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Minimizing the environmental impact of unused pharmaceuticals: Review focused on prevention

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Pharmaceuticals are essential for human health, but they become an environmental concern when entering the environment which occurs when residues are excreted after consumption or when unused pharmaceuticals are discarded improperly. Although there are no developed detection methods for all pharmaceuticals that reach the ecosystem, certain groups have been proven to cause adverse effects on ecosystems, including increased mortality in aquatic species and changes in physiology, behavior, or reproduction. Particular attention is devoted to these groups of pharmaceuticals and their environmental impact. In this review, the authors suggest measures for the reduction of unused pharmaceuticals in the environment, with a strong emphasis on prevention. Various policy interventions are recommended across the lifecycle including source-directed, user-orientated, and waste management measures, to prevent the creation of household pharmaceutical waste and to ensure environmentally friendly ways of pharmaceutical household waste disposal. Preventive measures include rational pharmaceutical consumption, prescribing greener drugs, or designing pharmaceuticals that are benign and easily biodegradable, improved disease prevention, personalized medicine, enhanced dimensioning of pack sizes, and marketplaces for redistribution of unused pharmaceuticals. The next step is to prevent unavoidable waste to reach the environment, so proper collection and disposal of unused pharmaceuticals is of utmost importance. Finally, educating health professionals and the public and partnership between environmental and healthcare scientists are of vital significance in all stages of the pharmaceuticals' lifecycle. Minimalization of the level of pharmaceuticals in the environment will benefit human life.

KEYWORDS

unused pharmaceuticals, environmental impact, waste prevention, waste reduction, pharmaceutical waste disposal

1 Introduction

Demographic, epidemiological and lifestyle changes such as aging population, the increase of chronic diseases, the availability of inexpensive generic treatments and ease of access to vast amounts of over-the-counter drugs have been key drivers for increased pharmaceutical consumption (González Pena et al., 2021; European Commission, 2019). The global increase in pharmaceutical consumption has led to an enhanced international awareness of the issue of unused pharmaceuticals (UPs) in households and the harmful environmental and health effects of their improper disposal (Paut Kusturica et al., 2016; Mitkidis et al., 2022). Pharmaceuticals in the environment are a challenge to manage as they are designed to interact with a living system and produce a pharmacological response at low doses, which makes them of environmental concern even at low concentrations. Secondly, pharmaceuticals are designed to be stable in order to reach and interact with target molecules, meaning that either they are very slow to degrade or their constant use leads to continuous release into the environment at rates above degradation rates. Also, conventional wastewater treatment plants are not designed to fully remove pharmaceuticals from wastewater (OECD, 2019).

There are two main ways by which pharmaceuticals enter the environment: excretion and improper disposal (OECD, 2022). In both cases, pharmaceuticals end up in sewage treatment plants that are generally not designed to remove such pollutants from wastewater (Thomas,Felicity and WHO, 2017). Pharmaceuticals have been detected primarily in surface waters, but also in groundwater, soil, manure and even drinking water. The presence of pharmaceuticals in freshwater and terrestrial ecosystems can result in the uptake of pharmaceuticals into wildlife with the potential to bioaccumulate (Zenker et al., 2014). Humans are subsequently exposed to pharmaceuticals *via* drinking water, and ingestion of its residues in plant crops, fish, dairy products and meat. The consequences of pharmaceuticals in the aquatic environment are an issue of rising concern, with impacts that can range from molecular alterations to effects at the population level (Queirós et al., 2021). Given that this is a growing environmental and health concern globally, this review pursues to answer the following questions: 1) which pharmaceuticals have been proven to cause detrimental effects on the environment 2) what are the options to reduce detrimental environmental impact of UPs before they reach the environment.

2 Effect of pharmaceuticals on the environment and human health

Human pharmaceuticals are listed as emerging contaminants by UNESCO. Their detection and elimination represent the crucial step according to the "2030 Agenda for Sustainable Development" Goal Targets (UNESCO 2020). The concentrations of drugs found in the environment are under therapeutic levels. In water surfaces that receive treated wastewater, pharmaceuticals are detected in concentrations less than 100 ng/L (Vumazonke et al., 2020; Björklund and Svahn, 2021; Li et al., 2021). These low concentrations are the reason for the difficult assessment of their toxic effects on the ecosystem and human health. The vast majority of pharmaceuticals have not been sufficiently explored for their long-term toxic effects, presence and fate in the environment (aus der Beek et al., 2016). However, certain pharmaceutical groups such as beta-blockers, antibiotics, anticancer drugs and endocrine disruptors (Nie et al., 2013; Kovács et al., 2015; Godlewska et al., 2021; Ortuzar et al., 2022) have been shown to cause devastating effects on the ecosystem including increased mortality, and impairment of the physiological and reproductive functions of aquatic species. Also, devastating effects are reflected on human health because it is impossible to separate humans from nature. Still, the scale of the problem remains highly unknown, due to the huge number of pharmaceuticals and the challenges of evaluating risks related to multi-compound exposure at low doses and over long periods of time (Kümmerer, 2019). The German Environment Agency (UBA) announced that 10% of medicines on the market represent potential environmental risk. Even though there are no developed detection methods for all pharmaceutics that reach the ecosystem some of them are predominantly present and proven to cause negative adverse effects on ecosystems (Küster et al., 2010). These groups include hormones, antibiotics, antidepressants, anti-inflammatories and analgesics, beta-blockers and anticancer pharmaceuticals (Monteiro and Boxall, 2010).

