Drug Safety
https://doi.org/10.1007/s40264-024-01497-3

EDITORIAL

Call to action: Pharmaceutical residues in the environment: threats to ecosystems and human health

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Accepted: 6 November 2024
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1 Overview

The increasing production and consumption [1] of pharmaceutical products by humans has led to measurable residues in the environment. They contaminate surface waters (freshwater and marine waters), soil, and groundwater, and traces may be present in treated drinking water. These residues originate from:

- human excretion (urine and faeces) from households and hospitals
- leaching from agricultural land and landfill sites
- unsafe disposal of medicines
- point source discharges from pharmaceutical manufacturing
- point-of-use emissions of anaesthetic gases and pressurised metered-dose inhalers.

Current water-treatment technology does not completely remove such residues, and untreated wastewater is discharged directly into the environment in many parts of the world [2, 3]. Evidence shows the potential for harmful effects on aquatic life and ecosystems, posing direct and indirect risks to humans, other organisms, and ecological chains.

These risks have been reported for up to three decades, and newly emerging evidence has been extensively documented, but little, if any, global coordinated effort has been made to address them adequately [4, 5]. The science concerned with monitoring and mitigating the effects of pharmaceuticals on the environment is known as ecopharmacovigilance. The growing body of evidence but absence of global initiatives to effectively tackle the problem indicates a pressing need for urgent, concerted, and global action.

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Published online: 10 December 2024

2 The Problem and the Evidence

Multiple studies have shown the presence of pharmaceutical contaminants in water sources and most environmental compartments across the world [6, 7]. Effects of pharmaceuticals on wildlife species exposed in the laboratory have been extensively reported, and some demonstrate measurable effects at concentrations that can be found in the environment (e.g. hormones EE2). However, there is little evidence of these predicted effects being observed in the wild, and no evidence so far of direct effects on humans [8]. All countries and global regions are known to be affected, and although most of the available monitoring data have been collected in high-income countries (primarily Europe and the USA), the highest levels of contamination are reportedly in low- and middle-income countries, associated with poor wastewater and waste management infrastructure and poor control of pharmaceutical manufacturing emissions [7].

The disposal of pharmaceuticals as solid waste in landfills poses a significant and often overlooked environmental hazard. Pharmaceuticals that are disposed into landfill may degrade, adsorb, or enter leachate, impacting the environment [6, 9]. Recent studies have underlined the gravity of this issue, showing that pharmaceutical waste in landfill sites can leach into the underlying groundwater and nearby water bodies and reach levels higher than the accepted safe concentrations [10]. Landfill leachates containing pharmaceuticals pose a threat to soil and groundwater, and—without proper treatment—could adversely impact human and aquatic life [6].

Monitoring of water quality in multiple locations across the world has revealed measurable concentrations of human pharmaceutical residues (in the form of unmodified active substances and their metabolites and transformation products) in surface water, groundwater, soil, and even drinking water [7]. Among many others, these include frequently detected substances such as carbamazepine, metformin, and diclofenac, as well as antidepressants, non-steroidal anti-inflammatory drugs, antibiotics, and hormonal products. Reports of concerning findings include the following.

- Active substances in oral contraceptives have been shown to damage the reproductive cycles and development of fish and amphibians, leading to concerns for ecosystem balance [11–13].
- There is a plausible link between a decline in human male fertility since the 1990s and oestrogens in the environment, although this remains a controversial topic [14–17]. Although oral contraceptives may be one contributing factor, many contaminants such as phytoestrogens, industrial chemicals, personal care products, and others are also receiving attention [18].
- Psychoactive drugs such as fluoxetine is affecting fish behaviour, making them less risk averse and more vulnerable to predators [8].
- The use of diclofenac in India led to the virtual extinction of vultures, with a resulting loss of biodiversity and the ecosystem services that vultures provided, in turn having a measurable, consequential effect on human mortality [19, 20].
- The overuse and discharge of antibiotics to water bodies exacerbates the risks of antimicrobial resistance [21] and potentially impairs the role of bacteria in metabolizing organic substances in water and soil [22].
- Concerns over diffuse, chronic, low-level human exposure to residues of multiple pharmaceuticals via consumption of drinking water, crops, fish, dairy, and meat products [5, 23, 24]. Levels of compounds such as carbamazepine, trimethoprim, and sulfamethoxazole in some crops may in fact be high enough to exceed risk thresholds for human consumption.

