic matter degradation [89, 90] and thus underlying that composting biomasses are either tolerant to such level or develop resistance mechanisms including degradation ability. In some cases, the antibiotic removal was correlated to several parameters such as total organic carbon, total nitrogen, phosphorus, total organic carbon / total nitrogen, total organic carbon / phosphorus and metallic trace elements [90]. However, some authors showed also that the heat release and organic matter degradation can be delayed by increasing antibiotic concentration. The effect of antibiotics on composting performances depends on the type of antibiotic and the level of concentrations. At 35 mg kg^{-1} dry matter, erythromycin affected the peak temperature while oxytetracycline, norfloxacin and tylosine did not [91]. In addition, it was shown that high antibiotics mixture concentrations (50 mg kg^{-1} chortetracycline + 10 mg kg^{-1} sulfadiazine + 5 mg kg^{-1} ciprofloxacin), delayed the organic matter decomposition and affected the removal of ciprofloxacin by comparison to the complete chortetracycline and sulfadiazine removals [92]. In a more recent study [93], high antibiotics concentrations (50-250, 20-100 and 10-50 mg kg^{-1} dry matter for tetracyclines, macrolides and fluoroquinolones respectively) decreased the thermophilic stage duration, temperature increase and decrease as well as the heat release. Additionally, the efficiency of the composting system and the compost quality (organic matter degradation and C/N ratio) were altered for the highest antibiotic concentrations.

The thermophilic conditions occurring during composting seemed to have a huge impact on the tetracyclines elimination [94, 95]. Arikan et al. [94] showed a very fast removal of chortetracycline at 55°C by comparison to 25°C. It was confirmed by Wu et al. [95] with chortetracycline, oxytetracycline and tetracycline removals of 74%, 92% and 70% respectively during the thermophilic phase. The degradation kinetics of these three antibiotics fitted with a first order model and allowed to calculate half-live for chortetracycline, tetracycline and oxytetracycline of 8.2, 11 and 10 days, respectively, indicating that chortetracycline was the more degraded compound [95]. Liu et al. [83] showed similar results for sulfonamides with highest dissipation rate at high temperature. The effect of thermophilic condition on antibiotics removal could be enhanced by the type of the substrate. For example, sulfonamide removal is more important in swine manure than chicken manure. In addition, sulfonamide transformation could be more pronounced in chicken manure at 30°C rather than 60°C [96]. These results suggested that the microbial community composition, related to the used substrate, played a crucial role in removing antibiotics. The microbial intensity regarding antibiotic removal is not conditioned, in all times, to high temperature. The microbial intensity could be enhanced on the basis of other parameter than temperature. The acclimatized sludge could play an important role in the biodegradation of antibiotics in the microbial fuel cell. The faster oxidation of the co-substrate to produce more electrons for sulfamethoxazole leading to their accelerated degradation [97].

The substrates used during composting play an important role regarding antibiotics elimination. The fate of chortetracycline, sulfamethazine and tylosine at 3 concentrations (2, 10 and 20 mg kg^{-1} dry matter) showed that chortetracycline and sulfamethazine removal depends on the presence of straw but tylosine removal did not [98]. At high temperature, straw provides a wide range of additional biding sites favorable for the chortetracycline and sulfamethazine adsorption. Antibiotics adsorption on co-substrates (palm rachis matrix for example) could reduce the bioavailability of antibiotics towards the microorganism involved during composting, and then explain why composting process was not entirely inhibited by high antibiotic concentration [93].

The coexistence of other pollutants with antibiotics and their influence on the elimination of antibiotics during composting was the object of a study carried out by Liu et al. [83]. Indeed, these authors showed that the dissipation of sulfonamides was slightly delayed in the presence of 2000 mg kg^{-1} of copper. This inhibitory effect could be explained by the toxicity of copper to microorganisms involved in the sulfonamides degradation.

The reported data in the Table 2 showed that the tetracycline family is the most studied. Generally, the most of tetracycline molecules are degradable after composting. Then, the compost could be used safely in soil as it was reported in several studies [92, 94, 123]. The recalcitrant molecules to the degradation (fluoroquinolone) are less studied, probably due to several analytical challenges that we have revealed in some of our current studies. So, the future studies need to focus on recalcitrant antibiotics and how the composting process could be optimized to improve their removal. Extensive studies including the role of temperature and time could provide more interesting data on the removal of recalcitrant antibiotics. In the same way, the potential risks of recalcitrant antibiotic after the use of composts in the agriculture soil (fauna and flora) must be investigated. A lot of studies reported in the Table 2 focused on the removal on extractible parent forms of antibiotics and concluded that compost could be safely used in the soil. However, the elimination of parent compounds are not sufficient. The presence of transformation products (metabolites) with active forms need to be investigated to ensure the safety of the final products. Antibiotics, and more particularly fluoroquinolone family and their transformation products represent an important environmental concern, and must be the subject of the future regulation dealing with sludge or compost valorization.

c. The mechanisms of elimination of antibiotics during composting

The physicochemical properties of antibiotics (Table 1) drive their fate (persistence, mobility) during composting. Moreover the physicochemical conditions and the degradation of organic matter occurring during the composting process may influence the fate of these molecules by changing their availability, i.e., their chemical form and their interactions with the organo-mineral matrix. Indeed, several processes could be implied in their removal, i.e., volatilization, abiotic and biotic transformation, mineralization, sequestration (formation of bound residues, non-extractible by the analytical methods). On the described literature in Table 2, very few papers provide information on the mechanisms of antibiotics elimination, for example by using abiotic controlled reactors (to assess abiotic transformation or sequestration), or radiolabeled compounds (mineralization proved by production of radiolabeled carbon dioxide, quantification of non-extractible residues), by quantifying transformation products. For Wu et al. [95], the removal of tetracyclines, which are considered unstable because of their chemical structure, could be linked to abiotic transformations like epimerization or dehydration. In this work, the transformation products (4-epichlortetracycline, 4-epioxytetracycline, 4-epitetracycline, anhydrotetracycline demeclocycline) were quantified and their removal also assessed. In the experiment of Kim et al. [98], the addition of sawdust to manure composting had a significantly positive effect on the removal of chortetracycline; the authors hypothesized that sorption plays a main role in this removal due to great quantity of divalent cations present in these organic matrices and the possible formation of chelates complexes with organic substances. In counterpart, tyosine do not form complexes with metal ions, but can form strong chemical bonds with negatively charged compounds in manure [98], accelerating the decline of the extractible antibiotic levels. Paesen et al. [99] described the hydrolysis of A-Tylosine to B-Tylosine under acid conditions. Under neutral and alkaline conditions, the compound produces Tylosine-A-aldol at the same time as other polar decomposition products. The hydrolysis of tylosine is reported to be high over the whole pH range from 2 to 13. For the sulfonamides, the decline in concentration of these molecules could be linked to the presence of organic substances, which generate adsorption sites at high temperatures during the composting process rendering them less extractible [100]. Humic substances play also an important role in the elimination of antibiotics. The production of humic substances leads to the sequestration of antibiotics within organic and inorganic matter that render them less extractable as hypothesized by Ho et al. [101] for various antibiotics during 40 days broiler manure composting.

