Environmental Science & Technology

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Article

# Pharmaceutical and Personal Care Products (PPCPs) in Global Surface Waters: Risk and Drivers

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Cite This: *Environ. Sci. Technol.* 2025, 59, 19146–19159

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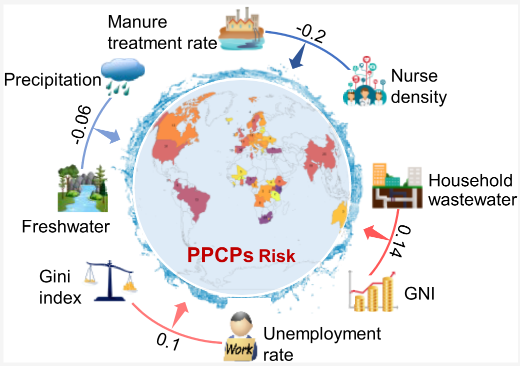
**ABSTRACT:** Pharmaceuticals and personal care products (PPCPs) are significant contaminants of global concern, yet their aquatic ecological risks and associated driving factors remain poorly understood. Here, we analyzed 190 PPCPs in surface waters across 60 countries on five continents, screened the priority PPCP list, and identified key ecological risk driving factors. Results showed that antihyperglycemics and antibiotics dominated concentration profiles, while hormones and nonsteroidal anti-inflammatory drugs (NSAIDs) posed the most severe ecological risks. 76 PPCPs exhibited potential risks in at least one country, with ibuprofen, 17$\beta$-estradiol, and carbamazepine identified as critical compounds, and estrone posing high risks to aquatic ecosystems globally. Across income levels, PPCP concentrations peaked in lower-middle-income countries, while ecological risks were highest in upper-middle-income regions. PPCP risks were correlated with multiple factors such as environmental infrastructure, healthcare systems, unemployment rates, and the Gini index. In addition, hydrological dilution and PPCP usage were also important driving factors that might be affected by climate change. Here, we offer the perspective that enhancing treatment capacity, improving healthcare accessibility, mitigating socioeconomic disparities, and adapting to climate change are imperative to mitigate PPCP risks while advancing across many of the United Nations Sustainable Development Goals.




**KEYWORDS:** *contaminants of global concern, aquatic ecological risk, global scale, socioeconomic, driving factors*

## 1. INTRODUCTION

Contaminants of global concern (CGCs) pose significant challenges to water quality, with potentially profound implications for human health and ecosystem integrity.[1,2] Within this critical domain, pharmaceuticals and personal care products (PPCPs), encompassing therapeutic agents for human and animal treatments and chemical constituents of personal care products, stand out as a particularly concerning class of CGCs owing to their widespread presence and potential environmental impact.[3] In 2021, global markets for pharmaceuticals and personal care products (PCPs) reached \$1340 billion[4] and \$270 billion,[5] respectively. With ongoing economic development, population growth, aging demographics, and healthcare advances, both the diversity and the volume of PPCPs are expected to increase. However, the removal of PPCPs in treatment processes is compound-dependent and typically incomplete,[6] and PPCPs enter aquatic ecosystems through multiple pathways, such as wastewater treatment plants (WWTPs), aquaculture facilities, industrial effluents, food/feedstock processing plants, and urban stormwater runoff,[7,8] creating a 'pseudopersistent' exposure state.[9] PPCPs released in the environment might induce toxicity at any level of biological hierarchy, such as cells, organs, organisms, populations, ecosystems, or the ecosphere, due to their inherent ability to induce physiological effects in organisms.[10] Numerous studies have indicated that PPCPs can significantly impact aquatic ecosystems at environmental concentrations.[11−15]

The concentrations and compositional profiles of PPCPs in surface waters are governed by a complex interplay of factors, including production magnitude and consumption patterns,[16,17] emission pathways via wastewater treatment facilities and agricultural runoff, hydrological processes affecting dilution and degradation processes, and socioeconomic determinants including regional healthcare practices.[18−20] These influences shape the spatial and temporal distribution of PPCPs in aquatic environments, impacting their ecological and human health implications. A global study revealed that active pharmaceutical ingredient (API) pollution in surface waters correlates positively with multiple median age, unemployment, and poverty rates, while negatively correlating

Received: April 28, 2025
Revised: August 13, 2025
Accepted: August 14, 2025
Published: August 29, 2025




https://doi.org/10.1021/acs.est.5c05659
*Environ. Sci. Technol.* 2025, 59, 19146−19159

with mortality.[12] Furthermore, ecological risks from PPCPs have been revealed to be associated with urbanization[21] and land use patterns.[22] These factors underscore the intricate linkages between environmental contamination and key Sustainable Development Goals (SDGs) indicators, particularly SDG 3 (Good Health and Well-being) and SDG 6 (Clean Water and Sanitation), highlighting the critical need for integrated approaches to mitigate PPCP-related environmental and health risks.

Although PPCPs have been widely detected in aquatic environments, current research is constrained by sampling strategies and geographical limitations. Since PPCP concentrations exhibit significant spatiotemporal variations, nonrepeated grab sampling and regional-scale studies cannot accurately represent the actual contamination levels, which limit our understanding of their ecological risks globally.[23] Moreover, there remains a notable gap in quantitative research examining the key drivers behind the aquatic footprints of PPCPs and their associated ecological impacts. Therefore, comprehensive large-scale data analysis is urgently needed to overcome these limitations and to accurately assess PPCP exposure patterns across broader geographical and temporal dimensions. In line with the One Health framework, a holistic global assessment of PPCP contamination would not only reveal the true extent of the problem but also enable the development of unified monitoring and mitigation strategies. Such a global perspective would ultimately inform more effective management approaches to protect both environmental and human health worldwide.[24]

In this study, we compiled measured concentration data for 190 PPCPs from the published literature over a 13-year period. We evaluated the aquatic ecological risk of PPCPs in freshwater systems at country and global scales, analyzed the distribution of PPCPs stratified by therapeutic classifications, and investigated the pathways leading to ecological risks using structural equation modeling (SEM), with SDG indicators as key explanatory variables. Our primary objectives were to establish a priority control list for PPCPs and identify key drivers of risks at the global scale. The findings enhanced our understanding of PPCP contamination, provided valuable insights for policymakers, and contributed to advancing the SDGs.[25]

## 2. MATERIALS AND METHODS

**2.1. Data Collection and Processing.** *2.1.1. Environmental Concentration Data.* The measured concentration data of PPCPs dissolved in water reported between 2010 and 2022 were retrieved from government reports and peer-reviewed publications. These materials were obtained through the German UBA "Pharmaceuticals in the Environment" database (https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0), and Web of Science searches using keywords such as "PPCPs," "API," "cosmetics," and "surface waters." Notably, the global pharmaceutical monitoring data set using consistent methods was included.[12] To ensure a comprehensive assessment, concentrations from both receiving waters and drinking water sources were included, encompassing various water body types such as rivers, lakes, and reservoirs.[11] Evidence suggests that sampling uncertainty typically exceeds analytical uncertainty in pharmaceutical monitoring studies.[26] Therefore, to maximize data coverage, measurements from all quantitative analytical methods, such as liquid chromatography−tandem mass spectrometry (LC−MS/MS), gas chromatography−mass spectrometry (GC−MS), etc., were included in our data set. Chemicals reported in at least three countries were selected to avoid potential bias from limited geographical coverage and to ensure robust data comparability across regions. For data quality assurance, several criteria were applied: (1) all included studies implemented quality control methods such as calibrations, reagent blank analyses, and replicate analyses; (2) only studies employing methods with sufficient sensitivity to detect environmentally relevant concentrations were included; (3) studies from "grey" literature (e.g., conference abstracts, nonpeer-reviewed technical reports) were excluded; (4) original literature that could not be found or was marked as "questionable" in the UBA database was excluded.[26,27]

