Fitness costs of environmentally relevant concentrations of pharmaceuticals and personal care products in freshwater fauna: a systematic review and meta-analysis

Running Title: Meta-analysis of PPCP effects on freshwater fauna

Anita Tarandek[1,2,*], Sandra Hudina[2], Marina Veseli[1], Ivan Senta[1], Danijela Žanko[1], Antonia Smolić[1], Jelena Bujan[1], Ana Previšić[2,3], Antica Čulina[1,4,*]

[1]Division for Marine and Environmental Research, Ruđer Boskovic Institute, Zagreb, Croatia

[2]Department of Biology, Faculty of Science, University of Zagreb, Croatia

[3]Collaborative Research Centre 1357 Microplastics, Faculty of Biology, Chemistry & Earth Sciences, University of Bayreuth, Bayreuth, Germany

[4]Netherlands Institute of Ecology, Royal Netherlands Academy of Arts and Sciences, Wageningen, Netherlands

*Corresponding authors: Antica Čulina (aculina@irb.hr), Anita Tarandek (anita.tarandek@irb.hr)

ORCID ID:

Anita Tarandek https://orcid.org/0000-0001-7362-0049

Sandra Hudina https://orcid.org/0000-0003-4793-8154

Marina Veseli https://orcid.org/0009-0004-8544-0626

Ivan Senta https://orcid.org/0000-0002-3308-5122

Danijela Žanko https://orcid.org/0009-0005-0436-0796

Antonia Smolić https://orcid.org/0009-0001-3685-4126

Jelena Bujan https://orcid.org/0000-0002-7938-0266

Ana Previšić https://orcid.org/0000-0002-0332-7522

Antica Čulina https://orcid.org/0000-0003-2910-8085

Abstract

Pharmaceuticals and personal care products (PPCPs) are now ubiquitous in freshwater ecosystems, entering water bodies through widespread use and incomplete removal during wastewater treatment. These compounds include psychoactive substances, antibiotics, anti-inflammatory drugs, hormones, chemotherapeutic drugs, fragrances, preservatives, UV filters, plasticizers and others. Although many studies report negative effects on survival and reproduction in non-target freshwater organisms, the overall magnitude and consistency of these impacts have remained unclear. We thus conducted the first systematic review and meta-analysis of PPCP effects at environmentally relevant concentrations across freshwater taxa. Our objectives were to quantify the overall effects of PPCP exposures on the fitness of freshwater fauna, and to test how the effects vary across taxa, and with developmental stage, sex, and

experimental context. We synthesized data from 96 peer-reviewed experimental studies and open datasets spanning 28 species and 65 PPCP compounds. Our meta-analysis shows that exposure to environmental levels of PPCPs consistently reduced fitness components, with survival showing the strongest decline. Among compounds, pharmaceuticals—and particularly antibiotics—produced the largest effects. However, the responses were context dependent. Our synthesis also revealed a substantial gap in taxonomic and compound coverage. We found little statistical evidence of publication bias in our dataset and the results were robust to sensitivity analyses. This study provides the first quantitative, cross-taxon synthesis of PPCP impacts on freshwater animals. By integrating heterogeneous ecotoxicological evidence, our findings strengthen the basis for prioritizing high-risk compounds and improving environmental risk assessment and regulatory decision-making.

Key words: freshwater organisms, chemical pollution, evidence synthesis, meta-regression, environmental pollution, water contamination

