All India Institute of Medical Sciences Rajkot

Clinical Pharmacology & Therapeutics

e – Bulletin

"Panacea"

Volume 2, Issue 2, August 2023

Published by
Department of Pharmacology
All India Institute of Medical Sciences (AIIMS), Rajkot

Contents

Ecopharmacology

- **Ecopharmacology"** [1] (Ecosystem + Pharmacology) describes the entry of chemicals or drugs into the environment through any route and at any concentration disturbing the balance of ecology (ecosystem), as a consequence.
- A broader term describes the entry of both 'Pharmaceutics and Personal Care Products (PPCPs)' and 'Industrial And Chemical Pollutants (IACPs)' into the environment by any route and at any concentration disturbing the balance of ecology (ecosystem), as a consequence.
- It includes
  - Drug - Environment interaction
  - Toxin - Environment interaction
  - Gene-Environment interaction

Environmental pharmacology [2]

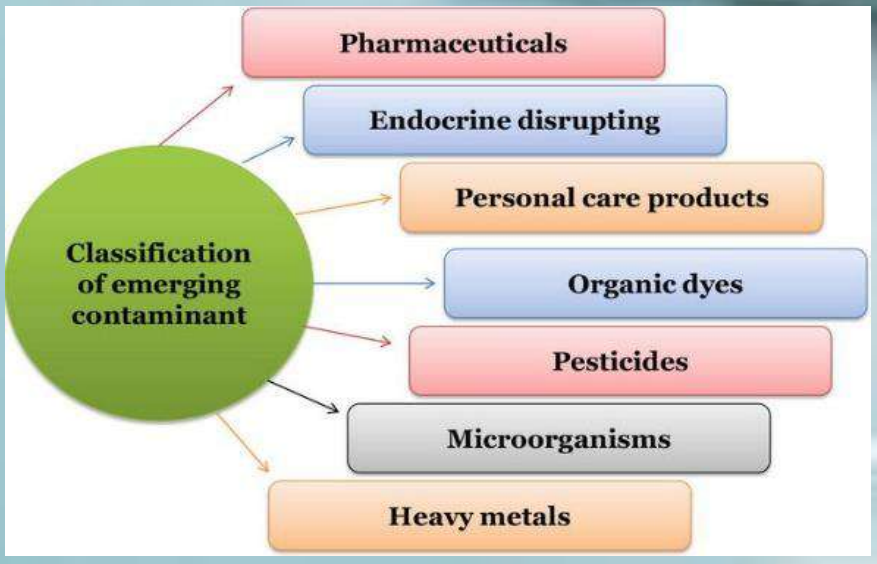
"The effect of pharmaceuticals and house care products on the environment and ecosystem"

Terminologies related to Ecopharmacology

Personal Care Product (PCPs)[3] are mainly used to improve the quality of daily life which include lotions, detergents, hair dyes, lipsticks, cosmetics, creams, bath soaps, dental care products, shampoos, toothpaste, sunscreens, fragrances, and other household items, etc.

Pharmaceutical Contaminants (PCs)[4] - arise from pharmaceutical industries that are biologically active compounds used to prevent, cure, or treat diseases.

Emerging Contaminants (ECs) [5]- a wide range of unregulated chemicals of synthetic or natural origin found in contaminant water or environment



Historical Background- Ecopharmacology

1981

Feminisation of **male fish** in UK due to **estrogenic compound.**[6]

1994

Clofibric acid was identified in drinking water in Berlin and Germany.[7]

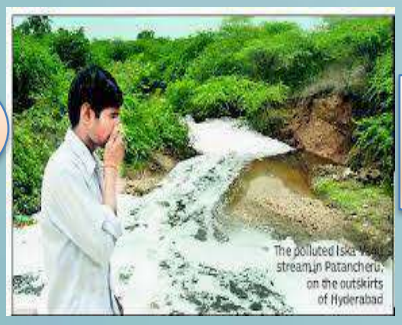
2004

Massive **death of Vulture** in India due to consumption of carcases containing **diclofenac.**[8]

2005

Traces of **cocaine** found in **Thyme river.**[9]