Based on the screening criteria, a total of 190 PPCPs were selected (compound lists are provided in Table S1). For simplicity and consistency, the concentration units reported in mg/L and $\mu$g/L were converted to nanograms per liter. The compiled data were processed through a systematic analytical approach (Figure S1). Site-specific chemical concentrations were processed as follows: values above method detection limits (MDL) were used as reported; values below MDL were substituted with MDL/2; nondetects were set to zero. Mean concentrations at the country-level were calculated by averaging site-specific measurements for each PPCP. The cumulative PPCP concentration ($\sum$PPCP) was then derived by summing these mean concentrations of all detected compounds in each country (Table S2). The frequency of detection for each PPCP was calculated as the ratio of countries where the compound was detected to the total number of countries surveyed worldwide. In addition, the 190 PPCPs were classed into nine therapeutic classes: antibiotics (55), antiepileptics (7), antihyperglycemics (2), antivirals (7), blood lipid regulators (23), hormones (15), NSAIDs (14), PCPs (11), and others (56). Cumulative concentrations were calculated for each of the nine PPCP classes by country.

*2.1.2. Ecotoxicological Data Compilation and Environmental Threshold Derivation.* Ecotoxicological data for PPCPs' effects on freshwater organisms were obtained from the US EPA's ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/search.cfm). The selection of toxicity end points adhered to principles of accuracy, relevance, and reliability.[28,29] A hierarchical approach was implemented for toxicity data selection, prioritizing chronic toxicity end points over acute data. Specifically, no observed effect concentration (NOEC) or 10% effect concentrations ($EC_{10}$) were prioritized for the most sensitive biological responses.[30] In cases where NOEC or $EC_{10}$ values were unavailable, lowest observed effect concentrations (LOEC), median effect concentrations ($EC_{50}$), or median lethal concentrations ($LC_{50}$) were utilized with corresponding assessment factors (AFs) of 2, 10, or 100, respectively.[30,31]

PNECs were derived by applying AFs of 10, 20, 100, or 1000 to NOEC/$EC_{10}$, LOEC, $EC_{50}$, and $LC_{50}$ values, respectively.[31] In the absence of toxicity data, the lowest PNEC values from the NORMAN Ecotoxicology Database (https://www.norman-network.com/nds/ecotox/lowestPnecs Index.php) were prioritized. When these data were unavailable, chemical hazard values (CHVs) were calculated using EPI Suite 4.11 (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface) and subsequently converted to PNECs using an AF of 10. Specifically, for antibiotics, we considered not only traditional ecotoxicological end points but also the antimicrobial resistance (AMR) development in


https://doi.org/10.1021/acs.est.5c05659
Environ. Sci. Technol. 2025, 59, 19146−19159

aquatic ecosystems, because traditional end points were insufficient to fully protect ecosystems from antibiotic-specific risks.[12,32,33] Minimum inhibitory concentrations (MICs), used to derive protective threshold concentrations for AMR development, were collected from literature.[34,35] The MIC-based thresholds were prioritized when they were lower than PNECs derived from chronic toxicity data. Information on ecotoxicity data and PNECs derived from various end points is available in Table S4.

*2.1.3. Socioeconomic and Natural Parameters.* A country-level data set of socioeconomic and natural parameters was compiled and structured, including those associated with PPCP consumption and discharge (e.g., GNI, population, livestock production, health expenditure, household wastewater generated), PPCP usage patterns (e.g., life expectancy, percentage of population aged above 60 years), environmental infrastructure (e.g., manure treatment rate, wastewater treatment rate), and pollutant dilution (e.g., precipitation, dilution ratios). Parameters about health services (e.g., nurses and midwives per 1000 people), scientific and technological advancement (e.g., research and development expenditure), economic development (e.g., GNI per capita), and social system (e.g., unemployment rate, Gini index) were also collected because they could influence the lifecycle of PPCPs, including their consumption, regulation, disposal, and treatment efficiency. Data were sourced from authoritative repositories and databases, including the Sustainable Development Report 2024 (https://dashboards.sdgindex.org/downloads), the World Bank database (https://databank.worldbank.org/home), the United Nations database (http://data.un.org/), the FAO database (https://www.fao.org/faostat/en/#data/SDGB), and peer-reviewed publications.[36,37]

**2.2. Ecological Risk Assessment.** Ecological risks for each PPCP were evaluated using the risk quotient ($RQ$), calculated with the country-level mean concentration and PNEC (eq 1). The aquatic ecological risk of PPCP mixtures in a country was characterized using the cumulative $RQ$ of all evaluated chemicals.[38] Additionally, cumulative $RQ$s and percentage contributions were calculated separately for each PPCP class.

$$RQ = \frac{C}{\mathrm{PNEC}} \tag{1}$$

where C is the country-level mean concentration and PNEC is the predicted no-effect concentration.

The ecological risk for each chemical was assessed and classified using a tiered approach proposed in our previous study.[11] Initially, the maximum $RQ$ ($RQ_{max}$) of each chemical in the 60 countries was identified, and the chemical was included in the priority list if $RQ_{max} \geq 1$. Furthermore, the frequency of concentrations exceeding the PNEC (eq 2) and the prioritization index (PI) (eq 3) were calculated. PPCPs were of great concern if PI $\geq$ 1 and if they were detected in more than 20 countries. Finally, the aquatic ecological risk posed by these PPCPs of great concern on a global scale was evaluated using joint probability curves (JPCs). For each JPC, risk products were calculated (risk product = exceedance probability × magnitude of effect) at all points, and the maximum risk product (MRP) was identified. This MRP value was then used to categorize risk levels as de minimiz (MRP < 0.25%), low (0.25 ≤ MRP < 2%), moderate (2 ≤ MRP < 10%), or high (MRP ≥ 10%).

$$F = \frac{n}{N} \times 100\% \tag{2}$$

where $F$ is the frequency of PNEC exceedance, $n$ is the number of countries with concentrations above PNEC, and $N$ is the total number of countries that reported the chemical.

$$\mathrm{PI} = RQ_{\mathrm{max}} \times F \tag{3}$$

where PI is the prioritization index, $RQ_{max}$ is the maximum risk quotient in the 60 countries, and $F$ is the frequency of PNEC exceedance.

**2.3. PPCP Profiles across Income Groups.** To analyze the impact of income level on PPCP contamination and ecological risk, the 60 countries were divided into 4 income groups according to the World Bank. Scatter plots with confidence ellipses were used to visualize the distribution patterns of PPCP exposure (total concentration and detected number), toxicity (mean PNEC and the number of classes), and risk (total $RQ$ and the number of PPCPs with concentrations exceeding their PNECs) across the four income groups, and Spearman rank correlation analyses were performed to assess significant relationships between paired variables. Furthermore, for each class, pairwise comparisons of total concentration and $RQ$ between income groups were conducted using Student's $t$ test, with significant differences indicated by asterisks.