The presence of estrogens in the environment represents a serious contamination problem (Bilal and Igbal, 2019). The world's human population discharges approximately 30,000 kg/yr of natural steroidal estrogens and an additional 700 kg/yr of synthetic estrogens only from birth control pill practices. However, the abundance of these hormones in the environment mostly originates from the livestock industry due to the wide usage of a variety of growth-regulating steroids to enhance the production rate of meat. Undoubtedly, estrogens are essential for normal human physiology but can have serious adverse effects if accumulate in the environment and enter the human food chain (Adeel et al., 2017). These types of hormones are capable to perturb human and animal physiology and affect normal reproduction. Estrogens as pollutants are also linked with a higher incidence of breast cancer in women and prostate cancer in men (Nelles et al., 2011; Trevino et al., 2015).

Antimicrobial resistance represents a global public health issue, especially considering the increased use of antibiotics during the COVID-19 pandemic which led to the depletion of the last line of antibiotics (Lai et al., 2021). It has been noted that the application of antibiotics in human medicine, veterinary medicine and agriculture is related to the contamination of the different parts of the environment which contributed to an increase in antibiotic resistance and the occurrence of ecotoxicological effects (Zainaba et al., 2020). A lack of proper antibiotic disposal practices among patients by discharging them into the sewage systems represents also a growing environmental threat to public health (Anwar et al., 2020). Also, the strong impact of antibiotic pollution after long-term exposure can affect human health, especially in patients with chronic diseases including obesity, diabetes, and asthma (Ianiro et al., 2016).

The worldwide contamination with antidepressants significantly increased during the COVID-19 pandemic (Rabeea et al., 2021). To this day antidepressants have been detected in urban and non-urban water systems. Many different types of aquatic animals bioaccumulate different antidepressants in their tissues which leads to cytotoxicity, genotoxicity, stress response alteration, increase/decrease in weight and length, and liver and kidney damage (Castillo-Zacarías et al., 2021). Considering that the human and animal environments significantly overlap, antidepressant pollution (sertraline, fluoxetine) has also impacted human neurodevelopment and different psychiatric conditions (Abbey-Lee et al., 2018; Li et al., 2020). Although psychopharmaceuticals are generally present in wastewaters at subtherapeutic levels they are capable to induce biological effects at low doses, particularly in an environment is often presents a combination of several psychopharmaceuticals which increases the risk of their toxic effects (Chan et al., 2021).

Large amounts of non-steroidal anti-inflammatory drugs, including acetaminophen, acetylsalicylic acid, ibuprofen, diclofenac and naproxen significantly contribute to the pollution of the environment, particularly as they have been found in nanograms and micrograms in soil, wastewater, surface water, drinking water, groundwater (Tyumina et al., 2020). These drugs have chronic ecotoxic effects as they are very resistant to biological transformation in the environment due to their stable chemical structure. It is known so far that they mostly cause disorders in the organs of invertebrates and vertebrates by inducing oxidative stress and disrupting activity of detoxification enzymes (Hodkovicova et al., 2022). These pharmaceuticals can also cause cardiovascular abnormalities, and hepatotoxicity and disrupt oocyte maturation by an unknown mechanism (Lister and Van Der Kraak, 2009; Xia et al., 2017).

Beta-blockers represent pharmaceutical compounds that show the potential to be highly persistent and toxic in the environment (Kuster et al., 2010). While some data about their environmental adsorption are lacking, it is known that these pharmaceuticals demonstrate moderately high solubility in water and have been detected in surface waters at concentrations of μg/L. These compounds are very resistant to hydrolysis, bioavailable and mobile in the environment. Therefore, their accumulation in the environment can cause unexpected consequences to different living organisms. In accordance with European Union Directive 93/67EEC, metoprolol and propranolol represent adverse compounds to aquatic species. This indicates results from tests performed on green alga (*S. vacuolatus*) (Maszkowska et al., 2014).

