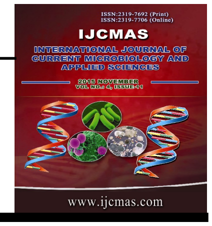

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Review Article

Antibiotics in the Environment: A Review

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A B S T R A C T

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Antibiotics are among the most successful drugs being used for human therapy. Besides being used for treating and preventing infectious diseases in humans, it is also used for animal farming and as well as for agricultural purposes. However, since antibiotics can challenge microbial populations it should be considered as a threat to our environment. Effluents from pharmaceutical manufacturing plants, hospitals and veterinary clinics; overland flow runoff, unsaturated zone transport from fields to which agricultural waste has been applied, and through leaky waste-storage structures contain antibiotics, their metabolites and antibiotic resistance genes that can contaminate natural environment. The major concerns regarding the presence of antibiotics in the environment are that the entire trophic levels will be wiped out in some ecosystems or that the multiple drug resistant bacteria will flourish and make its way into the food chain. Unfortunately, both of these fears have been realised. However, with more awareness of the effects of this type of pollution, the scientific community is beginning to recognize the importance of structuring plans to begin regulating as the need arises. This topic is going to be hot issue for years to come.

Introduction

Ever since the accidental discovery of penicillin by Alexander Fleming in 1928, hundreds of other antibiotics have flooded the market and are available for use (1) in humans and animals to treat infectious diseases, (2) as growth promoters and (3) to improve feed efficiency (Addison, 1984). Today, antibiotics play a major role in stimulating a physiological response in humans, animals, bacteria and other organisms and their use has been on rise in many developed countries.

The worldwide antibiotic consumption lies between 100,000 and 200,000 ton per annum (Wise, 2002). In 1996, about 10,200 ton of antibiotics were used in EU (European Union), of which approximately 50% was used in veterinary medicine and as growth promoters. In the United States, one estimate is that 50% of the 22,700 metric tons of all antibiotics prescribed annually are for humans and 50% for use in animals, agriculture and aquaculture. In India, between 2005 and 2009, the units of antibiotics sold in the country increased by about 40 %, points out the paper contributed by the Indian working group of the Global Antibiotic Resistance Partnership (GARP), chaired by N.K. Ganguly.

Over the past few years, concern has grown over the irrational use and disposal of antibiotics might potentially have on human health and environment. The selection and development of antibiotics resistant bacteria has led to worldwide social and scientific concern that the over prescription and misuse of antibiotics and the increased and worldwide use of sub-therapeutic doses of antibiotics in agriculture are responsible for this trend (Smith *et al.*, 2002). Since the late 1990s, the knowledge on antibiotic residues and antibiotic resistant bacteria is increasing. However, significant gap still exists in our understanding on the relationship between antibiotic residues, their metabolites and antibiotic resistant bacterial populations after their excretion.

Usage

Antibiotics are extensively used in human and veterinary medicine as well as in agriculture and aquaculture for the purpose of treating and preventing microbial infections.

Human medicine

Antibiotic prescription rates and intake without prescription vary markedly between countries (Mölstad *et al.*, 2002). According to World Health Organization (WHO) country specific data on the use for antibiotics of different groups in different countries are available as DDD (defined daily dose). Cars *et al.* (2001) obtained data for non-hospital antibiotic sales for 1997 from the 15 member states and analyzed these according to the Anatomic Therapeutic Chemical (ATC) classification system, and expressed them as defined daily doses per 1000 people per day. Sales of antibiotics varied more than four-fold: France (36.5), Spain (32.4), Portugal (28.8), and Belgium (26.7) had the highest sales, whereas the Netherlands (8.9), Denmark (11.3), Sweden (13.5), Germany (13.6), and Austria (12.4) had the lowest.