**2.4. Analysis of Drivers and Impact Pathways.** We hypothesized that the risk of PPCPs in each country was affected by regional natural and socioeconomic parameters through environmental exposure and toxicity profiles (Figure S2). Environmental exposure was characterized by total concentration and detected number, while the toxicity profile was represented by the coefficient of variation of PNEC. To identify the key drivers, hierarchical cluster analysis was conducted to group the 45 parameters into 4 major clusters and 7 subclusters. Within each major cluster, two parameters were selected from subclusters based on their statistical relationships with $RQ$ and other dependent variables. The clustering analysis and visualization were implemented using the 'pheatmap' package in $R$.[39]

Structural Equation Modeling (SEM) was performed using the partial least-squares path modeling (PLS-PM) approach. The path coefficients, outer loadings, and goodness-of-fit (GoF) indices were computed using the 'plspm' package in R. The statistical significance of path coefficients was assessed through bootstrapping with 1000 subsamples, appropriate for small sample sizes.[40] The procedure employed individual sign changes and two-tailed testing ($\alpha$ = 0.05) with 95% confidence intervals calculated using the bias-corrected and accelerated method.

**2.5. Statistical Analysis.** Statistical analyses were performed to investigate the distribution patterns and ecological risks of PPCPs across countries. Descriptive statistics were computed for the parameters of exposure and ecological risk of PPCPs. The Shapiro-Wilk test and distribution characteristics were used to assess the normal distribution of data sets. Spearman correlation was used to analyze the relationships among parameters of exposure and ecological risk of PPCPs in 60 countries. Visualization techniques included hierarchically arranged ridgeline plots for concentration and risk profiles, proportional alluvial diagrams for country-level distribution patterns arranged by cumulative percentages of predominant PPCPs classes, and global


https://doi.org/10.1021/acs.est.5c05659
Environ. Sci. Technol. 2025, 59, 19146−19159

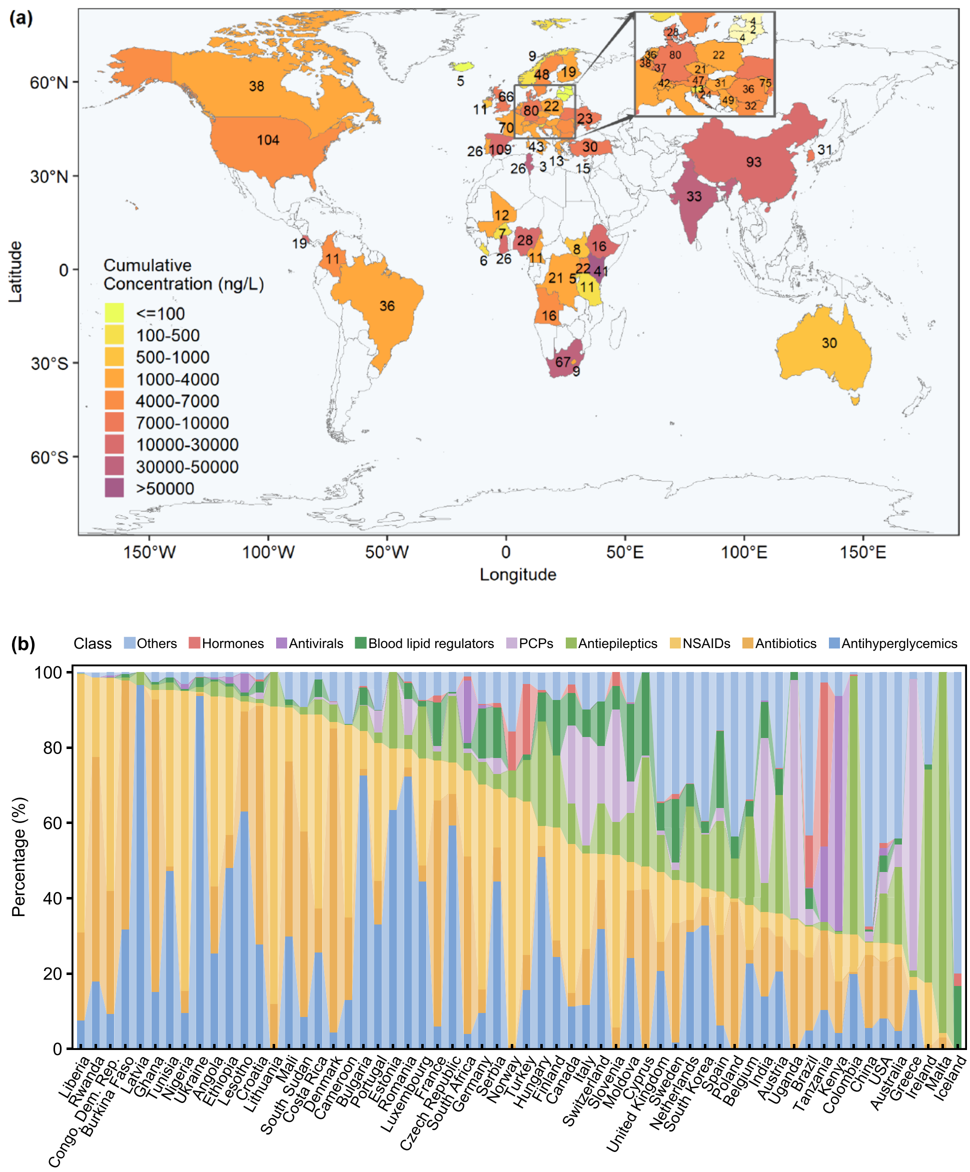



**Figure 1.** Occurrences of PPCPs in surface waters. (a) Cumulative concentrations and detected numbers of PPCPs globally. (b) Relative contribution of each class to the total concentrations. Countries are ordered by decreasing the combined contribution of the three dominant classes (antihyperglycemics, antibiotics, and NSAIDs).

distribution maps for spatial patterns. The influence of socioeconomic development on ecological risks was examined using local weighted regression (LOESS, span = 0.5) to model relationships between GNI per capita and both cumulative PPCPs concentration and *RQ*. To identify primary contributors to PPCPs risks across country contexts, linear regression models assessed relationships between observed variables and total *RQ*, while cluster analysis was conducted on eight influential factors across 60 countries. For indicators showing correlations with the *RQ* within specific ranges, outliers were removed before establishing linear regression models to improve model reliability and accuracy. All statistical analyses and visualizations were implemented in the R environment, with concentration and risk distribution maps specifically created using the maps package.

## 3. RESULTS

**3.1. Exposure of PPCPs in Surface Waters.** A total of 4489 mean concentration values at the country level for 190 PPCPs were compiled from 60 countries across all continents except Antarctica (Tables S1 and S2). Of the 190 PPCPs, 184 were detected above the MDL in at least one country, resulting in a total of 1852 detections. The detection rate for the types of PPCPs was 96.8% (184 out of 190), while the overall detection rate based on total data points was 41.3% (1852 out of 4489). The country-level mean concentrations of these detected PPCPs ranged from 0.01 ng/L for Estriol to 94,307 ng/L for Lamivudine, with a media concentration of 23.92 ng/L. The Shapiro-Wilk test results revealed that the logarithmic values of reported number, detected number, and total concentration in each country met the criteria for normality ($p > 0.05$). While the concentration at the country level did not pass the normality test, its skewness and kurtosis values suggested an approximate normal distribution (Table S3).



