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IMPACT OF PHARMACEUTICAL POLLUTION ON NATURE AND ITS MANAGEMENT: A GLOBAL ALERT

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ABSTRACT: Drugs taken by humans and animals find their way into rivers, lakes, and even drinking water and can have devastating effects on the environment. This review summarizes the research regarding pharmaceutical industry emissions and the health risks of pharmaceutical wastewater exposure.The present review is prepared by the extensive literature survey using different search engines like google.com, PubMed, SCOPUS, Medline, Ind Med, and the library of Galgotias University, Greater Noida. This review observed the consumption of medicinal products as one of the main sources of environmental contamination due to excretion (urine, feces) and improper disposal of unused or expired medicines (toilet, sink, litter). Some medicinal products, in particular anti-parasiticides, antimycotics, antibiotics, and estrogens, which can all have ecotoxicological effects, pose environmental risks in specific cases. The supervision of pharmaceutical waste poses a great challenge to policy planners, city administrators, medical personnel, and workers in the recycling industry. It is interdisciplinary, involving pharmacy, nursing, environment services, infection control, quality assurance, risk management, etc. According to the most recent data on water quality in India, the Yamuna at the Okhla and Nizamuddin bridges has the lowest quality and ranks eighth among rivers with the highest biochemical oxygen demand. A few examples of creative waste reduction initiatives that combine source reduction with reuse and recycling are presented for consideration in this regard. This paper concludes that the hazards and approaches to managing manufacturing-related and excretory-related environmental pollution can be reduced by some recent efforts by regulatory bodies around the world.

INTRODUCTION: On-going studies on pollution showed that worldwide associations and pharmaceuticals have inconvenient effects of drug items on the climate in the form of water and land pollution.

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Drug items are broadly utilized for the well-being of humans and in creature cultivation. These substances have been intended to be systemically dynamic and to cause fewer harmful impacts. During their production, use, and removal, Active Pharmaceutical Ingredients (APIs) just as other synthetic compounds are delivered into the climate.

Drug items (principally restorative items, yet additionally other individual consideration items) may be seen as natural poisons because of their general use in both human and veterinary medicine [1-3]. More than 559 unique medication biproducts

are found in biological territories, for instance, surface water, groundwater, soil, etc. There are around 3000 powerful medication biproducts affirmed in the European Union (EU) market, the remedial things for human use running someplace in the scope of 50 and 150g/capital/year [4]. The medications and their metabolites are released through crap and pee and end up in the maritime environment, either by discharge after part of a sewage water treatment plant, or by run-off from the surface, disposal methods for the soil, or drainage to the surface water ensuing to spreading of manure on the land [5]. Surprisingly, the direct appearance of veterinary medications in the environment may occur through application in aqua-farming (for instance, fish developing), yet likewise indirect contact through animals topically treated, and from run-off and separating through fields from manure spreading to agrarian fields and tamed animals' wastes [6]. Since, production of pharmacy pollution is amassed in express territories as the risks are not associated with use plans. A worldwide survey shows that more than 508 distinctive APIs have been recognized, sometimes at levels that represent a high danger to the climate.

According to the most recent data on water quality in India, the Yamuna at the Okhla and Nizamuddin bridges has the lowest quality and ranks eighth among rivers with the highest biochemical oxygen demand. Besides the deficiency of clean drinking water, poisonous froth from the lakes where the drug by-product is released is mostly due to the departures of numerous homes in Hyderabad [6, 7].

The major choices for discharge from accumulated and released drugs contrast in a couple of critical points. The particular responses for reducing the accumulation of effluents are not completely covered, but the consistent factor association and destructive nature of present-day pollutants give additional troubles [7]. The present review is prepared by the extensive literature survey using different search engines like google.com, PubMed, SCOPUS, Medline, Ind Med, library of Galgotias University, Greater Noida. In the current study, a short discussion concerning drugs on common defilements has been highlighted with all gauges that should be required to restrict the impact of medication on our mother nature given its socio-economic importance.

MATERIALS AND METHODS: To support the evidence-based representation of this review on this alarming global issue of pharmaceutical pollution, different information source engines were utilized such as Google.com, PubMed, SCOPUS, Medline, Ind Med, and the library of Galgotias University, Greater Noida. To make the global issue more scientific and useful some crucial aspects have been taken into consideration as follows.

A. Identifying the major health hazards due to pharmacy pollution were accumulated from the scientific research publications of the last twenty years.

