Review Article

Environmental Impact of Pharmaceuticals: A Comprehensive Review

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Abstract

This comprehensive review seeks to evaluate and synthesize the extensive literature regarding the environmental impact of pharmaceuticals, a growing area of concern within the realm of environmental science. Pharmaceuticals, including human and veterinary medicines, have been detected ubiquitously in the environment due to their widespread use and incomplete removal during wastewater treatment processes. These substances pose potential ecological risks due to their bioactive properties, but the magnitude and implications of these impacts are not yet fully understood. Our review covers the major aspects such as pathways of environmental entry, detection methods, potential impacts on flora and fauna, and potential human health implications of pharmaceutical contamination. We further explored the effectiveness of current wastewater treatment technologies in removing these substances and assess the potential of emerging technologies. The review concludes by discussing policy implications and the necessity for a global coordinated response. By encapsulating the breadth of research in this area, we hope to spur further research and foster greater awareness of the environmental implications of pharmaceutical waste.

Keywords: Ecological risks, environmental impact, pharmaceuticals, policy implications, wastewater treatment

Introduction

The use of pharmaceuticals, encompassing both human and veterinary medicines, has become indispensable in contemporary society. They play an integral role in disease management, control, and prevention, significantly improving the quality of life and life expectancy.[1,2] However, the environmental ramifications associated with these substances are becoming increasingly apparent and can no longer be overlooked.

Pharmaceuticals permeate the environment through an intricate web of pathways, underscoring the multifaceted nature of this escalating issue. These pathways are primarily classified into three categories: direct industrial release, indirect release through biological excretion, and inappropriate disposal of unused medications. Despite robust regulations, pharmaceutical manufacturing units often directly discharge effluents replete with active pharmaceutical ingredients (APIs) into wastewater streams, which, due to the lack of efficacious treatment protocols, lead to contamination of aquatic ecosystems. This issue is particularly pronounced in regions harboring dense concentrations of pharmaceutical production. Concurrently, the excretion of pharmaceuticals by humans and animals, a more diffused pathway, significantly contributes to environmental load. Postconsumption, the body expels unmetabolized pharmaceutical residues through urine or feces into sewage systems.[3] Veterinary pharmaceuticals further enter the environment through manure applied to agricultural fields. These wastes eventually converge at wastewater treatment plants (WWTPs), which, not originally designed to remove such substances, inadvertently release treated effluents and biosolids, often used as fertilizers, laden with these compounds back into terrestrial and aquatic realms. Ferrari *et al*. contended that due to their high production volumes

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and specific pharmacokinetic properties during standard therapeutic use (including half-life, urinary and fecal excretion, and metabolism), pharmaceuticals and their metabolites are frequently detected in wastewaters.[4] Pereira *et al*. posited that human excretion stands as the principal contributor to pharmaceutical residues in aquatic environments. As a result, WWTPs, which fail to completely remove these compounds, emerge as likely culprits for the omnipresent pharmaceuticals in environmental samples.[5] Following treatment, pharmaceuticals are discharged into various ecosystems in several forms, including unaltered parent compounds, metabolic by-products, and transformation products created during water treatment processes such as biodegradation, photolysis, or hydrolysis. This results in the contamination of diverse water bodies, including surface waters, seawaters, groundwater, and even certain drinking water sources.[6] Alternative routes of aquatic contamination encompass sewage overflow, aquaculture, and the leaching from agricultural lands due to the spreading of manure and the existence of livestock, further amplifying the complexity of the contamination issue. Finally, improper disposal practices of unused or expired medications, involving their discard into household trash or flushing down sinks and toilets, result in the direct introduction of pharmaceuticals into landfill leachate or domestic wastewater, bypassing any scope for removal or degradation before entering the environment.

