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Published in:
Environmental Monitoring and Assessment

DOI:
10.1007/s10661-022-09754-7

First published: 19/01/2022

Effects of Pharmaceuticals on the Nitrogen Cycle in Water and Soil: A Review

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Abstract

The effects of pharmaceuticals on the nitrogen cycle in water and soil have recently become an increasingly important issue for environmental research. However, a few studies have investigated the direct effects of pharmaceuticals on the nitrogen cycle in water and soil. Pharmaceuticals can contribute to inhibition and stimulation of nitrogen cycle processes the environment. Some pharmaceuticals have no observable effect on the nitrogen cycle in water and soil while others appeared to inhibit or stimulate for it. This review reports on the most recent evidence of effects of pharmaceuticals on the nitrogen cycle processes by examination of the potential impact of pharmaceuticals on nitrogen fixation, nitrification, ammonification, denitrification, and anammox. Research studies have identified pharmaceuticals that can either inhibitor or stimulate nitrification, ammonification, denitrification, and anammox. Among these, amoxicillin, chlortetracycline, ciprofloxacin, clarithromycin, enrofloxacin, erythromycin, narasin, norfloxacin, and sulfamethazine had the most significant effects on nitrogen cycle processes. This review also clearly demonstrates that some nitrogen transformation processes such as nitrification show much higher sensitivity to the presence of pharmaceuticals than other nitrogen transformations or flows such as mineralisation or ammonia volatilisation. We conclude by suggesting that future studies take a more comprehensive approach to report on pharmaceuticals' impact on the nitrogen cycle process.

Keywords Pollution, pharmaceuticals. nitrogen transformations. agriculture, antibiotics

1 Introduction

Societies around the world are placing increasing emphasis on managing and enhancing water soil and air quality in order to achieve widely shared sustainability goals (Folke et al., 2021). Maintaining water quality in marine ecosystems has become a critical focus of environmental management (Pashaei et al., 2015) and the importance of soil quality is rapidly emerging as a key indicator of sustainable land management practices (Sofo et al., 2021). However, emerging pollutants such as pharmaceuticals pose a significant threat. Pharmaceutical consumption has increased significantly in recent decades and they are now used for a wide range of therapeutic purposes; however, pharmaceutical compounds in wastewater, sewage sludge, and manure are transported to terrestrial and aquatic ecosystems via a range of pathways including disposal, discharge, and use as fertilizer amendments (DeVries & Zhang, 2016). Within both aquatic and terrestrial environments, pharmaceutical products can have negative impacts on the nitrogen cycle and therefore impact on soil fertility, crop nutrition and the wider transformations of nitrogen in our environment. For instance, fluoroquinolones and sulfonamides have been shown to partially inhibit denitrification in the environment, and the application of swine manure containing the antibiotic tylosin to soil has been shown to change the nitrogen behaviour mediated by these microbial communities (Grenni et al., 2018; Laverman et al., 2015; Roose-Amsaleg et al., 2016).

Nitrogen is essential for life. Nitrogen is the fourth most abundant element in cellular biomass and is required by all living organisms, accounting for 1–4% of living cells (Hirsch & Mauchline, 2015; Woodmansee et al., 1978). Currently, industrial fertilizers are used to produce food for about half of the world's population, and fertilizer use and legume cultivation have nearly doubled nitrogen input to terrestrial and marine ecosystems (Galloway et al., 2013; Kuypers et al., 2018). Nitrogen exists in the soil mostly in the form of organic compounds, which plants require for growth but organic-N cannot be directly utilized by plants because it must first be converted to ammonium or nitrate ions before it can be absorbed.. The transformations of nitrogen in the environment collectively known as the nitrogen cycle result from a wide range of transformations including nitrogen fixation, assimilation, nitrification, and denitrification (Fig. 1). Biologically available or reactive nitrogen is derived from both abiotic (approximately 3% from lightning and 30% from the fertilizer industry) and biotic inputs via biological nitrogen fixation mediated by diazotrophic bacteria (approximately 67% from both marine and terrestrial ecosystems) (Behar et al., 2005; Fowler et al., 2015; Nardi et al., 2002). The transformations of nitrogen play an important role in the nutrition of organisms and microorganisms. As a result, nitrogen is crucial in regulating primary production in the biosphere (Gruber & Galloway, 2008). However, nitrogen also represents a significant threat to the sustainable management of land, air, and water since nitrogen contained in fertilizers and manures is easily lost to the environment causing a wide range of negative impacts including greenhouse gas emissions, damage to air quality, water quality and soil quality and a loss of biodiversity (Sutton et al., 2011). This review investigates the effects of pharmaceuticals on the nitrogen cycle in water and soil and associated environmental issues.