B. Aggregating empirical findings on specific research on the major sources and causes of pharmacy pollution.

C. Identifying topics or questions requiring more investigation on pharmaceutical pollution.

D. Assessing and developing new frameworks on the major management alternatives of this hazardous pollution.

Antimicrobial Drug Contamination – Resistance to Antibiotics: Antimicrobial resistance is an interesting issue, with the gradual rise in multidrug contaminations as indicated by the World Health Organization (WHO). Findings from the survey in 2016 and 2017 centered around antibiotic contamination in India and China, reinforce this theory. Conceivable downstream contamination from assembling plants has been seen in the European Union and different pieces of the world. Samples, taken from sewers and different locales around mass medication manufacturing plants in Hyderabad and the actual city, indicated stunningly significant degrees of antimicrobial substances in the examples. The centralization of a wide range of antibiotics, ciprofloxacin, was sufficient to treat 44,000 individuals every day. Furthermore, more than 95 % of tests contained multidrug-safe bacterial strains. Anti-microbials that have been discharged into sewerage are likewise demonstrating a risky impetus for developing antimicrobial resistance. Studies taking a glimpse at metropolitan streams recommend choice for sub-populaces of safe microbes in light of significant degrees of antibiotics, for example, ciprofloxacin [6-9].

Impact of Pharmaceuticals on the Ecosystem: Determining the impact of the medications on the ecosystem might be challenging due to their low quantities. However, it is becoming more and more obvious that certain pharmaceuticals, particularly those with anti-parasitic idée, anti-mycotoxin, antibiotic, and estrogen properties all of which have the potential to have ecotoxicological effects pose a risk to nature under certain circumstances. For example, in India, vultures experienced a population crash between 1996 and 2007 due to exposure to the anti-inflammatory medicine diclofenac, which killed millions of birds and nearly drove them extinct. Since no one in India consumes beef, the medicine was given to cattle to treat fever and pain. Dead cattle, particularly those that had just received large dosages of diclofenac, were left for the vultures to feast on. It turns out that diclofenac primarily affects vultures in the genus Gyps, and between 10 million and 40 million of these birds perished from acute kidney failure and abdominal gout. In Asia, three Gyps vulture species are currently extremely endangered [10].

Doctors and pharmacists advise people not to combine ibuprofen with beta-blockers, but that isn't an option for a fish swimming in a muddy river that contains a soupy mixture of medications and other chemicals. There is insufficient data to draw a firm conclusion regarding the feminization of male fish in the wild by estrogen from birth control pills, nor is there any indication of population-level impacts. Numerous other hormone-like substances that may be in the water, such as bisphenol A, which has been demonstrated to have endocrine-disrupting qualities, can also have the same feminizing effects[9].Yamuna's water quality has declined and is severely contaminated as a result of the discharge of industrial and municipal waste water. The uppermost section of the Yamuna River, from its source to the Tajewala Barrage, has nearly perfect water quality and is free of all forms of contamination. The industrial, residential, and agricultural regions surrounding the river's lower course in Haryana contribute to pollution, which worsens as the river reaches the Delhi region. According to the most recent data on water quality in India, the Yamuna at the Okhla and Nizamuddin bridges has the lowest quality and ranks eighth among rivers with the highest biochemical oxygen demand [11, 12].

Prevention of Pharmaceutical Pollution - Role of Pharmacists: Drug specialists have a great job in lessening and controlling these drug contaminations. The presence of medications in surface waters, groundwater, and even marine frameworks has been affirmed at groupings of high to low levels. The most ideal approach to lessening contamination is to forestall drug toxins in the making. Certain organizations have creatively implemented contamination avoidance techniques that increase productivity and boost profits while minimizing environmental impacts. Even some smaller offices can overcome administrative barriers simply by reducing toxic discharges through aggressive contamination avoidance strategies. One way the company intends to reduce these wastes is through source reduction. That being said, the pharmaceutical industry may not implement source reduction strategies such as material replacements and measure modifications as easily as other assembly-related industries.

In their assembly offices, many drug companies have recently implemented contamination avoidance procedures. A few alternative methods for creative waste management reduction initiatives that combine the reduction of its source with recycling and reuse are presented for the scenarios that arise in this regard. Methylene chloride and other chlorinated solvents were used in several tablet covering operations in the tablet covering measure. Many enterprises have reduced the amount of hazardous waste in their air and emitting waste streams, as well as the cost of purchasing synthetic compounds, by switching to fluid-based covering films. Moreover, fluid-based cleaning solutions are increasingly being used for hardware cleaning in place of dissolvable-based solutions [14].

