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## Ecopharmacovigilance: An environment safety issue

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### Abstract

Ecopharmacovigilance includes science and activities pertaining to detection, assessment, understanding and prevention of adverse effects or other problems related to the existence of pharmaceuticals in the environment. These pharmaceuticals come into the environment through a variety of routes causing harmful effects. Some important examples of drugs causing harmful effects on environment are that of vultures' death after consuming carcass of animals treated with Diclofenac sodium, Ethinyl estradiol adversely affecting fish through its "feminization" of males, Progesterone producing sterility in frogs, Ivermectin adversely affecting growth of dung beetle, Fluoxetine causing behavioral changes in shrimps and bacterial resistance. Some corrective measures can be projected to lessen the amount of drugs entering the environment which includes reducing the amount of pharmaceutical waste generated, increasing efficiency of sewage treatment plants, green pharmacy and developing better drug disposal programs. Various attempts have been made by regulatory authorities to reduce the impact of pharmaceuticals in environment and these include Environmental Risk Assessment (ERA) of drugs, Resource Conservation and Recovery Act (RCRA) and Risk Mitigation Measures. We need to monitor the effects of drugs not only as a good medical practice, but also to safeguard our environment.

**Keywords:** Ecopharmacovigilance, pharmaceuticals, environment

### 1. Introduction

Environment is polluted not only by heavy metals, pesticides and emissions from gasoline engines, but also with pharmaceutical chemicals. These pharmaceuticals enter the environment through various routes causing harmful effects. The exorbitant decline in number of vultures in Indian subcontinent shook the environmental scientists and activists. Prior to this observation, research on the impact of chemical pollution was restricted to persistent organic pollutants. At this verge, attention has been drawn to the environmental impact of drugs giving birth to the subject of ecopharmacovigilance. <sup>[1]</sup>

Ecopharmacovigilance can be defined as science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment <sup>[2]</sup>. Some prominent examples of drugs causing harmful effects on environment are that of vultures' death after consuming carcass of animals treated with Diclofenac sodium <sup>[3, 4, 5]</sup>, Ethinyl estradiol adversely affecting fish through its "feminization" of males <sup>[6]</sup>. Thus, the science of ecopharmacovigilance can be discussed under following heads:

- Pharmaceuticals in the environment
- Consequences of environmental pollution by pharmaceuticals
- Approaches to reduce amount of pharmaceuticals released in the environment
- Ecopharmacovigilance and Drug regulations

### 2. Pharmaceuticals in the Environment

Drug use in both the human and veterinary population is escalating day by day. According to one estimate 100,000 tons of antimicrobials are consumed every year <sup>[7]</sup>. More than 30 billion doses of non-steroidal anti-inflammatory drugs (NSAIDs) are consumed annually in the United States only <sup>[8]</sup>.

In recent years, pharmaceuticals from numerous therapeutic classes have increasingly been detected in the environment, typically at ng/L to low mg/L in surface waters.

Most of the households contacted in a survey of pharmaceutical disposal practices either threw the materials in the garbage or rinsed them down the toilet or sink. Over 7% of respondents did not dispose off their unused medications, creating a household stockpile that may lead to accidental or deliberate wrongful ingestions <sup>[9]</sup>.

The potential routes of environmental entry of pharmaceuticals have been extensively reviewed by Kummerer <sup>[10]</sup>. These include:

### 2.1 Excretion of pharmaceutical ingredients from patients

Pharmaceutical ingredients are excreted either as parent compound or metabolites from patient. When a human or animal is given a drug orally, it may either be fully or poorly absorbed from the gastrointestinal tract. Clearly, unabsorbed drug will pass into the environment along with faeces. When humans or animals are given drugs parenterally or orally, the drug may be metabolized to a greater or lesser extent and excreted into the environment (including in exhaled air) as parent drug or metabolites, or as a mixture of both. It means that once they are excreted into the environment, they enter food chains and concentrate as they move upward into larger predators <sup>[1]</sup>.

