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Review article

# Chiral pharmaceuticals: Environment sources, potential human health impacts, remediation technologies and future perspective

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ABSTRACT

Chiral pharmaceuticals (CPs), including non-steroid anti-inflammatory drugs (NSAIDs), β-blockers and some herbicide and pesticides, are widely used in aquaculture, clinical treatment and many other fields. However, people are increasingly concerned about such ubiquitous pollutants, which can frequently be detected in contaminated soil and water. In large part, the significant sources of chiral pharmaceuticals stem from industrial processes, such as the direct discharge of untreated or incompletely treated wastewaters containing chiral pharmaceuticals, incorrect storage and use, animal wastes and biosolids. The main ways for human exposure to chiral pharmaceuticals are the disease treatment process and chiral pharmaceuticals contaminants. According to the results of a series of toxic studies, some diseases, even cancers, may be associated with exposure to certain chiral pharmaceuticals. Therefore, the treatment of chiral pharmaceuticals has become an important issue. The current advanced remediation techniques for chiral pharmaceuticals include the conventional method (sorption and sonolysis), biotransformation (an aerobic granular sludge-sequencing batch reactor and constructed wetland system) and advanced oxidation processes (ozonation and photocatalysis). Herein, in this review, we summarize the current status and sources of chiral pharmaceuticals, potential effects on human health, as well as the superiority, disadvantages and prospects of current advanced remediation technologies. Moreover, we also anticipate the prospect of the future research needed for chiral pharmaceuticals pollutant remediation.

## 1. Introduction

Chirality is also called stereoisomerism or enantiomerism or dissymmetry. It is a property of the substance that its mirror image cannot be superimposed on itself. It is just like your right and left hands (Nguyen et al., 2006). Because most of the pharmaceuticals contain a chiral carbon atom (four different substituent atoms covalently bond to a tetrahedral carbon), leading to the existence of enantiomers (Evans, 1992). Chiral compounds typically have two or more enantiomers, and the corresponding physical-chemical properties are manifested in the same compound enantiomers (Liu et al., 2008; Liu et al., 2005). A molecule that has at least one asymmetric carbon can be called as a chiral molecule. However, an asymmetric center atom is not only carbon but sulfur, phosphorus and so on. Even though there are present identical chemical structures in enantiomers, most enantiomers of racemic drugs show significant differences in other aspects (Nguyen et al., 2006). The enantiomers of chiral pharmaceuticals usually present stereoselectivity in many aspects, such as fate, toxicity and environmental occurrence (Amorim et al., 2016; Monteiro and Boxall, 2010). For racemic drugs, their pharmacological effects may be different. It can be similar, opposite, null or different (Nguyen et al., 2006).

Pharmaceuticals have now become the widely used compounds, which are usually employed for diseases treatment, animal husbandry and the controlling of pests in agriculture (Wang et al., 2010). Most analgesics, including aspirin, show a significant effect on relieving pain. Codeine and the more potent morphine, including the opioid analgesics are known as narcotic analgesics (Monteiro and Boxall, 2010). Among the chiral pharmaceuticals, NSAIDs, as a kind of painkiller, are

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commonly used in daily life and play a significant role in pain relief, anti-rheumatic and anti-inflammatory (Frost et al., 2014). Structures of some vital chiral pharmaceuticals are shown in Fig. S1.

Chirality research has become an essential part of academic research and drug development. Molecular chiral catalyst masters won the Nobel Prize in Chemistry in 2001 for their tremendous contribution to enantioselective separation (Long and Yarnell, 2001). On account of a variety of new technologies have been applied for separating enantioselective, US Food and Drug Administration (FDA) recommended to assess enantiomer activity in each of racemic drugs in the body and accelerate the development of chiral pharmaceuticals as single enantiomers (Liu and Liu, 2002; Nguyen et al., 2006).

A single enantiomer as the target product is produced under the action of catalyst (Shi et al., 2016; Tsubogo et al., 2015) or enzyme (Hühnerfuss et al., 2006; Kumar et al., 2017) in industrial production. It has been shown that some drugs can undergo enantioselective transformation (Sanganyado et al., 2017). The enantioselective transformation means a metabolic process which requires enzyme activity to convert one enantiomeric form into the other. Taking ibuprofen as an example, it can perform unidirectional enantioselective inversion. Its *R*-enantiomer will become the *S*-enantiomer, but the *S*-enantiomer will not be reversed to the *R*-enantiomer (Hao et al., 2005; Sanganyado et al., 2017). However, in different organisms, the degree of chirality and the direction of chirality may differ (Khan, 2014). But achieving high enantiomeric excess (ee $>$ 90%) is still challenging. Therefore, it is necessary to consider chromatography to separate enantiomers, and the content of chromatographic separation will be discussed in a later section.

In recent decades, due to the improper handling of chiral medicines in production, consumption and emission, the pollutant has been widely distributed in the environment. Chiral pharmaceuticals such as ibuprofen, venlafaxine, and propanol have become the chiral signatures that distinguish abiotic and biological processes in surface water and infer biological attenuation (Kasprzyk-Hordern and Baker, 2012; Li et al., 2013; Sanganyado et al., 2017). Due to human activities, chiral pharmaceuticals are brought into the environment. A range of biotic and abiotic processes are required before they reach the environmental matrices (Fig. 1) (Kasprzyk-Hordern, 2010). The biological effects of enantiomers may differ from the enantioselective interaction of biological systems, even though they have semblable thermodynamic properties (Amorim et al., 2016; De Andrés et al., 2009; Sun et al., 2014). According to the calculated risk quotients, ibuprofen was found to be in the medium to possess high risks in the larger rivers in northern China (Wang et al., 2010).