A few offices have set up projects where they can acknowledge controlled substances, and risky waste offices regularly acknowledge prescriptions. When areas gather undesirable prescriptions, the Environmental Protection Agency (EPA) prompts that drugs ought to be burned at managed offices to limit the defilement entering the climate. As a sort of medication organization for the climate, Eco Pharmacovigilance (EPV) underscores the source control of drug poisons. The youthful, grown-up respondents were found to focus closer on the natural issues presented by drug buildups and

become stronger of the EPV intercession overwhelmingly performed by drug ventures and drug specialists. Accordingly, it is critical to build up the standard medication removal conventions and instruct the overall population on the most ideal route for drug removal under the rule of EPV [15].

As indicated by the National Accreditation Board for Hospitals and Healthcare Providers (NABH) the medications' close/past expiry dates are removed, and no prescription past expiry date ought to be accessible in the drugstore. The emergency clinic ought to characterize what establishes "close to expiry." For instance, a quarter of a year before the expiry date. To achieve proficiency, the progression of prescriptions should be overseen from all viewpoints to defeat entanglements like overloading, expiry, and so forth drugstore inventory network is the territory wherein options and bargains are not worthy when inaccessibility emerges.

On the other hand, every pharmacy follows First in-First out (FIFO), which considers stock that enters the drugstore first and is additionally sold first. This typically happens when something is quick because of client requests. Always, Better, and Control (ABC) investigation is a strategy for grouping things or exercises as indicated by their relative significance. It is otherwise called "isolating the essential not many from the trifling many" because, for any gathering of things that add to a typical impact, a moderately couple of patrons represent a greater part of the impact. Vital, Essential, Desirable (VED) examination depends on the basic qualities and deficiency cost of the thing. Given their criticality, the things could be ordered into three classifications: indispensable, fundamental, and alluring. A blend of ABC and VED examination (ABC-VED lattice) can be productively utilized to develop an important command over the material supplies [16, 17].

Even though instructing the general population about appropriate medication removal is critical, drug specialists and understudy drug specialists should investigate beginning a prescription reclaim program. Drug specialists ought to inform patients about how they can manage undesirable medicines. Patients should take unused medicine to an office with a physician-recommended drug reclaim program. Every single pharmacy should have a noticeable solicitation for the patient to restore the office of unused medications with the bill, solution, and before its expiry, so it very well may be utilized by the following patient before going to the climate to ruin.

Drug specialists need to keep up, start, and rouse gift boxes at every single emergency clinic for unused medications for legitimate use by poor people and penniless and to help the climate be liberated from its contamination. By dispatching a reclaim program in various regions, the patients can benefit from outside intervention to find a way to restrict abuse issues and mishandle and forestall mischief to the climate. Medical Services Without Harm (HSWH) Europe, the European Commission's ecological danger evaluation of drug items (ERAPharm), is to bring issues to light of the negative connection between drugs and the climate and challenge the medical care industry to tidy up its creation [18].

In Australia, likewise, the Return Unwanted Medicines (RUM) Project, in Canada - British Columbia, accommodates undesirable and outdated prescriptions to be gathered by local area drug stores. Eleven European Union member countries have drug reclaim frameworks, all of which permit occupants to drop undesirable drugs at drug stores. This undertaking will create and execute a replicable pilot for gathering undesirable prescriptions at Household Hazardous Waste (HHW) assortments or in other provincial settings [19, 20]. Invert merchants oversee undesirable drugs from drug stores, medical clinics, and facilities. Some gathered drugs are gotten back to makers; others are bundled and shipped off-site for removal. This administration is painstakingly followed both as a support of the drug business and to meet legitimate prerequisites for the gathered controlled substances. Turn around merchants' bundle items, send them to makers, and give producer credits to drug stores [21].