2009

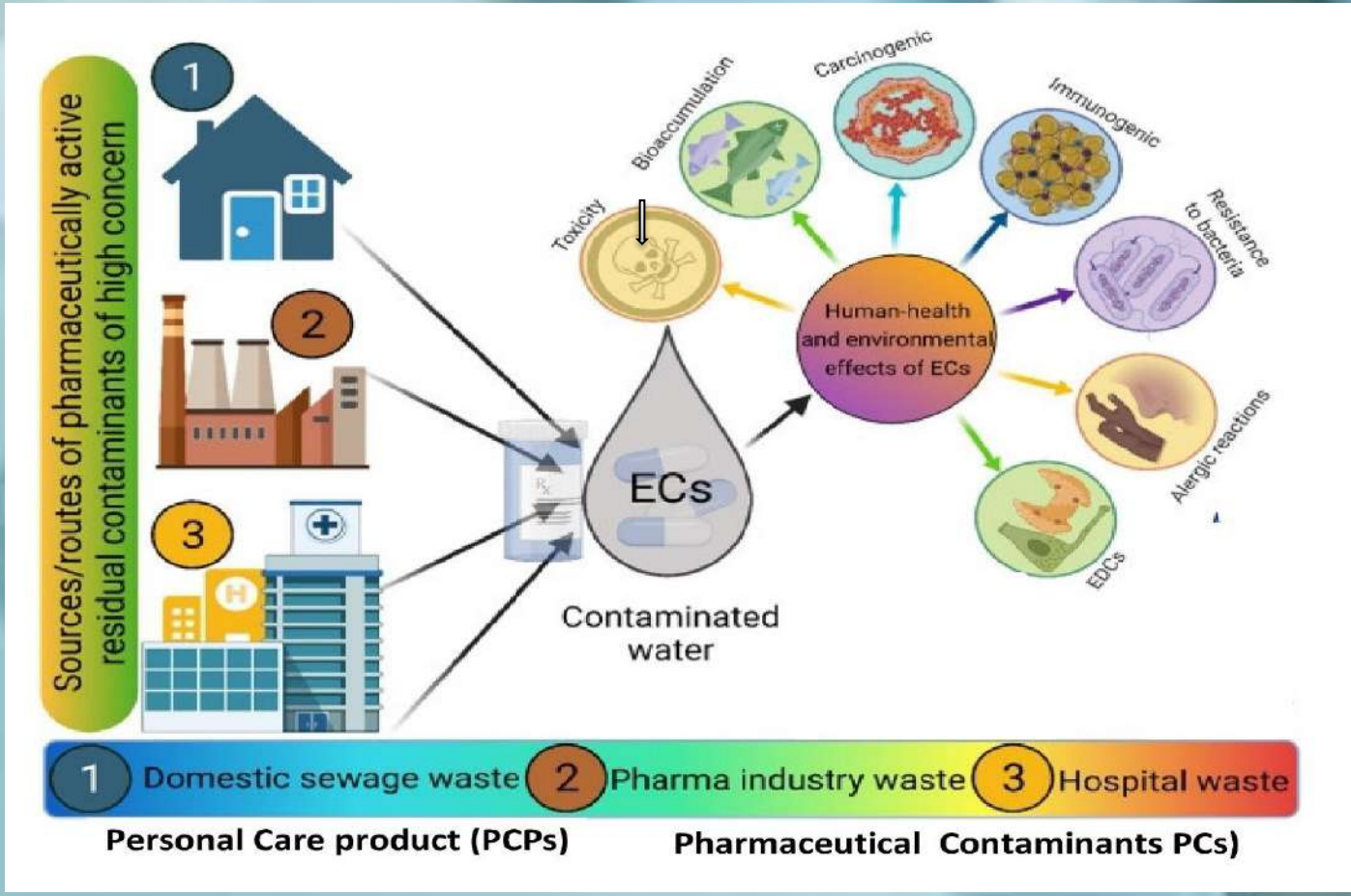


A high level of **ciprofloxacin** was detected in water in **Hyderabad.**[10]

2016

Alarming level of **azithromycin** and **erythromycin** was detected in Croatia's largest river- "**Superbug River**"[11]

Entry of PPCPs into environment [12]



Pharmaceutical and personal care products (PPCPs):

⇩

The compounds that **resist biodegradation** by microbes and persist in the environment in the active form called **Environmentally Persistent Pharmaceutical Pollutants (EPPP)**

⇩

External half-lives of these agents though dependent on the environment (water, air, soil, and sludge) are generally long and maybe more than one year for various compounds.

