Chemosphere 181 (2017) 178–189

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Review

# Eco-pharmacovigilance of non-steroidal anti-inflammatory drugs: Necessity and opportunities

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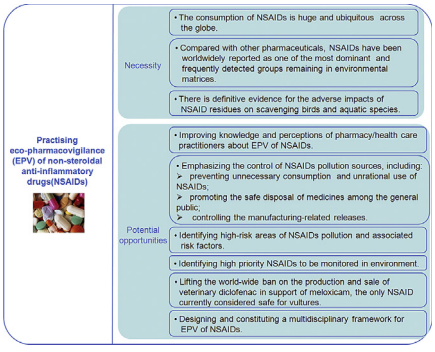
## HIGHLIGHTS

- EPV should target individual pharmaceuticals on a prioritised basis.
- The huge consumption, serious environmental pollution and high potential risks suggest the necessity of EPV of NSAIDs.
- Some advice and management practice options for EPV of NSAIDs were proposed.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

*Article history:*
Received 9 February 2017
Received in revised form
5 April 2017
Accepted 18 April 2017
Available online 21 April 2017

Handling Editor: Klaus Kümmerer

*Keywords:*
Eco-pharmacovigilance
Non-steroidal anti-inflammatory drugs
Pharmaceutical residues
Environment

## ABSTRACT

Eco-pharmacovigilance (EPV) is a practical and powerful approach to minimize the potential risks posed by pharmaceutical residues in environment. However, it is impracticable to practise rigorous and unitary EPV process for all the existing and new pharmaceuticals. Here, we focused on non-steroidal anti-inflammatory drugs (NSAIDs), and discussed the necessity and potential opportunities of practising EPV of NSAIDs. We found that the consumption of NSAIDs is huge and ubiquitous across the globe. NSAIDs were worldwidely reported as one of the most dominant and frequently detected groups in environmental matrices including wastewater, surface water, suspended solids, sediments, groundwater, even drinking water. Besides, there is definitive evidence for the adverse impacts of NSAID residues on scavenging birds and aquatic species. These data suggested the necessity of implementing EPV of NSAIDs. From the perspective of drug administration, we identified some things that can be done as management practice options for EPV implementation on NSAIDs:

- Improving knowledge and perceptions of pharmacy/health care practitioners about EPV of NSAIDs.
- Emphasizing the control of NSAIDs pollution sources, including preventing unnecessary consumption and unrational use of NSAIDs; promoting the safe disposal of medicines among the general public; controlling the manufacturing-related releases.
- Identifying high-risk areas of NSAIDs pollution and associated risk factors.
- Identifying high priority NSAIDs to be monitored in environment.

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http://dx.doi.org/10.1016/j.chemosphere.2017.04.084

- Lifting the world-wide ban on the production and sale of veterinary diclofenac in support of meloxicam, the only NSAID currently considered safe for vultures.
- Designing and constituting a multidisciplinary framework for EPV of NSAIDs.



**Contents**



## 1. Introduction

Owing to the rising production and consumption of medicines around the world, more and more pharmaceuticals are released into the sewer system via excretion after human and veterinary therapeutic use, manufacturing discharges, direct disposal of unwanted or expired drugs, etc., finally enter into the a variety of environmental matrices including surface water, groundwater, sediments, soil, even drinking water (Daughton, 2016; Holm et al., 2013). The pharmaceutical residues in the environment could contaminate food chain, and tend to accumulate within organisms. As a kind of biologically active compounds designed to be effective at low concentrations, pharmaceuticals in the natural environment could have possible adverse impacts to a variety of non-targeted organisms due to long-term exposures, including chronic toxicity, antibiotic resistance, endocrine disruption, toxic effects on reproduction of terrestrial and aquatic organisms, even become a growing public health concern (Nödler et al., 2014; Gao et al., 2012). To minimize the potential risks posed by pharmaceutical residues in environmental matrices, eco-pharmacovigilance (EPV) describing "the science and activities associated with the detection, evaluation, understanding and prevention of adverse effects of pharmaceuticals in the environment" has been proposed as a kind of pharmacovigilance for the environment (Holm et al., 2013). Based on the contamination sources of pharmaceuticals in the environment, some specific approaches to EPV have been encouraged, which mainly belong to green and sustainable pharmacy practice including environmental friendly drug design and process development, minimization of emissions in manufacturing, rational use of drugs, the take-back and management of unused drugs (Holm et al., 2013). Besides, some researchers who major in environics suggested that EPV should be maintained by a dynamic update mechanism to allow the environmental risk assessments to be regularly revised in the light of real-time data on the consumed amount, environmental levels, monitoring of pharmaceutical sources, etc. (Taylor and Senac, 2014; Silva et al., 2012). However, compared with pharmacovigilance, EPV is an emerging and more comprehensive science that is not regulated and has not formalized implementation model up to now (Holm et al., 2013).

Especially, in view of the diversity of pharmaceuticals in chemical, structural, biological or toxicological properties, it is impracticable to practise rigorous and unitary EPV process for all the existing and new pharmaceuticals. There is no justification for considering all the pharmaceuticals as a class of contaminants posing a problem (Taylor and Senac, 2014). And the constantly expanding number of new pharmaceuticals will result in a constantly expanding number of environmental contaminants. "Extensive and expanding spectrum of contaminants" has been considered as one of issues constraining policy and management for pharmaceutical residues (Naidu et al., 2016). Some scholars also have suggested that, to avoid waste of resources, the EPV should be implemented by targeting individual pharmaceuticals in the environment on a prioritised basis, instead of continuing to treat all the pharmaceuticals as a whole group of substances (Taylor and Senac, 2014). EPV focusing on a small subset of pharmaceuticals could offer a feasible and effective way to deal with the corresponding environmental risks on a case by case basis, further build or improve policy and/or regulations for the management of the environmental issues related to pharmaceuticals with more clear goals.

Obviously, there is a need for prioritised EPV for the pharmaceutical products with higher volume of use, more serious residue problems in environment and higher potential environmental risks. Therefore, in this paper, we focused on non-steroidal anti-inflammatory drugs (NSAIDs) in order to provide the background, area and activities to implement EPV. And several management practice options that can be taken for EPV implementation on NSAIDs were identified from the perspective of drug