Fig. 1 Nitrogen cycle process

2 Nitrogen cycle

The aquatic and terrestrial environments are the two most important reservoirs of reactive nitrogen. At a global scale the main inputs to reservoirs of reactive nitrogen are biological N fixation and the industrial manufacture of fertilizer nitrogen. These processes contribute to an annual addition of reactive N to the biosphere of fixed N of over 450 Tg N per year (Fowler et al. 2015). The residence time of this nitrogen in terrestrial and aquatic environments varies considerably, but the return of dinitrogen to the atmosphere from these environments is achieved by the microbial reduction of nitrate in soils and water to dinitrogen gas. The large uncertainties associated with estimates of biological N fixation and denitrification at a global scale make it difficult to determine whether these processes are currently balanced (Galloway et al., 2004; Vitousek et al., 2013).

2.1 Nitrogen cycle in water

The availability of inorganic and organic nitrogen compounds, primarily nitrate, ammonium, and dissolved organic nitrogen (DON), drives primary production in the oceans to a large extent (Voss et al., 2013). The nitrogen cycle in water is driven by complex biogeochemical transformations mediated by microorganisms, such as nitrogen fixation, denitrification, and assimilation, as well as anaerobic ammonia oxidation (Zehr & Kudela, 2011). Nitrogen reduction to ammonia is one of the most remarkable reactions catalysed by living organisms (a process known as nitrogen fixation) and a critical reaction in the nitrogen cycle (Rosca et al., 2009). The magnitude of biological nitrogen fixation and denitrification in the ocean, as well as the corollary question of how well these two processes balance each other, are currently hotly debated (Gruber & Galloway, 2008). Biological Nitrogen Fixation (BNF) is carried out by free living prokaryotes (bacteria) and a specialized group of symbiotic prokaryotes associated with leguminous plants.

2.2 Nitrogen cycle in soil

Nitrogen is a key nutrient needed by plants and, as a result, we use around 120 Tg of synthetically produced N fertilizers on an annual basis to support crop production (Gerten et al., 2020). This is supplemented by inputs of nitrogen provided by 88 Tg from BNF which in terrestrial environments is largely produced by leguminous plants (Davies-Barnard & Friedlingstein, 2020). The recent realization that the response of ecosystems to global environmental change will be heavily reliant on nitrogen dynamics has sparked renewed interest in the soil nitrogen cycle (Luo et al., 2011; Van Groenigen et al., 2006; Van Groenigen et al., 2015). Three characteristics of reactive nitrogen are of particular relevance to processes of transformation in soils: (1) the abundance of protein-based compounds in plants and soils, (2) the nature of the C–N bond in organic matter, litter and soil, and (3) the stoichiometry of various groups of organisms within ecosystems (Vitousek et al., 2002).

2.3 The characteristics of pharmaceuticals that impact on the nitrogen cycle

The nitrogen cycle in water and soil is being altered by pharmaceutical compounds, which are emerging pollutants. Many drugs, owing to their widespread human and veterinary usage, are being continuously added to ecosystems and can exhibit pseudo-persistence (Radke et al., 2010), and recently, widespread pharmaceutical detection in terrestrial and aquatic systems has sparked significant scientific and regulatory concern (Caracciolo et al., 2015; Cardoso et al., 2014; Zuccato et al., 2010). During this time, pharmaceuticals consumption, particularly during the COVID-19 epidemic, such as chloroquine, dexamethasone, favipiravir, hydroxychloroquine, lopinavir, oseltamivir, ribavirin, teicoplanin, umifenovir, etc., have increased, which has potentially significant implications for the nitrogen cycle process (Fig. 2). Pharmaceuticals differ from other chemical contaminants in the following ways: (1) they can be formed by an infinite number of complex molecules that differ in molecular weight, structure, functionality, and form, (2) they have the ability to pass through cellular membranes and, as a result, are relatively persistent if they are not inactivated before achieving the desired therapeutic effect, (3) they are polar molecules with more than one ionizable group, and their degree of ionization, among other things, is affected by the medium's pH, (4) they are lipophilic and some are water-soluble, (5) drugs such as erythromycin, naproxen, and sulfamethoxazole can remain in the environment for more than a year; others, such as clofibric acid, can remain in the environment for several years and become biologically active due to accumulation, (6) following administration, the molecules are absorbed, distributed, and subjected to metabolic reactions that can change their chemical structure (Quesada et al., 2019), (7) plastic particles can be absorbed by pharmaceutical compounds, increasing toxicity. Antibiotics are one of the most common pharmaceutical types found in high concentrations in water and soil. Antibiotic concentrations in natural environments, such as soil or water, range from a few nanograms per litre or kg soil to hundreds of nanograms per litre or kg soil, and the highest concentrations are typically found in areas subjected to high anthropogenic pressures, such as hospital effluents, wastewater influents, and effluents, and soils treated with manure or soils used for livestock (Grenni et al., 2018; Kay et al., 2004; Orya et al., 2016; Patrolecco et al., 2015; Verlicchi et al., 2015).