⇩

Imbalance of the ecosystem

Fate of PPCPs in the environment [14]

Remain unchanged

Environmentally Persistent Pharmaceutical Pollutants (EPPP)

Hormonal, Genetic and immunogenic effect

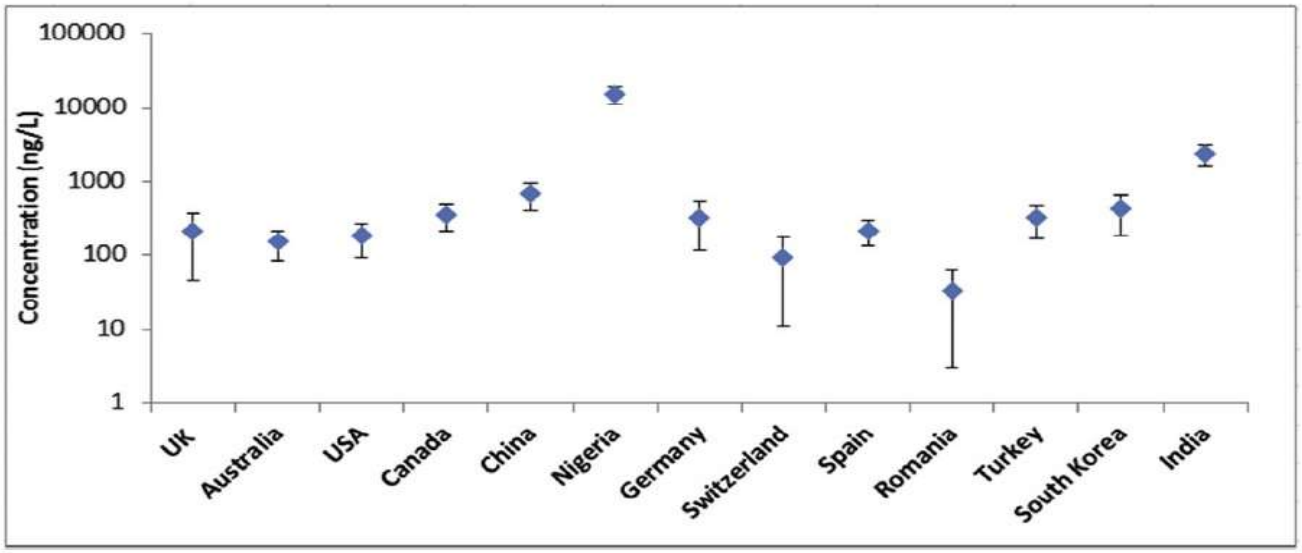
Undergoes degradation
Aerobic and anaerobic biodegradation

CO_2 and water or Metabolite

Degradation depends on: Age of the sludge and hydraulic retention time

Rate of removal of drugs form sewage treatment plan [15]

Drugs	Removal rate
Carbamazepine, Clarithromycin, Erythromycin, Estrone, Lincomycin, Spiramycin	0%
Atenolol, Benzafibrate, Clofibric Acid, Furosemide, Diazepam	10-30%
Amoxicillin, Ciprofloxacin, Enalapril, Ibuprofen, Ofloxacin	30-60%
Hydrochlorothiazide, Ranitidine, Sulfamethoxazole	variable



Concentrations (ng/L) of NSAIDs reported in surface water samples from different countries[16]

Harmful effects of PPCPs in the environment [17]

Aquatic and wild life

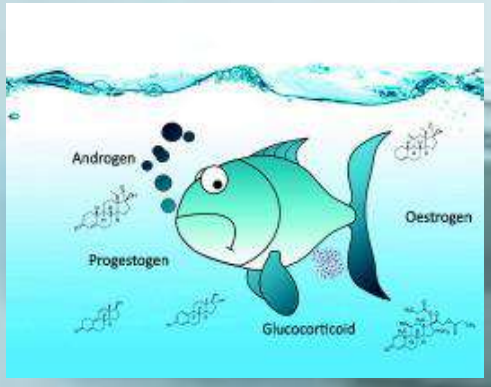
- Feminization of fishes
- The disappearance of dung beetles
- Developmental delay in amphibians
- Toxic effect of anti-parasites in fish farming
- Drug contaminants in biofilms