Other known and almost certainly some unknown effects, some of which may pose (as yet unknown) risks on humans or ecosystems, are also of concern.

3 The Causes

Causes of these residues include the following.

1. Unmodified substances and still-active metabolites are excreted by humans and animals and enter natural water and soils every day.
2. Unsafe disposal of unused medicines down the drain (i.e. sink or toilet) or waste to landfill.
3. Spreading of wastewater treatment sludge onto agricultural land; leaching from agricultural land and landfill sites into groundwater sources; direct use in fish farming.
4. Use of wastewater for irrigation of land (particularly in water-scarce regions).
5. Point-source discharges from hospitals and pharmaceutical manufacturing.

Conventional sewage and wastewater treatment plants are not 100% efficient at removing the residues of all pharmaceutical compounds; therefore, treated water remains contaminated when it is discharged into rivers and seas. Although individual substances are generally found at low (nanogram to microgram per litre) levels [7], their co-occurrence with many other contaminants such as personal care products, biocides, pesticides, and general chemicals [25], as well as their continuous presence (i.e. chronic exposure), may result in long-term cumulative or synergistic effects.

Additive, synergistic, and antagonistic effects are possible and would exacerbate the risk posed to humans and ecosystems.

4 Call for Action

4.1 Intensification of Monitoring and Research (Scale and Effect of the Problem)

Evidence of the problem is growing, but a much more intense and coordinated effort is needed to build a consistent picture of the facts at both the national and the global level and to investigate the direct and indirect effects on humans, amphibians, reptiles, fishes, birds, plants, bacteria, fungi, and—ultimately—ecosystems. New and standardised methods are needed to identify, assess, and monitor the combined effects of multiple substance residues, particularly the development and validation of effect-based methods [26].

4.2 Assessment of Severity and Probability of Risks (Prioritisation and Planning)

Evidence-based risk assessment approaches will allow the most urgent issues to be identified, providing immediate insight into the risks and informing long-term strategies for remedial action [27–30]. This needs to be balanced with the human right of patients to good health where access to medicine remains the priority in a risk–benefit assessment.

4.3 National and Global Regulatory Action (Preventive Measures and/or Behaviour Change)

Almost all aspects of the problem are amenable to regulatory (enforced, legal) action, prescription regulation, and behaviour change: at source, during use, at the point of disposal, and in the assessment of downstream impact. Regulatory measures can be directed at monitoring and reporting; setting and enforcement of standards (manufacturing standards, wastewater treatment); allocation of responsibility throughout the product lifecycle, including safe disposal; agricultural practices; and by considering the environmental impact of drug prescribing and dispensing.

Only a few national authorities provide requirements and guidance for environmental risk assessments to be conducted in connection with market approvals for medicinal products [31, 32]. In Europe, the pharmaceutical regulations and wider strategies are under revision [33], with a special focus on antimicrobial resistance and the presence of pharmaceuticals in the environment (through a One Health approach), and are encouraging the development of more environmentally sustainable medicines. It is also worth noting that some pharmaceuticals are now included in the proposed revisions of the Urban Wastewater Treatment Directive, Water Framework Directive, Groundwater Directive, and Environmental Quality Standards Directive [34, 35]. These proposals address some pharmaceutical compounds as contaminants of emerging concern. To the best of the authors' knowledge, global efforts to develop common standards are lacking. Therefore, a robust framework is needed to integrate environmental impacts into the risk–benefit assessments of pharmaceuticals, extending beyond water pollution to address broader concerns such as, for example, the impact of the anaesthetic gas desflurane on global warming. A foundational understanding of the environmental impacts of medicines should be ensured in the training of medical and pharmacy professionals, but this issue was not included in the most recent European directive regulating the training of future pharmacists.