Fig. 2 The negative impact of pharmaceuticals on the nitrogen cycle process in water and soil

3 Nitrogen fixation

Biological N fixation (BNF) is a microbial process that converts molecular N_2 gas to reactive, biologically available nitrogen forms (Marino & Howarth, 2009). Nitrogen fixation occurs when atmospheric nitrogen is converted to ammonia by nitrogenase, a pair of bacterial enzymes found in a few bacteria species, including cyanobacteria. However, most BNF is undertaken by Rhizobium bacteria which form a symbiotic relationship with leguminous plants (Herridge et al., 2008). Legumes are widely cultivated crop plants but also exist extensively in all ecosystems. The nitrogen fixed by biological fixation is first used to create ammonium (NH_4^+) ions which are subsequently incorporated into amino acids (Abu Shmeis, 2018).

3.1 Nitrogen fixation in water

Most of the reactive nitrogen in inland aquatic ecosystems comes from diffuse sources within the landscape ecosystems (via nitrate leaching), usually originating either directly or indirectly from the use of fertilizers or manures. However, BNF can also provide significant nitrogen inputs (Marino & Howarth, 2014). In aquatic environments, a wide range of prokaryotic organisms capable of nitrogen fixation exist, including bacteria that use organic carbon (heterotrophs), photosynthetic bacteria that fix inorganic carbon into biomass (autotrophs), and cyanobacteria (photoautotrophs) (Marino & Howarth, 2009). Although heterotrophs constitute a significant sink for primary production and thus an essential component of the marine nitrogen cycle (Berges & Mulholland, 2008) autotrophs while cyanobacteria also play a unique ecological role in aquatic ecosystems because they are the only organisms on Earth capable of fixing both inorganic carbon and nitrogen in an oxic (oxygen-containing) environment (Marino & Howarth, 2009). Marino & Howarth, (2014) found that heterotrophic bacteria and cyanobacteria are responsible for most nitrogen fixation in inland waters. Nitrogen fixation in reef ecosystems is a good example of nitrogen fixation in aquatic environments. Nitrogen fixation has since been proposed as a prominent component of the nitrogen cycle on coral reefs that may relieve N limitation and contribute significantly to overall marine N inputs (O'Neil & Capone, 2008).

3.2 Nitrogen fixation in soil

Nitrogen fixation in the soil can occur in a variety of ways, including anthropogenic processes, bacteria, etc. Biological nitrogen fixation is carried out by some free living microorganisms known as diazothrops, such as

Clostridium bacteria, which can be found in anaerobic soil environments, and oxygenic bacteria such as the cyanobacteria that are able to both fix nitrogen and carbon through photosynthesis. However, more important in most soils are the inputs of biologically fixed N by the Rhizobium bacteria which exist in symbiotic relationships within root nodules leguminous plant species (Sprent et al., 2017). In more intensively managed agricultural soils the inputs of synthetic fertilisers has been used to replace biological inputs for the production of food crops and forage (Van den Berg & Ashmore, 2008). Pharmaceutical contamination that is related to human activities can however inhibit BNF in soil. According to Gomes et al., (2018), rates of photosynthesis, nitrogen-fixation, and assimilation were reduced with, increased hydrogen peroxide accumulation, by the presence of ciprofloxacin in the plants.

3.3 Effects of pharmaceuticals on the nitrogen fixation

Pharmaceuticals, temperature, and light, as well as soil acidity, alkalinity, salinity, phosphorus, and water content status, all have a significant impact on BNF (Nandanwar et al., 2020). The potential impact of antibiotics on environmental bacteria is of significant concern, both from the perspective of enhancing the environmental reservoir of antibiotic resistance (the resistome) and through the inhibition of microorganisms that carry out important ecosystem services (Boxall, 2004; Brandt et al., 2015; Durso & Cook, 2014; Finley et al., 2013; Gaze et al., 2013; Griffiths & Philippot, 2013; Kumar et al., 2005; Revellin et al., 2018), especially for nitrogen fixation.