It is generally accepted that excretion of pharmaceuticals after human and veterinary therapeutic use dominates the global input of pharmaceuticals into the environment.

### 2.2 Release from the skin

The pharmaceutical ingredients can be released into the environment from washing of skin having medicinal application and from residues excreted through the skin via sweat.

### 2.3 Leftover medicines

Leftover medicines include all medications no longer being used for the original prescribed condition, constitute another dominating cause of environmental contamination because of improper disposal. The causes of accumulation of leftover drugs are numerous and two of the major factors are patient non-compliance (failure to take medications as directed) and dispensing of purportedly excessively large quantities (such as 90-day supplies).

### 2.4 Manufacturing units and hospitals

Through drug manufacturing units and hospitals a significant amount of drug enters the environment. Nevertheless, localized elevated drug concentrations can occur adjacent to discharges from hospitals and manufacturing sites if emissions are not properly treated and controlled <sup>[11]</sup>.

### 2.5 Discharges from drug formulations

Drug residuals from the formulations like transdermal patches also leave the significant amount of drug in environment <sup>[12]</sup>. Transdermal patches containing fentanyl are reported to retain 28-84% of the loaded drug after removal from skin <sup>[13]</sup>.

### 2.6 Animal carcass

Animal carcasses containing high levels of certain drugs and these drugs may be acutely toxic to animal scavengers <sup>[12]</sup>.

## 3. Consequences of Environmental Pollution By Pharmaceuticals

Medicines have an important role in the treatment and prevention of disease in both humans and animals. But it is because of the nature of medicines that they may also have unintended effects on animals and microorganisms in the environment. Although the side effects on human and animal health are usually investigated in thorough safety and toxicology studies, the potential environmental impacts of the medicines are less well understood and have only recently

become a topic of research interest. Following are some examples of impact of drugs through environment on various aquatic and terrestrial animals:

### 3.1 Vulture Population

In early 1990s, the Gyps vultures of India and South Asia were among the most abundant large raptors in the world. However, within a decade, the populations of three species, White-rumped Vulture *Gyps bengalensis*, Indian Vulture *G. indicus*, and Slender-billed Vulture *G. tenuirostris*, had declined so abruptly that all three are considered critically endangered. Surveys in India show that the country's Indian and Slender-billed Vulture populations declined by almost 97% between 1992 and 2007. White-rumped Vultures fared even worse, dropping by 99.9 percent, to just one thousandth of their 1992 population. Vultures are keystone species that perform a vital ecosystem service by disposing of carrion and their decline has had dramatic ecological and socio-economic consequences <sup>[14]</sup>.

Extensive research has identified the cause of the decline to be 'diclofenac', a Non-Steroidal Anti-Inflammatory Drug (NSAID) used to treat livestock. Vultures are exposed to the drug, when they consume carcass of animals that were treated with diclofenac shortly before death. Vultures die from kidney failure within days of exposure to diclofenac contaminated tissues, with post-mortem findings of extensive visceral gout. The extreme sensitivity of *Gyps* vultures was also unknown and unexpected <sup>[4]</sup>.

Acute effects have also been observed in the African white-backed vulture (*Gyps africanus*) and the Eurasian griffon vulture (*Gyps fulvus*) <sup>[15]</sup> as a result of diclofenac exposure. However, the North American species of vulture such as *Cathartes aura* appear to be less sensitive than *Gyps* vultures by exposure to diclofenac <sup>[16]</sup>.

### 3.2 Sterility in Frogs

Different kinds of progestogens have been identified in waterways in a number of countries. Levonorgestrel, a specific progestogen, can cause sterility in female frogs at concentrations not much higher than those measured in the environment.

Female tadpoles that swam in water containing low concentrations of levonorgestrel exhibited a greater proportion of immature ovarian egg cells and lacked oviducts, entailing sterility <sup>[17]</sup>.