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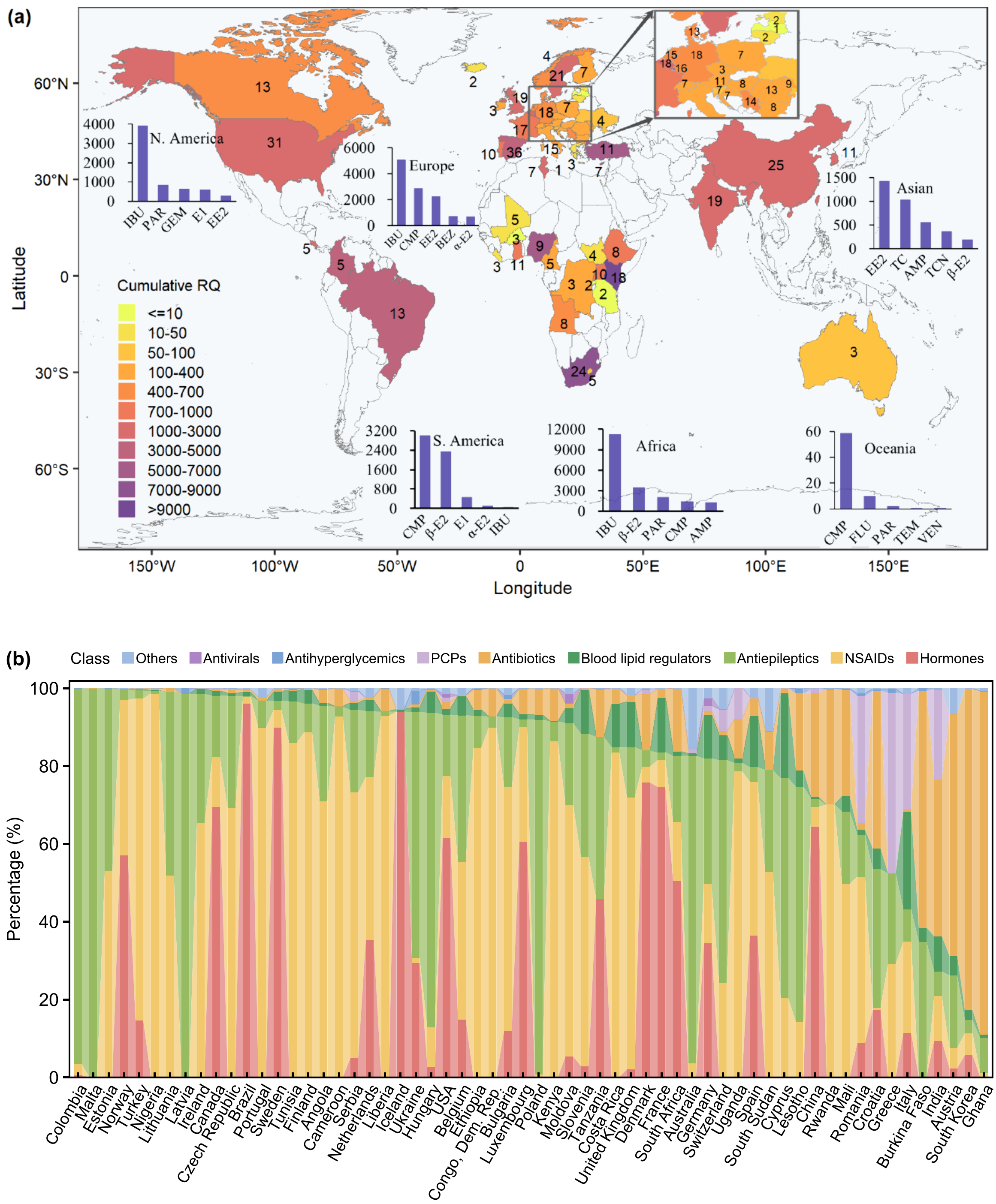


**Figure 2.** Global distribution of PPCP ecological risks. (a) Countries are shaded according to total *RQ*; numbers show PPCPs exceeding PNECs; inset charts display top five compounds by *RQ* per continent (AMP: Amoxicillin; BEZ: Bezafibrate; CMP: Carbamazepine; E1: Estrone; $\alpha$-E2:17$\alpha$-estradiol; $\beta$-E2:17$\beta$-estradiol; EE2: Ethinyl estradiol; GEM: Gemfibrozil; IBU: Ibuprofen; PAR: Paracetamol; TC: Tetracycline; TCN: Triclosan). (b) Percent contribution of PPCP classes to the total risk. Countries were ordered by decreasing the combined contribution of the three dominant classes (hormones, NSAIDs, and antiepileptics).

Regional PPCP contamination patterns revealed distinct hotspots worldwide. Europe had the highest diversity of PPCPs detected (184), but the highest cumulative concentrations were found in Africa (6 out of the top 10 countries). Within individual regions, substantial variability in contamination levels among countries could also be observed (Figure 1a), especially in Africa, where Kenya showed the highest cumulative concentration (159.5 $\mu$g/L), primarily from lamivudine (94.3 $\mu$g/L). By contrast, Rwanda had minimal contamination (0.1 $\mu$g/L), with 5 of 57 chemicals (8.8%) detected across eight sites in Kigali.[12] In the Americas, Costa Rica showed the highest total concentration (43 $\mu$g/L), and the US detected the most PPCPs, with 104 of the 118 monitored PPCPs being detected (88% detection rate). In Asia-Pacific region, India showed the highest total concentration (30.8 $\mu$g/L), while China detected the largest number of PPCPs (93). In Europe, Spain exhibited the highest total concentration (19.6 $\mu$g/L) with 109 compounds detected,


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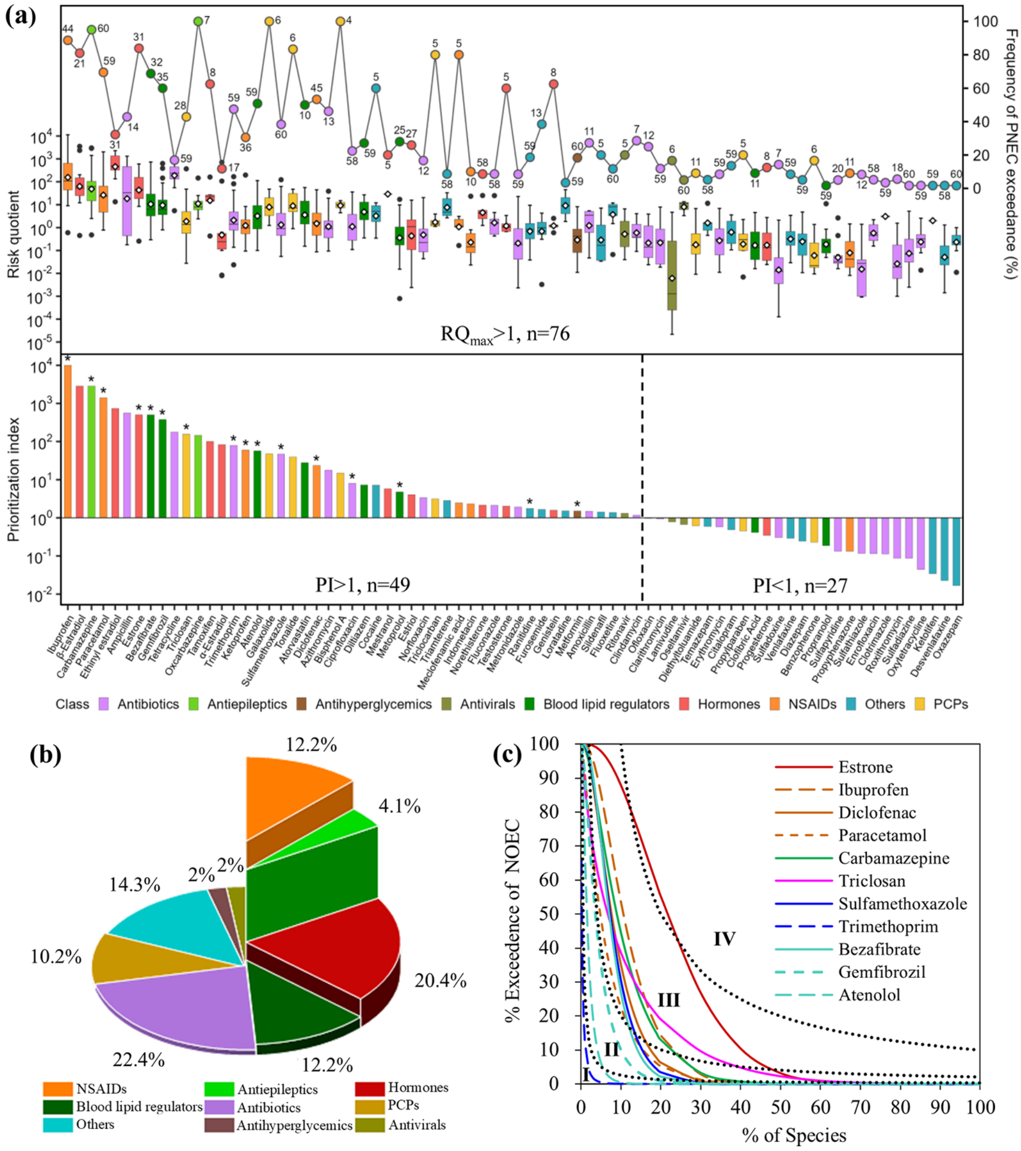