4 Nitrification

Nitrification takes place in soils, sediments, and aquatic environments (Butterbach-Bahl et al., 2011) and it is an oxidation process of converting ammonia (NH_3) to nitrite (NO_2^-) and then to nitrate (NO_3^-) (Casciotti et al., 2011). Ammonia oxidation ($NH_3 \rightarrow NO_2^-$) and nitrite oxidation ($NO_2^- \rightarrow NO_3^-$) are two consecutive nitrification steps, undertaken by two physiologically distinct clades of ammonia-oxidizing bacteria (AOB) and nitrite-oxidizing bacteria (NOB), whose close collaboration is required for complete ammonia-to-nitrate conversion (Hu & He, 2017). The ammonia-oxidizing bacteria, ammonia-oxidizing archaea, and nitrite-oxidizing bacteria are all autotrophic microorganisms that perform the nitrification process as well as nitrification, unlike ammonification and denitrification, is performed by a small number of organisms (Prosser, 2007).

$$\mathrm{NH_4^+ + O_2 + H^+ \rightarrow NH_2OH + H_2O}$$

$$\mathrm{NH_2OH + H_2O \rightarrow NO_2^- + 5H^+}$$

4.1 Nitrification in water

Nitrification has particular importance in aquatic environments. Nitrification reduces the demand for nitrogenous oxygen in wastewater effluents and nitrification is essential in wastewater treatment because it aids in the removal of ammonia, which is toxic to many fish (Ergas & Aponte-Morales, 2014). Nitrification is the final step in the regeneration of inorganic nitrogen from organic matter decomposition in the ocean, and it is tightly linked to organic matter flux in the water column and the majority of nitrification takes place near the surface layer namely the euphotic zone (Ward & Zafiriou, 1988; Ward, 2011). Nitrification rates in aquatic environments are determined by environmental factors such as salinity, temperature, oxygen, and pH. Nitrification in the water relies heavily on ammonia oxidation. Because many pharmaceuticals are often compounds that are resistant to biodegradation, their presence in raw sewage may have an impact on the performance of sensitive sewage treatment plant (STP) processes such as nitrification (Dokianakis et al., 2004). Ammonia-oxidizing bacteria (AOB) can be used for the removal of pharmaceutical residues which have become an emerging threat to the aquatic system in the last decades (Soliman & Eldyasti, 2018). Another study found that *N. europaea* and mixed ammonia-oxidizing bacteria (AOB) in nitrifying activated sludge could degrade triclosan and bisphenol A, but only mixed cultures could degrade ibuprofen, demonstrating that ammonia-oxidizing bacteria (AOB) can remove pharmaceutical residues whether in pure or mixed cultures (Roh et al., 2009; Soliman & Eldyasti, 2018). An important example of the negative impact of pharmaceuticals on the nitrogen cycle is related to nitrification and denitrification. Caracciolo et al., (2015) determined that at 250 mg/L concentrations, acetaminophen had a significant inhibitory effect (>25%) on nitrification and denitrification rates.

4.2 Nitrification in soil

Nitrification, or the oxidation of NH_4^+ to NO_3^-, occurs readily in oxic environments such as well-drained soils due to the activity of nitrifying prokaryotes, and this process is important for soil fertility because nitrate is easily assimilated by plants (Ergas & Aponte-Morales, 2014; Zhu et al., 2019). A range of conditions, such as soil temperature, moisture, and pH, influence rates of nitrification to occur in the soil (Izaurralde et al., 2012). However, nitrification in soil with low pH can occur (Hu et al., 2014). Soil, oxygen status and ammonium concentrations, play important role in rates of nitrification (Baggs et al., 2010; Butterbach-Bahl et al., 2013; Zhu et al., 2019). The ammonia oxidation pathway is the first and rate-limiting step in nitrification, converting ammonia to nitrite and it is the primary contributor to the ammonium:nitrate balance in the soil (Kowalchuk & Stephen, 2001; Beeckman et al., 2018).

