Received: 18 May 2024 | Revised: 8 February 2025 | Accepted: 21 February 2025

DOI: 10.1002/bcp.70046

ORIGINAL ARTICLE

Assessing the environmental impact of medicines in Italy using data from the Italian Medicines Agency

Valentina Giunchi[1] | Michele Fusaroli[1] | Agnese Cangini[2] | Filomena Fortinguerra[2] | Simona Zito[2] | Andrea Pierantozzi[2] | Carlotta Lunghi[1] | Elisabetta Poluzzi[1] | Francesco Trotta[2]

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[2]Italian Medicines Agency (AIFA), Rome, Italy

Correspondence
Valentina Giunchi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
Email: valentina.giunchi2@unibo.it

Present address
Carlotta Lunghi, Department of Life Sciences, Health, and Health Professions, Link Campus University, Rome, Italy.

Aim: This study builds on the environmental risk analysis presented in the 2022 National Report on Medicines Use in Italy by the Italian Medicines Agency and aims to assess the environmental risk posed by medicines in Italy and its regions.

Methods: The analysis selected 90 medicines based on three criteria: high utilization, low predicted no effect concentration (PNEC), and inclusion or candidacy for the European Watch List. For each medicine, the environmental risk was computed as the ratio between the predicted environmental concentration (PEC) and the PNEC. The PEC was derived following the approach of the Swedish Association of Pharmaceutical Industries and Italian drug utilization data. The risk was classified high if the ratio was greater than 10 and moderate if greater than 1.

Results: Overall, 13 medicines were identified as posing a high risk, including cardiovascular agents, antibiotics, analgesics, antidepressants and antiparasitic agents. The high risk was driven by either a very low PNEC (eg, estradiol and lacidipine) or high utilization (eg, amoxicillin, ibuprofen and diclofenac). Regional analysis showed higher risk due to high consumption for azithromycin and ofloxacin in central and southern Italy, and for levonorgestrel in northern Italy.

Conclusion: This study points to the need for prioritizing targeted sampling in surface waters for medicines estimated at high risk. To prevent and mitigate the risk, a more conscious clinical practice coupled with appropriate waste management are required.

KEYWORDS
drug safety, drug utilization, environmental impact of medicines, sustainability of medicines use

1 | INTRODUCTION

The use of medicines is one of the challenges posed by human activities to environmental sustainability.[1] After consumption, medicines are released into the environment through excretion in urine and faeces, either unchanged or as inactivated or still as active metabolites. Additionally, they can be released directly in wastewater in the case of topically applied formulations or improper disposal of medications through toilets. This enables medicines to enter wastewater and, subsequently, surface waters, potentially causing adverse effects on the fauna and flora in these environments.[1] The exposure of aquatic organisms to medicines can result in various adverse reactions that

Elisabetta Poluzzi and Francesco Trotta contributed equally to this work.

threaten the ecosystem. For example, exposure to hormonal agents may lead to the feminization of male fish, certain analgesics can induce nephrotoxicity in various animal species and the presence of antibiotics can contribute to the development of resistance in animals, plants and humans.[2–4]

At the European level, measures have been undertaken to assess the presence and environmental risk associated with medicines. These measures have concentrated explicitly on monitoring surface waters because they represent the first environment affected by the consequences of human medicine use. Since 2006 the European Medicines Agency (EMA) has required pharmaceutical manufacturers to include an Environmental Risk Assessment (ERA) as part of the European Public Assessment Report during the marketing authorization process for a pharmaceutical product. The ERA should provide information on the toxicity of the active pharmaceutical ingredients to aquatic organisms, along with details on the risk based on expected consumption.[5] Furthermore, in 2008 the European Commission introduced a compulsory monitoring system for surface water aimed at tracking a group of chemical substances, known as the Watch List, which may pose harm to the environment. The monitoring campaign began in 2015, periodically reviewing the list of monitored substances, which also includes human medicines.[6] In March 2019, the European Commission presented the "Strategic Approach to Pharmaceuticals in the Environment", which includes actions aimed at countering the negative effects of medicines on the environment throughout their entire lifecycle, from design and production to use and disposal.[7]

However, the task of monitoring medicines in surface waters is a resource-intensive endeavour that is often limited to a specific set of substances. Therefore, it is essential to prioritize the substances for monitoring by employing estimation methods that go beyond the pre-marketing estimates supplied by manufacturers seeking marketing authorization from the EMA. A commonly adopted measure for estimating the environmental impact of medicines is the risk quotient, calculated as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC).[5] The PNEC represents a tolerability threshold for organisms exposed to the medicines derived from in vivo tests,[8] while the PEC can be estimated in silico using various approaches. Currently, calculating the PEC commonly relies on the method proposed by the Swedish Association of Pharmaceutical Industries (Läkemedelsindustriföreningen [Lif]), which adapts the EMA's approach for postmarketing scenarios.[9,10] Lif has incorporated an environmental risk section on the Farmacevtiska specialiteter i Sverige (FASS) website (www.fass.se) as part of this approach, providing information on each pharmaceutical product supplied in Sweden. Building on this initiative, the Stockholm region has developed a dedicated web-based database for disseminating environmental information on medicines, including those found in FASS and other documents.[11,12] Inspired by the Swedish example, the Finnish Pharmaceutical Information Centre (Pharmaca) has integrated environmental information on medicines into the Pharmaca Fennica online service.[13,14] Other countries, such as Norway and Italy, have contributed to the development of their country-specific environmental risk assessments for medicines through publications in the scientific literature.[15,16]

What is already known about this subject

- Medicines represent a growing concern as a source of contamination in water systems.
- Traditional surface water samplings are resource-expensive and should be supported by estimation methods.
- The Italian Medicines Agency's National report on medicines use included for the first time in its 2022 version an assessment of the environmental impact.