The processes involved in antibiotics removal still remained not elucidated. Biodegradation could be responsible of the antibiotics decrease. Elsewhere, there is no study highlighting the real antibiotics biotransformation as a result of organic matter mineralization. Some abiotic processes could be also implied such as sequestration and/or chemical transformation. Indeed, biotic and abiotic processes are two concomitant removal pathways that have to be elucidated to gain better understanding and propose process optimization strategies.

4. The fate of antibiotics resistance genes during composting

Several researches investigated the fate of antibiotic resistance genes during composting (Table 4).These studies focused on the most important parameters involved in the antibiotic resistance genes removal during the composting of sludge or manure. A brief resume of the studied conditions is presented hereafter:

- 4 studies were conducted on sewage sludge whereas 20 studies were focused on different types of manure (swine, chicken, cattle, poultry, pig, cow, duck, bovine and dairy manure);

- The composting experiments were mainly conducted with lab-scale reactors and a duration ranging between 4 and 183 days;
- The most used co-substrates during the composting of sludge or manure are mushrooms, composting end-products, sawdust, rice straw, wheat stalks, wheat straw, medicinal herbal residues and cotton stalks;
- Antibiotic resistance genes conferring resistance to tetracyclines, sulfonamides, macrolides, fluoroquinolones and β-lactam are the most studied;
- To assess the fate of antibiotic resistance genes during composting, their removals are expressed in percentage (%) or by calculating the absolute or relative abundance (logs units, copies/16S rRNA, copies/g Total Solid or copies/g dry matter);

The main outcomes are:

- The addition of antibiotics, surfactants (biological or chemical), natural zeolite, biochar or metallic trace-elements are able to control the antibiotic resistance genes abundance and removal during composting;
- The bacterial communities, the abundance of transposons and horizontal gene transfer are some keys parameters implied in the antibiotic resistance genes removal.
- The composting stages (mesophilic, thermophilic and cooling phases) and their duration as well as physicochemical parameters (pH, moisture, ammonium nitrogen, and water-soluble carbon contents) play a crucial role regarding the antibiotic resistance genes removal.
- Some studies showed the effectiveness of composting on the antibiotic resistance genes removal but other ones showed the persistence and the increase of the concentrations of some antibiotic resistance genes after composting.

In the study of Selvam et al. [102], sulfonamides, tetracyclines and fluoroquinolones resistance genes represented respectively 10.28, 1.91 and 0.00022% of the 16S rDNA copies in the initial compost. After 42 days of composting, no antibiotic resistance genes were detected for the studied antibiotics. Yu et al. [103] found also a complete removal of tetracycline antibiotic resistance genes for the ribosomal protection protein groups in swine manure compost, and a reduction of 6 logs for others belonging to the ‘‘efflux” group. In the same way, Chen et al. [40] reported a reduction (7.3 logs) in the abundance of erythromycin antibiotic resistance genes during swine manure. Wang et al. [104] reported a partial removal of the tetracyclines antibiotic resistance genes (2.4 log copies/g dry matter) especially in the thermophilic stage (1.5 log copies/g dry matter). In these papers, a positive correlation was found between the antibiotic resistance genes reduction during composting and the temperature [102, 104-108]. Additionally, temperature was identified as an important parameter related to the transfer of a mobile plasmid (pIE732) [109]. In this study, chicken manure and compost were incubated separately at 23 and 50°C. The plasmid transfer from *E. coli* occurred in manure and compost at 23°C. At 50°C, plasmid transfer was not confirmed. High temperature is a main contributor in reducing (i) antibiotic resistance genes transfer and (ii) pathogen bacteria's [110].

Other studies showed contradictory results. Indeed, while a removal of 100% for oxytetracycline and sulfamethazine was reached during swine manure composting, a proliferation of the corresponding antibiotic resistance genes was observed by Wang et al. [111]. Another recent study conducted by Kang et al. [112] showed that the short-term thermophilic compost treatment could not remove the tetracycline resistance genes in pig manure.

The presence of heavy metals in sludge or manure at high level [113, 114] is considered as a co-selection factor for antibiotic resistance genes reduction [115-118]. Antibiotic resistance genes come into contact with heavy metals which could drive the selection and the evolution (increase/decrease) of antibiotic resistance bacteria [119]. The bioavailable fraction of heavy metals acts as a selective pressure on microbes [120]. Using a co-substrate such as biochar or superabsorbent polymers (sodium poly-acrylate) during composting could help to adsorb heavy metals, decreasing their availability and then contributing to reduce the selective pressure on antibiotic resistance bacteria [121, 22]. Nevertheless, the mechanisms involved on the dynamics of antibiotic resistance genes in the presence of heavy metals during composting are still unclear.

Basing on the reported data in the table 4, several studies confirmed that some antibiotic resistance genes were partially eliminated after composting and clearly demonstrated the contribution of high temperature, microbial community composition/changes and composting duration. Other studies revealed that the presence and the availability of other pollutants, such as heavy metals, could affect either the increase or the reduction of antibiotic resistance genes. Specific research on removal of these antibiotics resistance genes, including the role of temperature during extended periods of time are needed. In addition, very few information about the microbial mechanisms involved on antibiotic resistance genes transfer are reported.

In the same way, the associated risks of antibiotic resistance genes transfer after compost utilization are also very scarce. Hence, the fate of antibiotic resistance genes during sludge or manure composting still remains unclear and needs more detailed researches to determine optimizing removal strategies.

5. Conclusions and perspectives

The use of antibiotics in human or veterinary medicine is continuously increasing and leads to the emergence of these molecules as well as antibiotic resistance genes and antibiotic resistant bacteria on the whole environment compartments. The consequences on human health can involve countless deaths. The research on the mobility, the persistence, and the mechanisms of antibiotics elimination is still in progress. Although, developing common tools to assess the environmental proliferation or attenuation of antibiotic resistances and their impact on the environment and health is recommended.

Composting is a promising solution to eliminate or reduce the discharge of antibiotics and antibiotic resistance genes. However, lots of the studies were conducted at lab-scale under controlled conditions with very high antibiotics concentration (often spiked) and none of them elucidate the real mechanisms behind the removal performances, i.e., biotic or abiotic transformations, bound residues formation. This literature review highlighted the importance of process management (temperature, co-composting substrates) regarding the fate of antibiotics and antibiotic resistance genes. More research is still needed to better understand the driving mechanisms during antibiotics and antibiotic resistance genes removal as well as their interactions. This better understanding is a prerequisite for identifying better but compromised process management practices that simultaneously target antibiotics and antibiotic resistance genes, in order to reduce their load to the environment. The increase of the composting period can leave more time for antibiotics degradation especially during the maturation stage but may lead to proliferation of antibiotic resistance genes. Regarding the major role of sludge and manure land application in the dissemination of antibiotics and antibiotic resistance genes and the related environment and health issues, the establishment of standards regarding the authorized levels of antibiotics in sludge, manure and compost before the direct land application should be considered.