4.3 Effects of pharmaceuticals on the nitrification

To explain the impact of pharmaceuticals on nitrification, several examples can be reviewed (Table 1). The inhibitory effect of drugs on nitrifying microorganisms, in addition to being important for treatment plant efficiency, is relevant as a signal of potential negative effects on aquatic organisms when pharmaceutical-containing wastewater is discharged to a receiving water body (Carucci et al., 2006). In addition, at 250 mg/L concentrations, acetaminophen had a significant inhibitory effect (>25%) on nitrification and denitrification rates (Barra Caracciolo et al., 2015). On the other hand, the nitrification process is an important part of the removal process of pharmaceuticals. Various mechanisms are used to remove pharmaceuticals from water including photodegradation, sorption, biodegradation, and phytoremediation (Hijosa-Valsero et al., 2016). According to some studies, pharmaceuticals can be removed through the nitrification process (autotrophic biodegradation) (Peng et al., 2019). Indeed, it is known that nitrification can enhance pharmaceuticals removal (He et al., 2018). For example, there was high removal of diclofenac, ibuprofen, paracetamol, and metoprolol (60–100%), and partial removal of trimethoprim and carbamazepine (30 and 60%) (Köpping et al., 2020). Many studies also found that some pharmaceuticals had no effects on nitrification, such as tetracycline on nitrification (Jiang, et al, 2021).

Table 1 List of observed effects of pharmaceuticals on the nitrification rate

5 Ammonification

Ammonification is defined as any chemical reaction that converts NH_2 groups into ammonia or its ionic form, ammonium (NH_4^+), as an end product, and it is the final step of the nitrogen cycle that involves an organic compound and serves as a link between the depolymerization of large organic molecules and the nitrification step. In other words, the production of ammonium from organic matter is known as mineralization, which is sometimes referred to as ammonification (Kendall et al., 2013). Mineralization is known to be important in marine and terrestrial environments. Mineralization of bacteria and phytoplankton in sea water column can be an important source of nutrients in the water (Kendall et al., 2013).

5.1 Ammonification in water

The intensity of bacterial ammonification in water bodies is proportional to the amount of organic matter present (Billen & Fontigny, 1987; Podgórska & Mudryk, 2007). Because biological ammonium assimilation by bacteria, biofilms, and aquatic plants is preferable to nitrate assimilation, ammonification of organic nitrogen is an important process in water. When a plant or animal dies or an animal expels waste, the initial form of nitrogen is organic. Bacteria or fungi convert organic nitrogen from organic substrates back to ammonium (NH_4^+), in a process called ammunition or mineralization. The enzymes involved are: Glutamine synthetase (cytosolic and plastic); Glutamine 2-oxoglutarate aminotransferase (Ferredoxin and NADH-dependent) and Glutamine dehydrogenase, which have a minor role in the assimilation of ammonium, but are important in the catabolism of amino acids (Butnariu & Butu, 2019a). In this first stage of ammonification, nitrogenous organic residues are transformed into ammonia derivatives. This is done by bacteria such as *Bacillus*, *Bacterium*, or *Micrococcus*. In water, ammonia derivatives exist in two chemical forms (Butnariu & Butu, 2019b). The first is free molecular ammonia (NH_3), a rarefied gas that is formed especially if the pH of the water is greater than or equal to 7. At a pH of less than 7, ammonia associates with a water molecule and forms ammonium hydroxide (NH_4OH) (Vardanian et al., 2018). Ammonification starts right from the moment we introduce water into the aquarium because this environment is never 100% pure. The concentration of ammonia derivatives then increases progressively. Now, these derivatives are broken down by bacteria, present in large numbers. A recent study found that after 11 days, the ammonia concentration was already close to zero (Butu et al., 2020).

5.2 Ammonification in soil

Nitrogenous organic substances, which account for 99% of total N reserves of most soils (Butterbach-Bahl *et al.* 2011), are made up of humic reserves and other compounds that naturally accumulate in the soil as a result of the biological fixation of N_2 and the degradation of plant and animal organic residues, and manure. The bacterial cells themselves represent a mass of organic substance, predominantly protein, of about 6 tons/ha, to which are added about 20 tons represented by the rest of the microflora and microfauna. If this organic N remained unchanged, the N reserves available to plants would diminish year after year, eventually ceasing to allow plant growth. Normally, however, these substances undergo a mineralization process, at the end of which they are brought to the state of NH_3 (Jarvis *et al.* 2011). The ammonification process itself is preceded by the decomposition of protein molecules by hydrolysis, using extracellular proteases released by numerous species of aerobic and anaerobic microorganisms according to the general formula:

Protein $\rightarrow$ peptone peptides $\rightarrow$ amino acid under the influence of enzymes: proteinase, peptonase, peptidase and with the elimination of water.