Figure 3. Ecological risk ranking for PPCPs based on a multilevel system. (a) Ecological risk ranking for 76 priority PPCPs according to the prioritization indexes (PI). Numbers denote the total number of countries that reported the chemical. Asterisk (*) indicates PI > 1 with detected countries >20. (b) Stratified analysis of 49 high priority PPCPs by classes. In the 3D pie chart, the height represents the mean PI value for each category, while the angle represents the proportion of chemicals in each category relative to the 49 PPCPs. (c) Joint probability curves for 11 critical priority PPCPs. Three black dotted lines organize ecological risk into four levels: I. de minimiz, II. low, III. moderate, and IV. high risk.

whereas Cyprus, despite detecting only 15 PPCPs, ranked second (10.0 $\mu$g/L) primarily due to elevated sulfamethoxazole levels (4.1 $\mu$g/L). For the nine PPCP classes, antihyperglycemic drugs represented the greatest detected concentrations, followed by antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) (Figure S3). These three classes contributed more than 50% of the cumulative concentration in 37 countries (Figure 1b).

**3.2. Aquatic Ecological Risk of PPCPs by Country.** Ecotoxicity data for the 184 detected PPCPs were compiled, including 140 laboratory test data and 44 predicted toxicity values, with PNECs ranging from 0.003 to 8.55 × $10^8$ ng/L (Table S4). Among the 60 countries (Figure 2a), Kenya demonstrated the greatest total *RQ* of 15,249, followed by South Africa (8311) and Turkey (6248). The number of PPCPs that exceeded their respective PNECs varied among countries, ranging from 1 in Latvia and Malta to 36 in Spain. The Spearman correlation analysis (Table S3) indicated that the influence of the detected number on total *RQ* and the exceeded number was greater than that of the reported number. This suggested that actual contamination patterns (reflected by the detected number), rather than sampling intensity, more effectively explain the observed variations in PPCP risk across countries. At the continental scale, Oceania had the lowest risk, while South America faced greater risks than did Asia. The risk of PPCPs in Europe and Africa was highly uneven, with some countries confronting risks significantly higher than those of others.

Due to variations in toxicity effects among different PPCP classes (Figure S4), the primary contributors to the total *RQ*s were hormones, NSAIDs, and antiepileptics (Figure S5), which accounted for over 50% of cumulative *RQ*s across 54 countries (Figure 2b). Among the top 10 countries with the highest risk, there were four European countries, three Latin American

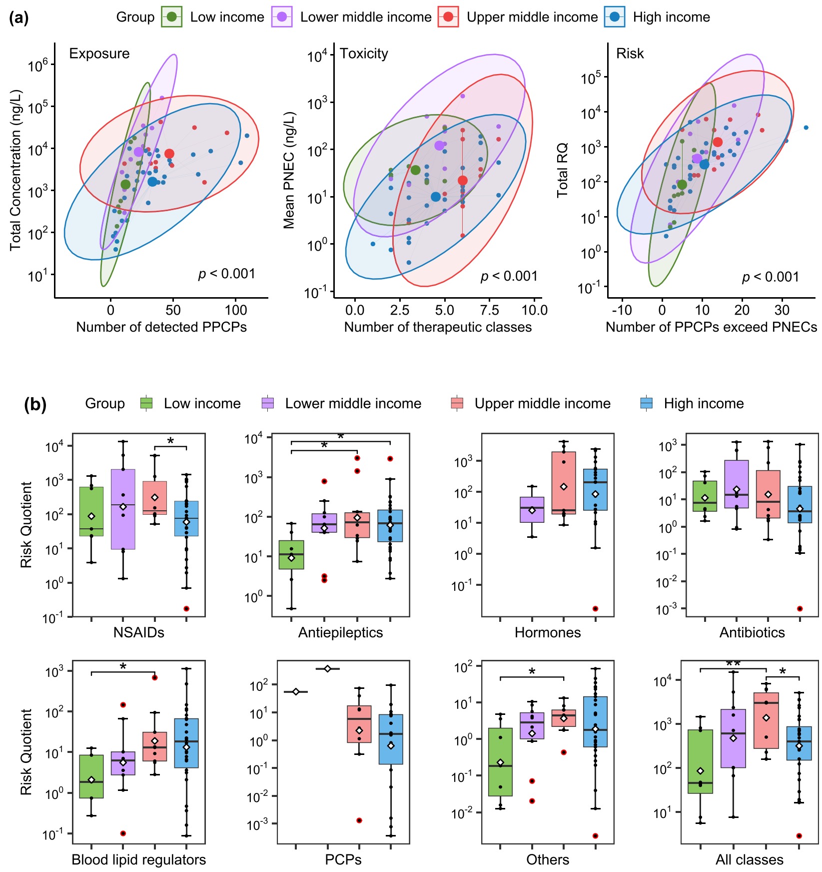


**Figure 4.** Distribution patterns of PPCPs across four income groups. (a) Exposure, toxicity and risk distribution for all PPCPs among different income groups. (b) Ecological risk distribution by PPCP class across income groups. $^{**}p < 0.01$, $^{*}p < 0.05$.

countries, and three African countries. A striking contrast was observed in India, which ranked fifth in global PPCP concentration but placed only 15th in ecological risk (total $RQ$: 1596). This discrepancy was likely explained by the dominance of PCPs, antibiotics, and antihyperglycemic drugs in India's PPCP profile (Figure 1b), substances that are generally less toxic to aquatic organisms (Figure S4). Conversely, Brazil's cumulative concentration (3.4 $\mu$g/L) was nearly 10-fold lower than India's, yet its total $RQ$ (3035) was approximately double, primarily due to hormones, which accounted for 96% of this risk.

### 3.3. Screening and Risk Ranking of Priority PPCPs.

Seventy-six PPCPs were identified as priority chemicals ($RQ_{max} \geq 1$), with frequencies of PNEC exceedance of 1.7−100% and PI of 0.02−10,025 (Figure 3a). Among these compounds, 49 were identified as high-priority chemicals (PI > 1). Ibuprofen, 17 $\beta$-estradiol, and carbamazepine were identified as the compounds of greatest concern worldwide due to their high $RQ_{max}$ (11,310, 3524, 3002) and exceedance frequency (89, 81, 95%). Notably, some PPCPs like bisphenol A exhibited small $RQ_{max}$ (15) but high exceed frequency (100%), while some PPCPs like tetracycline showed high $RQ_{max}$ (1040) but less exceed frequency (17%). Categorical analysis of the 49 high-priority PPCPs (Figure 3b) revealed NSAIDs as the highest-risk category, with six compounds (12.2%) showing the mean PI of 1921. Antibiotics constituted 22.4% of high-priority chemicals, yet displayed a lower mean PI (82). Conversely, antiepileptic agents demonstrated substantially elevated ecological risk (mean PI = 1499) despite comprising only 4.1% of compounds, represented by two chemicals (carbamazepine and oxcarbazepine).