Anticancer drugs stop the growth and division of cells and by their release into the environment, these pharmaceuticals affect the ecosystem through disruption of fertility and significant genetic alteration of living organisms. Anticancer drugs are prescribed in lower quantities but their effects even in ng/l concentrations are devastating, including mutagenic, carcinogenic, and teratogenic consequences to aquatic species. Due to their application and inappropriate disposal, cytostatic drugs are often detected in wastewater from pharmaceutical manufactories and hospitals. The detection frequency of anticancer drugs in hospital wastewater is 58% and cisplatin is marked as one of the most hazardous pharmaceuticals (Dan et al., 2021). The presence of cisplatin in waterbodies even at ng/l concentrations can cause toxic effects on aquatic species (Roque-Diaz et al., 2021) The surface water Watch List (WL) includes information about emerging pollutants that can cause a significant risk to aquatic organisms and humans upon consumption of contaminated drinking water. This list contains all the above-mentioned groups of pharmaceuticals (Gomez Cortes et al., 2022).

3 Measures to mitigate environmental impacts of UPs from households

Prior to seeking ways to improve the elimination processes of pharmaceuticals once they reach the environment, it is apparently more rational to act at source(Table 1). Considering that pharmaceuticals provide an unquestionable benefit to the health of humanity, great care must be taken not to restrict access to those pharmaceuticals that are necessary but to prevent their negative environmental impact (Argaluza et al., 2021).

3.1 Prevention of pharmaceutical waste

The findings from a recent study showed that more than one-third of UPs were classified as preventable pharmaceutical waste (Bekker et al., 2018). Given that 'prevention is better than cure' the priority is avoidance of pharmaceutical waste. Prevention of pharmaceutical waste could be performed through various measures such as improved disease prevention, personalized and precision medicine, and improved dimensioning of packaging sizes (Straub, 2016; Klatte et al., 2017; OECD, 2022).

Where the dose of pharmaceuticals must be calculated on a per-patient basis there exists a degree of wastage. The medication that is dosed based on the patient's weight or body size is often wasted due to the required dose not matching the vial size. Therefore, to encounter medication waste, manufacturers ought to facilitate more variety in package sizes and avoid large packages. Policymakers can urge manufacturers to stimulate a reasonable set of size options by requiring a maximum percentage of waste (Bach et al., 2016). Furthermore, the risk of accumulation of UPs in households can be reduced by reducing packaging sizes, particularly for new drug treatments and starter packs. Also, the appropriate range of pack sizes should be in line with the treatment duration and the posology in the summary of product characteristics (European Commission, 2021; OECD, 2022).

Pharmaceutical waste is only partially preventable, and should therefore be accompanied by other waste-minimizing approaches. Throughout society, recycling programs for the sustainable use of different resources have been implemented. A similar approach could be implemented for pharmaceutical waste, such as the redispensing of UPs that are within the expiration date (Bekker et al., 2018). Bekker et al. estimated that one-fifth of the returned medications were potentially suitable for redispensing. Returned UPs were considered eligible for redispensing if the package was unopened, undamaged and the period between the return and the expiry date was at least 6 months. One of the possible solutions for unused close-to-expiry-date pharmaceuticals is marketplaces that offer better matching of supply and demand. Although redispensing has the potential to contribute to waste minimization and monetary savings, it is still not applied in the practice due to concerns regarding counterfeits, quality assurance, and following legal restraints. However, some initiatives occur. In the Netherlands, there is a platform under the name PharmaSwap that allows certified pharmacists to sell undamaged UPs before their expiration date to other pharmacies, often at reduced prices. Likewise, two US start-ups are founded with the aim to collect and redistribute UPs to patients with low income (OECD, 2022). Redispensing is a promising way of UPs minimization, but requires a thoughtful implementation strategy with comprehensive communication with all stakeholders, paying particular attention to product quality assurance, financial handling, and legal aspects.

3.2 Collection schemes and take-back systems for household pharmaceutical waste

The practice of improper disposal of UPs from households represents a global phenomenon. Thus, effective collection schemes and take-back programs with the main purpose to offer an easy method for disposal of UPs represent an important measure to protect the environment (Paut Kusturica et al., 2016). Separate collection systems help avoid environmental leakage caused by flushing pharmaceuticals *via* drain or by mixing them with solid household waste that is destined for landfills without leachate collection (Masoner et al., 2016). The approaches used for collection differ among countries, but in general, pharmacies play an essential role. One-day collection events or mail-back envelopes are also available in some countries (e.g., United States). Some programs rely only on government funding (e.g., Australia) while others are financed by the pharmaceutical industry or pharmacies that provide support voluntarily or driven by extended producer responsibility (EPR) legislation (OECD, 2022).

