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SHORT COMMUNICATION

The environmental impact of pharmaceuticals in Italy: Integrating healthcare and eco-toxicological data to assess and potentially mitigate their diffusion to water supplies

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Pharmaceuticals can reach the environment at all stages of their lifecycle and accumulate in the ecosystem, potentially reaching toxic levels for animals and plants. In recent years, efforts have been made to map and control this hazard. Assessing country-specific environmental risks could drive regulatory actions towards eco-friendlier drug utilization and disposal practices. By starting from a list of 25 environmentally hazardous pharmaceuticals developed by Region Stockholm, we integrated eco-toxicological and 2019–2021 Italian drug utilization data to estimate the environmental impact of pharmaceuticals in Italy. We calculated the risk as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC). We found a high risk for levonorgestrel, ciprofloxacin, amoxicillin, azithromycin, venlafaxine, sertraline and diclofenac and a moderate risk for ethinyloestradiol, oestradiol and clarithromycin. This analysis can be periodically performed to identify the pharmaceuticals with the highest risk for the environment and ascertain if containment measures should be implemented.

KEYWORDS
drug safety, drug utilization, public health, toxicology

1 | INTRODUCTION

The global consumption of pharmaceuticals has increased significantly over the past decades and this trend is expected to continue in the coming years. This increase can be attributed to several factors, including the development of innovative pharmaceuticals for a wider range of conditions, the increasing number of elderly individuals who require treatment for age-related diseases, the inappropriate use of pharmaceuticals for both therapeutic and non-therapeutic purposes, and the promotion of illness for economic benefit by the pharmaceutical industry.[1–6] The increasing utilization of pharmaceuticals has triggered discussions about their environmental impact.[7] Several international frameworks address actions and goals for increased sustainability. Several of the Sustainable Development Goals (SDGs) of the United Nations Agenda 2030, adopted in 2015, affect pharmaceuticals research: SDG3 (Good health and wellbeing), SDG6 (Clean water and sanitation), SDG9 (Industry, innovation and infrastructure), SDG12 (Responsible consumption and production), and SDG14 (Life below water).[8]

Once consumed, most pharmaceuticals for human use are excreted in urine and faeces, either in unchanged condition or as metabolites. Moreover, unused pharmaceuticals can be disposed of in

inappropriate ways (e.g., by flushing them down the toilet or drain). Since most pharmaceuticals cannot be effectively eliminated in wastewater treatment plants, they are discharged to receiving water bodies, including surface water and groundwater. Here they can accumulate (usually ranging from μg/L to ng/L) and potentially lead to animal and plant toxicity.[9–11] For example, chronic exposure to ethinyloestradiol leads to sterilization and feminization in male fish and disruption of oogenesis in frogs.[12–16] Further, the accumulation of antimicrobials in water can lead to the selection and spread of resistant bacterial strains, which hamper our attempts to treat infections.[17,18] According to the World Health Organization (WHO), antimicrobic resistance will pose a major threat to human health in the near future.[19] To support eco-friendlier drug utilization and disposal, Article 8 of European Union Directive 2001/83/EC regulating pharmaceuticals for human use specifies the need to detail potential environmental risks for all new applications for marketing authorization.[20,21] To enter the market, most new pharmaceuticals must be assessed according to a two-tier environmental impact classification system called Environmental Risk Assessment. The first tier focuses on the environmental hazard considering intrinsic pharmaceutical properties, while the second focuses on environmental risk. Environmental risk is determined by the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) in surface water.[21] PNEC values are derived from eco-toxicological measurements in organisms in different environmental compartments.[21,22] In contrast, PEC values can be estimated considering the pharmaceutical consumption, the volume of wastewater produced, and the pharmaceutical disposal capability in a specific area (i.e., the removal in a wastewater treatment plant).[21,23] At the marketing authorization stage, the European Medicines Agency (EMA) requires the PEC estimation to be based on default parameters and predicted drug utilization.[21] Post marketing, actual drug utilization data can be used to estimate a more accurate PEC. Nonetheless, since pharmaceutical-specific wastewater production and dilution factors are difficult to obtain, these predicted concentrations may differ from actual samplings (i.e., measured environmental concentrations), which may be influenced by country-specific drug utilization patterns and disposal systems.[24] Monitoring systems can track pharmaceutical levels in surface water (and document inter-country heterogeneity), but their widespread application to a wide range of pharmaceuticals in the world's waters is time- and resource-expensive.[22,25–28]

