# TETRACYCLINES AND METABOLITES AS WASTEWATER CONTAMINANTS: FOCUS ON DETECTION AND POTENTIAL HAZARDS

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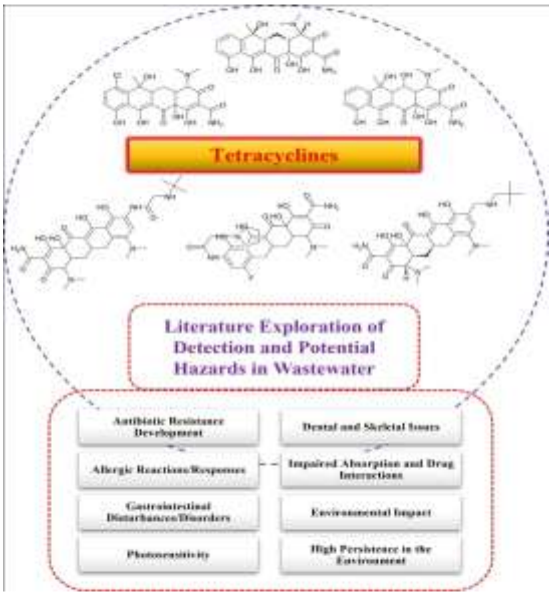


**Graphical Abstract**

**Abstract**

This review highlights the pervasive presence of tetracyclines, a class of antibiotics, and their metabolites in wastewater systems, arising from various way medical, veterinary, and agricultural usage. It delves into the analytical methods for detection, concentrations within treatment plants, fate, and transport mechanisms, including transformation processes and bioaccumulation. The core focus is on the profound environmental impacts, notably the development of antibiotic resistance, consequences for aquatic ecosystems, and potential risks to human health. Regulatory frameworks, mitigation strategies, and future research directions are discussed, emphasizing the urgent need for interdisciplinary efforts and global cooperation to address this critical issue and its far-reaching consequences for public health and the environment.

**Keywords:** Pharmaceutical Pollution, contamination, environmental concern, hazard, tetracycline.

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## 1. Introduction

In recent years, the spread of antibiotics in the environment has raised special concern. Antibiotics are indeed vital tools in the medical treatment of microbial infectious diseases, playing a pivotal role in safeguarding public health [1-8]. These life-saving medications are administered annually in substantial quantities to both humans and animals to combat a wide range of bacterial infections. However, the extensive use of antibiotics has led to unintended consequences, particularly their entry into the environment, which has ignited growing apprehension among scientists, environmentalists, and healthcare professionals alike [9-12]. This concern arises from the potential for antibiotics to persist in ecosystems, contribute to antibiotic resistance, and disrupt the ecological balance, all of which necessitate a careful examination of the environmental impacts of antibiotic dissemination.

Tetracyclines are a class of antibiotics widely used in human and veterinary medicine, as well as in agriculture. They are effective against a broad spectrum of bacteria and are used to treat various infections in both humans and animals. Tetracyclines work by inhibiting bacterial protein synthesis. While their medical and agricultural applications are essential for public health and food production, they can also lead to the presence of tetracycline residues and their metabolites in wastewater [1,13-16]. These compounds can enter the environment and have potential environmental impacts, including antibiotic resistance development and disruptions to aquatic ecosystems. The prevalence of tetracyclines and their metabolites in wastewater is a growing concern worldwide[17]. This contamination primarily arises from several sources, including the excretion of tetracycline-containing drugs by humans and animals, improper disposal of unused medications, and runoff from agricultural fields where tetracyclines are used as growth promoters for livestock [1,17].