Given that financial moment plays a significant role in UPs disposal systems, one of the valuable solutions is an implementation of the EPR laws which require that pharmaceutical manufacturers manage their products in all phases of their life cycle, including end-of-life treatment and waste management. Countries that have pursued an EPR approach shift the financial and organizational burden of UPs collection and disposal from the government to the pharmaceutical industry (Paut Kusturica et al., 2020). As a result, EPR implements the "producer pays principle", moving waste management costs from taxpayers to manufacturers. Companies can incorporate these costs in the price and provide services more cost-efficiently. European waste legislation currently provides a global framework for the implementation of EPR law in Europe and its policies have been designed and implemented in a very heterogeneous manner across Europe (OECD, 2022).

3.3 "Eco-prescription"

"Eco-prescription" or "green prescription" implies that the prescriber should consider the characteristics and environmental behavior of pharmaceuticals when prescribing (Daughton and Ruhoy, 2011). For instance, although oxazepam is considered a good option for the elderly due to its suitable pharmacokinetic profile, it is excreted unchanged *via* urine and accumulates for decades without biodegrading. From an environmental perspective, pharmaceuticals that are metabolized to inactive metabolites prior to elimination are preferable (Daughton, 2014). Incorporating environmental criteria in the use of pharmaceuticals is crucial, and it may represent a true revolution in pharmacology (Lertxundi et al., 2020).

The Stockholm County Council possesses an environmental classification of pharmaceuticals, created from a joint initiative between producers, authorities, and public health professionals. The classification indicates the risk and environmental hazards of pharmaceuticals determined based on the active pharmaceutical ingredient's persistence, bioaccumulation potential and toxicity. The risk refers to the likelihood that a pharmaceutical is toxic to aquatic organisms. Prescribers may incorporate this information when using pharmaceuticals for individual patients and choose

TABLE 1 Measures to mitigate impacts of UPs.

UPs mitigation	Measure	Description
UPs avoidance	Disease prevention	Communication and education activities and policy interventions aimed at reducing the development and severity of chronic diseases and other morbidities can reduce pharmaceutical consumption and UPs creation
	Personalized medicine	Fewer and more effective treatments can be achieved by using pharmaceuticals that are better targeted to patients' needs
	Dimensioning	Reducing packaging sizes for new drug treatments and starter packs can reduce risk of accumulation of UPs in households
	Marketplace for UPs	A marketplace for UFs that are close-to-expiry-date, unopened and undamaged provides better matching of supply and demand
Collection and safe final disposal of UPs	Collection in mixed municipal solid waste and controlled final disposal	Collection in mixed municipal solid waste and incineration in state-of-the-art incinerators
	Drug take-back programs	Take-back programs can prevent improper disposal of UPs from households
	EPR schemes	EPR implements the "producer pays principle", moving waste management costs from tax payers to pharmaceutical industry
"*Eco-prescription*"	Change prescriptions to more environmentally-friendly drugs	The "Wise List" incorporate environmental aspects to recommend drugs in ambulatory care prescribing
"*Green pharmacy*"	Development of more "environmentally friendly" pharmaceuticals	Designing more biodegradable pharmaceuticals that are less harmful for the environment ("benign by design")
Increase awareness and induce behaviour change	Information campaigns	They can be financed and managed by public authorities, the private sector, NGOs or be an accompanying requirement in the design of EPR schemes
	Incentives for returning UPs to pharmacies	Refunds or other rewards to nudge consumers for returning UFs to collection points
	Pharmaceutical ecolabelling	A mandatory information in EU countries
	Environmental classification schemes	Environmental classifications schemes allow doctors to make informed prescription choices

those that are environmentally friendly. To date, the "Wise List" (Kloka Listan) is the only multifaceted approach incorporating environmental aspects to recommend drugs in ambulatory care (Gustafsson et al., 2011).

3.4 New development or redesign of pharmaceuticals

To follow the concept of environmental protection, the pharmaceutical industry should develop promising concepts to minimize the content in excretion while ensuring sufficient pharmacologically active concentrations in the patient. "Green pharmacy" recognizes the potential for designing new more biodegradable pharmaceuticals that are less harmful to the environment (Daughton and Ruhoy, 2011). "Greener drugs" also contribute to the Sustainable Development Goals 6 (Clean Water), 3 (Health), 9 (Sustainable industries), 11 (Sustainable cities) and 12 (Responsible production and consumption) of the United Nations (Kummerer, 2019). There are already some examples of the development of more "environmentally friendly" pharmaceuticals, such as glufosfamide and green drug delivery systems (Dai et al., 2016; Banik, 2020). Scientists are currently developing an effective and environmentally friendly variant of the antibiotic ciprofloxacin which is a very stable pharmaceutical. Through computer modeling, the existing active substance is analyzed and changed theoretically for improved biological degradability and lower toxicological effects. The most promising candidates will be synthesized and tested *in vitro* (Kummerer, 2019).