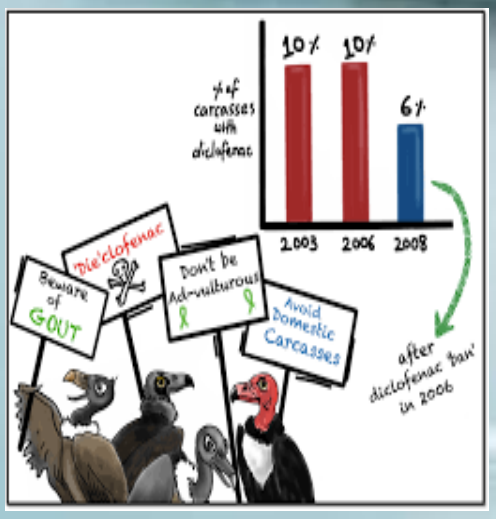
Human life

- Auto-immune disorders
- Endocrine abnormalities
- Impact of Epigenetic Changes
- Emergence of antimicrobial resistance

Examples of harmful effects on aquatic life

- The presence of **diclofenac and ketoprofen** resulted in **cardiovascular defects** and cardiac anomalies in freshwater fish *Clarias gariepinus* and *Danio rerio*. NSAIDs tend to contribute to changes in **gene expression and DNA damage**.[18]
- Synthetic **estrogen** used in oral contraceptive pills **harm the reproductive health** of fishes.
- **Ivermectin** residues **inhibit the growth of flies** so there is disappearance of the dung beetle which negatively affects the food chain by reducing the food source for birds.[19]
- Untreated sewage water with **fluoxetine** lead to **delayed development of tadpoles** in and behavioral changes in other aquatic species was observed Swimming activity of shellfish has been altered by fluoxetine.[20]





High Vulture mortality due to diclofenac use in cattle

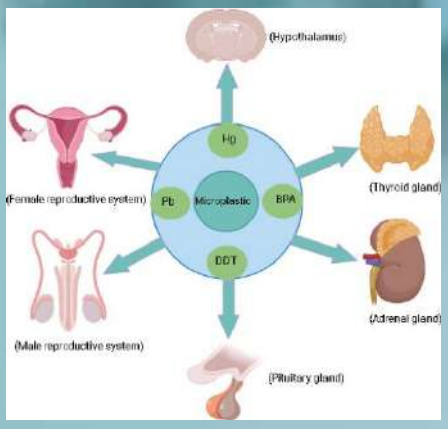
Examples of harmful effects on human life

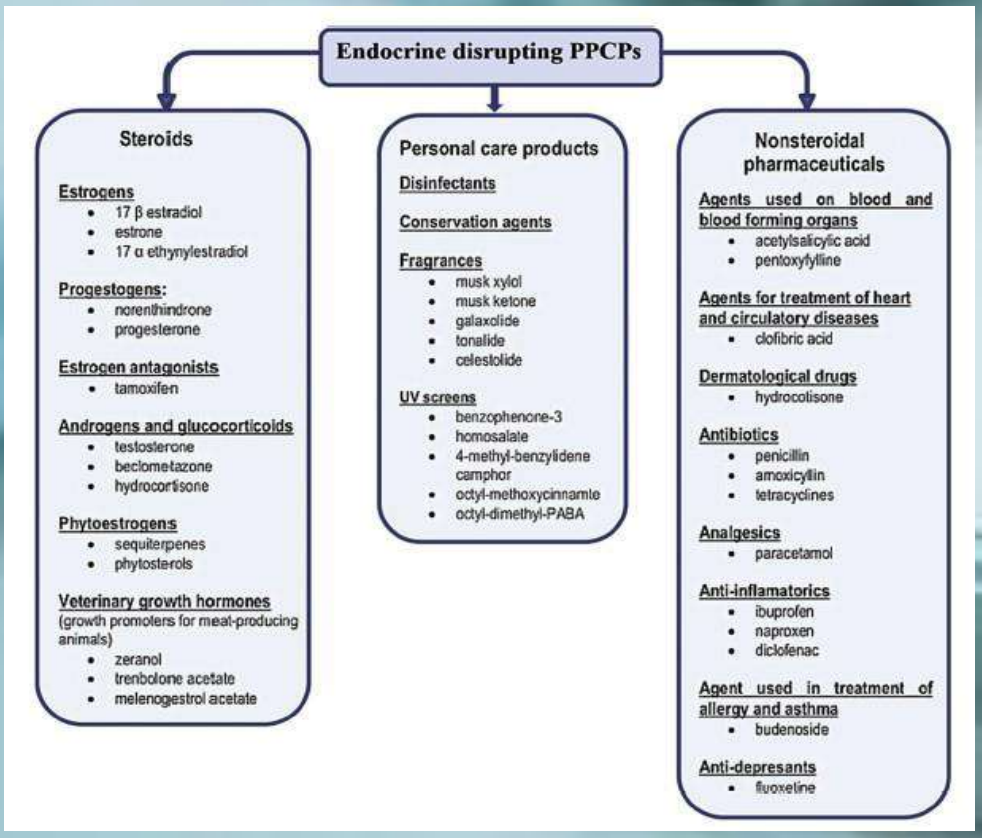
Autoimmune disorder: [21]

PPCPs like crystalline silica exposure is associated with the development of systemic sclerosis (SSc), systematic lupus erythematosus (SLE), rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody (ANCA) related vasculitis.

