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Bioaccumulation and analytics of pharmaceutical residues in the environment: A review☆

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ABSTRACT

The presence of pharmaceutical residues in various environmental compartments is an issue of increasing concern. The widespread occurrence of these compounds in water and soil samples has been demonstrated in a number of analytical studies. However, the data about their concentrations in biota samples is scarce. Moreover, the trophic transfer of pharmaceuticals remains largely unexplored, despite increasing evidence of the potential bioaccumulation of those compounds. Therefore, the main aim of this review is to present an overview of the current state of data about the bioaccumulation and analytical methodologies used for the determination of pharmaceutical residues in biota samples. This work focuses on the most commonly found pharmaceuticals in the environment: antibiotics, analgesic and anti-inflammatory drugs, steroid hormones, antihypertensives and antidepressants. We do hope that the collected data will allow a better understanding of pharmaceutical pollution and the exposure of non-target organisms. However, although impressive progress has undoubtedly been made, in order to fully understand the behavior of these chemicals in the environment, there are still numerous gaps to be filled in our overall knowledge in this field.

1. Introduction

Pharmaceuticals cover a large group of substances that belong to different chemical families. These compounds are introduced into the environment as a result of medical and veterinary use. Hence, in the course of the last decade they have been recognized as relevant environmental contaminants [1–3]. These immanently bioactive compounds are detected in various environment compartments at low or very low concentrations (ng L^{-1} to μg L^{-1}) but their continuous input into the environment may lead to prolonged exposure and thus they may cause adverse effects on non-target organisms. Moreover, their introduction rates in the environment exceed their degradation rate, hence they are considered to be pseudopersistent contaminants [4]. The amount of data proving the presence of pharmaceutical residues in different environmental compartments (mainly water bodies, soils and sediments) is still increasing [5–8]. It is caused by recent developments and improvements in advanced instruments and analytical methodologies, which have made the detection of these chemicals at low concentration levels possible.

However, the knowledge about their occurrence in biota samples is scarce, probably due to the complex experimental work involved in the analysis of such samples. Moreover, experimental bioconcentration test results are also limited, despite the fact that some physico-chemical properties of pharmaceutical compounds may indicate their tendency towards bioaccumulation. The term bioaccumulation is not defined precisely; sometimes it is presented as the simple uptake of substances from the environment but also as an accumulation over time or retention of a substance. It is therefore agreed that the bioaccumulation is estimated from the ratio of the chemical's concentration in the biota sample (plant, animal) to its concentration detected in the surrounding media (e.g. soil, sediment or water) [9,10]. Bioaccumulation is normally presented using factors: Bioaccumulation Factor (BAF)—the ratio of the contaminant in an organism to its concentration in the environment at a steady state, where the organism can take in the contaminant through ingestion with its food as well as through direct contact; or Bioconcentration Factor (BCF)—equivalent to BAF (steady-state distribution of chemical between aquatic organism and water), but with no dietary intake of contaminant, mostly investigated in laboratory conditions. Both BAF and BCF values are presented in L kg^{-1},

☆ Dedicated to Prof. Roman Kaliszan, a great scientist, who pushed chromatography into the dimension of a stand-alone scientific field.

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however this unit is normally omitted (also in this review). Biomagnification is the process whereby the tissue concentrations of a contaminant increase as it passes up the food chain through two or more trophic levels and is presented as Biomagnification Factor (BMF) (unit kg g^{-1}).

According to the OECD (Organisation for Economic Co-operation and Development) the main criteria for predicting the bioaccumulation potential is through a comparison to the chemical's lipophilicity, usually represented as the octanol–water partition coefficient ($\log K_{ow}$). The $\log K_{ow}$ values higher than or equal to 3 characterize compounds with the ability to partition into the lipid portion of organisms and bioaccumulate [4,10], which can also be observed for some pharmaceuticals [9]. Therefore, in order to better understand the risk that may be posed to terrestrial and aquatic organisms due to the presence of pharmaceuticals it is necessary to determine their BAF factors. It would only be possible if proper reliable and routine analytical tools were available for the determination of vast groups of pharmaceuticals in various environmental and biological matrices.

Therefore, the aim of this review was not only to present the current state of knowledge on the bioaccumulation and toxicity of pharmaceuticals. In addition, we also present a comprehensive overview of the current state of knowledge about the analytical methodologies used for the determination of pharmaceutical residues in biota samples. Today, the attention of the scientific community has mainly been concentrated on the presence of following pharmaceuticals in milieu compartments: antibiotics, analgesic and anti-inflammatory drugs, steroid hormones, antihypertensives and antidepressants [11]. Therefore, this review will focus on the drugs belonging to the therapeutic classes listed above.