4.4 Active Involvement of Doctors and Medical and Pharmacy Personnel

The concerns associated with the presence of pharmaceuticals in the environment are shared by environmental scientists, but awareness among healthcare professionals is still very low [36–38]. The environmental protection aspect, specifically related to pharmaceuticals' environmental impact, urgently needs to be integrated into academic curricula and continuing education courses for all professionals handling pharmaceuticals, such as medical doctors and pharmacists [39]. In this context, it is also important to consider the consequences of inappropriate prescribing leading to polypharmacy, mainly in the elderly [40]. Moreover, the environmental impact of each medicine should be considered and included in decision-making tools to guide more environmentally conscious prescribing practices.

4.5 Active Public Health Communication (Awareness and Behaviour Change)

The rising awareness of pharmaceutical pollution and potential for exposure via environmental sources might negatively affect public perception of medications and jeopardise patient adherence to prescribed courses of necessary medication. To ensure that the public's confidence in medicines is not undermined, patients and other members of the public need to have better awareness of mitigating action they can take. These can include, primarily, returning unused and/or expired medicines to a pharmacy or via take-back schemes but also never placing them in unsorted trash and not flushing medicines down the toilet. This applies to all forms of medicinal products (pills, cremes, gels, transdermal patches, and devices such as asthma inhalers). People need to be sensitised to the risks associated with pharmaceutical products