Endocrinal disturbance: [22]

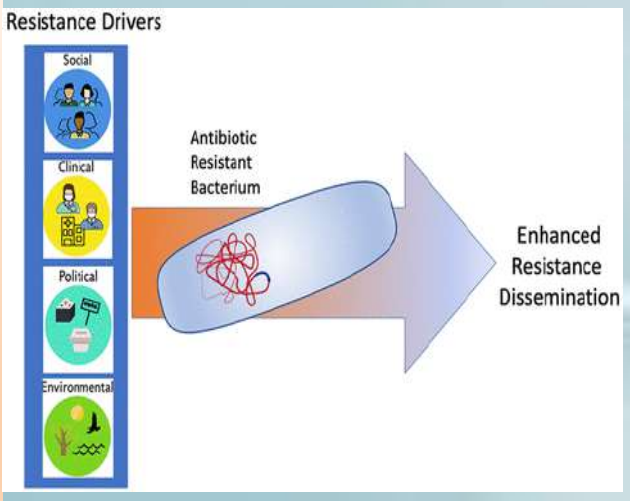
This environmental bioaccumulation of endocrine disrupting PPCPs exacerbates the abnormal hormonal control causing reproductive impairments, decreased fecundity, increased incidence of breast and testes cancers.





Antimicrobial resistance [23]

- Antibiotic residues can alter the human microbiome and cause health disturbances, such as allergic reactions, chronic toxic effects and disruption of the digestive system.
- Antibiotic-resistant pathogens including the resistant opportunistic pathogen *Pseudomonas aeruginosa*, *Escherichia Coli* carrying ESBL and Vancomycin-resistant enterococci (VRE) are enhanced
- The term **Ecoshadow** has been introduced to describe the environmental impact of antibiotics. Broad-spectrum antibiotics that are stable will have a larger impact on the bacterial flora (a long eco-shadow) than those with a narrow antibacterial spectrum which dissociates more rapidly (a short eco-shadow)



Regulatory Framework- Global Scenario

India [24]

- Indian Government - The Ministry of Environment and Environmental Pollution Control Board.
- It formed the recommendations and amended the Bio-Medical Waste Manufacturing and Handling Rules in 2018.

The **USA Food and Drug Administration (FDA)** have regulated pharmaceuticals in the environment since 1977 under the auspices of the National Environmental Policy act of 1969. [25]

The European Medicines Agency (EMA) issued guidelines in 2006: **Environmental Risk Assessment (ERA)**[26]: A regulatory requirement prior to launch of a new drug- To access the environmental fate and effect produced by pharmaceuticals- toxicity to aquatic life

- **Risk Quotient:** Ratio of **Predicted Environmental Concentration (PEC) and Predicted -No Effect Concentration (PNEC)**
- If Risk Quotient is > 1 than risk management is required

United states of America [27,28]

- **Drug enforcement administration (DEA):** DEA mandates disposal of drugs listed in CSA (controlled substances act) either by the return of the drug to the manufacturer or by destroying it with certain guidance and proper recording.
- **Resource conservation and recovery act (RCRA):** RCRA monitors appropriate safe practices in the manufacture, storage, transportation, treatment and disposal of hazardous pharmaceuticals.