### 3.3 Feminization of Male Fish

The potential impact of natural and synthetic estrogens on aquatic ecosystems has become a subject of vast interest in recent years. Field reports of reproductive problems in some European freshwater fish populations have led to concern over the possible role of environmental estrogens as relevant factors. Synthetic estrogens like 17- $\alpha$ -ethinylestradiol, which is widely used in contraception and related pharmaceutical purposes, have also been shown to enter the aquatic environment via effluent discharges from sewage treatment works and its very low concentration in aquatic environment causes feminization of male fish.

Ethinyl-estradiol in concentrations of 10 ng/L in water could induce the synthesis of vitellogenin in immature cyprinids and at levels as low as 0.1 ng/L in rainbow trout. Vitellogenin synthesis is an estrogen receptor-mediated response, occurring naturally in female fish following endogenous estrogen exposure via blood plasma. Vitellogenin induction in

juvenile or adult male fish can therefore be used as a biomarker of exposure to exogenous steroidal estrogens<sup>[18, 19]</sup>

### 3.4 Ivermectin and Dung Beetle

Ivermectin is used as anthelmintic in veterinary practice and gets excreted through faeces and subsequently affects other organisms like dung beetle adversely<sup>[20]</sup>. Scientist<sup>[21]</sup> reported that ivermectin elicit many sub-lethal responses in dung invertebrates, such as reduction of growth rate, inhibition of pupation and the disruption of mating.

As dung from livestock contains diverse fauna and provides a fruitful foraging habitat for other species, ivermectin may therefore indirectly affect other species by depleting the quality and quantity of their food source.

### 3.5 Fluoxetine and Marine Animals

One of the most prevalent environmental pharmaceuticals in North America and Europe is the antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI) and the active ingredient of Prozac. Fluoxetine is regularly detected in streams and lakes, which receive sewage effluent from wastewater treatment plants<sup>[22]</sup>.

#### 3.5.1 Fish

Fluoxetine and its active metabolite norfluoxetine are found to bioaccumulate in fish, particularly in the brain and adversely affect reproduction, growth and behavior<sup>[23]</sup>.

#### 3.5.2 Shrimps

Prozac in the water is affecting certain kinds of shrimp. These shrimp, when exposed to Prozac, may be more likely to put themselves in mortal danger. Shrimp normally gravitate toward safe, dark corners. But when exposed to fluoxetine, the animals were five times more likely to swim toward a bright region of water; this behavior makes them much more likely to be eaten by a predator, such as a fish or bird<sup>[24]</sup>.

### 3.6 Bacterial Resistance

Widespread use of antibiotics to prevent and treat infections in people and animals as well as for promoting growth in livestock is causing environmental contamination. There is a risk that bacteria found naturally in the environment will develop resistance to antibiotics commonly used to treat human or animal diseases. 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.

Scientist<sup>[25]</sup> reported that ampicillin-resistant bacteria were found in every U.S. river tested in 1999. In a 2000 study, all samples taken from the Ohio River contained *Escherichia coli* with some resistance to penicillin, tetracycline and vancomycin.

Researchers<sup>[26]</sup> investigated the possible increase in antibiotic-resistant bacteria in sewage associated with the discharge of wastewater from a hospital and a pharmaceutical plant by using *Acinetobacter* species. Findings of the experiment indicated that while the hospital waste effluent affected only the prevalence of oxytetracycline resistance, the discharge of wastewater from the pharmaceutical plant was associated with an increase in the prevalence of both single- and multiple-antibiotic resistance among *Acinetobacter* species in the sewers.