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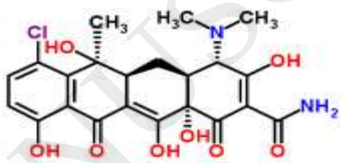
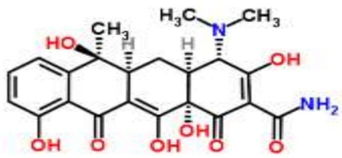
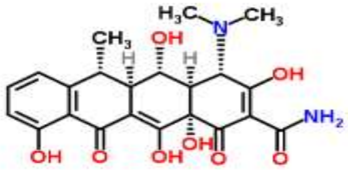
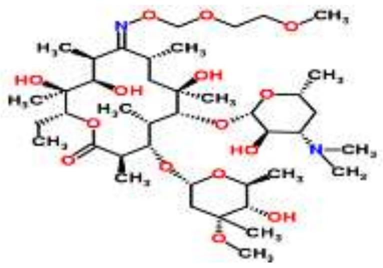
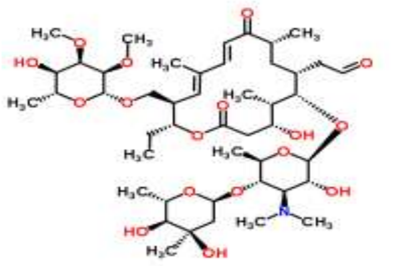
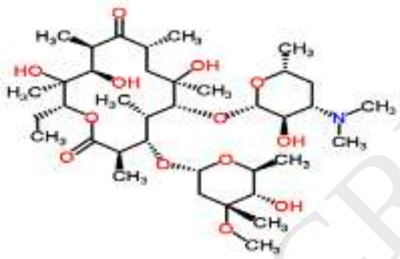
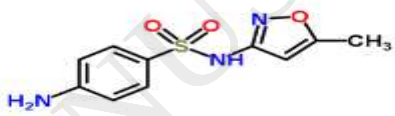
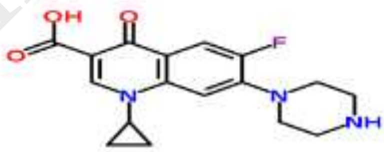
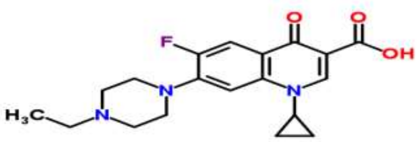
List of tables and figures

Table 1. Selected examples of commonly used human and veterinary antibiotics and their physical and chemical properties

Families	**Molecules**	**pKa (25°C)**	**Chemical structure**	**Usage**
Tetracyclines	Oxytetracycline	4.5		Humans and animals
	Chortetracycline	4.5		Animals
	Tetracyline	3.3		Humans and animals
	Doxycycline	-		Humans and animals
Macrolides	Roxythromycine	12.45		Humans

	Tylosine	13		Animals
	Erythromycin	8.8		Humans and animals
Sulfonamides	Sulfamethoxazole	5.7		Humans
Fluoroquinolones	Ciprofloxacin	6.09		Humans
	Enrofloxacin	2.74		Animals
	Norfloxacin	6.34-8.75		Humans

	Ofloxacin	5.97		Humans

Table 2. The fate of antibiotics during composting

Molecules	Disposal of composting	Compost mixture	Moisture % (M) and C/N ratio before composting	Compost quantities	Spiking of the initial mixture before composting	Initial antibiotics concentration (mg/kg DW)	Maximal temperature (°C)	Duration of composting (days)	Elimination (%)	Parameters related in antibiotics removal	References
Oxytetracycline	Self-heating laboratory composting	Beef manure, sawdust	M : 72.4 C:N= 29	3.3 kg	Beefs were medicated by 22mg/kg/day for 5 days	115	60	35	99.8	The basis on the oxytetracycline removal is not known. After composting, oxytetracycline residues have been rendered biologically inactive or unavailable.	[123]
Chlortetracycline	Pile and vessel composting	Turkey manure, blend of aspen, shavings and sunflower	M : 40% C:N=12.-12.9		Yes	1.5	60	35	>99	Thermophilic temperature resulted in a reduction in chlortetracycline, monensin and TYL concentration. Biotic and abiotic factors contributed to antibiotic degradation during composting.	[129]
Monensin						11.9			54		
Sulfamethazine						3.7			No degradation		
Tylosine						10.8			76		
Chlortetracycline	self-heating laboratory composter	Manure-Straw-Woodchips	M :68.3 C/N=25.5	3.5 kg	Beefs were medicated by 22mg/kg/day for 5 days	-	55	30	98	Abiotic process is responsible of chlortetracycline elimination.	[94]
Chlortetracycline	Lab vessel composter	Broiler and Hog manure	M= 50-60	4 kg	No	94.72 (Broiler Manure) 879.6 (Hug manure)	55 58	42	92.59 27.33	Antibiotics depletion is depending on carbon, nitrogen and phosphorus.	[90]
		Layer-Hen manure			Yes	50 100 150	55		100 94.92 94.51		
Chlortetracycline	Self-heating composter (60L)	Hen manure and straw	M= 65 C/N=13.2	45 kg	Yes	60	55	45	98.5	Not indicated	[89]
		Pig manure and straw	M= 65 C/N=17.7				62		95.7 97.3 96.2		
OTC		Hen manure and straw	M= 65% C/N=13.2				55		97.2		
Tetracycline							55		93.8		
Chlortetracycline	Pilot scale composting	Manure-mushroom residues	M : 56.9 C/N=11.02	5m^3	No	2.9	55-60	52	74	Antibiotics elimination predominately took place in the thermophilic stage. Transformation products indentification	[95]
OTC						1.6			92		
Tetracycline	Open-air windrow manually turned					0.4			70		
Chlortetracycline	Bench-scale composting conducted in computer controlled 20-L reactors	Swine manure-Sawdust	M : 55 C/N=29 Aeration rate: 0.5 L/kg DW/min	7 kg	Yes	50	60-64	56	100	High level of antibiotics delayed the initial decomposition that also affected the nitrogen mineralization	[92]
						5			100		
Sulfadiazine						10			100		
						1					
Ciprofloxacin						10			83		
						1			69		
Chlortetracycline	lab-scale	Manure-	M : 70	30 kg	Yes	2	50	40	96	Binding sites resulted in the reduction	[98]