Pharmaceutical Polluted Water Management: Prior research documented the administration of endocrine products and medications with increased shelf life in the past few years. Wastewater from chemical and fermentation processes is the focus of

the majority of treatment technologies. Certain substances that a single stage of treatment cannot entirely remove have been treated with hybrid methods. The primary purpose of hybrid technology use is to virtually eliminate the pollution or keep it within safe discharge limits. The pre-treatment step, which consists of sophisticated oxidation procedures, is the most often used treatment technology for both wastewater streams. Its primary purpose is to eliminate recalcitrant and refractory chemicals, which are occasionally non-biodegradable. The waste can then be efficiently handled using biological treatment techniques, such as aerobic and anaerobic processes, ultra-filtration membranes, etc [22, 23]. Research are still going on to achieve significant removal of these pharmacy pollutants based on their stimuli-responsive catalysis after appropriate early detection. Electrochemical biosensors are being fabricated with different receptors to analyze pharmaceuticals. Major outcomes are achieved by adopting an electroactive nano-system of desired requirements to develop proper health and environment management strategies. Nanofiltration membranes, Nonabsorbent, Photocatalysis and Advanced Oxidations Processes (AOP), and electrochemical degradation are adopted as a means to purify the pharmacy pollutants from the contaminated water [24]. The management of pharma pollution is demonstrated in **Fig. 1.**

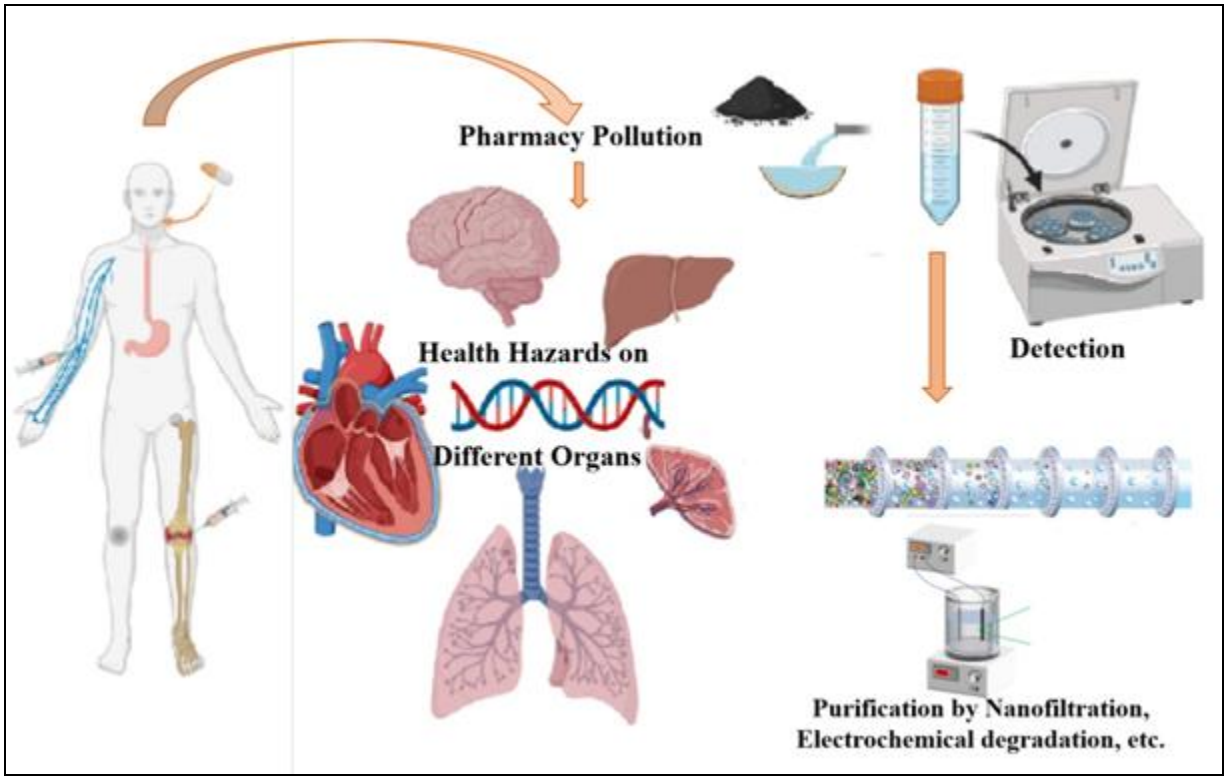

FIG. 1: MANAGEMENT OF PHARMACY POLLUTION

Drugs in Environmental Matrices: Approximately 700 different drug types' residues have been found in several environmental compartments, primarily in wastewater, surface, and groundwater, but also in soil, air, and biota, as well as in our drinking water from the tap [25]. Regarding psychiatric medications specifically, entire books have been written about their environmental presence [26]. Because of its widespread distribution, carbamazepine has even been proposed as a marker for wastewater-influenced aquatic bodies. Nanofiltration membranes for the removal of pharmaceutical contaminants from wastewater are still being developed by scholars globally **Table 1**. Additionally, once in nature, parent drugs (or metabolites) continue to change and go through intricate metabolic processes carried out by various organisms and physicochemical mechanisms (adsorption to solids, photo-degradation, etc.), resulting in the formation of transformation compounds [27].