Despite their bioactive properties, the environmental concentrations of pharmaceuticals are usually low; however, their continuous input and persistence can lead to significant ecological impacts. These substances have the potential to cause sub-lethal effects on nontarget organisms, impacting various levels of the biological hierarchy from individuals to ecosystems. Furthermore, the potential human health implications of pharmaceutical contamination in the environment are only just beginning to be understood, with the issue of antimicrobial resistance (AMR) of paramount concern.[7]

In undertaking this comprehensive review, a rigorous examination of the existing body of literature was carried out, focusing on a wide array of research papers. While numerous studies have addressed the environmental impact of pharmaceuticals, delineating the sources, pathways, detection methods, and potential repercussions for flora, fauna, and human health, a significant gap has been identified. Most previous research has concentrated on delineating the problems without offering practical and actionable solutions to mitigate the challenges associated with pharmaceutical pollution. The present study seeks to bridge this critical gap by providing an in-depth and well-rounded overview of the current understanding, along with identifying research lacunae concerning the environmental consequences of pharmaceuticals. It does not only delineate the sources and pathways of pharmaceuticals' entry into the environment but also evaluates the effectiveness of conventional and emerging wastewater treatment technologies. More importantly, it considers the policy implications and offers strategic recommendations to reduce the environmental impact of pharmaceuticals.

The aim of this review is to foster increased awareness, stimulate further research, and contribute to the development of informed and effective policies. By focusing on both the problems and potential solutions, this review strives to create a robust foundation for future endeavors aimed at combating the increasingly pressing issue of pharmaceutical pollution in the environment.

Sources of Pharmaceutical Pollution

The contamination of our ecosystems with pharmaceutical residues is a complex issue, largely attributable to three primary sources: Pharmaceutical Manufacturing, Human and Animal Excretion, and Improper Disposal of Medications.[8]

Pharmaceutical manufacturing

The first significant source of pharmaceutical pollution is the industry itself, where the production of these compounds occurs on a massive scale. Despite rigorous regulations, manufacturing plants often directly release effluents into wastewater streams. These effluents, laden with APIs, find their way into aquatic environments when proper treatment protocols are not in place or are ineffective. This issue is exacerbated in regions with a high concentration of pharmaceutical production, resulting in severe localized pollution.[9]

Human and animal excretion

The second prominent source of pharmaceutical pollution is much more diffused and extends to virtually every household: The excretion of pharmaceutical residues by humans and animals. Not all APIs consumed are fully metabolized by the body; significant quantities are expelled via urine and feces, which eventually enter sewage systems. This issue is magnified with the use of veterinary pharmaceuticals, where residues can be directly introduced into the environment through the application of manure on the agricultural land. Such contributions make human and animal excretion a widespread and challenging source of pharmaceutical pollution to tackle.

Improper disposal of medications

Finally, the improper disposal of unused or expired medicines poses a significant threat to environmental health. Unused pharmaceuticals are often discarded into household trash or flushed down toilets and sinks. This practice results in these compounds directly entering landfill leachate or domestic wastewater, bypassing any chance for removal or degradation before they infiltrate environmental matrices. This seemingly insignificant act, when multiplied by the scale of global medication usage, represents a substantial and pervasive source of pharmaceutical pollution.

Understanding these sources is the first step toward designing effective strategies to mitigate the environmental impact of pharmaceuticals. As such, each warrants a detailed investigation and an urgent call for sustainable solutions.

Pathways to the Environment

Understanding the diverse ways through which pharmaceuticals make their way into the environment is a crucial step in grappling with this complex problem. These pathways are as varied as they are numerous, but four key conduits stand out for their pervasive influence: WWTPs, direct release into water bodies, soil contamination via fertilizers, and leaching and runoff.

Wastewater treatment plants

WWTPs are the linchpins in our management of wastewater, yet they were not designed with pharmaceutical removal in mind. As a result, these facilities are a substantial conduit for pharmaceutical residues to enter the environment. A large part of pharmaceuticals consumed by humans and animals is not fully metabolized, and the resulting compounds both the original substances and various metabolites are expelled through urine or feces. These waste products enter the sewage system, winding up in WWTPs.[10]

However, conventional treatment processes in WWTPs, mainly biological degradation and physicochemical separation, fail to completely eliminate pharmaceutical compounds. Although they are quite efficient in removing conventional pollutants, these processes are ill-equipped to deal with the complex chemical structures and resilient nature of many pharmaceuticals. Consequently, these compounds persist in the treated wastewater.[11]