### 1.1 History

The family of tetracyclines (Figure 1) has a rich history of discovery and development (Table 1). In 1945, Benjamin Duggar made a groundbreaking discovery, isolating the first member of the tetracycline family, which he named aureomycin, or chlortetracycline [18]. This antibiotic was naturally produced through the fermentation of the bacteria Streptomyces aureofaciens, commonly found in soil. Subsequently, in 1947, another tetracycline, terramycin (oxytetracycline), was isolated, and synthesized by the bacteria Streptomyces rimosus [20]. A significant milestone occurred in 1953 when the tetracycline molecule, with its simple yet effective structure, was obtained. This achievement resulted from a combination of biological and chemical processes. A precursor molecule was first generated through fermentation, followed by a chemical reaction to introduce functional groups, ensuring its therapeutic functionality [19]. It was noted that both aureomycin and terramycin shared this basic structure, leading to the proposal of the generic name tetracycline. The pursuit of novel tetracyclines began, building upon the foundation of the original three tetracycline antibiotics: tetracycline, oxytetracycline, and chlortetracycline. Researchers sought to derive less toxic drugs with improved therapeutic applications. Between 1950 and 1970, a plethora of tetracycline family members, whether natural or semisynthetic, were discovered and developed. During this period, tetracyclines solidified their position as some of the most widely utilized antibiotics in medical and veterinary practice, demonstrating their enduring importance in the field of medicine.

This review aims to provide a comprehensive overview of the state of knowledge regarding tetracyclines as wastewater contaminants and their environmental impacts. By understanding the prevalence and effects of tetracycline contamination, we can work toward more sustainable practices to minimize their adverse effects on the environment and human health.

### 1.2 Uses of Tetracyclines

Tetracyclines are indeed among the most commonly used antibiotics due to their versatility and affordability. Their wide-ranging effectiveness against a broad spectrum of bacteria makes them indispensable in both human and veterinary medicine. Here are some key points highlighting the extensive use of tetracyclines [1,17-24]:

- Versatile Antibiotics: Tetracyclines are valued for their ability to combat a diverse array of bacterial infections. They are employed in the treatment of various conditions in humans and animals, including skin infections, respiratory tract infections (such as chest infections), urinary tract infections, genital infections, and lymph node infections. This versatility makes them a first-line choice for many clinicians.
- Combination Therapies: Tetracyclines are often used in combination with other medications to enhance their effectiveness. For instance, they are utilized in conjunction with acid-reducing drugs to treat stomach ulcers caused by Helicobacter pylori infection. Additionally, tetracyclines are employed as part of malaria prevention strategies in regions where this mosquito-borne disease is prevalent.
- Prominent Use in Farming: In countries like New Zealand, Poland, and China tetracyclines play a significant role in the farming industry. They are commonly administered to farmed animals such as pigs, chickens, sheep, and cows to prevent and treat

bacterial infections. This practice is essential for maintaining the health and productivity of livestock, which contributes to the food supply.

- Companion Animal and Aviary Use: While tetracyclines are primarily associated with livestock, they are also utilized in smaller quantities for companion animals like cats and dogs, as well as aviary birds. These applications help ensure the well-being of pets and birds by treating infections and preventing disease transmission.

The widespread use of tetracyclines underscores their importance in modern medicine and agriculture. However, it is crucial to manage their use responsibly to mitigate the risk of antibiotic resistance and the potential environmental impact, as tetracyclines, like other antibiotics, can find their way into the environment through excretion and agricultural runoff. Balancing their benefits with prudent antibiotic stewardship and environmental considerations is crucial to maintaining their efficacy and safeguarding public health and ecosystems.

**Table 1:** Milestones in the History of Tetracyclines antibiotics.

| Milestones in the History of Tetracyclines | Year | Ref. |
|---|---|---|
| Discovery of tetracyclineand chlortetracycline (aureomycin)by Benjamin Duggar | 1945 | [18] |
| Discovery of oxytetracycline (Terramycin) by Schatz & Waksman | 1948 | [17,18] |
| Broad-spectrum effectiveness of tetracyclines recognized | 1950s | [18] |
| Development of doxycycline, a semisynthetic derivative | 1960s | [18,19] |
| Development of minocycline, another semisynthetic derivative | 1970s | [18,20] |
| Development of Rolitetracycline | 1970s | [20] |
| Development and FDA Approval of Tigecycline | 2000s | [21] |
| FDA Approval of Eravacycline | 2016 | [22] |
| FDA Approval of Sarecycline | 2018 | [23] |
| FDA Approval of Omadacycline | 2018 | [24] |