Furthermore, 16 PPCPs were identified as critical priority chemicals due to their widespread detection across more than 20 countries. To assess their global ecological impact, JPCs were constructed for 11 compounds (Figure 3c), excluding five compounds with insufficient toxicity data. These curves integrate concentrations (Table S5) with chronic toxicity effects across various species (Table S6), indicating the probability of exceeding effect thresholds of different magnitudes. Data sets for each chemical were tested for normality using the Shapiro-Wilk test ($p < 0.05$) prior to application of parametric statistics (Table S7). Estrone (hormone) demonstrated the highest risk to aquatic ecosystems, with a MRP of 11.13 and a 61.83% probability of exceeding the NOEC for 18% of aquatic species. Seven PPCPs (ibuprofen, diclofenac, paracetamol, carbamazepine, triclosan, sulfamethoxazole, and bezafibrate) presented moderate risk levels (Figure 3c), with MRPs ranging from 1.83 to 5.34%.

### 3.4. Disparities in PPCP Risks across Income Levels.

Comparing the distribution of all PPCPs among four income groups (Figure 4a), results showed that total concentrations were highest in middle-income countries (both lower- and upper-middle groups). In contrast, mean PNEC values of detected PPCPs were lowest in more developed regions (upper-middle and high-income groups). Consequently, PPCPs in the upper-middle-income group demonstrated the highest ecological impact. Furthermore, significant correlations



https://doi.org/10.1021/acs.est.5c05659
Environ. Sci. Technol. 2025, 59, 19146−19159

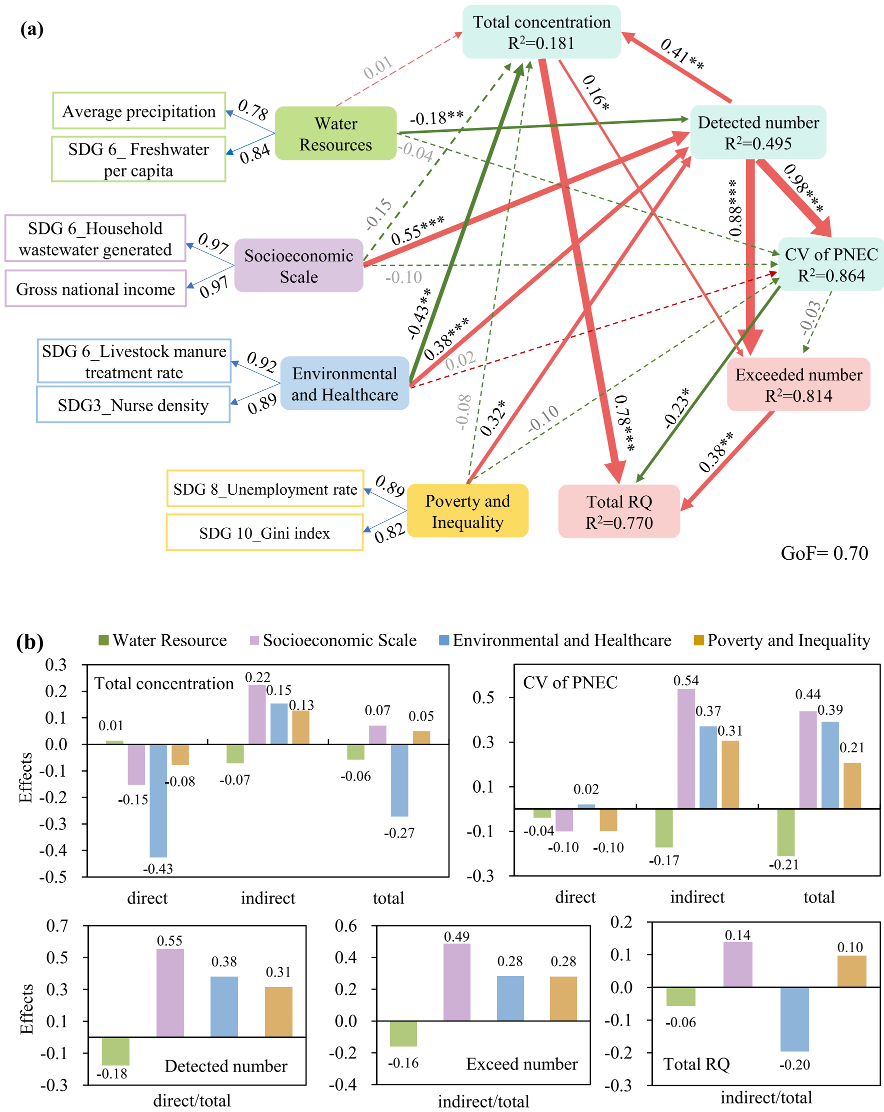


**Figure 5.** Results of structural equation modeling (SEM) analysis. (a) Path diagram showing the relationships among *water resources*, *socioeconomic scale*, *environmental infrastructure and healthcare systems*, and *poverty and inequality* on PPCP occurrence and ecological risks (GoF = 0.70). Solid and dashed lines represent significant ($p < 0.05$) and nonsignificant relationships, respectively. Path coefficients are shown with significance levels (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$). Red and green arrows represent positive and negative correlations, respectively. (b) Effect decomposition analysis showing direct, indirect, and total effects of four major variable groups.

($p < 0.001$) were observed between paired variables for exposure, toxicity, and risk.

Analysis by PPCP classes revealed that disparities in concentration (Figure S6a) and risk (Figure 4b) were primarily driven by compounds with higher concentrations or lower PNECs. While total PPCP concentrations in high-income countries were comparable to those in low-income countries, total *RQ*s were higher in high-income countries due to variations in antiepileptics and hormones, which exhibited higher risks despite lower concentrations. Similarly, compared with upper-middle-income countries, the lower-middle-income group showed higher pollution but lower ecological risk, attributed to differences in hormone and blood lipid regulators. Furthermore, the upper-middle-income group exhibited notably higher total concentration and total *RQ* than the high-income group, primarily due to NSAIDs, which contributed substantially to both cumulative concentration (Figure 1b) and *RQ* (Figure 2b) in both groups, with higher concentrations detected in the upper-middle-income countries.

It was noteworthy that the number of PPCPs reported by low-income and lower-middle-income countries was significantly lower than that reported by upper-middle-income and high-income countries (Figure S6b). This observation suggested that the total concentration and total *RQ* in these countries may have been underestimated. However, given the lower detection rates in these two groups, the impact was likely minimal. Additionally, the analysis indicated no significant differences in the minimum detected concentrations of PPCPs across income groups, suggesting that the influence of variations in analytical methodologies on the concentrations of PPCPs was limited.