In response to the problem of drugs directly accessing to the environment, treatment in sewage disposal plant has become a fundamental method. However, these chemical compounds may get to aquatic ecosystems through discharging sewage which is not entirely disposed of in wastewater treatment plants (WWTPs), directly discharging untreated raw wastewaters and promptly excreting in farming, agriculture, and aquaculture (Wang et al., 2010). Apart from immediate release from WWTPs, drugs can also get into the environment when fertilizer was composed by digested sewage sludge in agricultural land or from other places resulting in groundwater pollution (Matamoros et al., 2008).

Some antibiotics and psychotropic substances can cause more significant harm to human health through the enrichment of the food chain (Ding et al., 2015). For example, Liu et al. found that the concentration of sulfamethoxazole and trimethoprim is positively correlated with trophic levels, and the trophic magnification factors (TMF) are 2.19 and 2.40, respectively (Liu et al., 2017). According to the hazard quotients (HQ) suggested by Vragović et al. (2011), the HQ value of enrofloxacin (HQ = 0.07) in seafood (2014 and 2015) in the Laizhou Bay exceeds the standard of obvious risk (HQ $>$ 0.05). The HQ values of ciprofloxacin (HQ = 0.01) and clarithromycin (HQ = 0.01) in urban residents and enrofloxacin (HQ = 0.04) in rural residents are higher than the considerable risk (HQ $\geq$ 0.01) (Liu et al., 2017). In a previous report, the number of mothers who had breast-feeding fell from 69% to 35% during the first week to the first month after giving birth and medication is the second reason to stop breastfeeding after lack of support (Rigourd et al., 2014). The enrichment of one enantiomer over the other can be attributed to selective adsorption and microbial transformation (Sanganyado et al., 2017). Table 1 shows the monitoring data accumulated in aquatic organisms (Gao et al., 2012; Li et al., 2012a; Li et al., 2012b; Liu et al., 2017).

Nowadays, the development and application of the scientific and practical methods for the treatment of these pollutants have become a matter of concern to the whole world. Specific repair techniques include treatment in a sewage treatment plant, sorption, constructed wetland system, ozonation, sonolysis, and photocatalysis. And their advantages, weaknesses, feasibility, and prospects will appear in later sections. Here, the purpose of this review is to compile and analyze the characteristics, sources, and potential health effects of some of the more critical chiral pharmaceuticals, and to summarize some of the tools for restoration and the prospects for future research on chiral pharmaceuticals. This paper mainly includes three sections: a) properties, sources and health impacts on human; b) remediation technologies; c) future research prospects.

## 2. Properties, sources and health impacts on human

Pharmaceuticals are organic compounds that generally possess highly polar and resistant characteristics (Amorim et al., 2016; Ribeiro et al., 2012b). Depending on the result from a previous survey, from January to August 2003, the distribution of pharmaceuticals was approved by FDA. The results indicated that the single enantiomers were the most substantial part, at 64%, the achirals accounted for 22%, and the rest were racemates, which accounted for 14% (Caner et al., 2004; Ribeiro et al., 2012b). China is known as the largest producer and consumer of medicines, using about 162,000 tons of antibiotics in 2013 (Zhang et al., 2015; Zhu et al., 2013). The high demand for drugs may also have adverse impacts on non-target organisms, even the concentrations of them are residual (Kasprzyk-Hordern, 2010; Petrie et al., 2015; Ribeiro et al., 2012a).

In November 2006 and April 2007, urban surface waters samples taken from drinking water circuit and their sources in Karachi and Pakistan were contaminated with harsh industrial chemicals and pharmaceutical and personal care products (Scheurell et al., 2014). This indicated that the drinking water circuit in Karachi entered an alarm condition and led to the main pollutants being not the typical parent compound, but some conversion products still found in drinking water (Scheurell et al., 2009; Scheurell et al., 2013).

Chiral pharmaceuticals are a class of compounds that play an essential role in the pharmaceutical field and are often used extensively. There is a high worldwide distribution of chiral pharmaceuticals as veterinary and human pharmaceuticals, so it can be expected that they can publicly occur in the environment (Kasprzyk-Hordern, 2010). There are many ways for the sources of chiral pharmaceuticals contamination, such as emissions from manufacturing, the improper storage and discharged from medical units in wastewater and so on (Huang et al., 2014; Monteiro and Boxall, 2010). The way for a human to touch chiral pharmaceuticals is via drinking water or food, surgical treatment, and breathing. Among them, wastewater is the all-important environmental exposure pathway for drugs (Luo et al., 2014; Sim et al., 2011; Wang et al., 2018). The critical related factors to environment contamination mainly depend on geographical distributions of source types, climatic conditions and source strengths and so on (Huang et al., 2014). Therefore, drugs in the aquatic environment have attracted much attention from the scientific community and the general public, because of their potential impact on human health and ecological environment (Wang et al., 2010).