Sulfamethazine	composting apparatus	Sawdut				10	55		99	of residual antibiotic concentrations.	
Tylosine						20	55		95		
Doxycycline	Plastic containers	Broiler manure	M : 50-60 C/N=8	5 kg	Yes	13.64 30.64 62.57	45.7	40	99.80	pH, compost temperature, total organic carbon, nitrogen, C/N ratio, phosphorus, Na, Cr, Cu, Zn, Fe and Cd are suggested to have a possible effect on the degradation of antibiotics.	[101]
Sulfadiazine									>99.99		
Tylosine									>99.92		
Sulfamethazine and Sulfamethaxazole	Composting containers	Manure-straw	M : 50-60 C:N= 22.9	2 kg	Yes	20	55	35	>99.99	Thermophilic stage contributes on reducing sulfonamides.	[83]
Chlortetracycline	Small-scale composting	Manure	M: 55-65 C:N= 25-30	20-22	Medicated hereford steers	-	Up to 55	42	71-84	Static and turned composting is effective for reducing antibiotics. After composting, some antibiotics apparently more recalcitrant than others.	[85]
Tetracycline									66-72		
Sulfamethazine									97-98		
Pirlimycin									100		
Florfenicol	pilot-scale static pile thermophili c composting	Manure and wastewater biosolids/woo d-product (1.3 v/v)	M: 73	1.7 m^3	Yes	0.1	66-73	28	95-99	Thermophilic composting effectively degrades parent antibiotic compounds in manure and biosolids.	[88]
Sulfamethaxazole						0.2			98		
Sulfamethazine						0.8			97-99		
Tylosine						0.8			96-98		
Chlortetracycline	Open-air windrow	Manure from beef cattle	-	-	Medicated beef	-	40	2 years	94.5-99	composting leads to dissipation of antibiotics, the microbial composting process could be inhibited by the presence of antibiotics.	[86]
Sulfamethazine									59-93.2		
Tylosine									93.7		
Sulfamerazine	Cylindrical plastic containers	Manure (chicken and hog), sawdust and rice straw	M: 65	-	Yes	-	64	35	100	Adding conditioners improved the removal of 4 kinds of sulfonamides during composting	[124]
Sufachlorpyridazi ne									100		
Sulfadimoxine									100		
Sulfaquinoxaline									94.7		
Ciprofloxacin	windrow	Anaerobic sludge mixed with peat	-	-	No	1520[ab]	-	12 months	0.3[b]	The decomposition rate of antibiotics depends on the applied sludge treatment technology.	[125]
Norfloxacin						580[ab]			0.1[b]		
Ofloxacin						134[ab]			0.03[b]		
Sulfadimethoxine						73[ab]			Nd		
Sulfamethaxazole						22[ab]			0.01[b]		
Ciprofloxacin		Sewage sludge mixed with tree bark				442[ab]			70[b]		
Norfloxacin						439[ab]			64[b]		
Ofloxacin						157[a]			8[b]		
Sulfadimethoxine						32[ab]			nd		
Sulfamethaxazole						16[ab]			2[b]		
Norfloxacin	Windrow	Sludge-treebark	-	Volume ratio 2:3	No	0.0-110[ab]	-	12 months	0.0-22[b]	The degradation of antibiotics depends on the compost mixture.	[126]
Ciprofloxacin						2.6-111[ab]			0.0-20[b]		
Ofloxacin						0.5-39[ab]			0.0-3.2[b]		
Sulfamethaxazole						0.0-2.8[ab]			0.0-0.9[b]		
Sulfadimethoxine						0.0-7.9[ab]			0.0-4.2[b]		
Norfloxacin		Sludge-peat		Volume		0.0-162[ab]			0.0-5.4[b]		

Ciprofloxacin				ratio 4:3		0.0-426[ab]			0.0-7.1[b]		
Ofloxacin						0.0-38[ab]			0.0-0.5[b]		
Sulfamethaxazole						0.0-6.0[ab]			0.0-0.3[b]		
Sulfadimethoxine						0.0-20[ab]			0.0-0.2[b]		

nd: not determined

[a]: concentrations in sludge before composting; [b]: concentrations expressed by µg/kg dry matter.

Table 3. Antibiotics half-live during composting of sludge or manure

Families	Molecules	Half-live (days)	References
Tetracyclines	Chlortetracycline	1-86.8	[94, 95]
	Oxytetracycline	3.2-30	[94, 128]
	Tetracycline	4.5-105	[95, 129, 130]
	Doxycycline	<350	[23]
Macrolides	Tylosine	19	[127]
		2-105	[26, 35, 127]
Sulfonamides	Sulfamethazine	2.01 and 2.12	[73]
	Monensin	17	[87]
	Sulfadiazine	42-80	[131]
	Sulfamethaxazole	64-133	
Fluoroquinolones	Norfloxacin, Ofloxacin and Ciprofloxacin	217-2500	[23, 132]

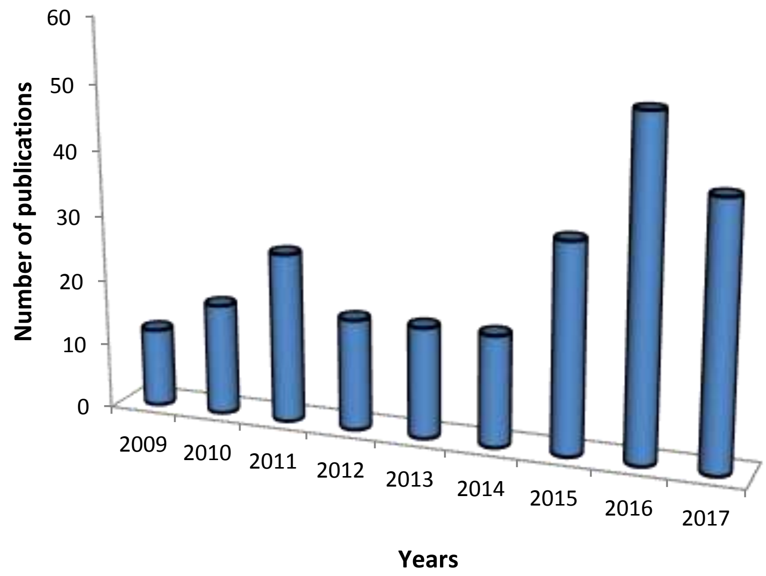
Table 4. Synthesis on recent studies on the fate of antibiotic resistance genes during composting of sludge or manure