This treated wastewater is either released back into rivers, lakes, or seas, or reused as irrigation water in agriculture, leading to the contamination of both aquatic and terrestrial ecosystems. It is important to underscore that this pathway is not merely a linear flow from consumption to environmental release; it's a cyclical problem. These pharmaceuticals can re-enter the human food chain through crops irrigated with contaminated water or seafood from polluted water bodies, demonstrating the pervasive and self-perpetuating nature of this issue.[12]

Direct release into water bodies

While WWTPs act as a significant indirect source, pharmaceuticals also find their way into our ecosystems through direct release. This release is often via industrial effluents, untreated or inadequately treated sewage, and stormwater runoff. Pharmaceutical manufacturing plants, in particular, can be a significant source of this direct release, especially when the factories are located in countries with less stringent environmental regulations.

In regions lacking adequate wastewater treatment infrastructure or regulatory oversight, the direct release of pharmaceuticals into water bodies becomes a primary pathway. The consequences of this direct release are profound and manifold. Aquatic organisms in these ecosystems bear the immediate brunt of this pollution, leading to various sub-lethal effects, alterations in biodiversity, and potential shifts in ecological balance. In the long term, this pollution can alter the structure and function of these ecosystems, with consequences that are hard to predict and even harder to reverse.

Soil contamination via fertilizers

Fertile soil is the lifeblood of terrestrial ecosystems and our agricultural practices. However, it also serves as a significant sink for pharmaceutical residues. The application of treated wastewater and biosolids from WWTPs in agriculture introduces a complex cocktail of pharmaceuticals into our soils. Although these substances are intended to enhance soil fertility and crop growth, they also carry the unintended consequence of soil contamination.

Pharmaceuticals present in the soil can be taken up by plants, potentially entering the food chain. They can also leach into groundwater or runoff into nearby water bodies, contaminating these vital sources of freshwater. Moreover, the soil acts as a complex chemical reactor, where pharmaceuticals can undergo various transformations due to biological, chemical, and physical processes. These transformations can lead to the formation of new compounds, whose environmental behavior and toxicological effects are often unknown.

Leaching and runoff

Leaching and runoff act as critical links connecting terrestrial and aquatic ecosystems in the context of pharmaceutical pollution. Leaching refers to the process where water percolates through the soil, dissolving and carrying with it various substances, including pharmaceutical residues. This process is particularly relevant in agricultural fields where manure or biosolids containing pharmaceuticals are applied, or in areas with extensive livestock operations.[13]

Pharmaceuticals leached from the soil can contaminate the groundwater, a vital source of drinking water. On the other hand, runoff, accelerated by precipitation events, transports surface-bound pharmaceuticals into local streams, rivers, or lakes. This pathway is particularly concerning as it can lead to sudden, episodic surges in pharmaceutical concentrations in aquatic ecosystems, presenting a severe threat to the organisms residing in these habitats.

These pathways, in all their complexity and interconnectivity, serve as a stark reminder of the omnipresence of pharmaceuticals in our environment. By recognizing these pathways, we pave the way for the development of targeted, efficient strategies to monitor, regulate, and mitigate this far-reaching problem. This understanding forms the foundation for advancements in treatment technologies, improvements in waste management practices, and the formulation of informed regulatory policies.

Persistence and Transformation of Pharmaceuticals in the Environment

Pharmaceuticals released into the environment are not inert; they undergo a series of transformations driven by physical, biological, and chemical processes. These transformations can change the pharmaceuticals' properties, behavior, and potential ecological impacts. However, it is important to note that many pharmaceuticals are designed to resist rapid breakdown in the human body to perform their therapeutic functions, contributing to their persistence in the environment.[14]

Physical processes (photolysis and hydrolysis)

Physical processes play a crucial role in the fate of pharmaceuticals in the environment. Among these, photolysis and hydrolysis are the key transformation mechanisms. Photolysis refers to the breakdown of compounds under the influence of sunlight. The intensity and wavelength of light, along with the optical properties of the environmental medium, significantly influence this process.[15] Pharmaceuticals in surface waters or shallow soils are particularly susceptible to photolysis.[16]