## 2. Occurrence of Tetracyclines and Metabolites in Wastewater

### 2.1 Medical and Veterinary Use

One significant source of tetracyclines in wastewater arises from their extensive utilization in medical and veterinary settings. Tetracyclines are indispensable antibiotics used to combat various bacterial infections in both humans and animals. In medical practice, they are prescribed to treat a wide spectrum of illnesses, including skin infections, respiratory tract infections, urinary tract infections, and sexually transmitted diseases. Similarly, in veterinary medicine, tetracyclines are administered to livestock, such as cattle, pigs, and poultry, to prevent and treat bacterial infections that can afflict these animals. While the use of tetracyclines is crucial for preserving human and animal health [1,25], a portion of these drugs is excreted by patients and animals, eventually finding their way into wastewater systems. This effluent, laden with tetracycline residues and their metabolites, poses a direct route for these antibiotics to enter the environment, leading to concerns about antibiotic resistance development and ecological consequences.

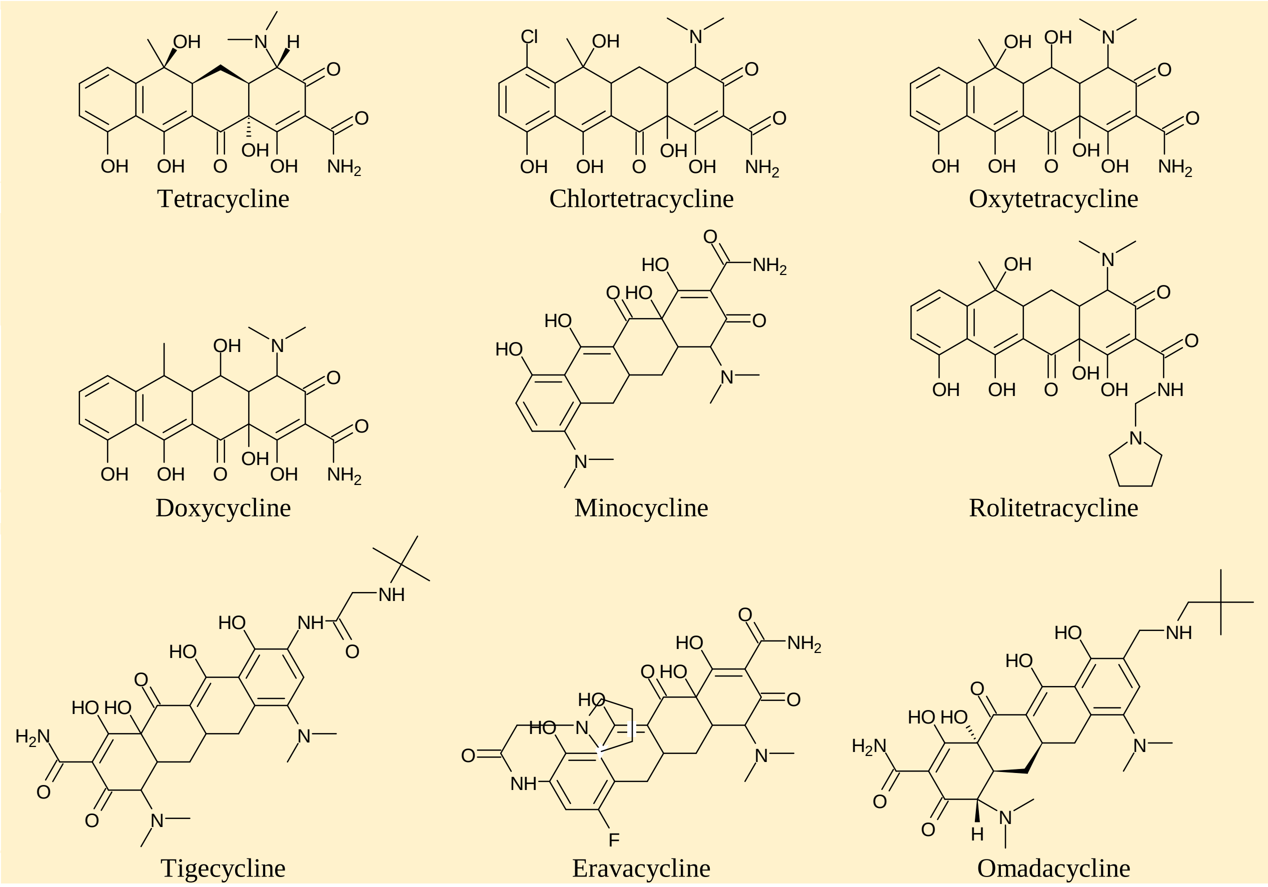


**Figure 1:** Chemical structures of Tetracyclines.

### 2.2 Agricultural Overflow

Another substantial source of tetracyclines in wastewater is agricultural runoff. Tetracyclines are employed in agriculture as growth promoters for livestock and as prophylactic measures to prevent bacterial infections among animals in crowded farming environments. When these antibiotics are administered to animals, they can be excreted and subsequently contaminate manure. When this manure is applied to agricultural fields as fertilizer or when runoff from these fields enters water bodies, it carries with it tetracycline residues and metabolites. This runoff is a conduit for tetracyclines to reach natural aquatic ecosystems, potentially affecting aquatic life and microbial communities [26,27]. Furthermore, it contributes to the overall environmental burden of antibiotic contamination. Understanding these two major sources of tetracyclines in wastewater is crucial for developing strategies to mitigate their environmental impact. Efforts to address this issue involve responsible antibiotic use in medical, veterinary, and agricultural contexts, as well as improved wastewater treatment methods to minimize the release of these antibiotics into the environment.