Antibiotic resistance genes	Compost mixture	Composting conditions	Antibiotics Spiking of the initial mixture	Initial concentrations of antibiotic resistance genes	Fate of antibiotic resistance genes after composting	Key parameters implied in the antibiotic resistance genes removal	References
Tetracycline (*tetG*, *tetW* and *tetX*) Sulfonamide (*sulI* and *sulII*) Fluoroquinolone (*aac(60)-Ib-cr*) B-lactam (*blaCTX-M* and *blaTEM*) Macrolide (*ereA*, *ermB*, *ermF* and *mefA*).	-Dewatered sewage sludge and mushrooms -Compost mixture quantity: 45kg (at a ratio of 1 :3 (v/v))	-Lab-scale composting reactor -Three composting experiments: the control (A), natural zeolite addition (B) and nitrification inhibitor addition (C). -Composting duration: 183 days	No	-	-The total antibiotic resistance genes copies were enriched 2.04 and 1.95 times in reactors A and C. -The total antibiotic resistance genes copies were reduced by 1.5% in the reactor B. -Some antibiotic resistance genes were reduced by 0.3-2 logs, while others increased by 0.3-1.3 logs after composting.	-Addition of natural zeolite; -The thermophilic and cooling stages; -The bacterial community structure and changes.	[60]
Tetracycline (*tetA*, *tetB*, *tetC*, *tetG*, *tetL*, *tetM*, *tetQ*, *tetO*, *tetW*, and *tetX*) Macrolide (*ermB*, *ermF*, *ermT*, *ermX*, *mefA*, and *ereA*) Aminoglycoside (*aacA4*, *aadA*, *aadB*, *aadE*, *aphA1*, *strA*, and *strB*) Sulfonamide (*sul1*, *sul2*, and *sul3*).	-Dewatered sewage sludge mixed with composting end-products at a ratio of 1:3 (v/v). -Compost mixture quantity: 200 tons	-Industrial hyperthermophilic and conventional composting in piles. -Composting duration: 45 days	No	-Tetracycline and sulfonamide (the most dominant antibiotic resistance genes): 5.1×10^{11} and 1.1×10^{10} gene copies per gram (dry weight) in the initial raw sludge.	-The relative abundance of antibiotic resistance genes were of 0.05 and 0.14 copies/16S rRNA genes respectively after hyperthermophilic and conventional composting.	-Hyperthermophilic condition.	[105]
23 antibiotic resistance genes encoding tetracyclines, sulfonamides, quinolones, β-lactam antibiotics, macrolides, florfenicol and multidrug resistance	-Sewage sludge	-Lab-scale thermophilic composting reactor. -Composting duration: 15 days	No	-	Removal efficiency (%): **Tetracycline** *tetA*,50.03; *tetB*, 100; *tetD*,92.00; *tetE*,100; *tetG*,85.23; *tetH*,66.41; *tetM*,62.36; *tetQ*,98.10; *tetX*,83.43 ; *tetZ*,63.70; *tetBP*,100 ; *tcrB*,100 **Sulfonamides:** *sul1*,93.93; *sul2*,97.17 **Quinolones:** *qnrS*,N.A; *qnrD*,97.28; *aac (6´)-lb-cr*,81.61 **Macrolides**: *ermB*,20.39; *ermC*,N.A. **Beta-lactam:** *blaTEM*,96.18; *blaCTX*,100; *blaSHV*,80.02 **Florfenicol:** *floR* 80.12 **Multidrug:** *oqxA* 63.39	-Thermophilic composting; -Combining thermophilic composting with anaerobic digestion.	[108]
156 antibiotic resistance genes and MGEs conferring resistance to a broad range of antibiotics (tetracyclines, multidrug, macrolide, lincosamide, streptogramin B and Aminoglycosides)	-Dewatered sewage sludge, sawdust and rice straw.	-Lab-scale composting in-vessel. -Composting duration: 50 days	No	-	-The antibiotic resistance genes were significantly higher at the last stage of composting. -The enrichment of antibiotic resistance genes was observed during composting.	-Bacterial phylogenetic; compositions.	[136]
Tetracycline (*tetM, tetO, tetQ, tetS, tetT, tetWtetB/P; tetC, tetE, tetG, tetH, tetY*and*tetZ*) Sulfonamide (*sul1*, *sul2, sul3, dfrA1*, *drfA2* and *drfA7*) Fluoroquinolone (*gyrA* and *parC*)	-Swine manure and sawdust mixed at a ratio of 1:1 (v/v).	-Lab-scale reactor -Composting duration: 56 days	Yes (Spiking at two levels)	-Resistance genes of tetracycline, sulfonamide and fluoroquinolone represented 0.02–1.91, 0.67–10.28 and 0.00005–0.0002%, respectively, of the total 16S rDNA copies in the initial compost mass.	No detection of antibiotic resistance genes except *parC*	-Thermophilic stage; -The addition of antibiotics; -The bacterial diversity.	[102]
Tetracycline (*tet*A, *tet*B, *tet*C, *tet*L, *tet*O, *tet*M, *tet*W and *tet*X).	-Swine manure mushroom and red mud. -The windrow size is about 27 m^3.	-Two windrows by adding the red mud (RM) and a control (CK) without adding the red mud.	No	-	-antibiotic resistance genes in swine manure were removed after composting (by 2.4 log copies/g TS), especially during the	-Bacterial community; -The addition of red mud.	[104]

		-Composting duration: 53 days			thermophilic stage (by 1.5 log copies/g TS)		
Tetracycline (*tetC*, *tetG*, *tetW*, and *tetX*), sulfonamide (*sul1*, *sul2*, *dfrA1*, and *dfrA7*) Macrolide (*ermB*, *ermF*, *ermQ*, and *ermX*).	-Chicken manure (C), wheat stalks (K) and bamboo charcoal (BC). -Compost mixture quantity: 3 kg	-Lab-scale reactor. -3 different proportions of BC -Composting duration: 26 days	No	-	- Relative abundance of *tetC*, *tetG*, *tetW*, *tetX*, *sul2*, *drfA1*, *drfA7*, *ermB*, *ermF*, *ermQ*, and *ermX* decreased by 21.6-99.5%, while the relative abundance of *sul1* increased by 7.5–17.7 times. - Relative abundance of antibiotic resistance genes (except *sul1*) in the mixture CK showed an elimination of 0.85 logs. -Adding 5, 10 and 20% of BC in the CK mixture increased the average reductions in the relative abundance of antibiotic resistance genes by 1.05, 1.08, and 1.15 logs, respectively.	-Temperature; -Adding biochar.	[121]
Tetracycline (*tetC*, *tetG*, *tetQ*, *tetW*, and *tetX*), Sulfonamide (*sul1*, *sul2*, and *dfrA7*) Macrolide (*ermF*, *ermQ*, and *ermX*) Quinolone (*qnrS*, *qnrD*, and *aac(6´)-ib-cr*).	-Swine manure and wheat straw mixture at a ratio of 1:1 (v/v).	-Lab-scale composting reactor. -Sodium polyacrylate (SP) was added at two levels + control without SP (CK). -Composting duration: 35 days	No	- Absolute abundance of antibiotic resistance genes in the initial material were ranged from 10^7 to 10^{10} copies g^{-1} DW.	-The absolute abundance of all the antibiotic resistance genes detected in the CK decreased by 8.12–96.70%. -Greater reductions in the absolute abundance of antibiotic resistance genes were obtained in the H treatment than the other two treatments.	-pH, moisture and bacterial community; -Addition of sodium polyacrylate.	[122]
144 antibiotic resistance genes encoding potential resistance to macrolide, lincosamide, streptogramin B, aminoglycoside, multidrug, tetracycline, and β-lactam.	-Cattle manure and sawdust.	-Conventional composting by windrow.	No	-The average number of ARGs in raw manure : 103.3	-The average number of antibiotic resistance genes in mature compost : 71.3	-The thermophilic stage; -Sawdust addition; -Bacterial community.	[133]
Tetracycline (*tetA*, *tetB*, *tetC*, *tetE*, *tetG*, *tetM*, *tetO*, *tetQ*, *tetT*, *tetW*, and *tetX*) Sulfonamide (*sul1*, *sul2*, *sulA*, *dfrA1*, and *dfrA7*) Macrolide (*ermA*, *ermB*, *ermC*, *ermF*, *ermQ*, *ermT*, and *ermX*) Fluoroquinolone (*aac(60)-Ib-cr*, *gyrA*, *parC*, *qnrC*, and *qnrS*).	-Swine manure medicinal herbal residues (MHRs) and wheat straw. -Compost mixture quantity: 5 kg	-Laboratory-scale composting. -Two composting experiment -Composting duration: 40 days	No	-	-The absolute abundance of*aac(60)-Ib-cr* and *tetW* decreased in both of the final composting products by 1.29 and 1.82 logs in SW, respectively, and 2.10 logs and 2.82 logs in SWC. -The absolute abundance of *int1*, *tetG*, *qnrA*, and *qnrS* increased by 1.56, 2.08, 3.16, and 3.25 times in SW, respectively, but they decreased by 34.1–84.0% in SWC.	-MHRs; -Changes in the microbial communities.	[134]
ARGs conferring resistance to multidrug, aminoglycoside, betalactam, tetracycline, vancomycin, macrolide, lincosamide and streptogramin B, fluoroquinolone, chloramphenicol and sulfonamides.	-Cattle, poultry, and swine manure mixed with rice straw.	-Large-scale commercial composting.	No	-Abundance of antibiotic resistance genes in raw cattle and poultry manure: 1.9 and 5.5 copies/cell.	-Abundances in the final cattle and poultry mature composts : 0.2 and 1.8 copies	-Thermophilic composting ; -Some antibiotic resistance genes persist after composting; -Optimal conditions and composting duration.	[106]
Tetracycline (*tetA*, *tetB*, *tetC*, *tetE*, *tetG*, *tetK*, *tetL*, *tetM*, *tetO*, *tetQ*, *tetW* and *tetX*) Sulfonamide (*sulI*, *sulII* and *sul Ⅲ*) Fluoroquinolone (*gyrA*, *gyrB*,*parC* and *parE*) Macrolides (*ermB*, *ermC*,*ermE*and*ermF*).	-Pig manure and sawdust (ratio of 5 :1 (v/v)). -Compost mixture quantity: 8.5 kg	-Polymethyl methacrylate reactors. -Composting duration: 90 days	Yes Manure was spiked by chlortetracycline at two levels	-	-The total ARGs copies number reduction was 0.21, 0.34 and 0.11 logs, respectively, in CK, T1 and T2.	-Microbial community.	[135]
Macrolide (*ermB*, *ermF*, *ermQ*, *ermT*, and *ermX*) Tetracycline (*tetC* and *tetX*) Sulfonamide (*sul1*and *sul2*)	-Cotton stalks and pig manure	-Composting chamber -Two treatment : pig manure with GM or non-GM -Composting duration: 40 days	No	-	-The absolute abundance of ARGs, intI1, and intI2 were reduced by 41.7 and 45.0% in the non-GM and GM experiments respectively.	-Temperature and ammonium nitrogen.	[107]