The amino acids resulting from this degradation enter the bacterial cells, where they undergo a deamination process, which results in NH_3 and the corresponding organic acid. There are several types of deamination, namely: (1) hydrolytic deamination, (2) hydrolytic and decarboxylation deamination, (3) reducing deamination, (4) reducing decarboxylation deamination (anaerobic), (5) oxidative deamination with decarboxylation, and (6) desaturation with desaturation .

Such reactions, in addition to N mineralisation, result in organic acid formation: acetic, formic, propionic, butyric, valerian. Depending on the environmental conditions and the nature of the microflora, these acids can be completely oxidized to CO_2 and H_2O (in the aerobic environment), accumulated as such, transformed into alcohols. Ammonification in the strict sense can therefore be defined as a biological process in which NH_3 is released into the soil, as a result of the action of soil microflora on amino acids resulting from the decomposition of protein substances (Butterbach-Bahl *et al.* 2011). In this sense, the release of NH_3 under the action of temporary root mycoflora is not included in the ammonification. In this process NH_3 can be reused as such by a whole range of microorganisms. Most of it still undergoes a transformation absolutely necessary for life in the soil, in forms accessible to plants, and the rest can be fixed in the soil, especially in acid soils or evaporate into the atmosphere. The microflora capable of producing ammonification of protein substances is numerous and diverse, and it acts as follows over time: aerobic bacteria enter the picture early on in the process, such as *Bacillus cereus var. micoides*, *B. subtilis*, *B. thermoproteolyticus*, unsporulate species such as *Serratia marcescens*, *Arthrobacter*, etc, and facultatively anaerobic species such as *Proteus vulgaris*, *Pseudomonas fluorescens*, *Escherichia coli*, *Sarcina lutea*, etc. After 2-3 days, anaerobic species such as *Clostridium putrefaciens*, *C. perfringens*, and some actinomycetes such as *Streptomyces violaceus*, and *Micromonospora chaleea* come into action, which begin to predominate and make the release of NH_3 to be maximum. Moulds invade the environment and the release of NH_3 decreases because they use NH_3 for protein synthesis and produce a lot of acids that neutralize the ammonia. Urea hydrolysis is performed by a large group of microorganisms capable of producing the enzyme urease (Mekonnen et al., 2021). In this group we find species of the genera: *Achromobacter* sp., *Bacillus* sp., *Clostridium* sp., *Corynebacterium* sp., *Pseudomonas* sp., Actinomycetes, and filamentous microfungi. To these is added the urobacteria group, which is distinguished by resistance to high concentrations of urea and alkaline pH, as well as the ability to release large amounts of NH_3. Urobacteria include *Bacillus (Urobacillus) pastures*, *Micrococcus ureae*, *Planosarcina ureae*, and others. The ammonifying activity of urobacteria is very important because urea contains 47% N_2 - which would otherwise be unused by plants.

5.3 Effects of pharmaceuticals on the ammonification

The nitrification process is more sensitive to different chemicals such as pharmaceuticals than the ammonification process partly because of the diversity of organisms associated with ammonification (Cycon et al., 2016). Various pharmaceuticals have a negative impact for instance, Cycon et al., (2016) reported that stimulation happened in 1 $mg \cdot kg^{-1}$ soil of naproxen and ketoprofen after 1, 15, and 30 days, while diclofenac and ibuprofen had no effect on the rate of ammonification (Table 2).

Table 2 List of observed effects of pharmaceuticals on the ammonification rate

6 Denitrification

Denitrification is the microbial process of converting nitrate and nitrite to gaseous nitrogen forms, primarily nitrous oxide (N_2O) and nitrogen (N_2). The availability of N oxides, nitrite (NO_2^-), or nitrate (NO_3^-), which are formed from the autotrophic nitrification pathway substrate, ammonia (NH_3), which is derived from ammonium (NH_4^+), is the key to denitrification as defined (Martens, 2004). The nitrate ion acts as a terminal electron acceptor in the absence of oxygen during the process of respiration, leading to a sequence of reduction reactions which ultimately produce N_2:

$$NO_3^- \rightarrow NO_2^- \rightarrow NO \rightarrow N_2O \rightarrow N_2$$

Denitrification is a process that occurs in all of our terrestrial and aquatic ecosystems, including tropical and temperate soils, natural and intensively managed ecosystems, marine and freshwater environments, wastewater treatment plants, manure storage facilities, and aquifers. The factors that determine the rate of denitrification are nitrate availability, the availability of an oxidisable organic substrate, and the oxygen concentration (indirectly determined by soil water content) (Butterbach-Bahl et al., 2011).