## 3. Analytical Methodologies for Detecting Tetracyclines and Its Metabolites

The availability of analytical instruments and equipment in the laboratory influences the choice of method. Laboratories equipped with advanced liquid chromatography-mass spectrometry (LC-MS) or gas chromatography-mass spectrometry (GC-MS) systems may favor these techniques for their superior sensitivity and specificity. However, for labs with limited resources, alternative methods like HPLC with UV detection or ELISA can still provide valuable information [28]. The proficiency of laboratory personnel and their familiarity with specific analytical techniques are critical. Skilled analysts are often more adept at optimizing and troubleshooting their chosen method, ensuring reliable and accurate results. Thus, the availability of trained personnel can influence the method selection. Regulatory authorities and standards may dictate specific methods or guidelines for the detection of tetracyclines and other antibiotics in certain applications, such as food safety or environmental monitoring. Laboratories must ensure that their chosen method complies with these regulations. In practice, many analytical laboratories adopt a flexible approach by using a combination of techniques to comprehensively assess tetracycline residues and metabolites in different sample types. For example, they might use ELISA for initial screening due to its speed and cost-effectiveness and then confirm the findings with more precise and sensitive methods like LC-MS/MS or GC-MS [29]. This multifaceted approach not only improves the overall accuracy of the analysis but also allows laboratories to adapt to various sample matrices and specific research or monitoring objectives. It ensures that the chosen methods are well-suited to the unique challenges presented by tetracycline analysis in diverse environmental and biological contexts.

Analytical methods for detecting tetracyclines and their metabolites in various matrices, such as water, soil, and biological tissues, are essential for monitoring and assessing their presence and concentration [30,31]. Several analytical techniques are commonly employed for this purpose, including:

- High-Performance Liquid Chromatography (HPLC): HPLC is one of the most widely used methods for tetracycline detection. It involves the separation of tetracyclines and their metabolites from a sample matrix using a liquid chromatographic column. The compounds are then detected by a UV or fluorescence detector. HPLC offers high sensitivity and selectivity and is suitable for complex matrices like biological fluids and environmental samples.
- Liquid Chromatography-Mass Spectrometry (LC-MS): LC-MS combines liquid chromatography with mass spectrometry to provide accurate identification and quantification of tetracyclines and their metabolites. This method is highly sensitive and can differentiate between different compounds with similar structures. LC-MS is particularly valuable for trace-level analysis in environmental and biological samples.
- Gas Chromatography (GC): GC is primarily used for volatile compounds, and while tetracyclines are not highly volatile, their derivatization can make them amenable to GC analysis. Derivatization involves chemically modifying the compounds to increase their volatility and thermal stability. GC is commonly coupled with mass spectrometry (GC-MS) for enhanced detection and identification.
- Enzyme-Linked Immunosorbent Assay (ELISA): ELISA is an immunological technique used for the rapid screening of tetracyclines and their metabolites. It relies on the interaction between specific antibodies and the target compounds. ELISA is a cost-effective method with relatively high throughput, making it suitable for large-scale monitoring but with slightly lower sensitivity compared to chromatographic techniques.
- Capillary Electrophoresis (CE): CE is an analytical technique that separates ions and small molecules based on their charge and size in a narrow capillary tube. It can be used for tetracycline analysis and offers advantages such as short analysis times and high resolution. CE is often coupled with various detection methods, including UV, fluorescence, and mass spectrometry.
- Nuclear Magnetic Resonance (NMR) Spectroscopy: NMR is a powerful technique for structural elucidation and can be used to confirm the identity of tetracyclines and their metabolites. While it may not be as commonly employed for routine quantitative analysis, it can be valuable in research and compound characterization.
- Tandem Mass Spectrometry (MS/MS): MS/MS techniques, such as triple quadrupole or ion trap mass spectrometry, can provide exceptional sensitivity and specificity for tetracycline analysis. They are often used in combination with liquid chromatography or gas chromatography for targeted quantification.

The selection of the most suitable analytical method for detecting tetracyclines and their metabolites is a critical decision that depends on several key factors. Different sample matrices, such as water, soil, biological tissues, and food products, may require different analytical methods due to variations in matrix complexity, composition, and potential interferences. For example, environmental samples like water and soil may contain various organic and inorganic compounds that can affect the accuracy and selectivity of the analysis. Therefore, the choice of method should consider the specific characteristics of the sample matrix. The desired level of sensitivity and specificity plays a pivotal role in method selection. Some applications require ultra-sensitive detection, especially when analyzing trace levels of tetracyclines and their metabolites in environmental samples. High-performance techniques like LC-MS/MS are often preferred in such cases. On the other hand, ELISA assays, while less sensitive than mass spectrometry, offer rapid and cost-effective screening, which can be valuable for initial assessments.

## 4. Potential Hazards

Tetracyclines, a class of antibiotics, have several potential hazards associated with their use. These hazards severely affect both individuals taking tetracycline medications and the environment. These hazards include antibiotic resistance development, allergic reactions, gastrointestinal disturbances, photosensitivity, dental and skeletal issues, impaired absorption, and environmental impact (Figure 2) [32]. One of the most significant concerns with tetracyclines is the potential for antibiotic resistance development. Prolonged or inappropriate use of these antibiotics can lead to the emergence of antibiotic-resistant bacteria, making infections more challenging to treat effectively. Allergic reactions are another potential hazard, with some individuals experiencing mild to severe allergic responses, including skin rashes and anaphylactic reactions. Common side effects of tetracyclines include gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal discomfort. These side effects can be bothersome and may require discontinuation of the medication. Additionally, tetracyclines can increase the skin's sensitivity to sunlight, resulting in an elevated risk of sunburn and skin damage when exposed to UV radiation [33]. Therefore, individuals taking tetracyclines should take precautions to minimize sun exposure.

In terms of developmental hazards, tetracyclines can affect dental and skeletal development in fetuses, infants, and young children. They may lead to tooth discoloration and impact bone growth if taken during pregnancy or early childhood. Furthermore, tetracyclines can impair the absorption of certain minerals in the gut and interact with other medications, potentially reducing their effectiveness or causing adverse effects. The environmental impact of tetracyclines is a growing concern. The release of these antibiotics into the environment, often through wastewater from human and animal excretion and agricultural runoff, can disrupt aquatic ecosystems, contribute to antibiotic resistance in environmental bacteria, and harm non-target organisms. Tetracyclines can persist in the environment for extended periods, leading to long-term contamination of water bodies, soils, and sediments. Their presence in the environment exerts selective pressure on bacteria, promoting the survival and proliferation of antibiotic-resistant strains. With the high resistance of antibiotics, in Greece, the campaign was made as the experience of a multifaceted regional campaign[34].