The environmental risk estimate proposed by the EMA can be extended to overcome these drawbacks using post-marketing drug utilization data.[29] In Sweden, two initiatives provide knowledge support on pharmaceuticals in the environment: Lif—the Swedish Association of the Pharmaceutical Industry (FASS)—and the Region Stockholm (Sweden capital region). FASS collects risk information from environmental risk assessment reports made by manufacturers.[30] Region Stockholm creates risk summaries based on the information from FASS, EPAR (European Public Assessment Reports) and peer-reviewed literature.[7,31]

The Region Stockholm Environmental Program 2017–2021 sampled a wide range of pharmaceutical concentrations at different sites in Sweden, and identified a list of 25 plausibly environmentally hazardous pharmaceuticals.[32] Focusing on these pharmaceuticals, we applied the Region Stockholm and FASS method to Italian drug utilization data to assess their environmental risk within Italy for 2019, 2020 and 2021.

On this subset of environmentally hazardous pharmaceuticals, we implemented a tool to timely and cheaply estimate the environmental risk of pharmaceuticals in Italy, combining eco-toxicological and consumption data. While non-exhaustive, this subset allows us to face the important challenges that should be taken into account when designing and performing a wider study (i.e., on a larger number of pharmaceuticals and countries). Once refined, this tool could be routinely applied to complement water samplings towards a better monitoring and mitigation of hazards related to pharmaceuticals in surface water.

What is already known about this subject

- Due to the worldwide increase in pharmaceutical consumption, pharmaceutical residues in surface water may reach toxic levels for the environment and lead to health-related problems.
- Despite this, surface water samplings of pharmaceutical concentrations are infrequent and only performed in specific geographical areas.

What this study adds

- We implemented a method to timely and cheaply estimate the environmental risk determined by pharmaceutical residues in Italian surface water combining eco-toxicological and consumption data.
- We identified a relatively high or moderate environmental risk for three hormones, four antibiotics, two antidepressants and one anti-inflammatory agent.
- Continuous monitoring may help stakeholders target interventions towards eco-friendlier pharmaceutical use and disposal.

2 | METHODS

We integrated drug utilization and eco-toxicological data to assess the environmental risk of the 25 selected pharmaceuticals[31,32] on surface waters in Italy. Drug utilization data were extracted from the OsMed (Medicines Utilization Monitoring Centre) reports on drug utilization for the years 2019, 2020 and 2021,[33–35] and from the OsMed reports on antimicrobial consumption for the years 2019 and 2020.[36,37]

These reports are published annually by the Italian Medicines Agency (AIFA) and provide summaries of data on drug utilization retrieved from both the Italian National Health Service (i.e., for reimbursed prescriptions and hospital-use pharmaceuticals) and wholesalers (i.e., sales of over-the-counter pharmaceuticals). When drug utilization data were unavailable in the OsMed reports, we did not compute a risk estimation.

The eco-toxicological PNEC values, describing the concentration below which no toxic effect on aquatic organisms is expected, were, depending on their availability, extracted from the Region Stockholm Pharmaceuticals and Environment database,[7,31] FASS website,[38] NORMAN database,[39] European Commission Watch List working materials,[40,41] or published literature. When multiple PNEC values regarding different animal species, among those approved in the OECD guidelines, were available for one pharmaceutical, the lowest or the one that referred to the most suitable species, according to the EMA guidelines, was prioritized.[21,42]

For each pharmaceutical, we used the FASS formula[23] to estimate Italian PEC values, quantifying the concentration of the pharmaceutical in the environment:

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

where

- $A\,(\mathrm{kg/year})$ is the quantity of pharmaceutical sold in Italy, based on OsMed reports for 2019, 2020 and 2021.[33–37] They present Italian drug utilization data as DDD/1000 inhabitants per day (ipd), where DDD is the defined daily dose, that is, the assumed average maintenance dose per day. We extracted the DDD/g conversion for the oral administration route from the WHO Collaborating Centre for Drug Statistics Methodology website[43] (Tables S1–S6). We converted DDD/1000 ipd drug utilization to kg/year as follows: $A(\mathrm{kg/year}) = \frac{A\left(\frac{\mathrm{DDD}}{1000}\mathrm{ipd}\right) \times 365 \times P}{1000} \times \frac{\frac{\mathrm{DDD}}{\mathrm{g}}\mathrm{conversion}}{1000}$.
- $R\,(\%)$ is the removal rate, due to absorption, volatilization, hydrolysis or biodegradation in disposal systems. Since generally no data on removal (R) were available, we assumed it to be null.
- P is the population to which drug utilization is referred to, that is, the total number of Italian inhabitants on 1 January of each year under analysis (Tables S1–S6).
- $V\,(\mathrm{L/day})$ is the daily wastewater volume per capita. Following the European Chemical Agency (ECHA) default value, we set it at 200.[44]
- D is the dilution factor of wastewater by surface water flow. Following the ECHA default value, we set it at 10.[44]

We also performed a sensitivity analysis using available data on Italian wastewater production and dilution. The Italian wastewater volume per capita was defined as 138.78 L/day using the domestic water use for 2008 as a proxy, while the Italian wastewater dilution factor was defined as 34.22.[45]

We calculated the environmental risk for each pharmaceutical as the ratio between its PEC and PNEC. Finally, we assigned FASS risk categories (high, >10; moderate, >1; low, >0.1; insignificant, ≤0.1)[23] to the pharmaceuticals studied.

The analyses and the graphical representations were performed through R software (version 4.2.1).[46]

3 | RESULTS

We integrated drug utilization and eco-toxicological data to assess the environmental burden of pharmaceuticals on Italian surface waters in 2019, 2020 and 2021. The environmental risk was assessed as the ratio between PEC and PNEC values.

We extracted PNEC values from public online databases and published literature gathering environmental hazard indexes. Among the 25 pharmaceuticals investigated, the most hazardous ones (i.e., the ones with the lowest PNEC) were ethinyloestradiol (0.000035 μg/L), levonorgestrel (0.00001 μg/L) and oestradiol (0.0008 μg/L), while irbesartan (704.0 μg/L), trimethoprim (312.45) and glibenclamide (99.4 μg/L) had the highest PNEC values. The complete list of PNEC values, with source and test information, is reported in Table S10.

We found a high risk for one hormone (levonorgestrel: PEC/PNEC = 207.80 in 2019, 189.97 in 2020, 236.04 in 2021), three antibiotics (ciprofloxacin: 80.00 in 2019, 70.00 in 2020, 70.00 in 2021; amoxicillin: 34.78 in 2019, 26.36 in 2020, 25.24 in 2021; azithromycin: 10.50 in 2019, 11.25 in 2020, 10.50 in 2021), two antidepressants (venlafaxine: 29.51 in 2019, 30.33 in 2020, 31.15 in 2021; sertraline: 22.61 in 2019, 23.67 in 2020, 24.73 in 2021), and one anti-inflammatory agent (diclofenac: 18.40 in 2019, 17.42 in 2020, 17.00 in 2021). We found a moderate risk for two hormones (ethinyloestradiol: 6.86 in 2019, 7.13 in 2020, 6.77 in 2021; oestradiol: 2.76 in 2019, 3.07 in 2020, 3.24 in 2021), and one antibiotic (clarithromycin: 4.58 in 2019, 3.13 in 2020, 2.71 in 2021). All the other pharmaceuticals had a low or insignificant risk, as presented in Figure 1.