3.5 Education and information campaigns

The limited consumers' awareness of proper disposal practices weakens their impact on disposal practices in many countries (Paut Kusturica et al., 2016). Information campaigns can increase the awareness and use of environmentally friendly ways of pharmaceutical waste from households. A good example is The #Medsdisposal campaign, a European initiative jointly coordinated by several European supply chain and healthcare organizations and supported by media campaigns in different languages. The initiative aimed to combat the detrimental impacts of mishandled pharmaceuticals on the environment by educating consumers about proper disposal routes and available take-back systems in different European countries. The German campaign entitled: "No pharmaceuticals down the toilet or sink!" is also considered a cost-efficient and effective educational campaign (OECD, 2022).

Furthermore, awareness and behavioral change can be achieved with special instructions for disposal that appear on the outer packaging or in the information leaflet of the drug, which is mandatory in EU countries. Incentives for returning UPs to collection points, such as various rewards to encourage consumers to adopt proper disposal practices are also useful approaches. For example, in Sweden, most pharmacy chains offer bonus credit points to consumers who return UPs to collection points. Furthermore, eco-labels on the environmental impact of different pharmaceuticals can influence consumer choice and awareness and help doctors make a decision while prescribing medications. The aforementioned environmental classification schemes include about 200 pharmaceuticals that are available online for consumers and prescribers (Stockholm County Council, 2014). The advice on proper drug disposal should also routinely follow drug dispensing. Pharmacists can play a key role in educating their customers on proper medication disposal methods (Paut Kusturica et al., 2016).

4 Conclusion

Environmental pollution with pharmaceuticals is a complex public health challenge that entails scientific doubts and involves a great number of stakeholders with various interests and at different organizational levels: governments, non-governmental organizations, scientific institutions, manufacturers, industry and households.

Various policy interventions should be implemented across the pharmaceutical lifecycle including source-directed, user-orientated and waste-management activities. The most valuable solutions should be implemented at source before pharmaceuticals reach the environment. These measures include rational pharmaceutical consumption, prescribing greener drugs, or designing pharmaceuticals that are benign and easily biodegradable. Improved disease prevention, personalized medicine, enhanced dimensioning of packaging sizes, and marketplaces for redistribution of UPs can to some extent prevent pharmaceutical waste creation. The next step is to prevent unavoidable waste to reach the environment, thus appropriate collection and disposal of UPs is essential and needs to be tailored to the national context and local challenges. Finally, educating health professionals and the public and partnership between environmental and healthcare scientists are of crucial importance in all phases of the pharmaceuticals' lifecycle. The heart of all joint efforts should be the "One Health" approach to tackle pharmaceutical waste and enhance human, animal, and environmental health that are strongly interconnected.

Author contributions

MPK: conceptualization. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Abbey-Lee, R. N., Uhrig, E. J., Garnham, L., Lundgren, K., Child, S., and Løvlie, H. (2018). Experimental manipulation of monoamine levels alters personality in crickets. *Sci. Rep.* 8, 16211. doi:10.1038/s41598-018-34519-z

Adeel, M., Song, X., Wang, Y., Francis, D., and Yang, Y. (2017). Environmental impact of estrogens on human, animal and plant life: A critical review. *Environ. Int.* 99, 107–119. doi:10.1016/j.envint.2016.12.010

Anwar, M., Iqbal, Q., and Saleem, F. (2020). Improper disposal of unused antibiotics: an often overlooked driver of antimicrobial resistance. *Expert. Rev. anti. Infect. Ther.* 18, 697–699. doi:10.1080/14787210.2020.1754797

Argaluza, J., Domingo-Echaburu, S., Orive, G., Medrano, J., Hernandez, R., and Lertxundi, U. (2021). Environmental pollution with psychiatric drugs. *World. J. Psychiatr.* 11, 791–804. doi:10.5498/wjp.v11.i10.791

aus der Beek, T., Weber, F. A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., et al. (2016). Pharmaceuticals in the environment—global occurrences and perspectives. *Environ. Toxicol. Chem.* 35, 823–835. doi:10.1002/etc.3339

Bach, P. B., Conti, R. M., Muller, R. J., Schnorr, G. C., and Saltz, L. B. (2016). Overspending driven by oversized single dose vials of cancer drugs. *BMJ* 352, i788. doi:10.1136/bmj.i788

Banik, B. K. (2020). *In advances in green chemistry, green approaches in medicinal chemistry for sustainable drug design*. Netherland: Elsevier.