What this study adds

- Ninety medicines with high utilization, low predicted no-effect concentration or present in the European Watch List were included.
- Thirteen medicines were at high environmental risk because of either their high toxicity to aquatic species or their high consumption in Italy.
- Regional differences potentially reflect various social and prescribing habits.

The Italian Medicines Agency (Agenzia Italiana del Farmaco) recently joined this initiative to map the environmental impact of medicines. In its 2022 annual Medicines Utilization Monitoring Centre (OsMed) report on national drug utilization (English version released in December 2023), a section was dedicated to estimating the environmental risk in Italy based on drug utilization data.[17]

This study aimed to assess the environmental risks of medicines used in Italy at the national, macro-area and regional levels.

2 | METHODS

2.1 | Selection of medicines

The environmental risk assessment was carried out for medicines that fulfilled the following criteria:

1. The first 30 medicines for human use most consumed in Italy in 2022.
2. Medicines for human use included in or candidates for at least one version of the Watch List.[18–21]
3. Medicines for human use with the highest toxicity to aquatic animals and plants, based on the PNEC value of each active ingredient.[22] Some medicines meeting this criterion have been excluded from the analysis as they are not currently available on the Italian market (see Supporting Information Table S1).

2.2 | Drug utilization sources

All Italian reimbursement categories, including over-the-counter and hospital sales, were taken into account to ascertain the total sales volume of each selected medicine. Data were extracted from the OsMed database, which contains information on the number of packages and related doses supplied in 2022. The extracted data included the amount, in kilograms, of each medicine purchased across the entire Italian territory and in each Italian region. Regional purchases were then aggregated to determine the total quantity of medicines purchased in each Italian macro-area (North, Center, and South and Islands). The total kilograms for each active ingredient was estimated without considering the administration route or the ATC code.

2.3 | Risk computation

The environmental risk of medicines for surface waters was assessed by calculating the ratio between the PEC and the PNEC. It was computed for the whole Italian territory, the three main macro-areas of Italy and each Italian region in 2022. Based on this assessment, environmental risk was classified as high when the PEC/PNEC ratio was greater than or equal to 10, moderate when between 1 and 10, low when between 0.1 and 1, and negligible when less than or equal to 0.1.[10]

The PEC of each pharmaceutical was computed using the Lif approach[10]:

$$Risk\ (\mu g/L) = \frac{A \times 10^9 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where A is the total amount (in kilograms) of pharmaceutical supplied and R is the pharmaceutical removal rate (%) through volatilization, hydrolysis or biodegradation. Since specific information is not available, a value of 0% is assumed by default.[8] P is the population size, calculated as the average between the residents on 1 January 2022 and the residents on 1 January 2023.[23,24] V is the volume of daily per-capita wastewater production (L/day). It is by default set to 200 L/day according to the EMA proposal.[5] D is the wastewater dilution factor produced by river flow and was set to 10, following the EMA proposal.[5]

The PNEC values were extracted from an open-access PNEC repository (https://osf.io/xtg8z/),[22,25] which retrieved them from the NORMAN ecotoxicology database "lowest PNEC",[26] the Watch List working documents,[18–21] the web-based database of the Region Stockholm "pharmaceuticals and environment"[12] and, where needed, the scientific literature. When multiple values were available for the same medicine, the lowest value was selected.[5]

2.4 | Link with ATC classification

Medicines were categorized according to the World Health Organization - Anatomical Therapeutic Chemical (WHO-ATC) classification (2023 version).[27] This is a hierarchical classification system used to categorize medicines based on the organ or system they target, their therapeutic use and their chemical characteristics.[27] In cases where an active ingredient was associated with multiple ATC codes, preference was given to the most frequently used code.

All the analyses were conducted using R[28] between January and March of 2023.

3 | RESULTS

A total of 90 medicines were identified based on our selection criteria and thus included in this analysis for environmental risk assessment (see Supporting Information Table S2). The majority of medicines belonged to cardiovascular agents (ATC C, n = 21), anti-infectives for systemic use (ATC J, 16), and antineoplastic and immunomodulating agents (ATC L, 14). Six medicines, namely allopurinol, diclofenac, estradiol, ethinylestradiol, levonorgestrel and metformin, were selected based on more than one criterion.

At the Italian level, 13 medicines were identified as posing a high risk to surface waters (see Figure 1 and Supporting Information Table S3), among them two cardiovascular agents (ATC C, olmesartan and lacidipine) and four antibiotics (ATC J, rifaximin, ofloxacin, azithromycin and amoxicillin). Other substances at high risk included the oestrogen estradiol (ATC G), two nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac (ATC M), two antidepressants, venlafaxine and sertraline (ATC N), the ectoparasiticide permethrin and the antiprotozoal atovaquone (ATC P). Furthermore, 23 medicines were categorized as having a moderate risk. The remaining 54 medicines were identified to have a low or insignificant risk according to assessments at the Italian level (see Figure 1 and Supporting Information Table S3).

The high risk stemmed from a very low PNEC for permethrin, estradiol, lacidipine and atovaquone. Although permethrin and atovaquone are not frequently used, their high amount of grams contained in a defined daily dose (DDD) (2.25 g) contributed to the risk profile. In contrast, estradiol and lacidipine are more commonly used, albeit with a lower quantity per dose. Conversely, other medicines at high risk, namely amoxicillin, azithromycin, ofloxacin, diclofenac and ibuprofen, have high PNEC values, but their widespread use and the high amount of grams per DDD exacerbated their risk (see Supporting Information Table S3).