**3.5. Key Risk Drivers of PPCPs.** To investigate the potential drivers of the ecological risk of PPCPs, 45 parameters were compiled, encompassing 35 SDG indicators, three natural parameters, four social parameters, and three economic parameters (Table S8). Hierarchical cluster analysis systematically categorized these parameters into four major categories and seven subcategories (Figure S7). The four major categories represented water resources, socioeconomic scale, environmental infrastructure and healthcare systems, and social system structure. These categories represent distinct aspects influencing PPCPs through hydrological dilution capacity, PPCP consumption and emission, treatment and management, and usage patterns, respectively. Based on subcategory results and correlations with PPCP risk characteristics (Table S9), eight parameters were selected and integrated into four latent constructs for multilevel SEM analysis (Figure 5a). The detailed information for the SEM model is presented in Table S10. The GoF of 0.70 indicated a strong alignment with the data, and the stability of the model parameters was confirmed through 1000 bootstrap samples, reinforcing its robustness and reliability. The explanatory power ($R^2$) for the key variables ranged from 0.181 to 0.864, indicating the model's effectiveness in explaining the ecological risk of PPCPs, which accounted for 86.4% of the variance in the exceeded number and 77% of the variance in total *RQ*. Results showed that the total *RQ* of PPCPs was positively associated with total concentrations ($\lambda = 0.78$, $p < 0.001$) and exceeded number ($\lambda = 0.38$, $p < 0.01$), and negatively correlated with the CV of PNEC ($\lambda = -0.23$, $p < 0.05$). Additionally, the detected number was involved in shaping total concentration ($\lambda = 0.41$, $p < 0.01$), the CV of PNEC ($\lambda = 0.98$, $p < 0.001$), and exceeded number ($\lambda = 0.88$, $p < 0.001$). Among these parameters, the socioeconomic scale showed the most significant impact on the number of detections ($\lambda = 0.55$, $p < 0.001$).

In a global context, the latent variable *environmental infrastructure and healthcare* systems demonstrated a significant direct negative effect on total concentration ($\lambda = -0.43$, $p < 0.01$) and a significant direct positive effect on the detected number of substances ($\lambda = 0.38$, $p < 0.001$). This seemingly contradictory pattern can be explained by the dual nature of environmental infrastructure and healthcare systems development: better performance on these indicators (higher livestock manure treatment rates and more nurses per capita) reduces PPCP concentrations through improved waste treatment and pharmaceutical management, while simultaneously being associated with higher GNI per capita, which leads to more diverse PPCP consumption and thus a greater variety of substances detected in the environment. Consequently, its overall effects on total concentration and total *RQ* were relatively modest, with total effect values of −0.27 and −0.20, respectively (Figure 5b). Both latent variables, *socioeconomic scale* and *poverty and inequality*, contributed more to total *RQ* than to total concentration, as they positively affected both the detected number and total concentration, while exhibiting greater indirect effects on the exceeded number compared to the CV of PNEC. The latent variable *water resources* displayed a significant direct negative effect on the detected number ($\lambda = -0.18$, $p < 0.01$) and a substantial total effect on the CV of PNEC (−0.21), but its effects on concentration (−0.06) and risk (−0.06) were minimal. This indicates that hydrological dilution effects can cause some substances to fall below detection limits, but the effects on concentration and risk remain minimal due to high PPCP loads in certain regions or high toxicity of some PPCPs (e.g., hormones).

## 4. DISCUSSION

**4.1. PPCPs' Pollution Challenges the Environmental Kuznets Curve (EKC).** The EKC posits that there is an initial increase in environmental pollution when a country's per capita income is low, but this falls over time as income per capita grows.[41] Among the four income groups, total concentrations peaked in lower-middle-income countries, while total *RQ* reached maximum levels in upper-middle-income countries. High-income countries exhibited concentrations similar to those of low-income countries but ecological risks comparable to those of lower-middle-income groups. However, detailed regression analysis using continuous GNI per capita data revealed additional complexity within the high-income group. The local regression analysis identified secondary peaks in both metrics near the $33,000 GNI per capita threshold (Figure S8), which falls within the high-income category, challenging the traditional EKC. These divergences suggested that reductions in PPCP concentrations may not proportionally decrease ecological risks. This can be explained by the disparate profiles of PPCP classes that dominate cumulative concentrations (Figure S6) and risks (Figure 4b), attributable to divergent consumption capacities/patterns and treatment infrastructure across income groups, coupled with chemicals' varying toxicity and degradability. First, disease profiles drive different PPCP demands across the income groups. Low-income countries demonstrate heightened antiviral and antibiotic usage linked to prevalent infectious diseases, which have lower aquatic toxicity.[14] In contrast, high-income countries show predominant use of age-related therapeutics (antiepileptics, lipid regulators, and hormonal medications),[42] which have higher aquatic toxicity and resistance to biodegradation.[43] Second, PPCP consumption differs across economic groups, even for a similar health problem, particularly in the case of expensive and novel chemicals. For example, NSAID concentrations were higher in the lower-middle-income group but posed higher risks in the upper-middle-income group. This spatial disparity stems from paracetamol's dual characteristics as the most ubiquitous NSAID and its high biodegradability in WWTPs, resulting in elevated environmental concentrations in lower-middle-income countries and effective attenuation in upper-middle-income countries with advanced WWTP infrastructure. In addition, upper-middle-income countries employ a more diverse NSAID portfolio encompassing high-toxicity compounds, such as ibuprofen, and treatment-resistant pharmaceuticals, such as diclofenac and indomethacin.

**4.2. Multiple Factors Drive PPCP Risks at the Country Level.** To identify the key drivers for each country, we performed a correlation analysis between the variables and total *RQ* (Figure S9) and conducted cluster analysis to divide the 60 countries into six groups (Figure S10). In the correlation analysis, three factors (livestock manure treatment rate, $R = -0.31$; the Gini index, $R = 0.38$; unemployment rate, $R = 0.34$) showed significant correlations at the global scale, and two factors (nurses density, $R = -0.31$; household wastewater generated, $R = 0.22$) demonstrated significant correlations with PPCP risks after removing outlier data. In addition, the per capita freshwater resources showed a negative correlation ($p = 0.054$) in 49 countries with freshwater below 12,000 $m^3$. Cluster analysis revealed four groups characterized by extreme values, with Iceland exhibiting exceptionally high freshwater resources, the US and China demonstrating substantial socioeconomic scales, six countries showing notably elevated unemployment rates, and three countries experiencing extreme precipitation levels. Based on environmental infrastructure and healthcare systems indicators, the remaining 48 countries were classified into two distinct clusters. One cluster


https://doi.org/10.1021/acs.est.5c05659
Environ. Sci. Technol. 2025, 59, 19146−19159

was primarily composed of high-income countries, while the other cluster consisted of African countries. This clustering pattern reflects the strong correlation between these indicators and economic development levels. In the first cluster countries, the PPCP risk is primarily attributable to insufficient hydrological dilution capacity, resulting from freshwater scarcity and the presence of hormonal contaminants. Additionally, three countries (Spain, Serbia, and Italy) showed notably high unemployment rates, which may increase pharmaceutical abuse. Countries in the second cluster exhibited low waste treatment rates, inadequate healthcare systems, and high economic inequality. Surprisingly, the high-income country Cyprus fell into this category, exhibiting a low livestock manure treatment rate and limited nursing staff, and restricted freshwater availability. These findings demonstrate that even high-income countries may face significant PPCP challenges involving specific natural and socioeconomic factors.

