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Review article

Diclofenac and its transformation products: Environmental occurrence and toxicity - A review

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ABSTRACT

Diclofenac (DCF) is a prevalent anti-inflammatory drug used throughout the world. Intensive researches carried out in the past few decades have confirmed the global ubiquity of DCF in various environmental compartments. Its frequent occurrence in freshwater environments and its potential toxicity towards several organisms such as fish and mussels makes DCF an emerging environmental contaminant. At typical detected environmental concentrations, the drug does not exhibit toxic effects towards living organisms, albeit chronic exposure may lead to severe effects. For DCF, about 30–70% removal has been obtained through the conventional treatment system in wastewater treatment plant being the major primary sink. Thus, the untreated DCF will pass to surface water. DCF can interact with other inorganic contaminants in the environment particularly in wastewater treatment plant, such as metals, organic contaminants and even with DCF metabolites. This process may lead to the creation of another possible emerging contaminant. In the present context, environmental fate of DCF in different compartments such as soil and water has been addressed with an overview of current treatment methods. In addition, the toxicity concerns regarding DCF in aquatic as well as terrestrial environment along with an introduction to the metabolites of DCF through consumption as well as abiotic degradation routes are also discussed. Further studies are required to better assess the fate and toxicological effects of DCF and its metabolites and must consider the possible interaction of DCF with other contaminants to develop an effective treatment method for DCF and its traces.

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1. Introduction

Pharmaceutical industry has emerged as one of the largest and prominent industry worldwide. Large amount of pharmaceuticals of different categories are being used to cure and care human and animal health. In general, pharmaceuticals comprise compounds which include materials extensively used in medicine, agriculture and biotechnology, such as drugs, antibiotics and hormones. The worldwide average per capita consumption of pharmaceuticals per year is estimated to be about 15 g. In industrialized countries, the usage is even as high as 50 to 150 g (Alder et al., 2006). Pharmaceutically active compounds (PhACs) are one of the conspicuous classes of pharmaceuticals which by one route or another, enter the environment as the parent compound or as pharmacologically active metabolites (Halling-Sørensen et al., 1998). It is estimated that worldwide consumption of active compounds amounts to 100,000 tons or more per annum (Kummerer, 2004). Usually, drugs are developed with an intention of having a beneficial biological effect on the organism to which they are administered, though many such compounds will often pass into the environment where they may exert an unwanted biological effect (Halling-Sørensen et al., 1998). The global occurrences of pharmaceuticals and PhACs in aquatic environment have been arising as a problem with unknown consequences. PhACs have been reported to be present in different environmental compartments and often the short-term as well as long-term effects are obscure (Kunkel and Radke, 2012; Langford et al., 2011) Hence, it has been relatively recently that PhACs have become a subject of interest to environmentalists worldwide (Hao et al., 2007).

Among PhACs, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used throughout the world and detected in different environmental compartments at concentrations ranging from ng L^{-1} to low mg L^{-1} (Halling-Sørensen et al., 1998; Khetan and Collins, 2007). Moreover, NSAIDs are over-the-counter (OTC) drugs in most of the countries and this in turn increases the chances for consumption and hence, their presence in the environment. DCF is often recognized as the 'world's most popular pain killer' and is also the most commonly used NSAID, with a market share close to that of the next three most popular drugs combined (ibuprofen, mefenamic acid, naproxen) (McGettigan and Henry, 2013). The name diclofenac is derived from its chemical name: 2-(2,6-dichloranilino)phenylacetic acid. Diclofenac was discovered by Ciba-Geigy, a Swiss pharmaceutical company in 1973 (now merged to Novartis). Diclofenac is commonly used to reduce inflammation and to relieve pain in diseased conditions, such as arthritis or acute injury. It also works as antiuricosurics and analgesic. DCF can be applied to skin or it can be administered orally. DCF is supplied as or contained in medications under a variety of trade names. In Canada, DCF is sold as Voltaren Emulgel and some other common names are Votalin (China), Diclofenaco Normon (Spain), Volini (India), Diclofenac-Asteria (USA and Korea), Diclo-Denk (Germany) Voltaren (Argentina, Australia, Belgium, Egypt, France, Germany, Israel, New Zealand, Norway, Portugal, Russia, South Africa, Sweden, Turkey) (sources - www.drugs.com/diclofenac, www.drugbank.ca, www.scbt.com).

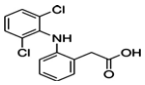
Pharmacological and physico-chemical properties of DCF are listed in Table 1. Often DCF is not completely removed from wastewater treatment plants (WWTP) due to its poor degradation and higher consumption rates (Fatta-Kassinos et al., 2011; Zorita et al., 2009). Hence, DCF is frequently detected in rivers, sediments and sludges (Kunkel and Radke, 2012; Langford et al., 2011). Relatively recently, DCF has drawn much more attention due to its frequent occurrence in drinking water sources (Gros et al., 2010) and its potential harmful effects on many organisms at significant concentration (Cleuvers, 2004; Oaks et al., 2004).

Diclofenac is normally used as salt of sodium or potassium for improved solubility and absorption. Until date, no literature is exclusively available on the environmental perspectives and concerns regarding the drug, DCF. Most of the previously published reviews have discussed the fate of diclofenac in WWTPs (Vieno and Sillanpää, 2014; Zhang et al., 2008). The objective of this review is to briefly summarize the current status of diclofenac in the environment, review the available information about its consumption, occurrence, toxicity, resistance, persistence and metabolites. In addition this review addresses the hypothetical possibility of potential interactions of DCF with other organic and inorganic contaminants, emerging contaminants along with its own metabolites. Major research gap in the current knowledge and future research need in diclofenac fate and transport in environment have also been highlighted.

2. Global consumption

It is fairly impossible to calculate the exact global consumption of diclofenac because of various reasons, such as use of different trade names for DCF, use for human and veterinary purposes and that the drug is an over the counter drug. Nevertheless, Zhang et al. (2008) estimated that about 940 tons of diclofenac is consumed globally on an annual basis from Intercontinental Marketing Services (IMS) health data (Zhang et al., 2008). About 877 tons of diclofenac were sold in 2007 in 76 major countries which are believed to account for about 96% of the global diclofenac pharmaceutical market (Zhang et al., 2008). In a 2012 report from "Fierce Pharma", diclofenac was listed as the 12th bestselling generic molecule globally. The total sales of diclofenac in

Table 1
Physico-chemical and pharmacological properties of diclofenac (in unionized form).

Properties		Reference
Structure		www.pubchem.ncbi.nlm.nih.gov, www.chemspider.com
Molecular formula and molecular weight	$C_{14}H_{11}Cl_2NO_2$, 296.16 g mol^{-1}	www.drugbank.ca, www.pubchem.ncbi.nlm.nih.gov
CAS no.	15307-86-5 15307-79-6 (disodium salt)	www.drugbank.ca, www.pubchem.ncbi.nlm.nih.gov
Water solubility	2.37 mg L^{-1} (25 °C)	www.drugbank.ca, www.chemspider.com
Henry's law constant	4.79×10^{-7} Pa m^3 mol^{-1} (25 °C)	www.scbt.com, www.pubchem.ncbi.nlm.nih.gov
Melting and boiling points	283–285 °C and 412 °C at 760 mm Hg (predicted) respectively	www.drugbank.ca, www.chemspider.com
p*K*a	4.15	www.drugbank.ca, www.chemspider.com
Log K_{ow} (logarithm of octanol-water partition coefficient)	4.51	www.scbt.com, www.pubchem.ncbi.nlm.nih.gov