Bekker, C., van den Bemt, B. J. F., Egberts, A. C. G., Bouvy, M. L., and Gardarsdottir, H. (2018). Patient and medication factors associated with preventable medication waste and possibilities for redispensing. *Int. J. Clin. Pharm.* 40, 704–711. doi:10.1007/s11096-018-0642-8

Bilal, M., and Igbal, H. M. N. (2019). Persistence and impact of steroidal estrogens on the environment and their laccase-assisted removal. *Sci. Total. Environ.* 690, 447–459. doi:10.1016/j.scitotenv.2019.07.025

Björklund, E., and Svahn, O. (2021). Total release of 21 indicator pharmaceuticals listed by the Swedish medical products agency from wastewater treatment plants to surface water bodies in the 1.3 million populated county skåne (scania), Sweden. *Molecules* 27, 77. doi:10.3390/molecules27010077

Castillo-Zacarías, C., Barocio, M. E., Hidalgo-Vázquez, E., Sosa-Hernández, J. E., Parra-Arroyo, L., López-Pacheco, I. Y., et al. (2021). Antidepressant drugs as emerging contaminants: occurrence in urban and non-urban waters and analytical methods for their detection. *Sci. Total. Environ.* 757, 143722. doi:10.1016/j.scitotenv.2020.143722

Chan, S. J., Nutting, V. I., Natterson, T. A., and Horowitz, B. N. (2021). Impacts of psychopharmaceuticals on the neurodevelopment of aquatic wildlife: A call for increased knowledge exchange across disciplines to highlight implications for human health. *Int. J. Environ. Res. Public. Health.* 18, 5094. doi:10.3390/ijerph18105094

Dai, L., Liu, K., Si, C., Wang, L., Liu, J., Heet, J., et al. (2016). Ginsenoside nanoparticle: a new green drug delivery system. *J. Mat. Chem. B* 4, 529–538. doi:10.1039/C5TB02305J

Dan, L., Hongxing, C., Hongsong, L., Schlenkc, D., Mue, J., Lacorte, S., et al. (2021). Anticancer drugs in the aquatic ecosystem: Environmental occurrence, ecotoxicological effect and risk assessment. *Environ. Int.* 153, 106543. doi:10.1016/j.envint.2021.106543

Daughton, C. D., and Ruhoy, I. S. (2011). Green pharmacy and pharmEcovigilance: prescribing and the planet. *Expert. Rev. Clin. Pharmacol.* 4, 211–232. doi:10.1586/ecp.11.6

Daughton, C. G. (2014). Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs. *Sci. Total. Environ.* 493, 392–404. doi:10.1016/j.scitotenv.2014.06.013

European Comission (2021). Guideline on the packaging information of medicinal products for human use authorised by the Union. Available at: https://health.ec.europa.eu/system/files/2021-04/2018_packaging_guidelines_en_0.pdf

European Commission (2019). *Directorate-general for environment, kümmerer, K., options for a strategic approach to pharmaceuticals in the environment: final report*. Brussels, Belgium: Publications Office.

Godlewska, K., Jakubus, A., Stepnowski, P., and Paszkiewicz, M. (2021). Impact of environmental factors on the sampling rate of β-blockers and sulfonamides from water by a carbon nanotube-passive sampler. *J. Environ. Sci.* 101, 413–427. doi:10.1016/j.jes.2020.08.034

Gomez Cortes, L., Marinov, D., Sanseverino, I., Navarro Cuenca, A., Niegowska Conforti, M., Rodriguez, P., et al. (2022). *Selection of substances for the 4th Watch list under the water framework directive*. Luxembourg: Publications Office of the European Union.

González Peña, O. I., López Zavala, M. Á., and Cabral Ruelas, H. (2021). Pharmaceuticals market, consumption trends and disease incidence are not driving the pharmaceutical research on water and wastewater. *Int. J. Environ. Res. Public. Health.* 18, 2532. doi:10.3390/ijerph18052532

Gustafsson, L. L., Wettermark, B., Godman, B., Andersén-Karlsson, E., Bergman, U., Hasselströmet, J., al., et al. (2011). The 'wise list'- A comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic. Clin. Pharmacol. Toxicol.* 108, 224–233. doi:10.1111/j.1742-7843.2011.00682.x

Hodkovicova, N., Hollerova, A., Blahova, J., Mikula, P., Crhanova, M., Karasova, D., et al. (2022). Non-steroidal anti-inflammatory drugs caused an outbreak of inflammation and oxidative stress with changes in the gut microbiota in rainbow trout (*Oncorhynchus mykiss*). *Sci. Total. Environ.* 849, 157921. doi:10.1016/j.scitotenv.2022.157921