The sensitivity analysis, performed with the Italian wastewater production and dilution factor, confirmed the high environmental risk of levonorgestrel (PEC/PNEC = 87.51 in 2019, 80.00 in 2020, 99.40 in 2021), ciprofloxacin (33.69 in 2019, 29.48 in 2020, 29.48 in 2021), amoxicillin (14.65 in 2019, 11.10 in 2020, 10.63 in 2021), and venlafaxine (12.43 in 2019, 12.77 in 2020, 13.12 in 2021). Sertraline was classified as high risk in 2021 and as a moderate risk in 2019 and 2020 (9.52 in 2019, 9.97 in 2020, 10.42 in 2021). Azithromycin (4.42 in 2019, 4.74 in 2020, 4.42 in 2021) and diclofenac (7.75 in 2019, 7.34 in 2020, 7.16 in 2021), previously classified as high risk, showed a moderate risk in the sensitivity analysis. The moderate environmental risk was confirmed for both the two hormones (ethinyloestradiol: 2.89 in 2019, 3.00 in 2020, 2.85 in 2021; oestradiol: 1.16 in 2019, 1.29 in 2020, 1.36 in 2021) and the antibiotic (clarithromycin: 1.93 in 2019, 1.32 in 2020, 1.14 in 2021). All the other pharmaceuticals showed a low or insignificant risk also in the sensitivity analysis (Figure 2).