Hydrolysis, on the other hand, involves the cleavage of chemical bonds in a molecule by the addition of water, altering the molecule's structure and properties.[17] It is a critical process in aqueous environments and highly dependent on factors such as pH, temperature, and the presence of catalytic substances. However, the impact of these physical processes varies greatly across different pharmaceuticals, depending on their chemical structure and environmental conditions.[18]

Biological processes (biotransformation and biodegradation)

Biological processes, primarily biotransformation and biodegradation, also significantly influence the fate of pharmaceuticals in the environment. Biotransformation refers to the process where microorganisms, plants, or animals modify the chemical structure of a substance, leading to changes in its properties and behavior. This process can either detoxify the substance or, in some cases, transform it into a more harmful form.[19]

Biodegradation, a specific form of biotransformation, involves the complete breakdown of a substance by microorganisms into simpler, harmless substances, such as carbon dioxide, water, and basic nutrients.[20] In terms of pharmaceuticals, biodegradation can serve as a natural attenuation mechanism. However, the efficiency of this process is heavily influenced by environmental conditions and the specific microbial communities present. Moreover, the complex and diverse structures of pharmaceuticals often present a significant challenge to their complete biodegradation.[21]

Chemical processes (oxidation and reduction)

In addition to physical and biological processes, various chemical reactions also affect the fate of pharmaceuticals in the environment. Oxidation and reduction, collectively known as redox reactions, are among the most influential of these chemical processes.

Oxidation involves the loss of electrons, which typically results in the formation of more polar and potentially more water-soluble products. In contrast, reduction involves the gain of electrons, often leading to less polar and potentially less water-soluble products.[22] These reactions can drastically alter the behavior of pharmaceuticals in the environment, influencing their mobility, bioavailability, and toxicity.[23]

The complexity of these transformation processes underscores the difficulty in predicting the environmental fate and impacts of pharmaceuticals. Furthermore, these processes can sometimes lead to the formation of transformation products that could be more harmful or persistent than the parent compounds. Understanding these transformation processes and their interactions is, therefore, crucial in assessing the environmental risk of pharmaceuticals and informing appropriate mitigation strategies.

Detection and Monitoring of Pharmaceuticals in the Environment

Detection and monitoring of pharmaceuticals in the environment is a crucial step toward understanding their fate, distribution, and ecological impacts. Over the years, methodologies have evolved significantly, transitioning from conventional methods to more advanced, emerging techniques. Despite considerable advancements, numerous challenges and limitations persist, highlighting the need for ongoing research and innovation in this area.

Conventional methods

Conventionally, the detection of pharmaceuticals in environmental matrices has relied on techniques such as gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS). These methods have provided the backbone for environmental monitoring of pharmaceuticals due to their ability to detect and quantify a wide range of compounds in diverse sample matrices.

LC-MS is particularly well-suited for pharmaceuticals due to its sensitivity and selectivity for polar and ionic compounds, which are common properties of these substances.[24] In contrast, GC-MS is typically used for more volatile and thermally stable compounds.[25]

Furthermore, sample preparation techniques such as solid-phase extraction and liquid–liquid extraction are often employed to concentrate pharmaceuticals and remove potential matrix interferences.[26,27] These conventional methodologies have made significant contributions to our understanding of the occurrence and distribution of pharmaceuticals in the environment.

Emerging techniques

Despite the utility of conventional methods, the trace-level detection, wide variety of pharmaceuticals, and complex environmental matrices present considerable analytical challenges. Consequently, researchers have turned to more advanced techniques to improve detection and quantification.