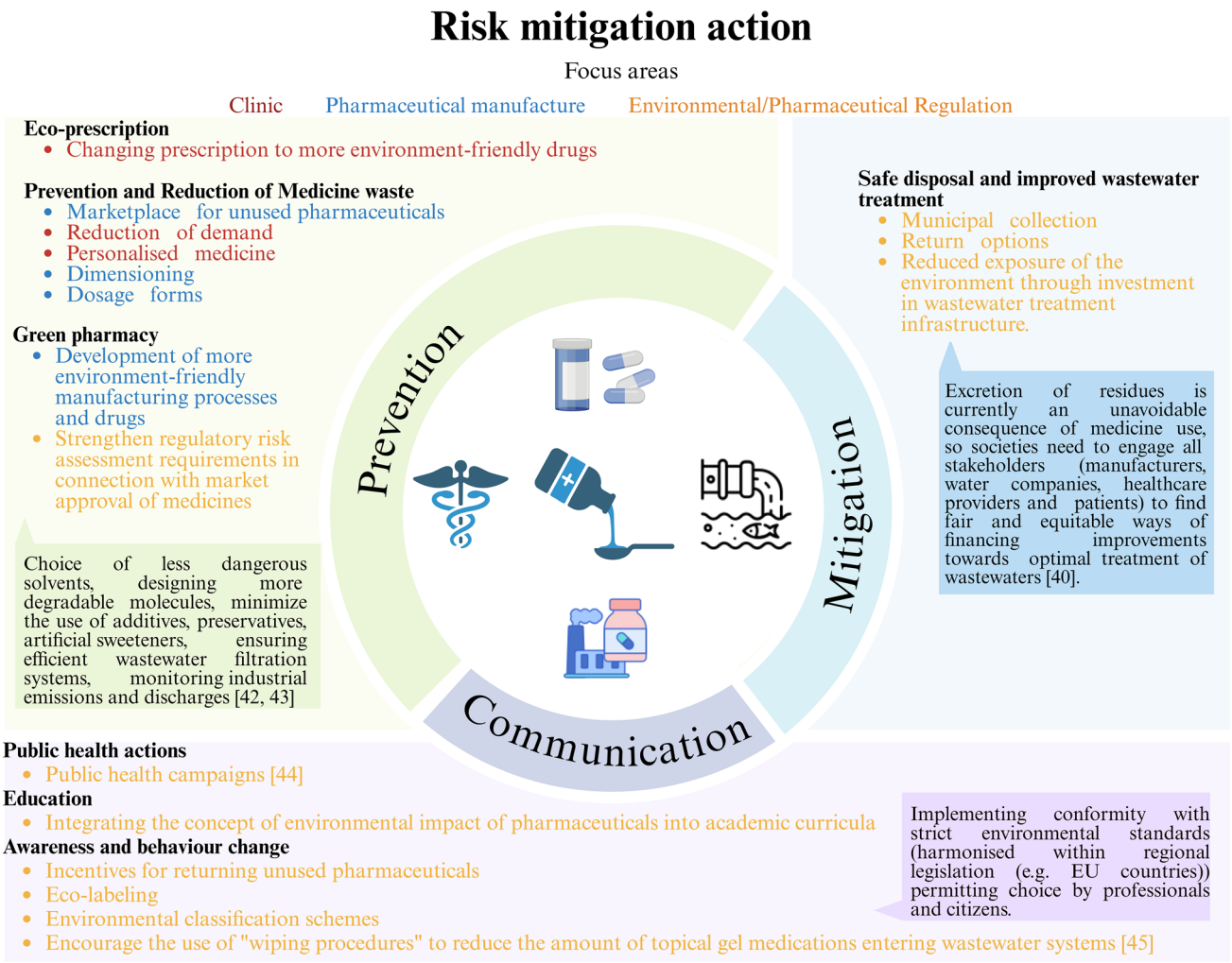

Fig. 1 Condensed overview of actions to prevent or mitigate risks from pharmaceutical residues in the environment. The figure was created in BioRender.com

entering the environment. On the other hand, patients should be encouraged to follow their prescribed treatments rather than wasting unused medicines. This could be aligned with existing and future awareness campaigns aimed at the prevention of antimicrobial resistance.

The topics presented in Fig. 1 are based on Paut Kusturica et al. [41], with substantial integrations and reformulations. The approaches suggested are unlikely to be exhaustive (or indeed comprehensive of all local initiatives already in train), and ongoing further development is welcomed and encouraged but should not delay the taking of measures available today.

5 Conclusion

Awareness and understanding of the potential risks to ecosystems and human health from pharmaceutical residues in the environment have been slow to emerge. However, they are unambiguous and demand attention. The risks known today are sufficient to prompt immediate action, and there is sufficient existing knowledge of potential future risks that require planning and mitigation now. These known risks are only one element in the broad spectrum of concerns about environmental pollution, but they are specific, identifiable, and real. As such, they require specific, coherent, radical, and urgent action by all stakeholders: politicians, regulators, scientists, medical personnel, and citizens worldwide.

Acknowledgements The group acknowledges the advisory and editorial support of Prof. Ralph Edwards, Dr. Marie Lindquist, and Bruce Hugman.

Declarations

Funding This manifesto was developed by a group of 30 experts from five countries meeting in Erice, Sicily, 25–28 September 2023. The workshop was organised and sponsored by The International School of Pharmacology 'Giampaolo Velo' at the Ettore Majorana Centre for Scientific Culture, Erice, Italy.

Conflict of interest Irene Bramke works for a company (AstraZeneca) that produces and sells pharmaceutical products. All the other authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics approval Not applicable. No new nor retrospective research is proposed in this article.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Code availability No specific software or custom code was used in this publication.

Authors' contribution Writing – original draft preparation: Carlotta Lunghi, Maria Rosa Valetto, Anna Barra Caracciolo; Irene Bramke, Mario Caroli, Paola Bottoni, Sara Castiglioni, Salvatore Crisafulli, Laura Cuzzolin, Paola De Ambrosis, Valentina Giunchi, Jacopo Grisotto, Antonio Marcomini, Ugo Moretti, Vitalia Murgia, Jayesh Pandit, Stefano Polesello, Elisabetta Poluzzi, Roberto Romizi, Nicoletta Scarpa, Giovanna Scroccaro, Raffaella Sorrentino, Anders Sundstrom, John Wilkinson, Giovanna Paolone*. Conceptualization: Irene Bramke, Stefano Polesello, Giovanna Paolone. Writing – review and editing: Irene Bramke, Stefano Polesello, Jacopo Grisotto, Giovanna Paolone. Funding acquisition: Ugo Moretti. Supervision: Giovanna Paolone. All authors read and approved the final version.

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