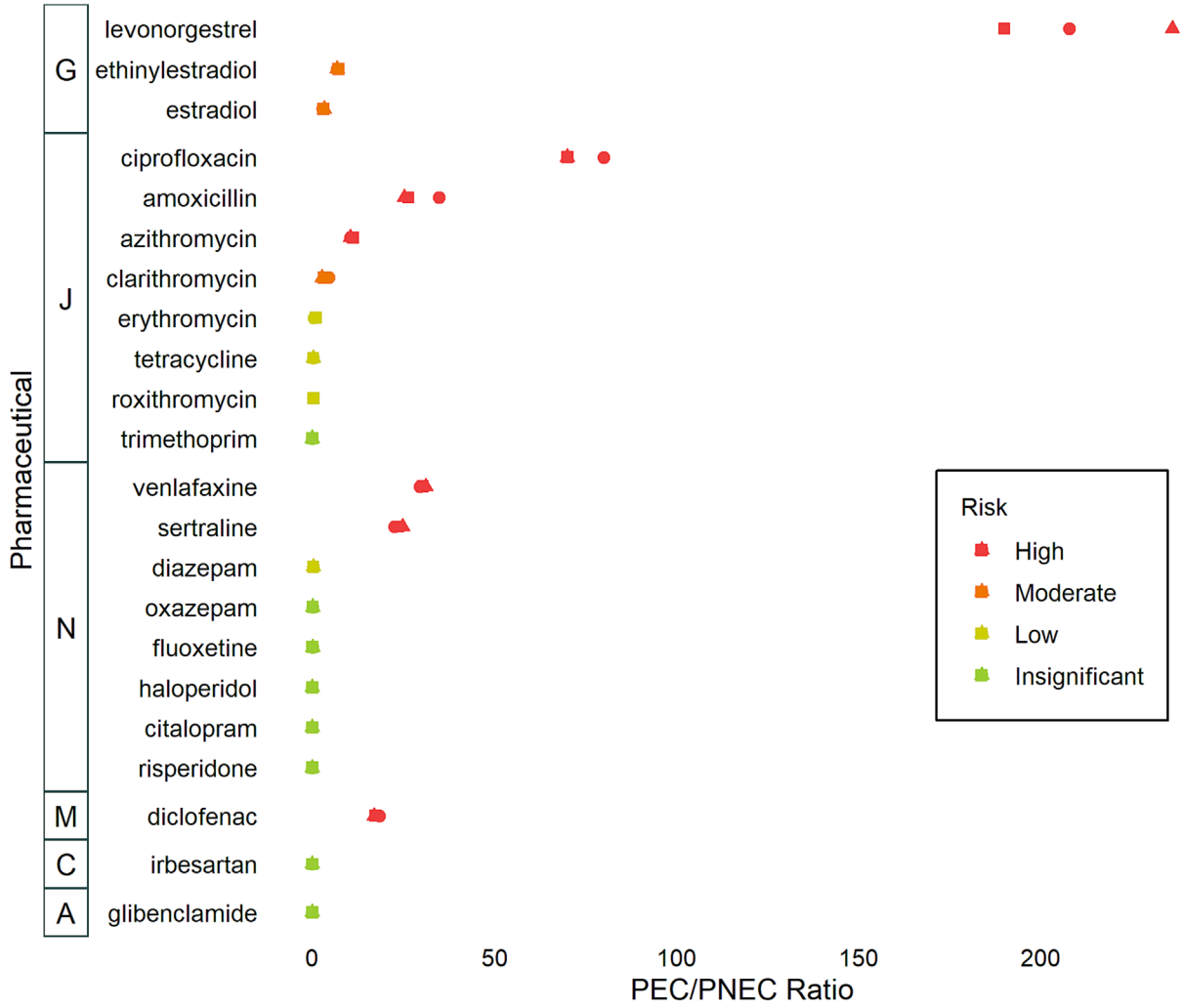

FIGURE 1 Risk quotient values for the environmental impact of selected pharmaceuticals on surface waters. 2019 values are indicated with ●, 2020 values with ■, and 2021 values with ▲. Meclozine, flupentixol and felodipine were not reported because it was not possible to derive the risk quotient due to missing values.

4 | DISCUSSION

Our study aimed to assess the environmental risk of 25 pharmaceuticals in Italy using Italian drug utilization data and both default and real wastewater production and dilution values. The environmental risk was estimated as high or moderate for 10 pharmaceuticals, and it decreased when considering Italian wastewater production and dilution values. Both primary and sensitivity analyses showed a high environmental risk for the hormone levonorgestrel, the antibiotics ciprofloxacin and amoxicillin, and the antidepressants venlafaxine and sertraline. The antibiotic azithromycin and the anti-inflammatory agent diclofenac passed from high risk in the primary analysis to moderate risk in the sensitivity one. Both analyses highlighted a moderate risk for the hormones ethinyloestradiol and oestradiol, and for the antibiotic clarithromycin. Based on previous eco-toxicological studies, these classes were expected to be environmentally hazardous.[12,14,18,25] The environmental risk was consistent throughout the years 2019, 2020 and 2021, with the only exception of sertraline in the sensitivity analysis (its risk was moderate in 2019 and 2020, and high in 2021). This consistency may be the result of a comparable consumption of these pharmaceuticals during the Covid-19 pandemic.[47]

The main challenges in this work concerned data retrieval, which required extraction from multiple heterogeneous sources. The FASS website provided information in Swedish, while some chapters of the OsMed reports were in Italian only. Some sources presented data in free text format, which hampers not only the use but also the preservation of data (e.g., glibenclamide PNEC value was lost in the last update of the FASS website), and no table format download was available. Inconsistencies in how data was organized across different sources further hampered data retrieval: the FASS organizes PNEC values based on brand names rather than on active ingredients. Despite these issues, through a time-consuming and challenging extraction process, we were able to extract the necessary data and provide a valuable table format for future analyses (Tables S1–S6, S10). Furthermore, although gathering data from multiple sources, there remained a lack or incompleteness of the data. For some