High-resolution MS, such as time-of-flight and Orbitrap-based systems, is increasingly being employed.[28] These techniques offer exceptional resolution, accuracy, and sensitivity, allowing for the detection and identification of not only parent pharmaceuticals but also their metabolites and transformation products.[29]

Moreover, the use of tandem MS (MS/MS) provides additional structural information, enhancing the confidence of compound identification.[30] The application of hybrid techniques, such as LC coupled with both MS and nuclear magnetic resonance spectroscopy, further augments the characterization and quantification capabilities.[31]

Another emerging area is the use of biosensors and bioassays for pharmaceutical detection. These methods are based on the interaction between pharmaceuticals and biological elements, such as enzymes or antibodies, to produce a measurable signal. They offer the advantages of speed, cost-effectiveness, and the ability to detect biological effects, but their application in complex environmental matrices is still a challenging task.[32]

Challenges and limitations

Despite advancements, several challenges and limitations persist in the detection and monitoring of pharmaceuticals in the environment. These include issues related to sample preparation, such as the potential for sample contamination and loss of analytes during extraction and concentration steps.[33]

The complexity of environmental matrices also poses challenges for the method of selectivity and sensitivity. Diverse and variable matrices can interfere with detection, making it difficult to identify and quantify low-level pharmaceuticals among numerous other substances.

Moreover, many emerging and advanced techniques require significant expertise and expensive, specialized equipment, limiting their accessibility, and widespread application. In addition, the sheer variety of pharmaceuticals, each with different chemical properties and behavior, complicates method development and standardization.

Furthermore, the detection of pharmaceuticals alone does not provide a complete picture of environmental risk. The presence of transformation products and mixtures of multiple pharmaceuticals, along with their potential synergistic or antagonistic effects, adds another layer of complexity to risk assessment.[34]

Reflecting on the key insights from this section, while strides have been made in the detection and monitoring of pharmaceuticals in the environment, numerous challenges and limitations necessitate continued research and technological innovation. Improvements in analytical methodologies and an integrated, holistic approach to risk assessment will be vital in tackling the environmental impact of pharmaceuticals.

Ecological and Human Health Impacts of Pharmaceuticals in the Environment

The ubiquity of pharmaceuticals in the environment presents significant concerns for both ecological and human health.[35] These compounds, initially designed to interact with biological systems in precise ways, can exert unintended effects on nontarget organisms and systems when present in the environment. This section will explore the impacts on aquatic and terrestrial wildlife, potential human exposure pathways, and the critical link to AMR.

Effects on aquatic and terrestrial wildlife

Scientists assert that our understanding remains limited when it comes to the biological destiny and ecotoxicological impacts of pharmaceuticals and their by-products on aquatic and terrestrial organisms, as well as other wildlife within their habitats (Arnold *et al*., 2013). It is established that aquatic organisms, which are exposed to substantial quantities of wastewater residues throughout their lifetimes, are susceptible to an array of chemicals carried within these residues. Pharmaceuticals can pose substantial risks to both aquatic and terrestrial ecosystems due to their bioactive nature. Water bodies, such as rivers, lakes, and oceans, often serve as the final destination for many pharmaceutical residues, posing significant risks to aquatic biota, including fish, amphibians, invertebrates, and phytoplankton. Pharmaceuticals can exert a variety of toxic effects, ranging from acute to chronic and can impact organisms at various biological levels from molecular to population levels.

For instance, synthetic estrogens found in contraceptives have been associated with the feminization of male fish, leading to skewed sex ratios and reproductive impairments.[36] Paut Paut Kusturica *et al*. reported that the global human population annually emits roughly 30,000 kilograms of natural steroidal estrogens, alongside an additional 700 kilograms of synthetic estrogens, stemming solely from the use of birth control pills. Nonsteroidal anti-inflammatory drugs, such as diclofenac, have been linked to the near extinction of several vulture species in Asia due to renal failure.[37,38] Antidepressants such as fluoxetine can alter the behavior of marine and freshwater organisms, affecting feeding habits, growth rates, and predator-prey interactions.[39]

Similarly, terrestrial wildlife, especially those closely associated with water bodies or those that utilize irrigated fields, is not spared from the exposure. Pharmaceuticals in the soil can be taken up by plants, presenting a potential route of exposure for herbivores. For example, veterinary pharmaceuticals, like antibiotics and hormones used in livestock production, can persist in manure and, when applied as fertilizer, can contaminate terrestrial environments, potentially affecting soil organisms and plant health.[40]

The ecological impacts of pharmaceuticals in the environment are complex and can have ripple effects throughout the ecosystems. These compounds can interact with each other or with other environmental contaminants, resulting in additive, antagonistic, or synergistic effects, further complicating the prediction and assessment of risks.[41]