Animal

In livestock antibiotics are routinely used at therapeutic levels to treat diseases and at sub-therapeutic levels to improve feed growth rate and increase feed efficiency (Kiser, 1976; Cohen, 1998). In the US, antibiotics used in animal feeding have increased from 91000 kg in 1950 to 9.3 million kg in 1999 (AHI, 2002). Of the 9.3 million kg antibiotics used, 8 million kg is used for treating infections and 1.3 million kg used as growth promoters. The use of antibiotics as growth promoters in the European Union is subject to Directive 70/524/EEC, covering additives in feeding stuffs and also includes a requirement that at the level permitted in animal feed does not adversely affect human, animal health, or the receiving environment (EU Directive 70/524/EEC, 1970). Sweden was the first to ban the use of antibiotics as growth promoters in 1986 and claimed that the number of antibiotic resistant bacteria remained lower than its neighbors and other countries during the period 1986-1995. Following the footsteps of Sweden, Danish animal food industries in 1998 decided to voluntarily discontinue further the use of all antimicrobial growth promoters in broilers, slaughter pigs and cattle (DANMAP, 2000).

Agriculture

Antibiotics have been in use since the 1950s to control certain bacterial diseases of high-value fruits, vegetable, and ornamental plants. Only two antibiotics, streptomycin and oxytetracycline, are registered by the United States Environment Protection Agency (USEPA) for use in plant agriculture. Vidaver (2002) estimated that 53,000 ha of fruits and vegetables are sprayed annually with antibiotics. In the USA, antibiotics applied to plants account for less than 0.5% of total antibiotic use (McManus *et al.*, 2002).

Aquaculture

In aquaculture, antibiotics have been used mainly for therapeutic purposes and as prophylactic agents. Antibiotics authorized for use in aquaculture are oxytetracycline, florfenicol, premix, sarafloxacin, erythromycin sulphonamides potentiated with trimethoprim or ormethoprim (Serrano, 2005).

Entry of antibiotics into the environment

Sources of antibiotic dissemination into our environment are not just restricted to patients excreting unabsorbed medications into the septic system and waste water treatment plants. But also includes effluents from pharmaceutical manufacturing plants, disposal of unused or expired drugs, overland flow runoff, unsaturated zone transport from fields to which agricultural waste has been applied, and through leaky waste-storage structures. Effluents from hospitals and veterinary clinics are also huge contributors to this problem (Rhodes *et al.*, 2000).

There are various routes through which antibiotics are introduced into the water. When fisheries use medicated foods or treat for disease outbreaks, antibiotics are directly released into the surface water. Routes of antibiotic introduction into the environment created by animal farming include manure used as fertilizer to waste water runoff. About 300,000 pounds of antibiotics are used in crop production each year (Halling-Sorensen *et al.*, 1998). Antibiotics are mainly sprayed on high value crops like fruit trees, ornamental plants etc. Not all of the spray remains on the plants; most are washed into the soil and eventually reach surface or ground water.

Effluent from waste water treatment plants is deposited directly into surface water. Leachate from septic systems and landfills is released into the unsaturated zone, but depending on soil conditions it may seep into groundwater or spread laterally until it meets a stream or other surface water.

Figure 1 shows different routes through which antibiotics enter into the environment.

Effects on the environment

The effects of antibiotics entering our water sources is not widely known; this is because it has been over the last few years that the scientific community have started to become concerned about the deleterious effects. Another reason is that the concentrations of antibiotics found in waters are usually quite low, in the low parts per billion range; and there have not been any reliable analytical methods to measure these low concentrations (Koplin, 2002).

Though individual antibiotic concentrations are low, there are so many different antibiotics that when combined they could lead to serious health and environmental problems. Little is known about the potential interactive effects that may occur from these complex mixtures, let alone the metabolites that can be formed as they break down (Koplin, 2002).

Some of the major concerns regarding the presence of antibiotics in the environment are that the entire trophic levels will be wiped out in some ecosystems or that the multiple drug resistant bacteria will flourish and make its way into the food chain. Unfortunately, both of these fears have been realised.

Effect on biota

Indigenous communities of microbial populations are very complex and they have the important task of cycling nutrients. For maintaining soil quality and sustainable use of agricultural land proper cycling of nutrients is necessary. Nitrogen is one of the important nutrients essential for agricultural systems and its cycling is driven by two genera of gram negative bacteria (e.g. *Nitrosomonas* and *Nitrobacter*). Gram-negative and wide spectrum antibiotics, such as sulphonamides and tetracyclines could seriously inhibit nutrient cycling if concentrations reached high enough levels. This result has been observed in laboratory studies, but no field studies have found antibiotic concentrations at levels that would seriously disrupt the nitrification process (Jensen, 2001).