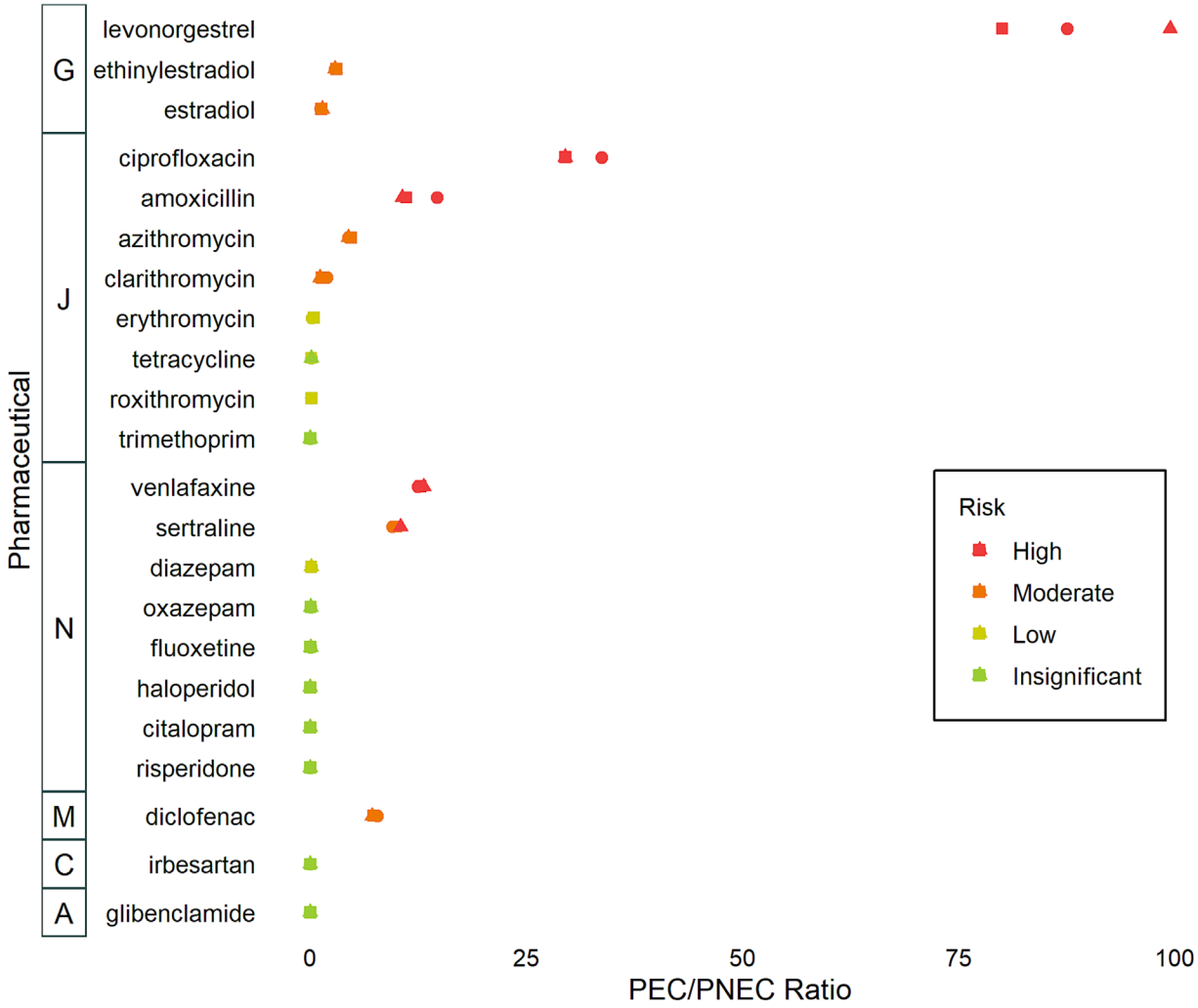

FIGURE 2 Risk quotient values for the environmental impact of selected pharmaceuticals on surface waters in the sensitivity analysis (real Italian values of wastewater production and dilution). 2019 values are indicated with ●, 2020 values with ■, and 2021 values with ▲. Meclozine, flupentixol and felodipine are not reported because it was not possible to derive the risk quotient due to missing values.

pharmaceuticals we were not able to retrieve information on species and assessment factors used to derive PNEC, and therefore we were unable to follow the EMA recommendation to use the lowest PNEC value among the ones provided for three organisms (one algae, one crustacean and one fish).[21] Similarly, the OsMed reports record only drug utilization values for the most used pharmaceuticals, potentially failing to track consumption of less used pharmaceuticals.

Furthermore, we acknowledge some limitations in the generalizability of our results. We proposed an estimation of environmental risk based on both the default wastewater disposal levels provided by the ECHA and the 2008 Italian wastewater production and filtering (as sensitivity analysis). They provided quite similar results, with some pharmaceuticals passing to a lower risk class in the sensitivity analysis, due to a lower wastewater production volume and a higher wastewater dilution. It is not excluded that updated country-specific values (which were not available to us) could result in different estimates. Moreover, environmental risks were computed for the overall Italian territory, but levels of pharmaceuticals in the aquatic environment may differ across areas (e.g., depending on urbanization and drug utilization patterns),[25] and among different year-periods (e.g., different temperatures may lead to different levels of water shortage and/or drought in the rivers).