Potential human exposure pathways

At present, no research delineates any enduring human health impacts arising from sustained exposure to low doses of pharmaceuticals in the water supply. Nevertheless, there are uncertainties and discrepancies associated with the quantitative methodologies employed to compute the predicted and actual environmental concentrations of APIs.[42] Human health can also be impacted by pharmaceuticals in the environment, primarily through exposure to contaminated water and food sources. Drinking water, including both surface water and groundwater, can be contaminated by pharmaceuticals. While wastewater treatment processes can remove a significant portion of pharmaceutical residues, some compounds resist degradation and can end up in the treated water released back into the environment. Pharmaceuticals have been detected in both source and treated drinking water, although typically at low concentrations.[43]

Pharmaceuticals can also enter the human food chain through the consumption of contaminated plants and animals. For example, plants irrigated with contaminated water or grown in contaminated soils can uptake pharmaceuticals, which may then be consumed by humans. Similarly, fish and other aquatic organisms can bioaccumulate certain pharmaceuticals in their tissues, presenting another potential route of human exposure.[44]

While the concentrations of pharmaceuticals in drinking water and food are generally considered low, the potential for long-term chronic exposure raises concerns. The effects of long-term exposure to low levels of pharmaceutical mixtures are not well understood and present a significant challenge in assessing potential human health risks. This sentiment was further echoed by Mackuľak *et al.*, (2019)[2] who posited in their research that determining whether heightened concentrations of certain drug metabolites in agricultural plants may ultimately pose a health risk to humans is a challenging task. However, they did note that the mere presence of pharmaceuticals or their metabolites in a plant could potentially lead to adverse effects on the plant's growth and development.

Link to antimicrobial resistance

The presence of antimicrobial compounds, including antibiotics, in the environment has been increasingly linked to the global health crisis of AMR.[45,46] Antimicrobials in the environment can exert selective pressure on microbial communities, promoting the survival of resistant strains and facilitating the horizontal gene transfer of resistance mechanisms.[47]

WWTPs, in particular, are the hotspots for the emergence and spread of antimicrobial-resistant bacteria, as they bring together high densities of diverse microbial communities, residual antimicrobials, and mobile genetic elements. Antimicrobial-resistant bacteria and resistance genes can then be released into the environment through treated effluent and biosolids.[48]

Resistance can spread through various environmental compartments, including water, sediment, and soil, impacting both environmental and human health. Humans can be exposed to resistant bacteria through direct contact with contaminated environments, consumption of contaminated water or food, or via vectors such as insects.[49] AMR represents a significant threat to the efficacy of our current antimicrobial therapies and is a major concern for public health.[50]

In all, the presence of pharmaceuticals in the environment has far-reaching and complex implications for both ecological and human health. Continued research is necessary to further our understanding of these impacts and to develop strategies to mitigate potential risks. Considering the global scale and complexity of this issue, a multidisciplinary approach integrating fields such as environmental science, toxicology, microbiology, epidemiology, and risk assessment is crucial moving forward.

Policy Implications and Future Directions in Managing Pharmaceuticals in the Environment

The presence of pharmaceuticals in the environment is not a new concern; however, the implications of this contamination and the required response present a relatively novel and complex challenge to policy and decision makers. This section will delve into current regulations and their effectiveness, provide recommendations for policy-makers, and outline areas for future research in addressing this multifaceted issue.

Current regulations and their effectiveness

The regulatory frameworks for pharmaceuticals in the environment are inconsistent and vary across countries, contributing to the complexity of the issue. At present, most pharmaceutical regulations focus on the approval process for new drugs, safety and efficacy in use, and control of manufacturing practices, but rarely consider the environmental fate and effects of these substances.

