

From excretion to ecology: The strategic imperative of eco-pharmacovigilance



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Abstract

As the widespread presence of active pharmaceutical compounds in the environment poses a growing threat to ecosystems worldwide, understanding & mitigating medicinal pollution has become crucial. Drugs in active form pose a serious threat to the environment as they enter the ecosystem through different channels. Some high-profile examples are the toxicity of Diclofenac that results in death of vultures from feeding on dead livestock due to consumption of Diclofenac, Ethinyl estradiol that causes feminization of males in fish species, progesterone that leads to amphibian infertility, Ivermectin that affects dung beetles' development process, and fluoxetine that affects shrimp behavior in addition to promoting microorganisms' resistance. In order to minimize this threat, the adoption of some measures such as reduction in pharmaceutical waste production, updating of wastewater management systems, green pharmacy initiatives, and proper pharmaceuticals disposal is imperative. Moreover, some regulations, including ERA, RCRA, and risk mitigation measures, are important.

Keywords: Eco-Pharmacovigilance, Medicinal Pollution, Eco-toxicology, green drug, Risk Assessment.

1. Introduction

Environment is not only polluted by smog, heavy metals or gaseous emissions but it is also harmed by the pharmaceutical drugs. Active ingredients of drugs are getting into the environment through various processes and causing significant harm to wildlife. (1)

The harmful effects of pharmaceutical ingredients in the environment were highlighted by the mysterious mass poisoning of vultures that occurred in South Asia several years ago. This incident, in which the use of Diclofenac by veterinarians led to the suppression of kidney function in the vultures, drew attention to the problem of the impact of drugs on the environment. As a result, eco-pharmacovigilance was created, a discipline that studies the

effects of drugs on the environment and develops measures to prevent them (for example, the hormone Ethinyl Estradiol, which turns male fish into females) (2).

Eco-pharmacovigilance includes four areas of study:

1. Pharmaceutical residues in the environment and their impact on it.
2. Approaches to reduce the number of pharmaceuticals released in the environment.
3. The development of green pharmacy.
4. Ecological and environmental aspects of drug use and regulation.

2. Pathways of pharmaceutical release into the environment

2.1 Patient Excretion (Human & Veterinary)

After therapeutic administration, drugs are excreted from the body as inactive molecules, broken-down metabolites, or a combination of both. Drugs that are administered via oral route but poorly absorbed are directly excreted with feces. Drugs that are either partially or totally absorbed are excreted as metabolites with urine, feces, or air. After their release with bodily fluids, pharmaceuticals enter the food chain, accumulating in higher-trophic-level organisms. Excretion of drug residues with the patient's fluid is the major source of pharmaceuticals in the environment since it occurs at both human and veterinary levels (4).

2.2 Wash-off and Sweat

Pharmaceuticals in topical formulations (creams, gels, patches) are washed off with water during bathing and enter the water system. Also, a small amount of therapeutics is released to the environment by the means of sweat.

2.3 Unused/Left-over Medicines

Leftover medicines include the medication no longer being used for the prescribed condition, constitute another cause of environmental pollution. The dispensing of larger quantities (e.g., 90-day supplies) and inappropriate management of the left-over medicines are some of the factors that contribute to this problem.

2.4 Industrial and Institutional Effluents

Large amounts of pharmaceuticals are released to the environment through industrial and institutional wastes. This pathway is serious as it provides a direct and concentrated source of chemicals to the local environment (5).

2.5 Animal Carcasses

The dead animals that have been treated with pharmaceuticals pose a significant hazard to the environment and also to the animal scavengers as their bodies carry high level of therapeutic drugs (6).

3. Biological diversity impact of pharmaceuticals

Pharmaceutical products play a crucial role in the treatment of both human beings and animals. But due to high biological activity of APIs released into the environment always lead to unpredicted toxic effects on flora and fauna. Though standard clinical tests provide all the necessary information about potential side effects and drug safety on target organisms, the effects of drugs on the environment after consumption are not well studied yet. Following are some examples of the toxic effects of pharmaceuticals on different animal species (8).

Table 1. Impact of Pharmaceuticals Across Species (8).