Concerning these issues, future improvements in the field of the environmental impact of pharmaceuticals are desirable. Developing public integrated databases with coded fields for eco-toxicological data (like PNEC), including detailed information on their derivation method and on animal and plant species used, may overcome the lack of information about native species, the insufficient information to estimate PNEC values, and the difficulty of retrieving data from free text. Promoting full public access to drug utilization data, including less used pharmaceuticals and regional sales, would allow for more exhaustive and region-specific environmental risk monitoring. Moreover, to obtain sub-regional estimates, actual and current indexes of wastewater production and filtering capacity and underlying differences between healthcare settings (e.g., hospitals, nursing homes, private homes) may be considered.

Our study sets the stage for an Italian-based investigation and the integration of eco-toxicological and drug utilization databases. While eco-toxicological studies, like measured environmental concentrations, are needed to further validate and refine this method, consumption-derived environmental risk estimates may complement and prioritize pharmaceutical samplings in the waters. Starting from this analysis setting and given the example of other initiatives, such as the Region Stockholm Pharmaceuticals and Environment web-based database,[31] we propose that a country-based information tool for the environmental risk posed by pharmaceuticals should be developed. To achieve this, both highly detailed and easy to understand aspects should be accounted for due to the need to provide information to the broader public. Stakeholders, including researchers in the field, may be interested in highly specific data available in ready-to-use formats. On the other hand, the awareness of these problems associated with pharmaceuticals in the environment should extend beyond the scope of research and academia and reach prescribers and decision-makers. Clinical pharmacologists already play an important role in improving patient care, both participating in the development of better medicines and promoting the safer and more effective use of pharmaceuticals.[48] Promoting more environmentally friendly drug utilization should also be an important concern. Active involvement and collaboration between all the stakeholders in environmental and healthcare settings are essential to deal with the environmental impact of pharmaceuticals[49] and to achieve the Agenda 2030 goals: by 2030, we should "ensure sustainable consumption and production patterns" (goal 12), and "conserve and sustainably use the oceans, seas and marine resources for sustainable development" (goal 14).[8] International Pharmaceutical Federation (FIP) guidelines for green pharmacy practice highlight the way in which pharmacists may be involved in minimizing the environmental effects of pharmaceuticals. They deal with green prescribing and dispensing, but also with environmentally friendly ways to dispose of unused or expired pharmaceuticals.[50] At the same time, other actions may be needed, such as the development of sewage treatment systems specifically designed to deal with pharmaceuticals and of greener pipelines for medicine development and production.[51,52]

AUTHOR CONTRIBUTIONS

All the authors contributed to the conceptualization and design of the study. Valentina Giunchi retrieved data necessary for the analyses. Valentina Giunchi and Michele Fusaroli performed the analyses and the graphical visualization. Valentina Giunchi and Michele Fusaroli wrote the original draft and Elisabetta Poluzzi supervised all the work. All authors contributed to the interpretation of the results, and to the review and editing of the draft. All authors read and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data and R script used for the analyses are available in the Supporting Information. Data supporting the findings of this study were derived from the following resources available in the public domain: OsMed reports on drug utilization for the years 2019, 2020 and 2021 and on antimicrobial consumption for the years 2019, 2020: https://www.aifa.gov.it/en/rapporti-osmed; Region Stockholm database on pharmaceuticals and environment: https://janusinfo.se/beslutsstod/lakemedelochmiljo/pharmaceuticalsandenvironment.4.7b57ecc216251fae47487d9a.html; FASS webpages on environmental information: https://www.fass.se/LIF/menydokument?userType=0&menyrubrikId=2432; NORMAN Ecotoxicology Database: https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php; WHO Collaborating Centre for Drug Statistic Methodology webpages on pharmaceutical dose information: https://www.whocc.no/atc_ddd_index/.

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SUPPORTING INFORMATION

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

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