Europe [29]

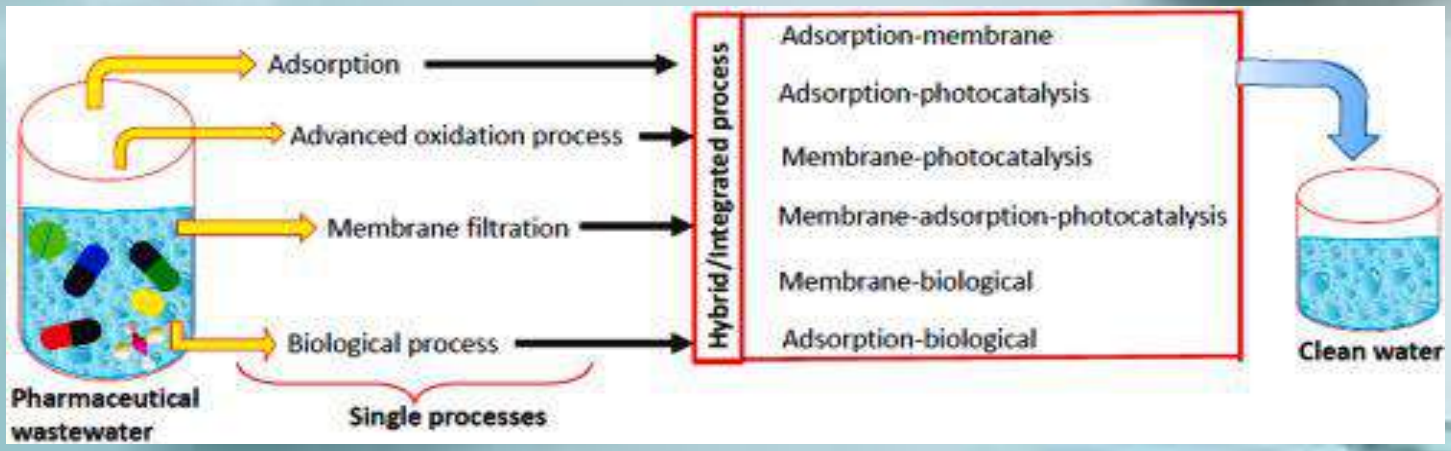
- **Environment risk assessment (ERA):** To assess environmental risk for every new drug in the pre-approval phase.
- Water framework directive (WFD)
- **Knowledge and new assessment on pharmaceutical products in environmental waters (KNAPPE)**

Treatment of pharmaceutical contaminants in Environment [30]

The removal of PPCPs/EDCs from contaminated water is a challenging task due to the complexity and persistence of the pollutants in water.

A number of the conventional wastewater treatment technologies have so far been reported as shown in image.

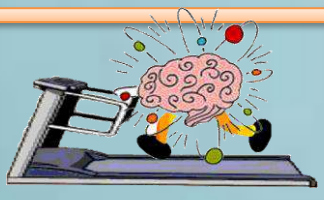
Routine toxicological analysis of drinking water should be done so as to establish the exposure limits to PPCPs in humans.



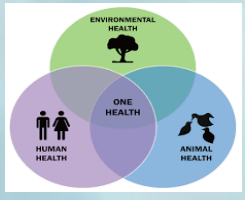
ECOPHARMACOVIGILANCE[31]

It as the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment.

- It monitors the harmful effects of pharmaceuticals on humans through nontherapeutic Exposure.
- To ensure significant issues associated with pharmaceuticals in the environment are identified and managed properly.



1. Which drug was banned by the Indian government for veterinary use for the protection of ecology?
   _____
2. Ecotoxicological studies of the drug is tested on _____?
3. Which pesticides caused neurotoxicity in animals and humans sprayed around cashew plantations in Kerala?



Take Home Message

Let's join hands for safe use of medicine and healthy environment for all.

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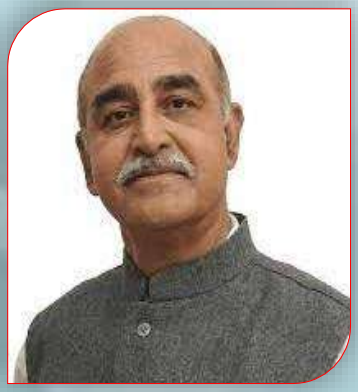
Ans: Diclofenac 2. Algae & Fish 3. Endosulfan

Prepared by: Dr. Kiran G. Piparva under the guidance of Dr. Rima Shah



Message from Executive Director.....

"I heartily congratulate the department of pharmacology for bringing this informative newsletter on "Ecopharmacology" – an emerging issue in clinical pharmacologyand therapeutics. My best wishes to the entire team.....

Dr. (Col) CDS Katoch, Executive Director, AIIMS, Rajkot.

Team Pharmacology

This is an effort to bring forward important information on "Ecopharmacology" emerging environmental risk by drugs and pharmaceutical products. We hope you enjoy reading this e-bulletin!

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(Associate professor, Department of Pharmacology)

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