## 4. Approaches to Reduce Amount of Pharmaceuticals Released To the Environment

Some remedial measures can be projected to reduce the amount of drugs entering the environment:

1. **To reduce generation of pharmaceutical waste:** The first priority should be to reduce the amount of pharmaceutical waste generated, rather than dealing with the pharmaceutical waste once it has been generated. Reducing the amount of pharmaceutical waste addresses the root cause of the problem as well as reducing overall health care cost<sup>[27]</sup>.
2. **To increase efficiency of sewage treatment plants:** Sewage treatment plants are generally not equipped to routinely remove medicines. Thus, measures should be taken to improve the efficiency of these sewage treatment plants so that pharmaceutical can be removed from sewage before it enters local waterways. However, livestock treated with veterinary drugs can and do excrete them into the environment and treated livestock that die and are left in the environment and consumed by scavengers, is a particularly difficult issue to deal with<sup>[27]</sup>.
3. **Use of Green pharmacy:** It is the design of pharmaceutical products and processes that eliminate or reduce significantly the use and generation of hazardous substances and the prevention / reduction of environmental safety and health impacts. Thus, new eco-compatible ways should be adopted to synthesize drugs. Biopharmaceuticals may be an alternative but still lack a scientific evidence to accept them as a complete substitute of drugs in practice<sup>[27]</sup>.
4. **Developing better drug disposal programs:** Over the counter and prescription medications should not be disposed down the drain because wastewater treatment facilities are not designed to remove pharmaceutical compounds and they may end up in local waterways and may eventually be found in drinking water. Properly disposing of unwanted and expired prescriptions and over-the-counter medications in the trash promotes a healthy aquatic environment and prevents accidental poisoning and intentional abuse. WHO<sup>[28]</sup> has given following guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies:
  - **Return to donor or manufacturer:** Wherever practical the possibility of returning unusable drugs for safe disposal by the manufacturer should be explored.
  - **Landfill:** Landfill means to place waste directly into a land disposal site without prior treatment or preparation. Properly constructed and operated landfill sites offer a relatively safe disposal route for municipal solid wastes, including waste pharmaceuticals. An appropriate landfill consists of an evacuated pit isolated from watercourses and above the water table. Each day's solid waste is compacted and covered with soil to maintain sanitary conditions.
  - **Waste immobilization:** Immobilization of pharmaceutical waste can be done by following two ways:
    - ❖ **Encapsulation:** Encapsulation involves immobilizing the pharmaceuticals in a solid block within a plastic or steel drum. Drums should be filled to 75% capacity with solid and semi-solid pharmaceuticals and the remaining space is filled by the mixture of lime, cement and water in the proportions 15:15:5 (by weight).

- ❖ **Inertization:** Inertization is a variant of encapsulation and involves removing the packaging materials, paper, cardboard and plastic, from the pharmaceuticals. Pills need to be removed from their blister packs. The pharmaceuticals are then ground and a mix with lime, cement and water in proportion of 65:15:15:5 respectively, to form a homogenous paste. The paste is then transported in the liquid state by concrete mixer truck to a landfill and decanted into the normal urban waste. The paste then sets as a solid mass dispersed within the municipal solid waste.
- ❖ **Incineration:** Pharmaceuticals are ideally disposed of by high temperature (i.e. above 1200°C) incineration. Such incineration facilities, equipped with adequate emission control, are mainly to be found in the industrialized world. Burning of pharmaceuticals at low temperatures or in open containers results in release of toxic pollutants into the air. Ideally this should be avoided [29].

#### 4.1 Household Disposal Steps

As per National Drug Control Policy, U.S.A. [30] the following steps can be adopted for household disposal of pharmaceutical products:

- a) Take your prescription drugs out of their original containers.
- b) Mix drugs with an undesirable substance, such as cat litter or used coffee grounds
- c) Put the mixture into a disposable container with a lid, such as an empty margarine tub, or into a sealable bag
- d) Conceal or remove any personal information, including Rx number, on the empty containers by covering it with permanent marker or duct tape or by scratching it off
- e) The sealed container with the drug mixture, and the empty drug containers, can now be placed in the trash

### 5. Ecopharmacovigilance and Drug Regulations

Various attempts have been made by regulatory authorities to reduce the impact of pharmaceuticals in environment such as:

#### 5.1 Environmental Risk Assessment (ERA) of drugs

The Food and Drug Administration (FDA) is required to consider the environmental impacts of approving drug as an integral part of its regulatory process. FDA's regulations in 21 CFR part 25 specify that Environmental Assessments (EAs) must be submitted as part of certain new drug applications. When a new drug is proposed for market, FDA requires the manufacturer to conduct a risk assessment that estimates the concentration that will be found in the environment. If the risk assessment concludes that the concentration will be less than one part per billion, the drug is assumed to pose acceptable risks.