S.No.	Affected species	Pharmaceutical contaminant	Primary and biological impact & mechanism	Specific consequences observed
1.	Vultures (Gyps species)	Diclofenac	Causing acute renal failure & visceral gout when consumed from treated animal's carcass	Leads to the population's decline of >97-99.9% in South Asia, creating an ecological catastrophe.
2.	Amphibians (Frogs/Tadpoles)	Levonorgestrel	Damaging reproductive tract development causing females to have short oviducts and arrested follicles	Sterility in female frogs when exposed to this pharmaceutical at trace levels similar to environment concentrations.
3	Aquatic life (Fish)	Fluoxetine (SSRI antidepressant)	Accumulates in the brain, and exposure is linked to altered behavioral responses to environmental cues.	Interfere with the growth and reproduction in fishes
4	Microorganisms	Various antibiotics (Ampicillin, Oxytetracycline, Vancomycin)	By promoting antibiotic resistance in environmental bacteria, it creates conditions for generating drug-resistant microbes. For example, Acinetobacter – a multi-resistant bacterium now	This resistance can in turn be passed on to bacteria that cause diseases in humans and animals, making it more difficult to control bacterial infections.

			present in water bodies.	
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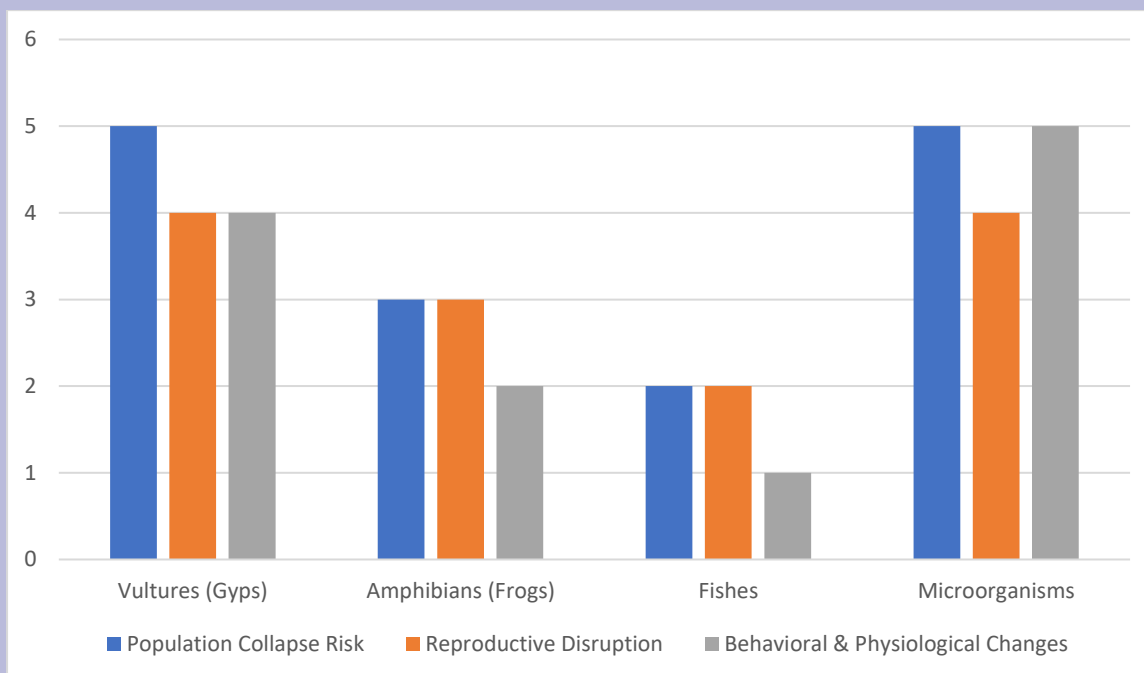


Figure 1. Ecotoxicity of Active Pharmaceuticals Across Species

4. Eco-pharmacovigilance

Eco-pharmacovigilance (EPV) is the science and practice of detecting, assessing, understanding and preventing the harmful effects of pharmaceuticals and chemical residues on ecosystems, animals and human health. Whereas pharmacovigilance deals mainly with the drug's impact on patients and human health, eco-pharmacovigilance goes further in terms of responsibility by also considering the effects of drugs and their ingredients on the environment after use. In other words, Eco-pharmacovigilance (EPV) refers to the entire post-consumer use of an active pharmaceutical ingredient that may endanger ecosystems and domestic animals as well as humans (9).

4.1 Objectives of Eco-pharmacovigilance

4.1.1 Ecosystem ecotoxicity profiling

This objective primarily focuses on the scientific and statistical analysis of the impact that the drug's ingredients have on the environment both before and after being launched. It requires:

- Calculation of concentration of drugs in the environment to establish exposure – predicted environmental concentration (PEC) which is done by comparing the PEC to the predicted no-effect concentration (PNEC) of water, soil, and biota.
- Identification of ecotoxicological hazards which aims to determine the most severe consequences on plants, fish, and other organisms when they are exposed to pharmaceuticals through the examination of acute and chronic toxicity of the ingredient, its bioaccumulation as

well as persistence in water, hormonal activity in fish and other species and ability to disrupt the water's endocrine functions in animals.

c) Regulatory gatekeeping falls under the competence of the European Medicines Agency (EMA), as well as the FDA and other drug regulatory agencies worldwide. The main task is to review and assess submissions on the potential risks posed by the drug to the environment. It ensures that the potential negative changes to the environment are taken into account during the approval process (10).