Tetracyclines (*tetA*, *tetB*, *tetL*, *tetM*, *tetW*, *tetQ*, *tetO* and *tetX*), sulfonamide (*sul1* and *sul2*) and chloramphenicol (*fexA*, *floR*,*cmlA*, *cfr* and *fexB*)	-Rice straw biochar (RSB), mushroom biochar (MB) and chicken manure -Compost mixture quantity: 5 kg	-Lab-scale composting reactor -Three composting experiments were carried out: composting with RSB, MB and a control without biochar (CM) -Composting duration: 42 days	No	-	-The average removal rate of antibiotic resistance genes was 0.86 log units in CM. -The average removal rate was 0.61 and 1.49 log units in (CM + RSB) and (CM + MB) respectively.	-The Microbial community ; -The bio-availability of heavy metals.	[118]
Tetracycline (*tetA*, *tetB*, *tetC*, *tetE*, *tetG*, *tetM*, *tetO*, *tetQ*, *tetT*, *tetW*, and *tetX*) Sulfonamide (*sul1*, *sul2*, *sulA*, *dfrA1*, and *dfrA7*).	-Cow manure and straw mixed at a ratio of 4:1 (v/v).	-Conventional composting by windrow. -Composting duration: 40 days	Yes The cow manure was spiked by oxytetracycline at 3 levels	-	- The RAs of *tetC*, *tetX*, *sul1*, *sul2*, and *intI1* increased 2–43 times, while those of *tetQ*, *tetM*, and *tetW* decreased by 44–99%. -The oxytetracycline addition increased the absolute abundance and RAs of *tetC* and *intI1*, while the highest concentration (200 mg/kg) of oxytetracycline also enhanced those of *tetM*, *tetQ*, and *drfA7*.	-The bacterial community; -Composting was not effective in reducing most of the ARGs.	[137]
Tetracycline (*tetC*, *tetG*, *tetM*, *tetQ*, *tetW*, and *tetX*), Sulfonamide (*sul1*, *sul2*, and *dfrA7*) Macrolide (*ermB*, *ermF*, and *ermX*) Quinolone (*aac(60)-Ib-cr*).	-Wheat straw and chicken manure, bio-surfactant (rhamnolipid, RL) and chemical surfactant (Tween 80, Tw)	-Rectangular bubble boxes. -Composting duration: 30 days	No	-	-The relative abundance of antibiotic resistance genes and intI1 were reduced by 1–4.7, 0.8–3.7 and 0.3–2.6 logs with the addition of Tw, RL and in the control experiments.	-Temperature and the water-soluble carbon contents; -RL and Tw.	[138]
12 ARGS (*tetB*, *tetL*, *tetM*, *tetW*, *tetQ*, *tetX; sul1*, *sul2*,*cfr*, *cmlA*, *fexA*, and*floR*)	-Pig and duck manure, sawdust, rice straw biochar (RSB) and mushroom biochar (MB).	-Rectangular foam container. -Composting duration: 42 days	Yes Animal feeding operations	-Total abundance of antibiotic resistance genes was 3.75×10^{-1} copies/g (duck manure) which is 3.7 times higher than in pig manure.	-The average removal of antibiotic resistance genes was 2.56 and 2.09 log units in duck and pig manure compost.	- Biochar addition; - The type of biochar and manure.	[139]
Tetracycline (*tetB*, *tetC*, *tetM*, *tetO*, *tetT*, and *tetZ*)	-Pig manure	-Petri dishes were incubated at 60°C -Thermophilic composting duration: 4 days	Yes Animal feeding operations	-	-	- Thermophilic composting cannot remove tetracycline resistance genes in pig manures.	[112]
bla_{tem}, *tet(M)*, *sul1*, *sul2*, *ermB*	-Chicken manure	-Composting heap -Composting duration: 6 weeks	Yes Animal feeding operations	-	-	-Colistin administration had no impact on the antibiotic resistance genes; -Composting is insufficient to eliminate ARGs.	[140]
109 antibiotic resistance genes conferring resistance to aminoglycoside, MLSB, tetracycline, β-lactame, multidrug, vancomycin, chloramphenicol, sulfonamide.	-Bovine, chicken and pig manure	-Industrial composting using 12 different composting mixtures -Composting duration: 15-90 days	-	-The total abundances (copies/16S rRNA) in bovine, chicken, and pig manure were 0.08–0.28, 1.71–3.07, and 0.54–1.49 respectively	-The total abundances (copies/16S rRNA) were 0.06–0.52, 0.08–0.36,and 0.11–1.17 in bovine, chicken, and pig composts respectively	-Animal species, the abundance of transposons, heavy metal concentration, total nitrogen level, dosage and duration of exposure to antibiotics; -Some antibiotic resistance genes were reduced after composting, but other antibiotic resistance genes were inconsistently influenced.	[141]
Tetracycline (*tetA*, *tetB/P*, *tetC*, *tetE*, *tetG*, *tetM*, *tetO*, *tetQ*, *tetT*, *tetW*, and *tetX*) Sulfonamide (*sul1*, *sul2*, *sulA*, *dfrA1*, and *dfrA7*) Fluoroquinolone (*gyrA*, *parC*, *qnrA*, *qnrC*, *qnrS*, and *aac(6')-ib-cr*) Macrolide (*ermB* and *ermQ*)	-Dairy manure and wheat straw	-Composting incubator -Composting duration: 40 days	-	-	-The abundances of the detected antibiotic resistance genes ranged from 6.2 $\times 10^5$ to 1.1×10^{11} copies per gram dry compost	-Thermophilic and mature phase of composting; -Bacterial succession and horizontal gene transfer.	[142]
Tetracycline (*tetB*, *tetC*, *tetL*, *tetM*, *tetW*) Erythromycin(*ermA*, *ermB*, *ermF*, *ermX*) Sulfamethazine(*sul1*, *sul2*)	-Cattle manure	-Lab-scale composter -Composting duration: 30 days	Feed and fortified treatments	-7.39, 8.14, 7.68, 9.23, 9.63, 8.63, 7.42, 8.01, 8.25, 9.31 and 9.38 Log_{10} copies g dry matter respectively for *tetB*,	-10.58, 7.60, 10.92, 5.43, 8.12, 6.61, 7.95, 10.06, 8.87, 8.80 and 8.64 Log_{10} copies g dry matter respectively for *tetB*, *tetC*, *tetL*, *tetM*, *tetW*,	-Oral administration; -Antimicrobial concentrations; -Mesophilic and thermophilic temperatures; -Longer thermophilic composting period.	[143]