To address these potential hazards, responsible antibiotic use is crucial. Healthcare professionals should prescribe tetracyclines judiciously, and patients should adhere to prescribed dosages and complete their courses of treatment. Proper disposal of unused medications and improved wastewater treatment methods can help reduce environmental contamination. Additionally, ongoing research into alternative antibiotics with lower ecological and health risks aims to address these concerns and ensure safer antibiotic practices.

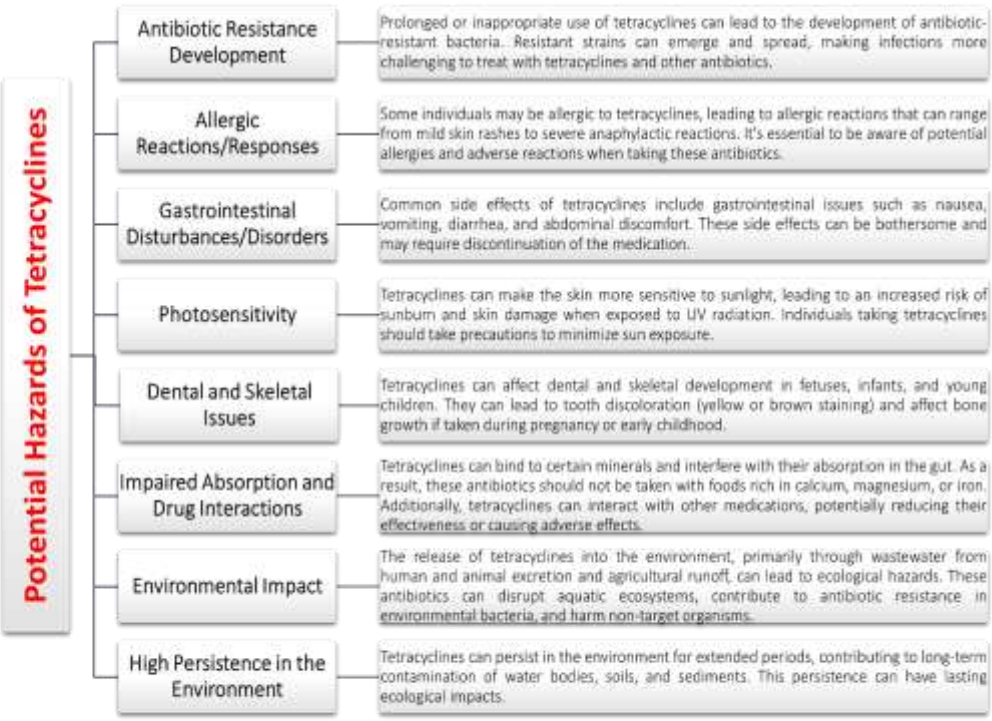


**Figure 2:** Several potential hazards associated with the use of tetracyclines.

### 4.1 Effects on aquatic ecosystems

#### 4.1.1 Disturbing Phytoplankton

Tetracyclines, a class of antibiotics widely used in human and veterinary medicine, pose significant hazards to aquatic ecosystems. One notable effect is their disturbance of phytoplankton populations, which play a crucial role in aquatic food chains and ecosystem balance [35]. When tetracyclines enter water bodies through various routes, such as wastewater discharge or runoff from agricultural areas, they can accumulate in aquatic environments. Even at relatively low concentrations, tetracyclines can inhibit the growth of phytoplankton, microscopic photosynthetic organisms that form the foundation of aquatic food webs. Phytoplankton serve as primary producers, converting sunlight and nutrients into organic matter, making them essential for supporting aquatic life. When their growth is disrupted by the presence of tetracyclines, it can lead to reduced primary productivity in aquatic ecosystems. This, in turn, can have cascading effects on the entire food web, affecting organisms at higher trophic levels, from zooplankton to fish and beyond.