The comparison of environmental risk among Italian macro-areas revealed differences likely driven by varying consumption patterns, as all other variables included in the PEC and risk computations were kept constant across macro-areas. Specifically, the risk of lacidipine, ofloxacin and azithromycin was high in Central and South Italy, while the high risk of atovaquone was observed only in Central Italy. Additionally, the high risk of levonorgestrel was confined to Northern Italy, and the high risk of clotrimazole, clindamycin, ciprofloxacin, imatinib, montelukast and ebastine was restricted to Central Italy. In contrast, miconazole exhibited a high risk in both Central and Southern Italy (see Figure 2, Supporting Information Figure S1 and Supporting Information Table S4).

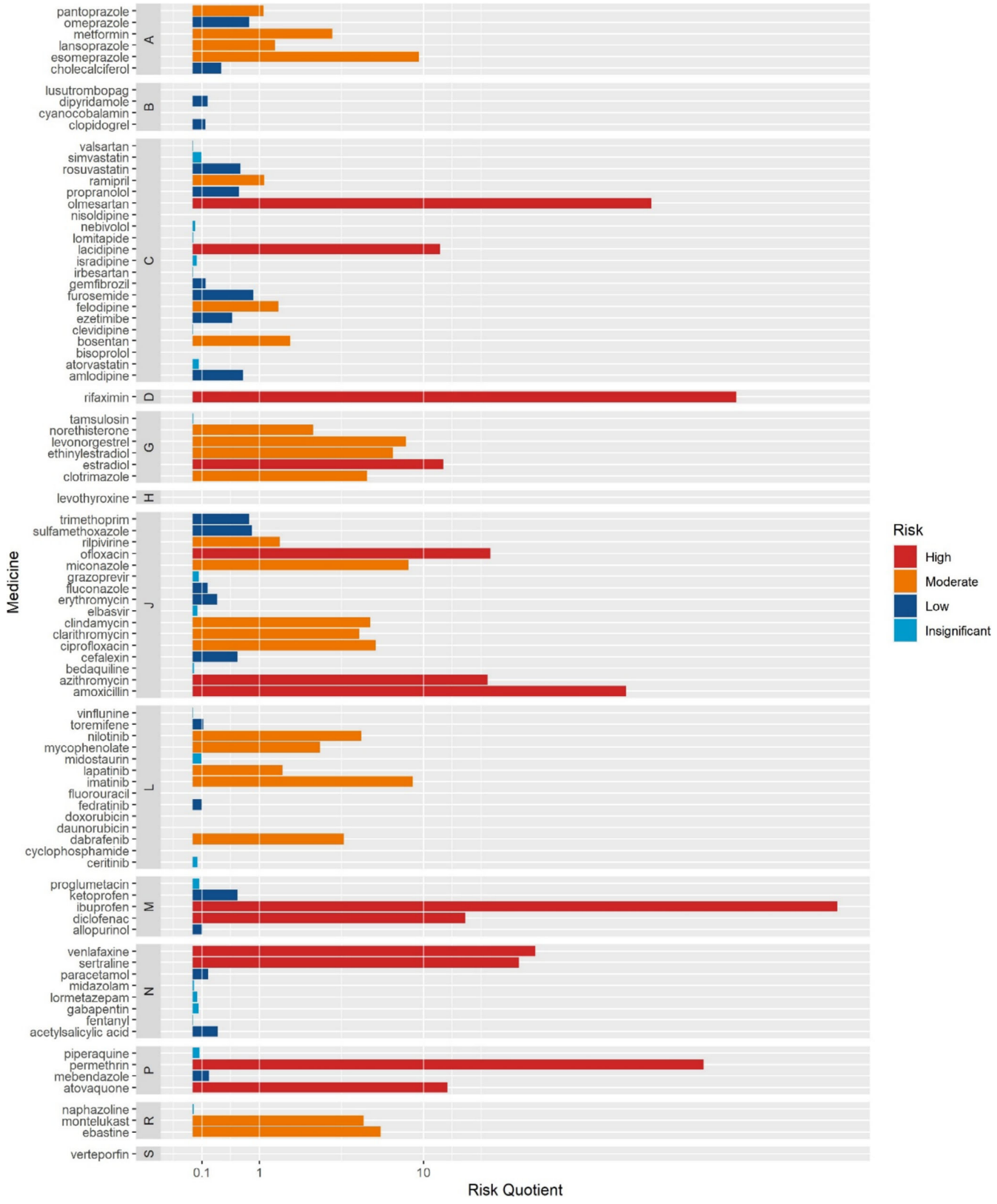

FIGURE 1 Risk level of the 90 selected medicines in Italy in 2022. Uppercase letters indicate ATC level I groups.