2. Antibiotics

2.1. Analytics of antibiotics in the environment

The term antibiotic is used to denote any drug, natural or synthetic, that has a selective toxic action on bacteria or other single-celled microorganisms [12]. The consumption of antibiotic substances worldwide is estimated in hundreds of thousands of tons annually. No specific value can be given on a global scale, since there is a lack of information in many countries and there are differences in the data collection systems. In human medicine, antibiotics are the third most frequently prescribed group of pharmaceuticals (~6%), in veterinary medicine, more than 70% of all consumed pharmaceuticals are antibiotic agents [13–18].

Antibiotics constitute a very large group of substances of different properties. Therefore many methods for the extraction and analysis of these compounds have been developed over the years. Table 1 contains a collection of summaries of these methods for different groups of antibiotics in different matrices [19–56]. In cases involving just the extraction of one or two groups (usually sulfonamides and fluoroquinolones) the extraction method is simple solvent extraction (SE) or solid phase extraction (SPE). However, when more numerous groups of substances are to be analyzed the procedure requires the use of stronger extraction methods like: ultrasonic assisted extraction (USE), pressurized liquid extraction (PLE), accelerated solvent extraction (ASE) or microwave assisted extraction (MAE). The usual solvents are methanol, acetonitrile or a phosphorous buffer (pH ~ 7). In most cases a clean-up step is applied using SPE. Antibiotics are most efficiently analyzed using high pressure liquid chromatography (HPLC). Here again, depending on the analyte group, either fluorescence detection (FLD), UV/vis or mass spectrometry (MS) is used, including tandem MS/MS variations. Alternative techniques have also been proposed: a study described the simultaneous analysis of sulfonamdies, penicillins and fluoroquinolones using capillary electrophoresis-mass spectrometry (CE-MS) [31]. Also in more recent publications ultra performance liquid chromatography coupled with mass spectrometry (UPLC–MS) was used in order to analyze diverse groups of antibiotic compounds.

2.2. Environmental presence, bioaccumulation and ecotoxicity of antibiotics

Antibiotics are a widely used group of pharmaceuticals, therefore they can be introduced into the environment via several pathways including human sources like: exertion, the flushing of old prescriptions, hospital waste, and wastewater treatment plant (WWTP) effluent. However, the largest environmental sources of antibiotics are agricultural ones, since they are used worldwide in the form of feed additives, not only for prophylactic and therapeutic purposes, but also to promote growth and increase feed efficiency. It must be noted that pharmaceuticals are metabolized in organisms to a different extent; in this case, most antibiotics are metabolized in the range of 30% up to 90%, the remaining unchanged parent compounds, and often biologically active metabolites, are discharged directly to soil via the usage of manure as fertilizer, or by pasture-reared animals excreting faeces and urine directly on the land. On the other hand, surface runoff and direct usage in aquaculture can lead to the contamination of aquatic environments [13,57,58].

Once in the environment, the fate and effects of these substances depends on several factors, such as their physical-chemical properties, climatic conditions, pH, soil type and a variety of other factors [13]. The varying chemical properties will influence the behavior of the chemical through wastewater treatment as well as its mobility, persistence and bioavailability in the matrix. For example, it is well known that most antibiotics can be effectively sorbed onto sludge particles [18,59]. Based on the available literature data, the present study highlights the most commonly used priority groups of antibiotics, residues of which are found in the natural environment: tetracyclines (TCs), penicillins (PEs), sulphonamides (SAs), macrolides (MAs), aminoglycosides (AMs), and fluoroquinolones (FQs). The basic structures of the mentioned groups, and the typical ranges of chosen physical-chemical properties are presented in Fig. 1. Fluoroquinolones (FQs) are antimicrobial agents effective in treating a broad-spectrum of bacteria. They are used both in human and veterinary medicine. FQs have very low Henry's Law constants, resulting in negligible volatilization [60]. The $\log K_{ow}$ values in the case of FQs vary up to 5.5 units with a median value of 2.5. However, it has been observed that they do have a high affinity for soil compartments such as sludge, sediments and soils [61]. Furthermore, FQs are moderately soluble in water and represent amphoteric compounds, which means they have different speciations depending on the pH of the solution. FQs are relatively stable in the environment, being insensitive to hydrolysis. They are primarily degraded via photolysis; however, this is quite a slow process, especially when considering FQ sorbed to aquatic sediments. Tetracyclines (TCs) are also broad-spectrum antibacterials, active against a range of organisms, such as *Mycoplasma* and *Chlamydia*, as well as a number of gram-positive and gram-negative bacteria. Both their parent compounds and degradation products are biologically active compounds, especially toxic to sludge bacteria. The molecule of tetracycline has several ionizable functional groups, and the charge of the molecule depends on the solution pH. TCs are relatively stable in acidic media, but not in alkaline conditions, and form salts in both media. In general, these compounds are moderately soluble in water; however, the solubility of the corresponding hydrochlorides is reported to be much greater. Furthermore, they are not volatile substances and they photodecompose easily [13,62,63]. Sulfonamides (SAs) are