Antibiotic resistance

Primary resistance is naturally present in the microorganisms. However, secondary resistance develops when microorganisms comes in contact with antimicrobials during therapy. Plasmid mediated resistance is transferable between microorganisms through the process of conjugation (horizontal resistance transfer). Resistance can then reach the environment with the potential of adversely affecting aquatic and terrestrial organisms (Kümmerer, 2009).

The most prominent medical examples are vancomycin-resistant *Enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and multi-resistant Pseudomonads. The transfer of resistant bacteria to humans could occur via water or food if plants are watered with surface water or sewage sludge, if manure is used as a fertilizer, or if resistant bacteria are present in animal products (Perretin *et al.,* 1997; Khachatourians, 1998; Salyers, 2002; Dolliver and Gupta, 2008).

The emergence of antibiotic resistant bacteria is worrisome because this problem is accumulating and accelerating while the world's tool for combating this problem is both decreasing in both number and power (Harrison and Lederberg, 1998; Finch and Hunter, 2006).

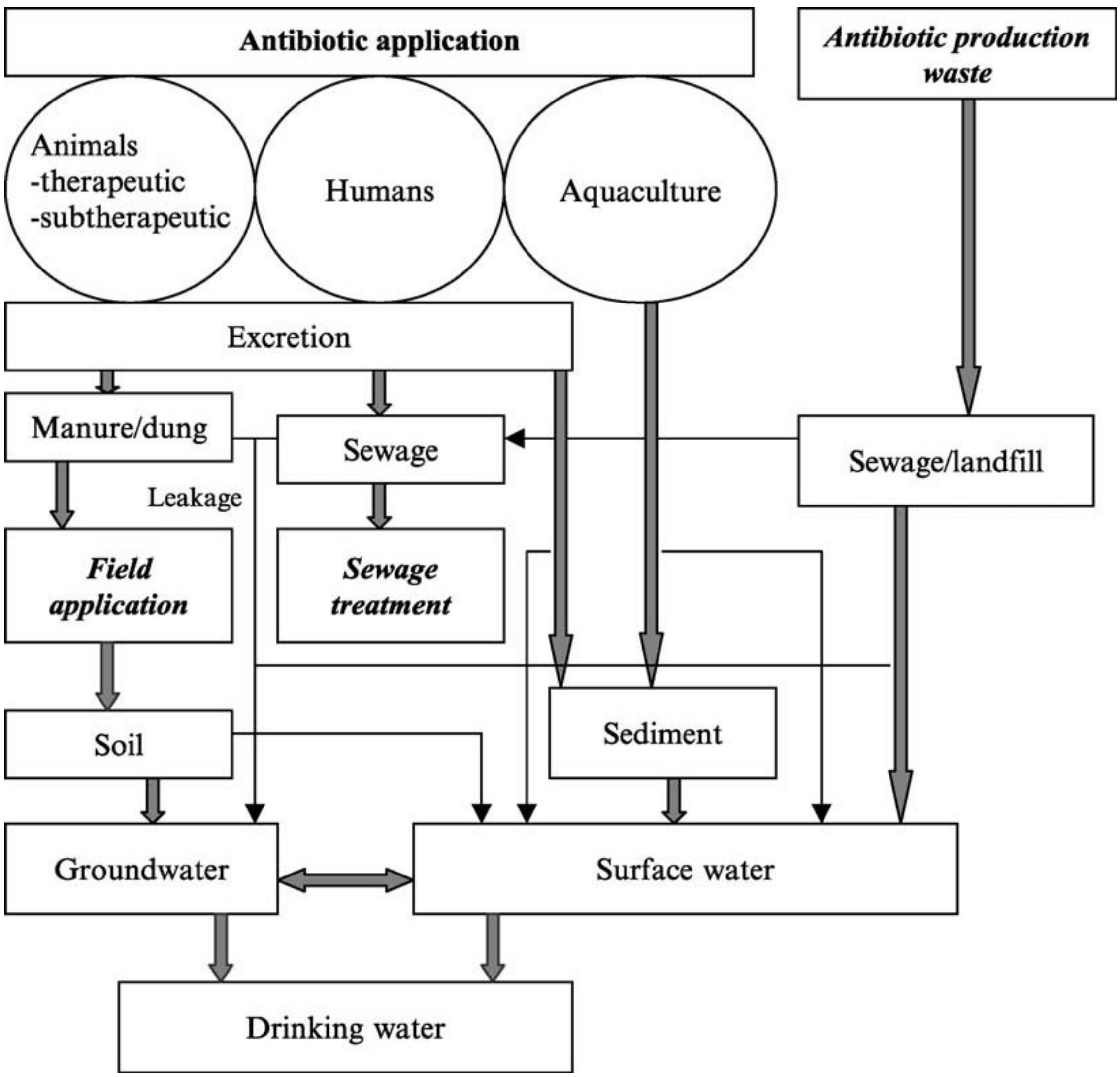
Genotoxicity and biodegradability of antibiotics