4.1.2 Targeted ecological hazard control

This objective involves various post-market control measures needed to prevent drug pollution. The measures include:

a) Eco-friendly design and prescribing initiatives which mainly move towards the promotion of chemical design, manufacturing, and prescribing policies that would reduce the quantity and toxicity of pharmaceutical waste. They include “Benign-by-design” philosophies, Eco-prescribing initiatives, pharmaceutical waste minimization strategies such as dose optimization, packaging optimization initiatives, take-back programs that facilitate the return and proper disposal of pharmaceutical waste.

b) Industrial, institutional, and municipal waste control which is primarily achieved through the implementation of more stringent effluent regulations for pharmaceutical manufacturers, hospitals, and other industrial institutions that play a role in introducing pharmaceutical compounds into the environment. Some of the measures include imposing strict control and regulations on the industries, developing more efficient waste treatment systems such as ozonation and activated carbon monitoring and controlling pharmaceutical pollution at the community level.

c) Implementation of policies and surveillance measures which focuses on periodic assessments of environmental hotspots and establishing monitoring plans that will ensure the continuous evaluation of the impact pharmaceuticals have on the environment. It also requires the introduction of regulations, restrictions, or warnings to cut down on environmental drug pollution when the surveillance results indicate that it is necessary (10).

5. Twin pillars of green drug design

5.1 Complete Absorption and Internal Metabolism

The first strategy focuses on designing the pharmaceutical products that can be completely metabolized in the body. Such drugs are integrated into the targeted nanoparticles to ensure that the drug is delivered directly to the target tissues and cells. This will help to reduce the initial dose as the nanoparticle system will actively participate in the delivery process. Ideally, 100 percent of the administered dose must be absorbed and metabolized inside the patient's body, resulting in harmless byproducts such as water and carbon dioxide. Not a single molecule of the drug remains unmetabolized and has to be excreted through the patient's urine, feces, or sweat, thus contaminating the environment.

5.2 Environmental Biodegradation (“Benign by Design”)

The second strategy is also based on the latest achievements in medicinal chemistry, that allows to modify the molecular structure of the drug in such a way that it can withstand the destructive action of patient’s body. However, once the drug is excreted with the urine, it is introduced to the environmental conditions and can be degraded by bacteria, sun light, or water. To do so, the researchers replace the strongest and most stable chemical bonds with weaker ones so that the drug will not last for long after being excreted. In this way, the pharmaceutical substance remains stable inside the patient’s body for a necessary timeframe, but once it enters the sewage system, it will degrade quickly and will not harm the environment (11,12).

6. Guardians of green healthcare: The strategic role of pharmacy in Eco-pharmacovigilance

Due to the leading role of pharmacists in health care delivery and social services, pharmacists play an important role in addressing pharmaceutical pollution from major five areas, including:

6.1 Educating the community: The first area is educating the community about the toxic hazards of pharmaceutical wastes on environment and motivating them to bring their expired and unwanted medicines to the pharmacies for proper disposal.

6.2 Take-back programs: Introducing take-back programs to help collect pharmaceutical wastes for safe and responsible disposal, thus preventing the expired or unused drugs from entering the environment through water resources and soil.

6.3 Eco-prescribing and waste reduction : Collaborating with other healthcare professionals, particularly doctors, to promote eco-friendly drug and appropriate prescription to reduce pharmaceutical pollutants, particularly antibiotics and ensure environmental sustainability.

6.4 Policies formulation and environmental management: The pharmacies may collaborate with other organizations to develop policies and regulations regarding industrial waste and water management and manage medical waste.

6.5 Advancement of sustainable healthcare initiatives: Advancing sustainable health care initiatives may involve the development of environmentally friendly pharmaceutical products and the reduction of plastic usage in the pharmacy (13,14).

7. Conclusion

For decades, the primary aim of drug development has been the maximization of therapeutic efficacy. Yet, the active principle of a pharmaceutical substance is increasingly found in water systems, in the food chain, and in wild animals. It turns out that the useful effects of a drug should not be exclusively aimed at patients – the health of the planet must also be maintained. Eco-pharmacovigilance helps to transform the pharmaceutical industry into a truly sustainable business by changing the definition of an ideal drug to one that is “good for patients as well as ecosystem”.

The concept of eco-pharmacovigilance allows for turning the pharmaceutical industry towards a more extensive and lasting commitment to environmental protection. Green drug design

principles help the pharmaceutical companies to change the nature of business by making medicines fit for purpose while being harmless to the environment: this is the goal of pharmacovigilance and pharmacy in everyday practice. The task of pharmacists and physicians is to ensure that drugs are used in terms of ecological safety: this includes dispensing medical advice, proper disposal of medicines, and raising awareness. The essence of green healthcare is to create the most favorable conditions for the patient, for whom the “medication is intended to be disposed of in a way that is safe for the environment, which will be rid of it.”

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