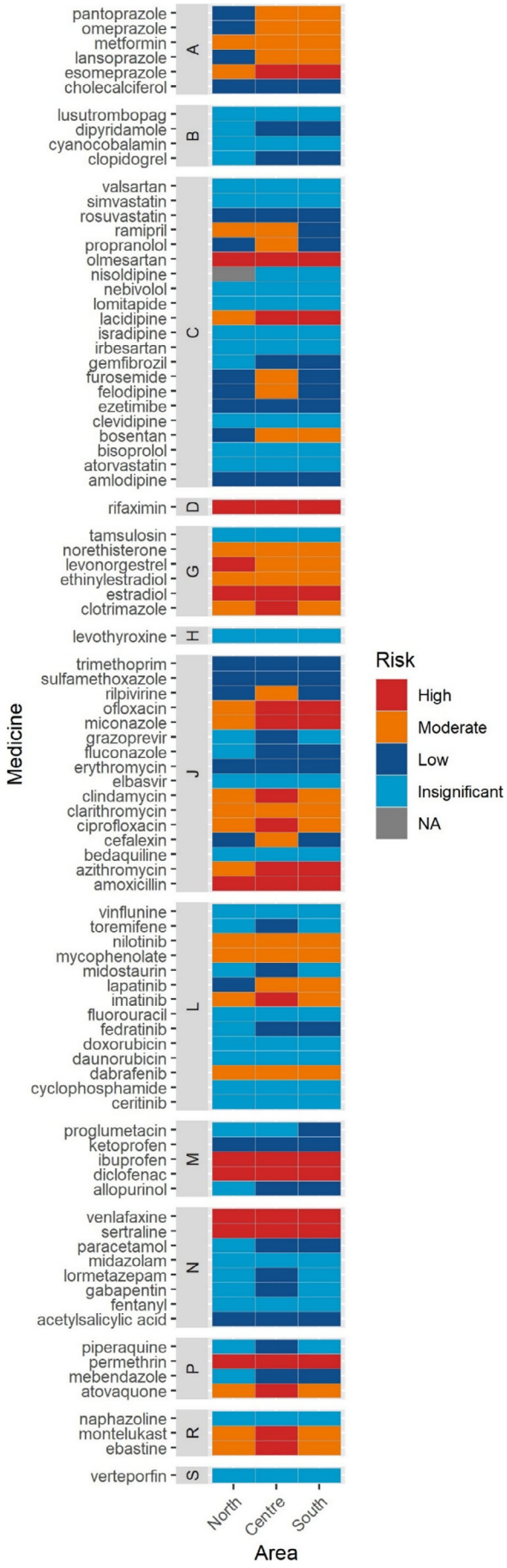

FIGURE 2 Risk level of the 90 selected medicines in 2022 divided by Italian macro-area. Uppercase letters indicate ATC level I groups.

4 | DISCUSSION

To our knowledge, this is the first study investigating the environmental impact of an extended range of medicines in Italy, starting from drug utilization data. We identified different high-risk medications, including NSAIDs, hormonal agents, antidepressants, cardiovascular drugs and antibiotics.

The majority of therapeutic classes considered in this analysis exhibited at least one medicine posing either a high or moderate level of risk. This suggested that the environmental risk was widespread and distributed across various types of medicines. Notably, the only classes that did not show any risk in this analysis were the ATC B class of blood agents and the ATC S class of sensory organs agents. However, it is important to acknowledge that the number of medicines from these classes included in the assessment was relatively limited and that most sensory agents have also another ATC code.

The method used to derive environmental risk relies solely on PNEC to assess the harmfulness of medicines to the aquatic environment. However, the physico-chemical characteristics of the medicines also play a role in determining the damage caused to aquatic organisms. These characteristics are typically exemplified by persistence, bioaccumulation and toxicity.[29] In the following, we will discuss the high- and moderate-risk medicines identified in our study, integrating known effects in terms of persistence, bioaccumulation and toxicity.

Commonly used medicines posing a high risk to Italian surface waters were the NSAIDs such as diclofenac and ibuprofen. The environmental impact of diclofenac has widely been studied and it is recognized to cause severe environmental damage,[30,31] with a high risk being acknowledged in different countries.[32] On the other hand, ibuprofen, despite its high risk, driven essentially by wide consumption, may have an overall lower environmental impact because it had a lower potential for bioaccumulation and persistence.[32,33] Otherwise, ketoprofen, acetylsalicylic acid and paracetamol, belonging to the same therapeutic area, showed a low risk. Despite their similarly high consumption, their PNEC values were higher compared to those of diclofenac and ibuprofen, resulting in a lower environmental risk.

Hormonal agents commonly employed for contraceptive purposes, and to a lesser extent for menopausal symptom treatment, were associated with either a high or moderate level of risk. These substances are widely acknowledged for their potential to cause harm when present in surface water because of their ability to disrupt the hormonal equilibrium of different aquatic species. For example, they can cause the feminization of male fish and consequently disrupt ecological equilibrium.[2] For instance, while the use of contraceptives has a definitive environmental impact, reducing their usage is not a viable option due to social consequences. These include the potential increase in birth rates, particularly among lower socioeconomic

groups, leading to adverse psychosocial effects, and the compromised efficacy of contraceptives if their use is diminished.[34] Therefore, alternative strategies to mitigate the environmental footprint should be explored.[35,36]

Another pharmaceutical compound identified as posing a high risk to the environment is permethrin, an antiparasitic agent commonly employed for the treatment and prevention of head lice and scabies.[37] Since permethrin is extensively utilized in agriculture as a broad-spectrum insecticide, the hazard to the environment is probably even higher.[38,39] Also, the antiprotozoal atovaquone has been identified as posing a high environmental risk. While these latter two medicines have been identified as potential high-risk emerging contaminants on the basis of PNEC values obtained in experimental conditions, their effects on real aquatic ecosystems have not been thoroughly studied.[40–42]

The antidepressants sertraline and venlafaxine, respectively a selective serotonin reuptake inhibitor and a serotonin-norepinephrine reuptake inhibitor, were identified as posing a high environmental risk. They are widely used to treat a broad spectrum of prevalent psychiatric disorders, including major depression and anxiety disorders.[43] The primary toxic effect observed in exposed fish was alteration in behaviour, although there are conflicting findings.[44–47] Clinical alternatives, such as citalopram and escitalopram, have higher PNEC,[22] potentially rendering their environmental risk lower.