Ianiro, G., Tilg, H., and Gasbarrini, A. (2016). Antibiotics as deep modulators of gut microbiota: Between good and evil. *Gut* 65, 1906–1915. doi:10.1136/gutjnl-2016-312297

Klatte, S., Schaefer, H. C., and Hempel, M. (2017). Pharmaceuticals in the environment – a short review on options to minimize the exposure of humans, animals and ecosystems. *Sustain. Chem. Pharm.* 5, 61–66. doi:10.1016/j.scp.2016.07.001

Kovács, R., Csenki, Z., Bakos, K., Urbányi, B., Horváth, Á., Garaj-Vrhovac, V., et al. (2015). Assessment of toxicity and genotoxicity of low doses of 5-fluorouracil in zebrafish (*Danio rerio*) two-generation study. *Water. Res.* 77, 201–212. doi:10.1016/j.watres.2015.03.025

Kümmerer, K. (2019). From a problem to a business opportunity-design of pharmaceuticals for environmental biodegradability. *Sustain. Chem. Pharm.* 12, 100136. doi:10.1016/j.scp.2019.100136

Küster, A., Alder, A. C., Escher, B. I., Duis, K., Fenner, K., Garric, J., et al. (2010). Environmental risk assessment of human pharmaceuticals in the European union: A case study with the β-blocker atenolol. *Integr. Environ. Assess. Manag.* 6, 1–523. doi:10.1897/IEAM_2009-050.1

Lai, C. C., Chen, S. Y., Ko, W. C., and Hsueh, P. R. (2021). Increased antimicrobial resistance during the COVID-19 pandemic. *Int. J. Antimicrob. Agents.* 57, 106324. doi:10.1016/j.ijantimicag.2021.106324

Lertxundi, U., Hernández, R., Medrano, J., and Orive, G. (2020). Drug pollution and pharmacotherapy in psychiatry:A "platypus" in the room. *Eur. Psychiatry.* 63, e33. doi:10.1192/j.eurpsy.2020.32

Li, Y., Miao, Y., Zhang, W., Yang, N., Niu, L., Zhang, H., et al. (2020). Sertraline inhibits top-down forces (predation) in microbial food web and promotes nitrification in sediment. *Environ. Pollut.* 267, 115580. doi:10.1016/j.envpol.2020.115580

Li, Z., Yu, X., Yu, F., and Huang, X. (2021). Occurrence, sources and fate of pharmaceuticals and personal care products and artificial sweeteners in groundwater. *Environ. Sci. Pollut. Res. Int.* 28, 20903–20920. doi:10.1007/s11356-021-12721-3

Lister, A. L., and Van Der Kraak, G. J. (2009). Regulation of prostaglandin synthesis in ovaries of sexually-mature zebrafish (*Danio rerio*). *Mol. Reprod. Dev.* 76, 1064–1075. doi:10.1002/mrd.21072

Masoner, J. R., Kolpin, D. W., Furlong, E. T., Cozzarelli, I. M., and Gray, J. L. (2016. Landfill leachate as a mirror of today's disposable society: Pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. *Environ. Toxicol. Chem.* 35, 906–918. doi:10.1002/etc.3219

Maszkowska, J., Stolte, S., Kumirska, J., Łukaszewicz, P., Mioduszewska, K., Puckowski, A., et al. (2014). Beta-blockers in the environment: part II. Ecotoxicity study. *Sci. Total. Environ.* 493, 1122–1126. doi:10.1016/j.scitotenv.2014.06.039

Mitkidis, P., Chrysochou, P., Obolevich, V., and Mitkidi, K. (2022). Effectiveness of environmental health and loss framing on household pharmaceutical take-back schemes. *Waste. Manage.* 143, 61–68. doi:10.1016/j.wasman.2022.02.017

Monteiro, S. C., and Boxall, A. B. A. (2010). Occurrence and fate of human pharmaceuticals in the environment. *Rev. Environ. Contam. Toxicol.* 202, 53–154. doi:10.1007/978-1-4419-1157-5_2

Nelles, J. L., Hu, W. Y., and Prins, G. S. (2011). Estrogen action and prostate cancer. *Expert. Rev. Endocrinol. Metab.* 6, 437–451. doi:10.1586/eem.11.20

Nie, X. P., Liu, B. Y., Yu, H. J., Liu, W. Q., and Yang, Y.-F. (2013). Toxic effects of erythromycin, ciprofloxacin and sulfamethoxazole exposure to the antioxidant system in Pseudokirchneriella subcapitata. *Environ. Pollut.* 172, 23–32. doi:10.1016/j.envpol.2012.08.013

OECD (Organisation for Economic Co-operation and Development (2022). *Management of pharmaceutical household waste: Limiting environmental impacts of unused or expired medicine*. Paris, France: OECD Publishing.