TABLE 1: DOCUMENTED PHARMACEUTICAL API IN DIFFERENT WATER BODIES AROUND THE WORLD [28-43]

S. no.	Country	Drugs Detected	Max. Concentration/metrics detected (effluent)	Year
1	China [28-31]	Antibiotics: Oxytetracycline	Effluent: 1065 mg l^{-1} & effluent: 19.5 mg l^{-1} surface water: 712 µg l^{-1}	1988 & 2008
		Penicillin G & its metabolites	Penilloic acid[a] 44 mg l^{-1}	2008
		Oestrogenic sex steroids	Surface water: Penilloic acid[a] 11.6 mg l^{-1}	2006
		Sulphonamides, NSAIDs and other drugs	Ethinyl oestradiol 51 ng l^{-1} Sulfamethoxazole 1.34 mg l^{-1}; ibuprofen 1.5 mg l^{-1}	2009
2	India [32-36]	Salicylic acid—anti-inflammatory	Effluent: 2270 mg l^{-1}	1993
		Fluoroquinolone antibiotics	Ciprofloxacin 31 mg l^{-1}	2007
			Ciprofloxacin 14 mg l^{-1}	2009
			Groundwater: cetirizine 28 µg l^{-1} surface water: ciprofloxacin 6.5 mg l^{-1} River sediment: ciprofloxacin 914 mg kg^{-1} organic material Groundwater: ciprofloxacin770 ng l^{-1} soil: ciprofloxacin 7.2 µg g^{-1} organic matter	2011 2014
3	Germany [37-39]	Phenazone and metabolites	Groundwater: phenazone 3.95 µg l^{-1} tap water: phenazone 0.4 µg l^{-1}	2002
			Groundwater: phenazone 2.5 µg l^{-1} tap water: phenazone 0.25 µg l^{-1}	2004
4	Switzerland [40, 41]	Venlafaxine antidepressant	Surface water: 0.8 µg l−1	2004
		Oseltamivir antiviral	Surface water: 160 ng l−1	2010
5	Israel [42, 43]	Venlafaxine and metabolites	Effluent: venlafaxine 11.2 µg l−1	2012
		Carbamazepine and Venlafaxine	Effluent: venlafaxine 11.7 mg l−1b	2013

Research on the impact of drug pollution on human health is still lacking. Drug concentrations in tap water shouldn't cause any health issues, according to a 2012 WHO report [44]. A subsequent study conducted in China validated these findings [45, 46].

However, drug exposure in nature may cause problems for the most vulnerable patient groups (allergic, for instance). There are still unanswered questions, especially in Regard to long-term (chronic) exposure to a range of contaminants, even though the evidence for any short term negative impact on human health is lacking. The primary exposure to these pharmaceuticals is vegetables, drinking water, meat, fish, dairy products and tubers [47].

The rise in antibiotic-resistant bacteria is probably the most well-known illustration of the detrimental effects of drug pollution on human health and is today regarded as the largest global public health issue. In this regard, we believe that the "One Health" concept, which holds that environmental and human health are intimately linked, is crucial [48]. However, we think that this strategy should be applied to other treatment classes, not just antibiotics, including psychiatric medications [49].

Regulatory Framework: The US Environmental Protection Act regulates pharmaceutical household trash. Certain current regulations must be considered while developing pharmaceutical take-back programs in the US. The Resource Conservation and Recovery Act (RCRA) and the Federal Resource Conservation and Recovery Act cover waste from pharmaceuticals and other hazardous products. It only governs pharmaceutical waste, which is an unsorted collection of unwanted medications, some of which may be utilized in the future, or it can be processed and reused. The reverse distribution industry is built on this foundation. Reverse distribution of pharmaceutical waste has been approved by the US EPA. Waste-like materials (such as a broken container or contaminated prescription) cannot be transported as products to a reverse distributor, according to the U.S. EPA permit, which expressly states that the industry is not to be used as a waste management system [50].