Among the ATC class C medicines, olmesartan, an angiotensin II receptor blocker,[48] and lacidipine, a calcium channel blocker also used for hypertension,[49] were estimated to pose a high environmental risk. In contrast, the angiotensin II receptor blocker valsartan resulted in an insignificant impact on the environment. Among the calcium channel blockers class, felodipine presented a moderate risk, while amlodipine and nisoldipine presented a low risk. Moreover, ramipril, an ACE inhibitor, was estimated to pose a moderate risk, while the beta-blockers bisoprolol, nebivolol and propranolol resulted in a low or insignificant environmental risk. Certain studies emphasized that medicines within the same therapeutic class may exhibit distinct behaviours during wastewater treatment. For instance, among angiotensin II receptor blockers, olmesartan degrades more slowly than valsartan, adding complexity to their risk assessment.[50] A few studies have identified adverse reactions, including reproductive problems and issues related to biochemistry, such as disturbances in lipid metabolism, oxidative stress and steroid levels,[51] but overall the effects of cardiovascular agents on aquatic organisms and plants remain insufficiently explored. Given the vast array of medicines available for the treatment of hypertension and the large number of people affected, it is crucial to consider the environmental impact in the overall assessment of these medications even at the moment of medical prescription. This should be included in a comprehensive assessment of their sustainability, along with their clinical risk-benefits, costs and accessibility to patients.

Finally, a high environmental risk was estimated for certain antibacterials and antibiotics. The penicillin amoxicillin, the macrolide azithromycin and the fluoroquinolone ofloxacin were identified as high-risk medicines. Rifaximin, an antibiotic mainly used to treat traveller's diarrhoea caused by *Escherichia coli*, was also classified as high risk. However, it is important to note that it could be purchased in Italy for use during travels abroad. Additionally, this medicine may be overused for the treatment of certain diseases, such as diverticulitis.[52] Moderate risk was estimated for ciprofloxacin (a fluoroquinolone) and clarithromycin (a macrolide), while erythromycin, another macrolide, was estimated as low risk. The elevated risk associated with commonly used antibacterials in Italy raised significant concerns, particularly regarding potential adverse impacts on aquatic flora and fauna.[53] Beyond posing immediate threats to the aquatic environment, these antibacterials also exhibit a worrisome capacity for bioaccumulation, further amplifying the risk. Moreover, the potential for the development of antibiotic-resistant strains adds a critical layer to the potential consequences, emphasizing the need for careful monitoring and management of antibiotic use to safeguard both environmental and public health.[4,54,55] Similarly, for cardiovascular drug classes, the environmental impact of each antimicrobial agent should be added to the clinical profile to provide physicians with additional information to make the appropriate therapeutic choice.

We identified some differences in the environmental risk of certain medicines across Italian regions. These differences reflected local drug prescription attitudes and consumption patterns, and may reflect different healthcare practices and socio-economic disparities. Regions with higher consumption rates of high-risk medicines may benefit from targeted initiatives aimed at both physicians and patients, promoting responsible drug prescription practices, raising awareness about the environmental consequences of improper drug disposal and implementation of advanced wastewater treatment systems.

4.1 | Limitations and future perspectives

OsMed data, with their extensive spatial coverage at national, macro-area and regional levels, along with their comprehensive coverage of all medicines supplied, offer an exhaustive picture of drug utilization in Italy and its associated risk on surface waters. This analysis may be useful for highlighting the differences between the geographic areas and for the establishment of a routine of environmental risk estimation.

The primary limitation of this study is the utilization of default values for both the volume of wastewater produced and the removal rate at wastewater treatment plants in the risk derivation approach employed. Further, this analysis assumes a worst-case scenario where all consumed medicines are hypothesized to end up in surface waters. Elements such as human detoxification, correct disposal and wastewater treatment, which have the potential to reduce surface water concentrations of medicines, were not included. This analysis is therefore useful as a first step in prioritization. Moreover, even for low-risk medicines, it is essential to consider that their active metabolites may pose a higher risk, therefore additional work should focus on estimating the impact of metabolites based on drug utilization data for the parent compound. Additionally, the computed PEC only accounted for human consumption, overlooking the potential contribution of

veterinary medicines. Although the impact of veterinary medicines on surface water is often indirect, primarily through soil contamination, it could be significant for certain therapeutic classes such as antibiotics and hormones. To enhance the accuracy of future assessments, efforts should be directed toward collecting this data at the Italian, macro-area and regional levels. Furthermore, we used both in vivo and in silico PNEC values without making a distinction between them. Specifically, in silico PNEC values, derived through a quantitative structure-activity relationship approach, were found to be the lowest for 28 out of the 90 medicines analysed, with 12 medicines having no other values available. All in silico PNEC values were sourced from the NORMAN database. Finally, we should not solely focus on substances with high or moderate risk. This is because several substances within the same class might share a toxic mechanism, potentially causing an effect when present together, even if each substance individually remained below the threshold of no effect. Additionally, different substances could exhibit a synergistic effect by acting at various points along the same pathway or they might combine to form new substances with different mechanisms or potencies.[56,57] Furthermore, low concentrations of medicines in the environment have the potential for bioaccumulation, subsequently leading to higher concentrations along the food chain, a phenomenon known as biomagnification. As a result, even medicines initially deemed low risk could impact secondary consumers.[58]