OECD (Organisation for Economic Co-operation and Development) (2019). *Pharmaceutical residues in freshwater: Hazards and policy responses, OECD studies on water*. Paris, France: OECD Publishing.

Ortúzar, M., Esterhuizen, M., Olicón-Hernández, D. R., González-López, J., and Aranda, E. (2022). Pharmaceutical pollution in aquatic environments: a concise review of environmental impacts and bioremediation systems. *Front. Microbiol.* 26, 869332. doi:10.3389/fmicb.2022.869332

Paut Kusturica, M., Golocorbin-Kon, S., Ostojic, T., Kresoja, M., Milovic, M., Horvat, O., et al. (2020). Consumer willingness to pay for a pharmaceutical disposal program in Serbia: a double hurdle modeling approach. *Waste. Manag.* 104, 246–253. doi:10.1016/j.wasman.2020.01.029

Paut Kusturica, M., Tomas, A., and Sabo, A. (2016). Disposal of unused drugs: Knowledge and behavior among people around the world. *Rev. Environ. Contam. Toxicol.* 40, 71–104. doi:10.1007/398_2016_3

Queirós, V., Azeiteiro, U. M., Soares, A. M. V. M., and Freitas, R. (2021). The antineoplastic drugs cyclophosphamide and cisplatin in the aquatic environment - Review. *J. Hazard. Mat.* 412, 125028. doi:10.1016/j.jhazmat.2020.125028

Rabeea, S. A., Merchant, H. A., Khan, M. U., Kow, C. S., and Hasan, S. S. (2021). Surging trends in prescriptions and costs of antidepressants in England amid COVID-19. *DARU. J. Pharm. Sci.* 29, 217–221. doi:10.1007/s40199-021-00390-z

Roque-Diaz, Y., Sanadar, M., Han, D., López-Mesas, M., Valiente, M., Tolazzi, M., et al. (2021). The dark side of platinum based cytostatic drugs: From detection to removal. *Processes* 9, 1873. doi:10.3390/pr9111873

Stockholm County Council (2014). *Environmentally classified pharmaceuticals 2014-2015*. Stockholm, Sweden: Stockholm County Council.

Straub, J. O. (2016). Reduction in the environmental exposure of pharmaceuticals through diagnostics, Personalised Healthcare and other approaches. A mini review and discussion paper. *Sustain. Chem. Pharm.* 3, 1–7. doi:10.1016/j.scp.2015.12.001

Thomas, Felicity & WHO (World Health Organization) (2017). *Pharmaceutical waste in the environment: a cultural perspective*. Regional Office for Europe. Available at: https://apps.who.int/iris/handle/10665/254734.

Trevino, L. S., Wang, Q., and Walker, C. L. (2015). Hypothesis: Activation of rapid signaling by environmental estrogens and epigenetic reprogramming in breast cancer. *Reprod. Toxicol.* 54, 136–140. doi:10.1016/j.reprotox.2014.12.014

Tyumina, E. A., Bazhutin, G. A., Cartagena Gómez, A. D., and Ivshina, I. B. (2020). Nonsteroidal anti-inflammatory drugs as emerging contaminants. *Microbiology* 89, 148–163. doi:10.1134/S0026261720020125

UNESCO (United Nations Educational, Scientific and Cultural Organization). 2020. *Emerging pollutants in water and wastewater*. Available at: https://en.unesco.org/emergingpollutantsinwaterandwastewater

Vumazonke, S., Khamanga, S. M., and Ngqwala, N. P. (2020). Detection of pharmaceutical residues in surface waters of the eastern cape province. *Int. J. Environ. Res. Public. Health.* 17, 4067. doi:10.3390/ijerph17114067

Xia, L., Zheng, L., and Zhou, J. L. (2017). Effects of ibuprofen, diclofenac and paracetamol on hatch and motor behavior in developing zebrafish (*Danio rerio*). *Chemosphere* 182, 416–425. doi:10.1016/j.chemosphere.2017.05.054

Zainaba, S. M., Junaidb, M., Xu, N., and Malik, R. N. (2020). Antibiotics and antibiotic resistant genes (ARGs) in groundwater: A global review on dissemination, sources, interactions, environmental and human health risks. *Water. Res.* 187, 116455. doi:10.1016/j.watres.2020.116455

Zenker, A., Cicero, M. R., Prestinaci, F., Bottoni, P., and Carere, M. (2014). Bioaccumulation and biomagnification potential of pharmaceuticals with a focus to the aquatic environment. *J. Environ. Manage.* 133, 378–387. doi:10.1016/j.jenvman.2013.12.017