Enick and Moore describe Environmental Risk Assessments (ERAs) as methodical processes grounded in scientific principles, wherein risk is optimally defined by the objective likelihood of a perilous occurrence.[51] Deblonde and Hartemann explained that ERA systems categorize environmental hazards into three primary classifications based on the drug's characteristics: persistence, which refers to the drug's resistance to degradation in the aquatic environment; bioaccumulation, the drug's potential to accumulate in the adipose tissue of aquatic organisms; and toxicity, the potential of the drug to pose toxic risks to aquatic life.[52] Jones *et al*. stated that despite the introduction of guidelines for new pharmaceuticals in the USA and proposed drafts for ERA of new pharmaceuticals in the European Union, it is unlikely these legislative measures will significantly impact the environmental levels of the many pharmaceutical products already approved for use.[53] In the European Union, an ERA is mandatory for the approval of new pharmaceuticals.[54] However, this is not the case in many other regions including the United States. Even where ERAs are mandatory, they often have limitations. For example, they are typically based on the predicted environmental concentration (PEC) and do not account for the complex and dynamic nature of environmental systems.[55]

Moreover, they do not consider the impacts of pharmaceutical mixtures, which is more representative of the real-world scenario. For instance, the study by Giunchi *et al*. identified a significant environmental risk for multiple pharmaceuticals in Italy, including levonorgestrel, ciprofloxacin, amoxicillin, azithromycin, venlafaxine, sertraline, and diclofenac, and a moderate risk for others, calculated solely on the basis of the ratio between the PEC and the predicted no-effect concentration.[56]

On the waste management side, current wastewater treatment regulations do not mandate the removal of pharmaceuticals, with existing standards focusing more on traditional pollutants. As a result, conventional wastewater treatment processes, not designed to remove pharmaceuticals, often fail to fully eliminate these substances, leading to their discharge into the environment.[57]

Thus, while current regulations have been effective in addressing traditional environmental contaminants, they have been largely ineffective in tackling the issue of pharmaceutical pollution, necessitating the development of more targeted and robust regulatory frameworks.

Areas for future research

Addressing the issue of pharmaceuticals in the environment necessitates a substantial research effort to close current knowledge gaps and to provide the evidence base necessary for policy development. Future research should focus on improving our understanding of the occurrence, fate, and effects of pharmaceuticals in various environmental compartments, including air, which has received less attention compared to water and soil. Studies should investigate the impacts of long-term, low-concentration exposure to pharmaceutical mixtures on both wildlife and humans. This includes research on sub-lethal effects, impacts on microbiomes, and potential links to chronic diseases in humans. Research is also needed on the role of the environment in the development and spread of AMR, and on strategies to mitigate this risk. In terms of detection and monitoring, research should aim to develop sensitive, cost-effective, and field-deployable methods for detecting pharmaceuticals in the environment. There is also a need for research on the social and economic aspects of pharmaceutical pollution, including public perceptions, behaviors, and willingness to pay for solutions, and on the cost-effectiveness of different policy options. The development and evaluation of advanced wastewater treatment technologies, green pharmacy approaches, and pollution prevention strategies represent another important area for future research.

Drawing together the principal arguments made thus far, addressing the issue of pharmaceuticals in the environment is a considerable challenge requiring comprehensive, integrative, and innovative approaches. While substantial progress has been made, much work lies ahead. It is essential that policy makers, researchers, industry, and the public work together toward solutions to ensure the sustainable management of pharmaceuticals and the protection of environmental and human health.

Recommendations

Addressing the escalating issue of pharmaceutical pollution calls for a comprehensive approach such as the Dutch chain approach proposed by Moermond and de Rooy that involves different stakeholders, ranging from consumers to policy-makers. One of the pivotal steps toward managing this problem begins with public education and awareness campaigns.[58] These programs can effectively highlight the environmental and health risks associated with the improper disposal of medicines. By informing the public about the significance of not discarding unwanted drugs down the toilet or sink, but instead returning them to pharmacies or designated collection points, we can substantially reduce the quantity of pharmaceutical pollutants that enter our water systems.

Beyond the role of the individual, certain systemic changes can also be instrumental in mitigating pharmaceutical pollution. For instance, the implementation of drug take-back programs by governments and pharmacies can provide a secure and environmentally friendly method for consumers to dispose of their expired or no longer needed medicines.