**4.1.2 Disruption of Microbial Communities**

Tetracyclines in aquatic ecosystems also disrupt microbial communities. These antibiotics can inhibit the growth of various bacteria, including both pathogenic and beneficial species. While the intended purpose of tetracyclines in medical and veterinary applications is to target harmful bacteria, their presence in water bodies does not discriminate between beneficial and harmful microbes [36]. This disruption can lead to ecological imbalances, as beneficial bacteria are critical for nutrient cycling, water purification, and overall ecosystem health. Disrupting these microbial communities can have far-reaching consequences, potentially affecting the breakdown of organic matter, the availability of essential nutrients, and the overall stability of aquatic ecosystems.

**4.1.3 Impact on Aquatic Life and Food Chains**

The hazardous effects of tetracyclines on aquatic life extend beyond phytoplankton and microbial communities. As these antibiotics persist in water bodies, they can directly impact aquatic organisms. Fish, invertebrates, and other aquatic species can be exposed to tetracyclines, either through the water they inhabit or by consuming contaminated prey. Tetracyclines can disrupt physiological processes in aquatic organisms, potentially leading to reduced growth, altered behavior, and impaired reproduction. Moreover, when aquatic species are exposed to antibiotics like tetracyclines, they can accumulate these compounds in their tissues. This can result in bioaccumulation up the food chain, ultimately affecting organisms at higher trophic levels, including species consumed by humans.

Therefore, tetracyclines and metabolite's hazardous effects on aquatic ecosystems encompass disturbances to phytoplankton populations, disruptions of microbial communities, and impacts on various aquatic life forms [34-36]. These ecological consequences can reverberate through aquatic food chains, affecting the health and functioning of entire ecosystems. Addressing these hazards requires responsible antibiotic use, improved wastewater treatment, and a holistic approach to safeguarding aquatic environments from the detrimental effects of antibiotic contamination.

**4.2 Potential risks to human health**

**4.2.1 Exposure Routes**

Tetracyclines, a class of antibiotics, have hazardous effects on human health, primarily when exposure occurs through various routes [37]. One common exposure route is the medical or veterinary use of tetracyclines to treat bacterial infections. While these antibiotics can effectively combat infections, their overuse or misuse can lead to antibiotic resistance, rendering them less effective in treating future illnesses. Another potential exposure route is through the consumption of food products originating from animals treated with tetracyclines in agriculture. Residues of these antibiotics can sometimes be present in meat, poultry, and dairy products. Although regulatory agencies establish safety standards for antibiotic residues in food, exceeding these limits can pose health risks, potentially leading to antibiotic resistance and other adverse health effects in humans. In addition, tetracyclines can inadvertently enter the environment through wastewater from human and animal excretion, agricultural runoff, and pharmaceutical manufacturing. This environmental contamination can result in the presence of tetracyclines in drinking water sources, exposing individuals to these antibiotics indirectly. Prolonged exposure to low levels of antibiotics in drinking water may contribute to the development of antibiotic resistance in human pathogens.

**4.2.2 Long-term Health Consequences**

The long-term health consequences of tetracycline exposure can be multifaceted and pose risks to human health. One prominent concern is the development of antibiotic resistance. Over time, frequent exposure to tetracyclines, either through medical treatments or environmental contamination, can select for antibiotic-resistant strains of bacteria in the human body. This can compromise the effectiveness of tetracyclines and other antibiotics when needed to treat bacterial infections, making infections more challenging to manage and potentially life-threatening. Additionally, tetracycline exposure has been associated with certain adverse effects on human health. The use of minocycline and doxycycline as potential treatments for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) has been a subject of research interest. However, the clinical trials and studies exploring their efficacy in these patient populations have yielded inconclusive results, and concerns have been raised regarding their long-term safety. Markulin et al.described an extensive review on repurposing tetracyclines for the treatment of Alzheimer's and Parkinson's disease [38]. Some key points to consider regarding the use of minocycline and doxycycline in AD and PD are as:

- Neuroprotective Effects: Initial studies in animals suggested that minocycline and doxycycline might have neuroprotective effects, which led to interest in investigating their potential clinical benefits in AD and PD patients.
- Inconclusive Results: Clinical trials in AD and PD patients have not provided clear evidence of significant therapeutic benefits from minocycline or doxycycline treatment. The outcomes have been mixed, with some studies showing modest improvements while others have not shown any significant effect.
- Safety Concerns: Safety is a major concern when considering long-term antibiotic therapy in patients with neurodegenerative diseases. There are two main levels of safety concerns- (a) Long-term antibiotic use can disrupt the balance of gut microbiota, potentially leading to gastrointestinal issues and other health problems. This is a particular concern in AD and PD patients, as gut microbiota has been linked to brain health and neurodegenerative diseases. (b) The widespread and long-term use of antibiotics in AD and PD patients could contribute to the development of bacterial resistance and pose a global health threat as these antibiotics are important for treating various bacterial infections.
- Sub-antimicrobial Doses: The idea of using sub-antimicrobial doses of doxycycline is a potential approach to mitigate some of the safety concerns associated with long-term antibiotic use. Such doses aim to provide potential benefits without causing significant disruption to the gut microbiota or promoting antibiotic resistance. To address the uncertainty surrounding the use of minocycline and doxycycline in AD and PD, more research is required. This should include rigorous studies to evaluate their efficacy, long-term safety, and impact on gut microbiota in these specific patient populations. Sub-antimicrobial doses should also be investigated further to assess their potential benefits and risks. The interest in using minocycline and doxycycline as potential treatments for AD and PD due to their neuroprotective effects, the current evidence is inconclusive, and safety concerns related to long-term antibiotic use must be carefully considered. Future research should focus on addressing these concerns and exploring alternative dosing strategies to better understand their potential in treating neurodegenerative diseases.

Prolonged use of these antibiotics can disrupt the natural balance of beneficial bacteria in the gut, potentially leading to gastrointestinal issues and affecting overall digestive health. In some cases, tetracyclines have been linked to skin sensitivities, making individuals more prone to sunburn and skin damage when exposed to sunlight.

Furthermore, exposure to tetracyclines during pregnancy or early childhood can lead to developmental issues. Tetracyclines can affect dental development, causing tooth discoloration in infants and children. In pregnant women, these antibiotics may impact skeletal development in the developing fetus, emphasizing the importance of cautious use during pregnancy. Addressing these potential health risks requires a responsible approach to antibiotic usage. Healthcare professionals must exercise discretion when prescribing tetracyclines, and patients should diligently follow prescribed dosages and complete their treatment regimens. Moreover, it is imperative to take proactive measures to reduce the environmental presence of tetracyclines and promote antibiotic stewardship programs. These efforts are vital for mitigating the enduring health consequences associated with these antibiotics.

## 5. Conclusion

In conclusion, the multifaceted nature of tetracyclines, as antibiotics offering both therapeutic benefits and associated hazards, underscores the need for a balanced and responsible approach. Tetracyclines are undeniably valuable in addressing bacterial infections, yet their overuse and inappropriate utilization have raised significant concerns, particularly regarding the emergence of antibiotic resistance as a global health crisis. Beyond the realm of healthcare, the discussion extends to the varied routes through which individuals are exposed to tetracyclines, including dietary intake and environmental contamination. These exposures carry an array of potential health risks, encompassing disruptions to the delicate balance of gut microbiota, heightened skin photosensitivity, and developmental concerns—especially pertinent for infants and expectant mothers. To navigate this intricate landscape effectively, it is incumbent upon us to embrace responsible antibiotic deployment. This involves not only the discerning use of tetracyclines in medical practice but also proactive efforts to mitigate their environmental presence. Promoting antibiotic stewardship programs is instrumental in orchestrating a holistic response to these challenges. In striving to strike a harmonious equilibrium between harnessing the therapeutic power of tetracyclines and exercising conscientious antibiotic stewardship, we can aspire to safeguard human health and the environment. Through these collective efforts, we aim to preserve the utility of tetracyclines as indispensable tools in the medical arsenal while minimizing the potential perils they pose to our well-being and ecological balance.

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**Conflict of Interest**
There is nothing to declare.

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