Results of these analyses showed that the PPCP risks were driven by multiple factors at the country level. For example, Kenya ranked highest in PPCP risk globally, and this phenomenon can be characterized by a low livestock manure treatment rate, few nurses and midwives, and limited per capita freshwater resources. South Africa (ranked second) faced these same three factors alongside a high Gini coefficient and unemployment rate. The high-income country, Spain, was ranked seventh due to its large socioeconomic scale, high unemployment rate, and limited precipitation. Moreover, PPCP risks are also affected by the pharmaceutical industry scale. Reports indicated that Kenya held a 50% market share in the Common Market for Eastern and Southern Africa.[44] India (ranked 15th) was the largest supplier of generic drugs globally,[45] while China (ranked 11th) led in API production and represents the second-largest consumer market.[46] Europe excelled in producing and exporting innovative and synthetic drugs, with Cyprus (ranked sixth) having the highest drug discovery costs per capita, followed by Luxembourg (ranked eighth), while the US (ranked 16th) was the second-largest API producer and a major pharmaceutical consumer.[47]

**4.3. Limitations.** While this study provides a comprehensive global assessment of PPCP ecological risks and their drivers, several methodological considerations should be acknowledged. First, PPCP exposure data across the 60 studied countries vary significantly in quality and geographical coverage, with abundant data from developed regions but limited information from many developing countries.[48] Although our synthesis of extensive historical data helps reduce random errors and captures temporal variations, differences in analytical methods and detection limits may still result in detection biases, particularly for trace contaminants. Second, our country-level approach necessarily overlooks within-country spatial heterogeneity in PPCP distribution, particularly relevant for geographically diverse countries such as China, the US, and Brazil. Studies at finer spatial resolutions would provide more targeted policy implications for identifying pollution hotspots and major emission sources. Third, current knowledge gaps regarding sensitive species responses, multigenerational impacts, and antimicrobial resistance profiles[49,50] limit risk characterization precision. Additionally, PPCP transformation products were not included in this study due to the limited availability of both occurrence and ecotoxicity data. Future research should not overlook these compounds, as they may be both more abundant and more potent than their parent compounds.[51,52] Furthermore, the assessment of mixture toxicity remains particularly challenging, as multiple PPCPs may pose unexpected synergistic risks even at low concentrations,[53−55] which can be amplified by prolonged exposure.[56] Future research should prioritize establishing standardized global monitoring networks, developing integrated databases connecting PPCP and transformation product exposure with socioeconomic factors at the subcountry scale, and advancing harmonized frameworks for mixture toxicity assessment, with particular emphasis on long-term cumulative impacts on ecosystem stability and public health. The trait-based community-level risk assessment method proposed in our previous study offers a promising approach for future ecological risk assessment.[57]

**4.4. PPCP Management Strategies for Sustainable Development.** Amid expanding socioeconomic scales, governments need to develop management strategies that account for their country-specific conditions to effectively address PPCP pollution and meet the SDGs. In developing countries, where ecological risks primarily stem from high exposure concentrations, priority should be given to developing efficient and cost-effective treatment technologies (supporting SDG 6), improving healthcare system capacity (supporting SDG 3), and mitigating socioeconomic disparities (supporting SDG 10). In developed countries, chemicals with high toxicity to sensitive species or limited removal efficiency in WWTPs significantly contribute to the total *RQ*. Therefore, emphasizing source reduction through green pharmaceutical design[58] and precision medicine approaches, and enhancing treatment efficiency in disposal systems is imperative (supporting SDG 3, 6). Additionally, enhancing employment and healthcare conditions in rural areas and urban slums remains crucial (supporting SDG 3, 8).

Furthermore, dilution and usage were also important drivers of the PPCP risks. In the context of climate action, natural parameters require careful attention, particularly in water-scarce regions and infectious disease-prone areas. Research showed that climate change intensified drought frequency and severity in humid tropical regions,[59] making effective water management essential for climate adaptation. Concurrently, shifting temperature and precipitation patterns are expanding suitable conditions for infectious disease transmission in many regions. Evidence showed that climate change exacerbated health risks in developing countries, including malnutrition, transmission of vector-borne diseases such as malaria and dengue fever, as well as direct morbidity and mortality resulting from heat waves and extreme weather events.[60] Meanwhile, extreme weather events can trigger acute mental health conditions such as anxiety, depression, and posttraumatic stress.[61] These interconnected challenges underscore the urgency of establishing a global action plan for disease prevention that bridges environmental stewardship (SDG 6) with precision public health interventions (SDG 3).

Overall, in alignment with the One Health perspective, PPCP pollution represents a complex challenge that spans public health, veterinary medicine, and ecological systems rather than merely an environmental issue. Success in managing PPCP pollution will require coordinated efforts across different sectors and stakeholders. These integrated management strategies not only promote the synergistic health of humans, animals, and ecosystems but also support the 2030 Agenda for Sustainable Development.


https://doi.org/10.1021/acs.est.5c05659
*Environ. Sci. Technol.* 2025, 59, 19146−19159

## 5. IMPLICATIONS

This study found that 184 PPCPs were detected in at least one country. The major contributors to total concentrations worldwide were antihyperglycemics, antibiotics, and NSAIDs, while the total *RQ*s were dominated by hormones, NSAIDs, and antiepileptics. Tiered risk assessment identified 76 priority PPCPs, with eight posing moderate-to-high risks to global aquatic ecosystems. Ibuprofen, 17$\beta$-estradiol, and carbamazepine emerged as critical compounds, characterized by elevated *RQ*s and frequent exceedance of PNECs. Given the heterogeneous PPCP composition across income groups, concentrations peaked in lower-middle-income countries, whereas ecological risks reached maximum levels in the upper-middle-income regions. Notably, local weighted regression revealed that both concentration and risk exhibit a secondary peak proximal to a per capita GNI of $33,000, which challenges the EKC hypothesis. This deviation occurs because PPCP ecological risks are predominantly driven by environmental infrastructure and healthcare system factors rather than solely by economic development at the global scale. Even high-income countries exhibit challenges with suboptimal pollutant treatment rates or healthcare resource constraints, compounded by substantial PPCP consumption, including persistent and highly toxic compounds. At the country level, PPCP risks were generally driven by multiple factors, such as freshwater scarcity, elevated unemployment rates, and pronounced socioeconomic stratification. Based on these findings, we propose constructive policy strategies to control PPCPs, contributing to the attainment of the 2030 Agenda Sustainable Development Goal targets.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.5c05659.

Collection and processing of PPCP concentrations in surface waters (Figure S1); a priori SEM used in this study (Figure S2); probability density distributions of cumulative concentrations of each class across 60 countries (Figure S3); comparison of PNEC values for various groups of PPCPs (Figure S4); distribution of cumulative *RQ* of each class across 60 countries (Figure S5); distribution patterns of PPCPs across four income groups (Figure S6); correlation-based hierarchical clustering heatmap of 45 driving factors (Figure S7); relationships between GNI per capita and total concentration and total *RQ* (Figure S8); correlations between the total *RQ* with driving factors (Figure S9); and hierarchical clustering heatmap showing the relationships between eight driving factors across 60 countries (Figure S10) (PDF)

List and classification of 190 reported PPCPs in surface waters of 60 countries (Table S1); exposure and ecological risks of PPCPs in 60 countries (Table S2); global analyses of PPCPs exposure and ecological risks (Table S3); toxicity data and PNECs of 184 PPCPs (Table S4); exposure concentrations for the 11 PPCPs in aquatic organisms (Table S5); toxicity values for the 11 PPCPs in aquatic organisms (Table S6); parameters of JPCs)for 11 PPCPs (Table S7); anthropogenic and natural parameters (Table S8); correlation coefficient of 45 factors with occurrence, toxicity, and ecological risk of PPCPs (Table S9); and SEM fit parameters (Table S10) (XLSX)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was financially supported by the National Natural Science Foundation of China (42322710, 42477299) and the National Key Research and Development Program of China (2021YFC3200105). We thank PhD students Zhenfei Yan, Ying Luo, and Yu Ma from Beijing Normal University for their help with the statistical analysis of data. We also thank Professor Yeyao Wang from the China National Environmental Monitoring Center and John P. Giesy from the University of Saskatchewan for their help with the review.

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*Environ. Sci. Technol.* 2025, 59, 19146−19159