#### 5.2 Resource Conservation and Recovery Act (RCRA)

The federal Resource Conservation and Recovery Act (RCRA) has been in place since 1976 for regulating the disposal of health care waste. Enforced by EPA, it regulates and tracks the disposal of solid waste, setting forth strict rules for facilities that generate, transport, store and dispose off hazardous waste. RCRA defines hazardous waste as chemicals or formulations so detrimental to the environment that they must be separated for special disposal and cannot be introduced into sewers or placed in landfills. Approximately 5% of all pharmaceutical agents are considered "RCRA hazardous." However, many more pharmaceutical agents have

RCRA-hazardous characteristics. One reason for this is due to the fact that the RCRA hazardous pharmaceutical agent list has not been updated as more agents have come to market [31].

#### 5.3 Risk Mitigation Measures (RMM)

If the ERA of a Veterinary Medicinal Product (VMP) indicates an unacceptable risk to the environment, i.e., the risk quotient (RQ) consisting of the ratio of PEC (Predicted Environmental Concentration) to PNEC (Predicted No Effect Concentration) is equal to or larger than one, and/or the risk-benefit balance is negative, i.e., the therapeutic benefit is outweighed by risks to the environment, safety or efficacy, the authorization can be refused. An exemplary performance of an ERA for a VMP is provided by Liebig *et al.* [32]. Risk mitigation measures (RMMs) can be applied to improve the prevention of exposure and the protection of the environment and in the case of risk indication within the ERA (i.e.,  $RQ \geq 1$ ), to reduce the RQ with a follow-up step of the RQ calculation.

Although an environmental risk-benefit assessment and refusal of authorization due to environmental concerns are not foreseen for Human Medicinal Products (HMPs), RMMs can also be applied to human pharmaceuticals. In Figure, the various options are shown when RMMs can be applied as part of the overall evaluation of the environmental concerns of HMPs and VMPs.

According to Adler *et al.* [33], the RMMs can be separated into three categories:

- Short-term measures; e.g., improved disposal and sewage treatment techniques, refusal of the spreading of contaminated manure
- Mid-term measures; e.g., modified risk perception and risk communication of producers and consumers of medicinal products
- Long-term measures; e.g., decisions that foster the concept of sustainable pharmacy.

Following flow chart showing the options to apply risk mitigation measures as part of the evaluation of environmental concerns of human (HMP) and veterinary medicinal products (VMP). Environmental concerns are addressed by calculating the risk quotient (RQ: the ratio of predicted environmental concentration to predicted no effect concentration), by conducting an environmental risk-benefit assessment and by improving the safety of marketed products through eco-pharmacovigilance.

### 6. Conclusion

Drug use has become an inevitable part of our lives but it is not imperative to compromise with the balance of ecosystem on any grounds. Solutions need to be suggested to save this only livable planet from ill effects of these chemicals. These may include better sewage treatment plants, education over rational use of drugs, and development of biodegradable products. Biopharmaceuticals may be an alternative but we still lack a scientific evidence to accept them as a complete substitute of drugs in practice. We need to monitor the effects of drugs not only as a good medical practice, but also to safeguard our environment. If we don't begin to address the environmental damage we are causing (both intentional and unintentional), it will be at the far greater cost of accelerated species extinction and disruption of the food chain. The research community, EPA, FDA and pharmaceutical manufacturers should work together to design educational

programs to better inform investigators, healthcare providers and patients about the potential environmental impacts of pharmaceutical use and appropriate disposal methods.

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