Proactive measures are essential for managing the high environmental risk associated with certain medicines and the appropriate actions may vary depending on the therapeutic class. For example, in classes such as NSAIDs and antibiotics, limiting overconsumption, overprescription and unnecessary self-treatment can lead to improvements in drug utilization. However, for medicines in classes like hormonal agents, where drug utilization may not be easily modifiable, it is crucial to take postutilization measures. This may include the implementation of filtering systems in wastewater treatment plants to mitigate the impact on the environment.[59,60]

AUTHOR CONTRIBUTIONS

V.G., M.F., E.P., C.L., A.C., F.F. and S.Z. conceptualized and designed the study. V.G., M.F., C.L., E.P., A.C., F.F., S.Z. and A.P. curated the drug utilization data. V.G. retrieved data other than drug utilization, and performed analyses and graphical visualization. V.G. wrote the original draft. M.F., C.L., E.P., A.C., F.F. and S.Z. revised and integrated the original draft. All the authors read and approved the final version.

ACKNOWLEDGMENTS

Part of the content was published in the OsMed 2022 report on medicines use in Italy (accessible at https://www.aifa.gov.it/en/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2022). V.G. and C.L. were supported by Italian Programma Operativo Nazionale funds on green research. E.P. was supported by institutional research funds (Ricerca Fondamentale Orientata). M.F. is supported by funds for a PhD for the University of Bologna. Open access publishing facilitated by Universita degli Studi di Bologna, as part of the Wiley - CRUI-CARE agreement.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data and scripts used in this analysis are available in the Supporting Information.

ORCID

Valentina Giunchi https://orcid.org/0000-0001-5841-8520
Michele Fusaroli https://orcid.org/0000-0002-0254-2212
Agnese Cangini https://orcid.org/0000-0002-1640-3993
Filomena Fortinguerra https://orcid.org/0000-0002-6587-9808
Carlotta Lunghi https://orcid.org/0000-0001-7636-6285

REFERENCES

1. Daughton CG. Chapter 2 Pharmaceuticals in the Environment: Sources and Their Management. In: Petrovic M, Barcelo D, Pérez S, eds. *Comprehensive analytical chemistry*. Vol.62. Analysis, Removal, Effects and Risk of Pharmaceuticals in the Water Cycle. Elsevier; 2013:37-69. doi:10.1016/B978-0-444-62657-8.00002-1
2. Porseryd T, Larsson J, Kellner M, Bollner T, Dinnétz P, Porsch Hällström I. Altered non-reproductive behavior and feminization caused by developmental exposure to 17α-ethinylestradiol persist to adulthood in three-spined stickleback (*Gasterosteus aculeatus*). *Aquat Toxicol*. 2019;207:142-152. doi:10.1016/j.aquatox.2018.11.024
3. der aus Beek T, Weber FA, Bergmann A, et al. Pharmaceuticals in the environment—global occurrences and perspectives. *Environ Toxicol Chem*. 2015;35(4):823-835. doi:10.1002/etc.3339
4. Grenni P, Ancona V, Barra Caracciolo A. Ecological effects of antibiotics on natural ecosystems: a review. *Microchem J*. 2018;136:25-39. doi:10.1016/j.microc.2017.02.006
5. EMA. *Revised guideline to assess risk of human medicines for the environment*. European Medicines Agency; 2018. Accessed 5 August 2023. https://www.ema.europa.eu/en/news/revised-guideline-assess-risk-human-medicines-environment
6. Commission Implementing Decision (EU) 2022/1307 of 22 July 2022 Establishing a Watch List of Substances for Union-Wide Monitoring in the Field of Water Policy Pursuant to Directive 2008/105/EC of the European Parliament and of the Council (Notified under Document C[2022] 5098) (Text with EEA Relevance). 197.; 2022. Accessed 5 December 2023. http://data.europa.eu/eli/dec_impl/2022/1307/oj/eng
7. European Parliament. Strategic approach to pharmaceuticals in the environment. Published online 2019. Accessed 5 April 2024. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0226_EN.html
8. ECHA. Guidance on information requirements and chemical safety assessment chapter R.10: characterisation of dose [concentration]-response for environment. Published online May 2008. https://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf/bb902be7-a503-4ab7-9036-d866b8ddce69
9. Ågerstrand M, Wester M, Rudén C. The Swedish environmental classification and information system for pharmaceuticals — an empirical investigation of the motivations, intentions and expectations underlying its development and implementation. *Environ Int*. 2009;35(5):778-786. doi:10.1016/j.envint.2008.12.001
10. Lif. Environmental classification of pharmaceuticals at www.fass.se. Published online 2012. Accessed 5 December 2023. https://www.lif.se/contentassets/b7cf255755504f78a906f3eba8a6ae38/environmental-classification-of-pharmaceuticals-att-wwwfassse.pdf
11. FASS.se. *Fakta om läkemedel och miljö*. FASSse; 2015. Accessed 5 August 2023. https://www.lif.se/sa-funkar-det/lakemedel-och-miljo/