The role of pharmaceutical companies in this issue cannot be overstated. These organizations can refine their manufacturing processes to reduce waste (Paut Kusturica *et al*., 2022) and limit the environmental impact of drug production.[37,59] Embracing technologies like "green chemistry" and promoting the development of "green" pharmaceuticals can make a significant difference. These "green" pharmaceuticals, effective in treatment but designed to break down rapidly in the environment postexcretion, can substantially decrease the environmental load of pharmaceuticals.[60]

Advancements in wastewater treatment technologies are also a crucial element in combating this problem. Governments and water authorities should actively invest in advanced methods that are capable of removing pharmaceuticals and their metabolites. The utilization of these innovative solutions could not only protect our water systems but also significantly lower the risk of pharmaceutical pollutants affecting aquatic ecosystems and ultimately human health.

Regulation also plays a vital role in controlling pharmaceutical pollution. A more stringent regulatory framework for ERAs of pharmaceuticals can help manage their release into the environment. This could encompass stricter regulations on pharmaceutical manufacturing and waste disposal, as well as the introduction of laws ensuring that pharmaceuticals are included in environmental monitoring programs. Paut Kusturica *et al.*(2022) posited that it seems more logical to address the issue of pharmaceutical pollution at the source rather than focusing on ways to improve the elimination processes once these substances have entered the environment. They also emphasized that, given the undeniable health benefits of pharmaceuticals to humanity, efforts should aim not to limit access to necessary medications, but to mitigate their detrimental impact on the environment.

Finally, the importance of research should be underscored. Ongoing studies into the effects of pharmaceutical pollutants on wildlife and humans, the pathways through which they infiltrate the environment, and effective strategies for their removal or mitigation are critical. This persistent quest for knowledge can lead to innovative solutions, while also informing policy and best practices.

To encapsulate the key points discussed, the fight against pharmaceutical pollution involves an interconnected web of strategies that span from the individual level to systemic changes. By fostering collaboration across sectors, investing in infrastructure and research, and maintaining a steadfast commitment to minimizing the environmental footprint of our healthcare practices, we can substantially curb pharmaceutical pollution, thereby safeguarding our environment and health.

Conclusion

The journey through this comprehensive review has underscored the complexity and significance of the issue surrounding the environmental impact of pharmaceuticals. From the detailed elucidation of the numerous pathways through which pharmaceuticals enter the environment to the intricate processes that facilitate their persistence and transformation, it is clear that the scope of the problem is vast and multifaceted. The fact that these pharmaceutical residues have been detected in various environmental compartments signifies the global and far-reaching impact of this issue. Our exploration of the effects of these pharmaceuticals on ecological and human health reveals a growing body of evidence suggesting significant potential risks. The documented impacts on aquatic and terrestrial wildlife, the potential exposure pathways to humans, and the link to AMR all provide compelling reasons for urgent attention and action. However, the review also reveals considerable gaps in our understanding of the problem. Many aspects of the environmental fate and effects of pharmaceuticals are not fully understood, and detection and monitoring techniques, while advancing, still face significant challenges. Furthermore, our understanding of the social and economic dimensions of pharmaceutical pollution is still in its infancy. This review has underscored the insufficiency of current regulations in addressing the issue of pharmaceutical pollution. Although regulations exist, their effectiveness is limited by their focus on traditional contaminants and their failure to fully incorporate the unique challenges presented by pharmaceuticals. Nevertheless, the potential for policy makers to drive change is substantial, and this review provides a clear blueprint for the necessary regulatory responses.

Our evaluation of future directions suggests a plethora of opportunities for further research and innovation. From the development of advanced wastewater treatment technologies and green pharmacy approaches, to the exploration of public perceptions and the cost-effectiveness of different policy options, it is clear that there is an exciting and critical research agenda to be pursued. Ultimately, this review paints a complex picture of a significant global challenge. The environmental impact of pharmaceuticals is an issue of growing concern that requires immediate and coordinated action. However, it also presents an opportunity: to drive innovation in pharmaceutical design and wastewater treatment, to rethink our relationship with pharmaceuticals, and to place the health of our environment at the center of our health-care systems. As we continue to grapple with this challenge, one thing is clear: our actions now will shape the legacy we leave for future generations.

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