				tetC, *tetL*, *tetM*, *tetW*, *ermA*, *ermB*, *ermF*, *ermX*, *sul1* and *sul2*. (concentration of 16S rDNA)	*ermA*, *ermB*, *ermF*, *ermX*, *sul1* and *sul2*. (concentration of 16S rDNA)		
tetM, tetO, tetQ, tetW, tetA, tetC, tetG, tetL, tetX, sul1 and *sul2*.	-Swine manure	-Composting piles -Composting duration: 32 days	Yes Manure was spiked by sulfamethazine and oxytetracycline	-	-	-Horizontal gene transfers; -Antibiotics concentrations; -Thermophilic composting failed to prevent the proliferation of antibiotic resistance genes.	[111]
Macrolide (*ermA* and *ermB*)	-Swine manure and wheat straw	-Lab-scale composter -Composting duration: 35 days	No	-	-The absolute abundance were decreased for *ermA* (0.4–1.2 logs) and *ermB* (1.2–1.6 logs).	-Temperature; -Bacterial community; -Copper addition.	[144]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Number of publications
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2011
2012
2013
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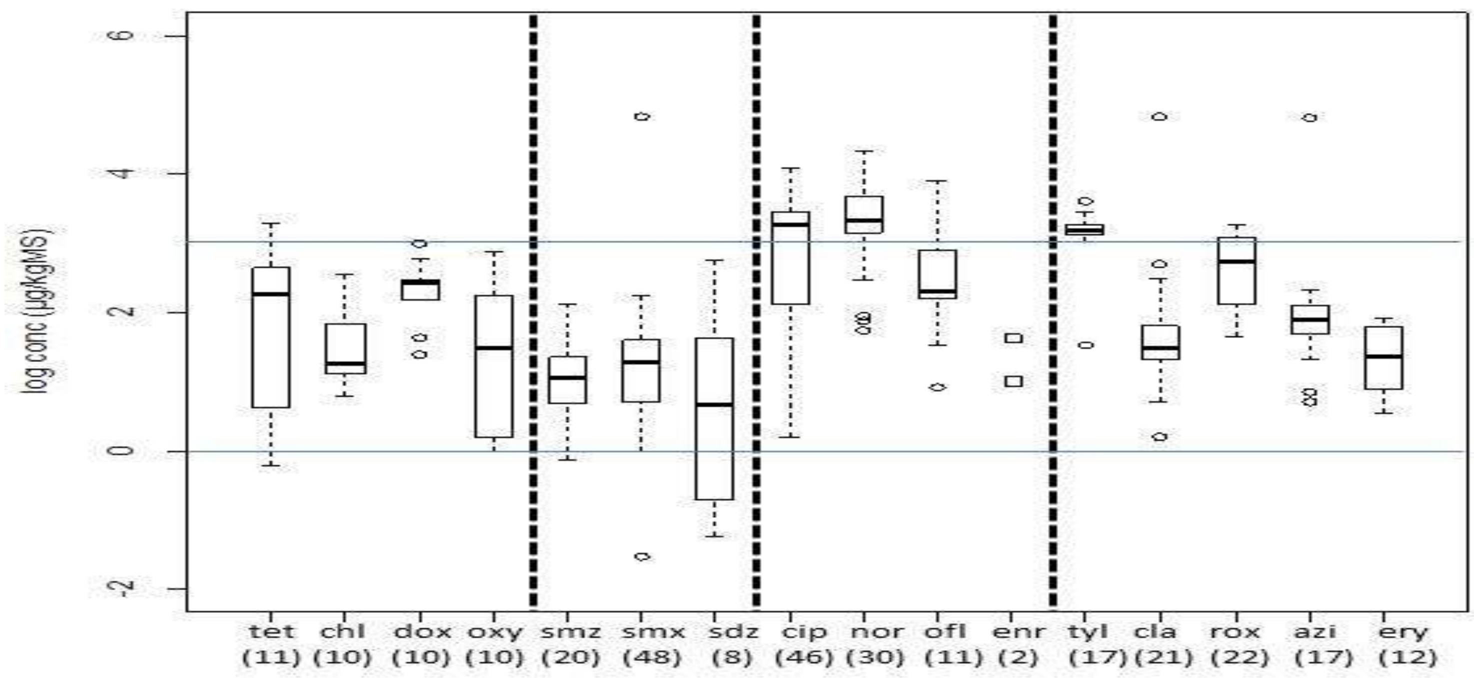
2015
2016
2017
Years

Figure 1.