12. Region Stockholm. Janusinfo – Environment and Pharmaceuticals. Accessed 5 December 2023. https://janusinfo.se/beslutsstod/lakemedelochmiljo/pharmaceuticalsandenvironment.4.7b57ecc216251fae47487d9a.html
13. Nordvall E. Environmental classification of medicines available for the first time in Finland. Pharmaca 12 January 2022. Accessed 26 October 2023. https://pharmaca.fi/en/environmental-classification-of-medicines-available-for-the-first-time-in-finland/
14. Pharmaca Fennica. Accessed 5 December 2023. https://pharmacafennica.fi/
15. Giunchi V, Fusaroli M, Linder E, et al. The environmental impact of pharmaceuticals in Italy: integrating healthcare and eco-toxicological data to assess and potentially mitigate their diffusion to water supplies. *Br J Clin Pharmacol*. 2023;89(7):2020-2027. doi:10.1111/bcp.15761
16. Welch SA, Olsen K, Nouri Sharikabad M, Tollefsen KE, Grung M, Moe SJ. Pharmaceutical pollution: prediction of environmental concentrations from national wholesales data. *Open Res Eur*. 2022;2:71. doi:10.12688/openreseurope.14129.2
17. National report on medicines use in Italy: year 2022. Accessed 5 December 2023. https://www.aifa.gov.it/en/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2022
18. Gomez CL, Marinov D, Sanseverino I, Porcel RE, Lettieri T. Selection of substances for the 4th watch list under the water framework directive. *JRC Publ Rep*. doi:10.2760/01939
19. Selection of substances for the 3rd watch list under the water framework directive – Publications Office of the EU. Accessed 20 August 2023. https://op.europa.eu/en/publication-detail/-/publication/a2ab9f86-d140-11ea-adf7-01aa75ed71a1/language-en
20. Loos R, Marinov D, Sanseverino I, Napierska D, Lettieri T. Review of the 1st watch list under the water framework directive and recommendations for the 2nd watch list. *JRC Publ Rep*. doi:10.2760/614367
21. Negrão DCR, Ceriani L, Ippolito A, Lettieri T. Development of the first watch list under the environmental quality standards directive. *JRC Publ Rep*. doi:10.2788/101376
22. Giunchi V. PNEC repository. Published online 22 August 2023. doi:10.17605/OSF.IO/XTG8Z
23. Indicatori demografici. 8 April 2022. Accessed 6 December 2023. https://www.istat.it/it/archivio/269158
24. Indicatori demografici - Anno 2022. Accessed 6 December 2023. https://www.istat.it/it/archivio/283229
25. Giunchi V, Poluzzi E. A collection of Predicted No-Effect Concentrations of human pharmaceuticals and their metabolites. Published online 13 December 2023:2023.12.12.571257. doi:10.1101/2023.12.12.571257
26. NORMAN. *NORMAN ecotoxicology database*. NORMAN ecotoxicology Database; 2023. Accessed 5 August 2023. https://www.norman-network.com/nds/ecotox/
27. WHO. WHOCC - ATC/DDD Index. Accessed 5 August 2023. https://www.whocc.no/atc_ddd_index/
28. R: The R Project for Statistical Computing. Accessed 2 February 2024. https://www.r-project.org/
29. Sangion A, Gramatica P. Pbt assessment and prioritization of contaminants of emerging concern: pharmaceuticals. *Environ Res*. 2016;147:297-306. doi:10.1016/j.envres.2016.02.021
30. Sathishkumar P, Meena RAA, Palanisami T, Ashokkumar V, Palvannan T, Gu FL. Occurrence, interactive effects and ecological risk of diclofenac in environmental compartments and biota: a review. *Sci Total Environ*. 2020;698:134057. doi:10.1016/j.scitotenv.2019.134057
31. Joachim S, Beaudouin R, Daniele G, et al. Effects of diclofenac on sentinel species and aquatic communities in semi-natural conditions. *Ecotoxicol Environ Saf*. 2021;211:111812. doi:10.1016/j.ecoenv.2020.111812
32. Welch SA, Moe SJ, Sharikabad MN, Tollefsen KE, Olsen K, Grung M. Predicting environmental risks of pharmaceuticals from wholesale data: an example from Norway. *Environ Toxicol Chem*. 2023;42(10):2253-2270. doi:10.1002/etc.5702
33. Villén J, Nekoro M, Sporrong SK, Håkonsen H, Bertram MG, Wettermark B. Estimating environmental exposure to analgesic drugs: a cross-sectional study of drug utilization patterns in the area surrounding Sweden's largest drinking water source. *Environ Adv*. 2023;12:100384. doi:10.1016/j.envadv.2023.100384
34. Cleland J, Conde-Agudelo A, Peterson H, Ross J, Tsui A. Contraception and health. *Lancet*. 2012;380(9837):149-156. doi:10.1016/S0140-6736(12)60609-6
35. Adeel M, Song X, Wang Y, Francis D, Yang Y. Environmental impact of estrogens on human, animal and plant life: a critical review. *Environ Int*. 2017;99:107-119. doi:10.1016/j.envint.2016.12.010
36. Guerrero-Gualan D, Valdez-Castillo E, Crisanto-Perrazo T, Toulkeridis T. Methods of removal of hormones in wastewater. *water*. 2023;15(2):353. doi:10.3390/w15020353
37. Permethrin topical uses, side effects & warnings. Drugs.com. Accessed 28 December 2023. https://www.drugs.com/mtm/permethrin-topical.html
38. Hill IR. Aquatic organisms and pyrethroids. *Pestic Sci*. 1989;27(4):429-457. doi:10.1002/ps.2780270408
39. Drago B, Shah NS, Shah SH. Acute permethrin neurotoxicity: variable presentations, high index of suspicion. *Toxicol Rep*. 2014;1:1026-1028. doi:10.1016/j.toxrep.2014.09.007
40. Almeida A, De Mello-Sampayo C, Lopes A, da Carvalho Silva R, Viana P, Meisel L. Predicted environmental risk assessment of antimicrobials with increased consumption in Portugal during the COVID-19 pandemic; the groundwork for the forthcoming water quality survey. *Antibiotics*. 2023;12(4):652. doi:10.3390/antibiotics12040652
41. Aubakirova B, Beisenova R, Boxall AB. Prioritization of pharmaceuticals based on risks to aquatic environments in Kazakhstan. *Integr Environ Assess Manag*. 2017;13(5):832-839. doi:10.1002/ieam.1895
42. DeMars C, Wang R, Grieneisen ML, Steggall J, Zhang M. Assessment of pyrethroid contamination and potential mitigation strategies in California central coast surface waters. *J Environ Manage*. 2021;278:111507. doi:10.1016/j.jenvman.2020.111507
43. Venlafaxine uses, dosage & side effects. Drugs.com. Accessed 28 December 2023. https://www.drugs.com/venlafaxine.html
44. Melvin SD. Effect of antidepressants on circadian rhythms in fish: insights and implications regarding the design of behavioral toxicity tests. *Aquat Toxicol*. 2017;182:20-30. doi:10.1016/j.aquatox.2016.11.007
45. Mennigen JA, Zamora JM, Chang JP, Trudeau VL. Endocrine disrupting effects of waterborne fluoxetine exposure on the reproductive axis of female goldfish, *Carassius auratus*. *Comp Biochem Physiol C Toxicol Pharmacol*. 2017;202:70-78. doi:10.1016/j.cbpc.2017.08.003
46. Campos B, Rivetti C, Kress T, Barata C, Dircksen H. Depressing antidepressant: fluoxetine affects serotonin neurons causing adverse reproductive responses in *Daphnia magna*. *Environ Sci Technol*. 2016;50(11):6000-6007. doi:10.1021/acs.est.6b00826
47. Sehonova P, Svobodova Z, Dolezelova P, Vosmerova P, Faggio C. Effects of waterborne antidepressants on non-target animals living in the aquatic environment: a review. *Sci Total Environ*. 2018;631:789-794. doi:10.1016/j.scitotenv.2018.03.076
48. Olmesartan uses, side effects & warnings. Drugs.com. Accessed 28 December 2023. https://www.drugs.com/mtm/olmesartan.html
49. Lacidipine: uses, interactions, mechanism of action|DrugBank Online. Accessed 28 December 2023. https://go.drugbank.com/drugs/DB09236
50. Bayer A, Asner R, Schüssler W, et al. Behavior of sartans (antihypertensive drugs) in wastewater treatment plants, their occurrence and