The genotoxicity and degradation of antibiotics has been investigated much more internationally. In different studies, a number of antibiotics were found to be genotoxic (Isidori *et al.,* 2005; Cavas and Gözükara, 2005). Antibiotics like quinolones, floroquinolones, ofloxacin, lincomycin etc. were found to be genotoxic using a variety of animal and microbial assays (McQueen *et al.,* 1991; Hartmann *et., al.,* 1998; Isidori *et al.,* 2005).

As far as the biodegradability of antibiotics is concerned, only a few of the antibiotics were partially biodegraded under test conditions in aquatic systems (Kümmerer *et al.,* 1999, 2000). Most were persistent. Different tests conducted for assessment of biodegradability of antibiotics like ciprofloxacin, metronidazole etc. showed that antibiotics were not easily biodegraded (Al-Ahmad *et al.,* 1999; Kümmerer *et al.,* 2000; Alexy *et al.,* 2004). Also most antibiotics tested to date have not been biodegradable under aerobic conditions (Al-Ahmad *et al.*, 1999; Kümmerer *et al.*, 2000; Alexy *et al.*, 2004). Biodegradability has been poor for most of the compounds investigated in laboratory tests – even some of the ß-lactum (Alexy *et al.*, 2004). Some antibiotics occurring in soil and sediment proved to be quite persistent in laboratory testing as well as in field studies. Some do not biodegrade well under anaerobic conditions (Gartiser *et al.*, 2007).

Despite these above studies, the knowledge on genotoxicity and biodegradability of antibiotics is still limited.

Figure.1 Anticipated exposure pathways for antibiotics in the environment



In conclusion, even if the occurrence, effects and fate of antibiotics have been put in the perspective of the scientific community, still little is known about the actual risk it possessed to humans and the environment. Significant gap exists in the understanding of the interaction between the antibiotics, their metabolites and the promotion of resistance after excretion (Kemper, 2008).

For proper risk assessment and management different measures need to be taken to reduce the emission of antibiotics in the environment. For this reason, unused or expired drugs should not be flushed down the drain and patients should be made aware that antibiotics are used for treating bacterial diseases and not for common cold caused by viruses. Doctors, patients and pharmacists play a pivotal role in reducing the release of antibiotics in the environment. Also prudent use of antibiotics in livestock farming will limit the risk factors of transferring antibiotics resistance from animals to humans.

In the current scenario, there are no regulations for the monitoring of any antibiotics in ground, surface or drinking waters. This is because concentrations of antibiotics are generally low, in parts per billion ranges. Regulations that are in effect now relate to the disposal of unused or expired antibiotics under the Current Good Manufacturing Practice (CGMP) regulations set forth by the FDA (FDA 1998). This regulation calls for the incineration of all disposed of antibiotics by the manufacturer (FDA 1998). However, with more awareness of the effects of this type of pollution, the scientific community is beginning to recognize the importance of structuring plans to begin regulating as the need arises. This topic is going to be hot issue for years to come.

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