6.1 Denitrification in water

An increase in nitrate concentrations in groundwater observed worldwide as a result of fertilizer use and industrial wastewater raises concerns due to the serious consequences for human health (Park et al., 2005). One of the most important applications of denitrification is in water treatment. For many years, denitrification has been utilized for treatment in aquatic environments especially for wastewater (Gayle et al., 1989). Moreover, nitrification and denitrification are the two most common items for removing inorganic nitrogen from wastewater (Zhu et al., 2016).

6.2 Denitrification in soil

Nitrates accumulated in the soil, as a result of the nitrification process or by application of fertilizers, are partly consumed by higher plants, and a variable amount is washed away by infiltration and runoff. Microorganisms can use nitrates in two ways: they can be assimilated during protoplasm synthesis (assimilation of nitrites) or they can be reduced to oxidize an organic or mineral substance (Butnariu & Butu, 2020). Denitrification is a process that closes the circuit by returning molecular N_2 to nature. The reduction of nitrates in the denitrification process creates either N_2 or NH_3, releases intermediate compounds such as the greenhouse gas N_2O. Optimal production conditions are achieved in water-saturated soils and in deep structures in which the following groups of microorganisms can react (Butu et al., 2021). The actual denitrifying bacteria that reduce NO_3^- to N_2 are *Pseudomonas stutzeri* and *Pseudomonas denitrificans*. *Bacillus megaterium*, *Escherichia coli*, *Pseudomonas aeruginosa*, and other microorganisms in the general soil flora are capable of reducing NO_3^- to NO_2^-, as are some sulfurous bacteria such as *Thiobacillus denitrificans*. It is certain that the reduction of nitrates to gaseous N_2 represents for the soil a real loss that can reach up to 120 kg N_2/ha/year, although some of the released N_2 can be taken up by anaerobic N_2 fixatives such as *Clostridium pasteurianum* (Bagiu et al., 2020a). It also is of environmental concern given that N_2O is a greenhouse gas with nearly 300 times the warming potential of CO_2. At the same time, incomplete reduction, up to the intermediate stages, of nitrites and NH_3 is less detrimental to the soil fertility, as NH_3 can be used by some heterotrophic microorganisms, while nitrites are taken up by nitrate bacteria and nitrate reoxidations (Bagiu et al., 2020b).

6.3 Effects of pharmaceuticals on the denitrification

The conversion of nitrates to gaseous nitrogen occurs in the production of alkalinity, leading to an increase of pH. The optimum values of pH are in 7-8 domain with different optimal values for different bacterial populations (Simek et al., 2002). In case that for the denitrification process is not enough organic substrate for his ensuring it can be used different organic compounds as: methanol, ethanol, acetic acid, residues of organic materials. Most used sources as electron donors are the organic matter from waste water and methanol. Their choosing is made having regard the economic part and the local availability. Table 3 combines several types of research that examined how pharmaceuticals affect denitrification in water and soil.

The widespread nature of denitrification in soils reflect the underlying diversity of soil microorganisms that are responsible (Butterbach-Bahl *et al.* 2013). This diversity of organisms is likely to mean that individual pharmaceutical products are unlikely to completely inhibit the denitrification process since in cases where jnhibition of individual species or genera occurs as there are usually other species that can take over the denitrifying role. For this reason the denitrification process appears to be less sensitive to the presence of pharmaceutical substrates than other N cycle processes.

Table 3 List of observed effects of pharmaceuticals on the denitrification rate

7 Anammox

The anammox process accounts for a significant portion of nitrogen conversion in the oceans (Chen et al., 2019). There appear to be some enzymatic similarities between anammox and aerobic NH_3 oxidation, and anammox has the same ecological significance as denitrification, i.e., the loss of fixed nitrogen in anoxic environments (Ward, 2008). Anammox (anaerobic ammonium oxidation), a reaction that oxidizes ammonium to dinitrogen gas under anoxic conditions using nitrite as the electron acceptor, was a significant discovery in the nitrogen cycle. Nitrite and ammonium are converted into dinitrogen gas in this process:

$$NH_4^+ + NO_2^- \rightarrow N_2 + 2H_2O$$

7.1 Anammox in water

Anaerobic ammonium-oxidizing (anammox) bacteria are one of the most recent additions to the biogeochemical nitrogen cycle and can produce more than half of the N_2 gas released (Jetten et al., 2009). There are five types of anammox bacteria: (1) Ca. Brocadia, (2) Ca. Jettenia, (3) Ca. Kuenenia, (4) Ca. Anammoxoglobus, and (5) Ca. Scalindua (Kartal et al., 2007; Kartal et al., 2008; Kuypers et al., 2005; Quan et al., 2008; Schmid et al., 2000; Schmid et al., 2003; Strous et al., 1999; Wu et al., 2019). Anammox bacteria exist in a variety of natural habitats, including anoxic marine sediments and water columns, freshwater sediments, water columns, freshwater marshes, rivers, meromictic lakes, and river estuaries (Dale et al., 2009; Humbert et al., 2010; Kuypers et al., 2005; Lam et al., 2009; Long et al., 2013; Philipot et al., 2007; Rich et al., 2008; Schmid et al., 2007; Schubert et al., 2006; Thamdrup et al., 2006; Trimmer et al., 2003; Zhang et al., 2007). Indeed, the anammox process offers an appealing alternative to current wastewater treatment systems for ammonia-nitrogen removal (Jetten et al. 2009). Moreover, anammox research has primarily focused on its role in the oceanic nitrogen cycle, with anammox contributing more than 50% of N_2 loss in some marine environments (Arrigo, 2005; Devol, 2015; Xi et al., 2016).

7.2 Anammox in soil

Anammox bacteria have also been detected in permafrost soils, reductisol, agricultural soils, peat soils, and rice paddy soils (Humbert et al., 2010; Long et al., 2013; Philipot et al., 2007; Zhu et al., 2011) and anammox bacteria were detected to be more common and phylogenetically diverse in terrestrial ecosystems than in most other environments (Humbert et al., 2010; Moore et al., 2011; Humbert et al., 2012; Zhu et al., 2011). For instance, anammox activity accounts for 1 to 37% of total N_2 loss from paddy soils (Sato et al., 2012; Xi et al., 2016; Zhu et al., 2011).

7.3 Effects of pharmaceuticals on the anammox

Several studies have found that pharmaceuticals have a negative effect on anammox bacteria (Table 4). Environmental factors such as temperature, heavy metals, nanomaterials, and antibiotics limit the growth of anammox bacteria (Li et al., 2019; Zhang et al., 2019; Zhang et al., 2021).

Table 4 List of observed effects of pharmaceuticals on the anammox rate

8 Conclusions

This review has demonstrated that pharmaceuticals can exert a wide range of stimulatory and inhibitory effects on nitrogen cycle processes in different environments, which may be modified by different concentrations and types of pharmaceuticals. Even at low concentrations, nitrification and denitrification appear sensitive to pharmaceuticals ($\mu g \cdot L^{-1}$). However, inadequate information exists regarding how pharmaceuticals can affect nitrogen fixation and ammonification or how they interact in the environment. It is likely that a range of mechanisms is responsible for the observed impacts of pharmaceutical products including direct stimulation or inhibition of microbial populations, alterations of rates of chemical reactions (through impacts on enzyme controlled metabolic pathways) indirect actions (such as reactions with substrates influencing to microbial activity, and other indirect impacts of pharmaceutical products. Such information is critically important if we are develop more sustainable use of nitrogen as a critical component of our food production systems. Future investigations will need to take a more systematic and comprehensive approach to address these concerns. We need to know more about the source, the pathways of transport and longevity of pharmaceuticals in the environment to fully understand their impact. The process of decomposition of biologically active molecules can also lead to the production of intermediate products that can have impacts on the environment. There is evidence that the effects of pharmaceutical exposure may not manifest themselves for as long as one year after initial exposure, underscoring the need for long-term studies that replicate pharmaceutical applications over time or deliver continuous exposure (DeVries & Zhang, 2016). Thus, future investigations will need to take a more systematic and comprehensive approach to address these concerns.

Acknowledgements

This research was supported by the Doctorate Study Programme in Ecology and Environmental Sciences, Marine Research Institute of Klaipeda University and Nicolaus Copernicus University in Torun. The authors gratefully acknowledge Prof. Monica Butnariu for editing this article.

Declarations

Consent to Publication

We confirm that all authors have read the manuscript and agree to its submission in *Environmental Monitoring and Assessment.*

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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