risk for the aquatic environment. *Environ Sci Pollut Res*. 2014;21(18):10830-10839. doi:10.1007/s11356-014-3060-z

51. Zhang K, Zhao Y, Fent K. Cardiovascular drugs and lipid regulating agents in surface waters at global scale: occurrence, ecotoxicity and risk assessment. *Sci Total Environ*. 2020;729:138770. doi:10.1016/j.scitotenv.2020.138770
52. Piccin A, Gulotta M, di Bella S, Martingano P, Crocè LS, Giuffrè M. Diverticular disease and rifaximin: an evidence-based review. *Antibiotics*. 2023;12(3):443. doi:10.3390/antibiotics12030443
53. Bojarski B, Kot B, Witeska M. Antibacterials in aquatic environment and their toxicity to fish. *Pharmaceuticals*. 2020;13(8):189. doi:10.3390/ph13080189
54. CDC. *Antibiotic resistance in the environment*. Centers for Disease Control and Prevention; 2022. Accessed 9 November 2023. https://www.cdc.gov/drugresistance/solutions-initiative/environment.html
55. García J, García-Galán MJ, Day JW, et al. A review of emerging organic contaminants (EOCs), antibiotic resistant bacteria (ARB), and antibiotic resistance genes (ARGs) in the environment: increasing removal with wetlands and reducing environmental impacts. *Bioresour Technol*. 2020;307:123228. doi:10.1016/j.biortech.2020.123228
56. Moreira DG, Aires A, de Lourdes PM, Oliveira M. Levels and effects of antidepressant drugs to aquatic organisms. *Comp Biochem Physiol Part C Toxicol Pharmacol*. 2022;256:109322. doi:10.1016/j.cbpc.2022.109322
57. Stuer-Lauridsen F, Birkved M, Hansen LP, Holten Lützhøft HC, Halling-Sørensen B. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere*. 2000;40(7):783-793. doi:10.1016/S0045-6535(99)00453-1
58. Zenker A, Cicero MR, Prestinaci F, Bottoni P, Carere M. Bioaccumulation and biomagnification potential of pharmaceuticals with a focus on the aquatic environment. *J Environ Manage*. 2014;133:378-387. doi:10.1016/j.jenvman.2013.12.017
59. Moermond CTA, de Rooy M. The Dutch chain approach on pharmaceuticals in water: stakeholders acting together to reduce the environmental impact of pharmaceuticals. *Br J Clin Pharmacol*. 2022;88(12):5074-5082. doi:10.1111/bcp.15509
60. Helwig K, Niemi L, Stenuick J-Y, et al. Broadening the perspective on reducing pharmaceutical residues in the environment. *Environ Toxicol Chem*. 2024; 43(3):653-663. doi:10.1002/etc.5563

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Giunchi V, Fusaroli M, Cangini A, et al. Assessing the environmental impact of medicines in Italy using data from the Italian Medicines Agency. *Br J Clin Pharmacol*. 2025;1-9. doi:10.1002/bcp.70046