a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sdz (8)
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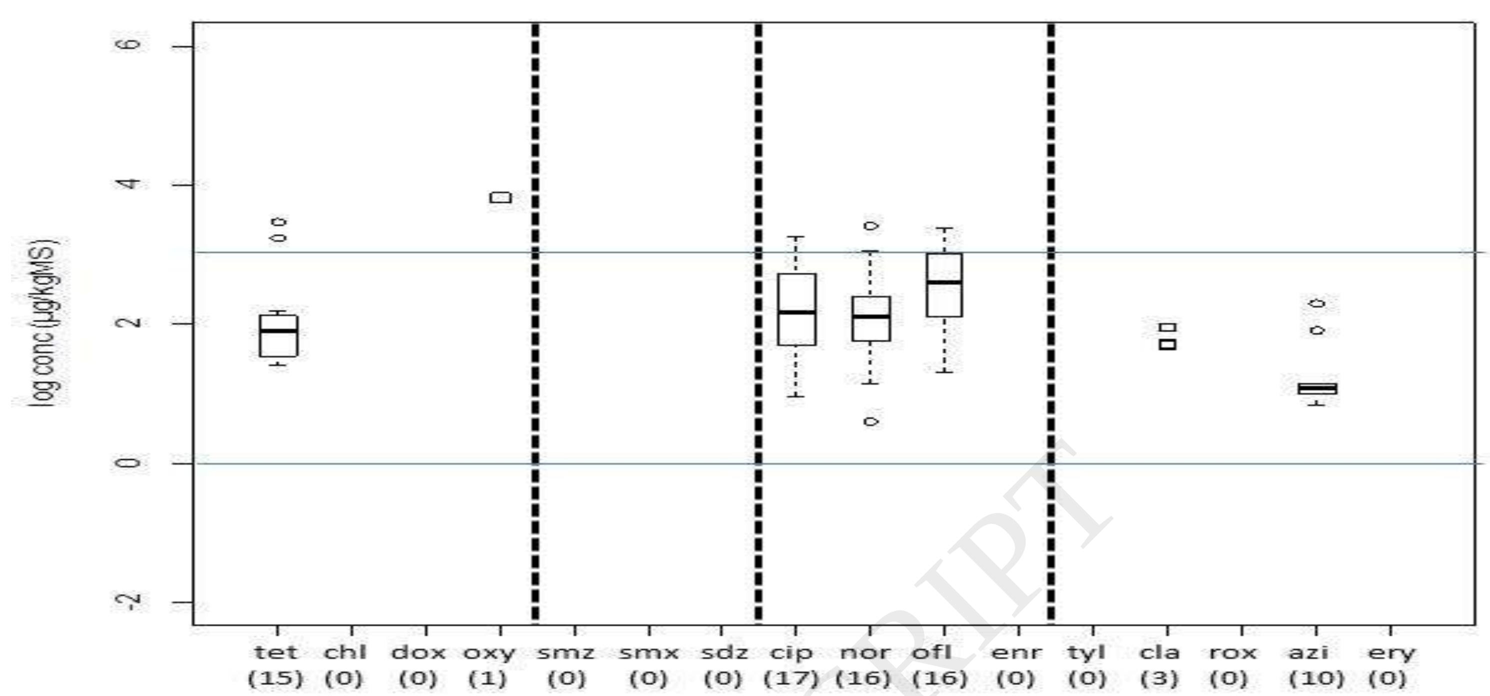
b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sdz (0)
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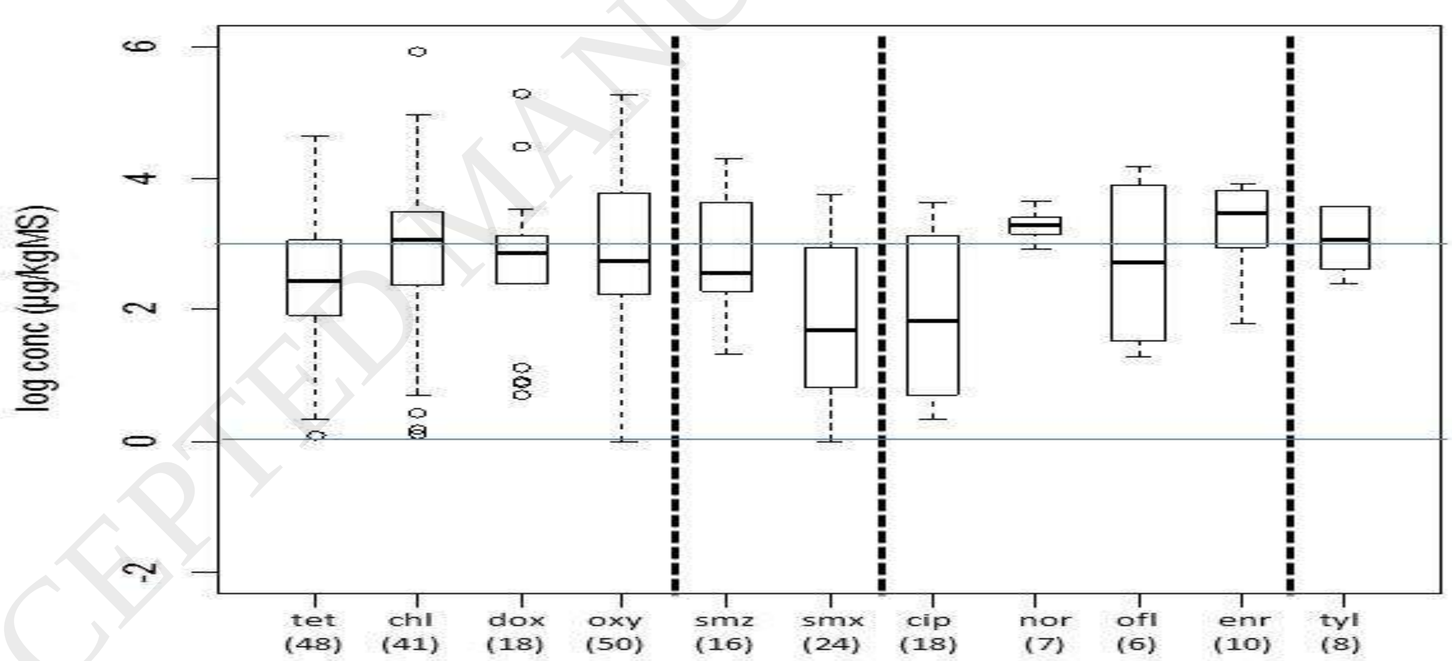
c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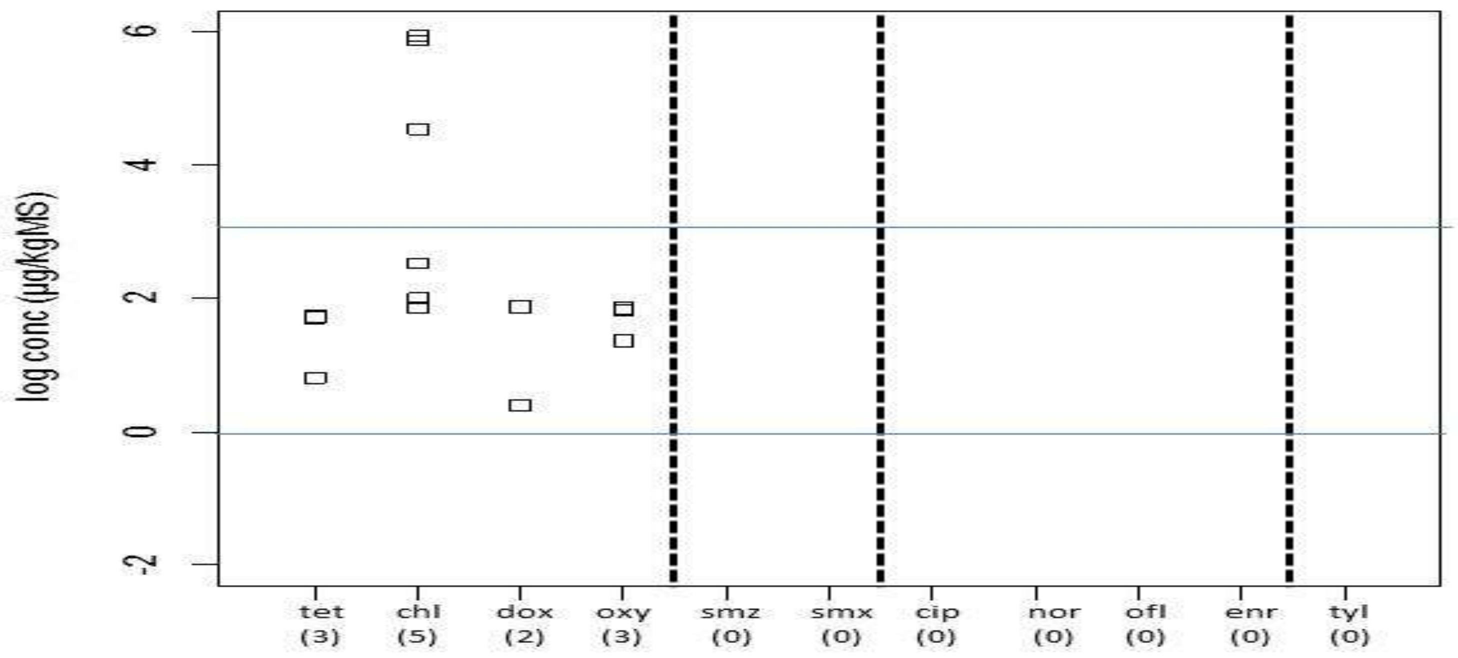
d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cip (0)
nor (0)
ofl (0)
enr (0)
tyl (0)

Figure 2.