US Drug Enforcement Administration (DEA): The Drug Enforcement Administration (DEA) of the United States regulates some pharmaceuticals, which are referred to as "controlled substances."

These are crucial for certain medicines that can be abused, like opioids and tranquilizers like codeine, Valium, Ritalin, anabolic steroids, and Lomotil. DEA uses five schedules to enlist prohibited drugs. Medications listed in Schedules II through V are prescribed to patients, while medications listed in Schedule I have no therapeutic benefit.

Health Insurance Portability and Accountability Act (HIPAA): A standard for safeguarding the privacy of personal health information is established by the Health Insurance Portability and Accountability Act (HIPAA), which is managed by the U.S. Department of Health and Human Services (DHHS). Prescription labels and other personally identifiable medical information must be secured by these standards. In theory, HIPAA only protects businesses associated with medical care providers, including pharmacies. Business associates may collect waste from pharmacies. A waste management contractor is considered a business associate by HIPAA regulations, and to safeguard confidential patient data, the pharmacy and the waste management contractor must sign a written agreement [51-52]. Numerous administrative bodies, organizations that buy mass medications, global speculation organizations, drugstores and medical care associations that purchase and disperse the eventual outcomes, can impact or make impetuses [52-53].

Control of pharmaceutical pollution is a major concern across the globe; therefore, the control policy and guidelines regarding pollution control are framed and controlled by different regulatory bodies around the world. Different countries have their regulatory bodies which are represented in **Fig. 2.**

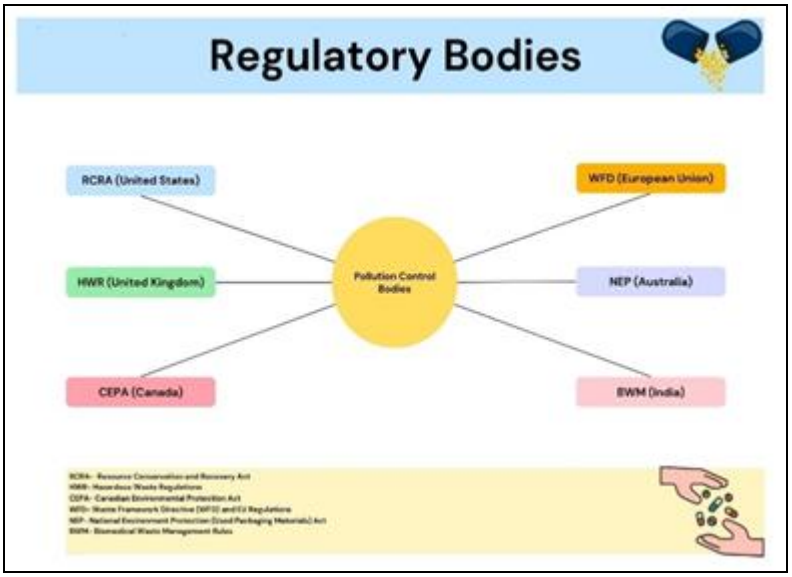

FIG. 2: REGULATORY ASPECTS OF DIFFERENT COUNTRIES FOR THE MANAGEMENT OF PHARMACY POLLUTION

CONCLUSION: From the current review, it has been certain that the drugstore industry and the worldwide drugstore individuals are playing a major role in keeping environmental pollutants free from pharmaceutical items. There are, nonetheless, some efficient observing projects or thorough, precise investigations on the event of drugs in drinking water, and limited information is one of the vital difficulties in surveying the potential dangers related to following groupings of drugs in drinking water. The pharmacist has to guide the patient and its attendant for proper disposal of the medicine. The pharmacy industry plays a crucial role in minimizing environmental contamination from pharmaceutical products. However, there is a lack of comprehensive monitoring programs or studies on the presence of pharmaceuticals in drinking water. Although current assessments suggest that low concentrations of these substances pose little risk to human health, there are gaps in understanding the long-term effects of exposure to low-level drug mixtures. Effective wastewater management and legal incentives for pharmaceutical manufacturers are essential to ensuring safe disposal levels. Pharmacies can contribute by promoting the return of unused

medications and educating customers on proper disposal methods. Additionally, cost-effective systems for waste management, public awareness, and further research into pharmaceutical pollution's impact on mother nature are needed to meet Sustainable Development Goals (SDG) for health and clean water. Campaigns are pushing for the pharma industry to reduce pollution through better waste practices and donation programs, while more studies on drug exposure effects are encouraged.

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