1. Introduction

Freshwater ecosystems play a critical role in biodiversity maintenance, aquatic food webs, and the life cycles of numerous species, and they provide critical ecosystem functions (Dudgeon et al., 2006; Lynch et al., 2023; Strayer & Dudgeon, 2010; Vári et al., 2022). Yet, they are increasingly threatened by multiple anthropogenic pressures, with pollution emerging as a key driver of freshwater biodiversity loss (Sayer et al., 2025). Chemical pollution is especially worrying, as thousands of chemicals, including pharmaceuticals and personal care products (PPCPs) are continuously released into freshwater environments (Meyer et al., 2019; Sigmund et al., 2023). PPCPs are a diverse group of compounds that are used to prevent or treat human and animal diseases or improve the quality of daily life (Boxall & Brooks, 2024). PPCPs enter freshwater systems through multiple pathways, such as agricultural runoff, improper disposal and wastewater effluents (Khalidi-Idrissi et al., 2024; Samal et al., 2022). Wastewater treatment plants often cannot remove these compounds completely, so they persist in surface waters (Michael et al., 2013). Even at low concentrations, their continuous input can lead to chronic effects for non-target freshwater organisms (Wydro et al., 2023).

PPCPs can affect freshwater organisms by disrupting endocrine systems, altering behavior, impairing immune function and affecting physiology. Such impacts are reflected in reductions in survival and reproduction (e.g. Ebele et al., 2017; Fabbri, 2015; Tijani et al., 2013) and can ultimately lead to population declines and evolutionary changes (Brommer, 2000; Flatt & Heyland, 2011; Stearns, 1992). Thus, many experimental studies aim at understanding such individual level fitness effects of PPCPs. Such studies are often conducted at relatively high concentrations, which may not reflect environmental exposure scenarios (Boxall et al., 2012). Therefore, experimental studies that expose animals to environmentally relevant concentrations are likely to better represent realistic environmental scenarios, making their results more pertinent for understanding the potential ecological and evolutionary consequences of PPCPs. Importantly, the magnitude and direction of PPCP effects on fitness can vary among species (Coleman & Edmands, 2024; Spurgeon et al., 2020) and depend on traits of exposed organisms such as their life stage (Hutchinson et al., 1998) or sex (Lafram et al., 2026). Furthermore, these effects can be modified by abiotic (experimental) conditions such as temperature, food availability, oxygen levels and exposure regime (Bundschuh et al., 2020; Cerveny et al., 2021;

Heugens et al., 2001; Holmstrup et al., 2010). Considering such context dependence is essential for understanding how PPCP exposure might translate from individual-level effects to population-level consequences in freshwater ecosystems.

The current evidence emerging from experimental studies on the impact of PPCPs on the fitness of freshwater animals is fragmented, and experiments are commonly conducted at small temporal scales within a narrow experimental context (e.g. single life stage or sex, acute exposure durations and constant laboratory conditions). As a result, the findings cannot be readily generalized across exposure categories, organism traits and environmental conditions (Boxall & Brooks, 2024). Further, the gaps in taxonomic coverage of studied organisms likely prevent more complete understanding of potentially dangerous effects on natural ecosystems. Given these gaps in understanding how PPCPs affect fitness of freshwater fauna at environmentally relevant concentrations, we conducted a systematic review and meta-analysis of existing studies on the topic. Systematic reviews and meta-analyses provide a powerful tool to integrate findings across studies by systematically collecting the existing evidence and assessing the magnitude of the outcomes across relevant primary studies and by analyzing the causes of variation among study outcomes (Gurevitch et al., 2018). Such syntheses are essential for advancing ecological understanding, identifying knowledge gaps, and for informing risk assessment, mitigation measures, and policy decisions (Collins et al., 2019; Nakagawa, Yang, et al., 2023).

Here, we present the first quantitative synthesis of the reported impacts of PPCP exposure on key fitness components in freshwater fauna. We consider fitness to include survival, reproductive output, and measures that are strongly linked to survival or reproduction (i.e. indirect fitness). Indirect fitness included time to reach a certain reproductive or developmental stage (e.g., age at first reproduction, time to hatch) and juvenile size, which are proxies for individual fitness and potential population performance traits (Nilsson-Örtman & Rowe, 2021; Shingleton, 2011). We specifically focused on the environmentally relevant concentrations of pollutants to ensure ecological relevance. Importantly, we included data extracted from published studies and openly available raw datasets, which allowed us not only to broaden the scope of evidence but also to compare whether effect sizes derived from raw data differ from those derived from published results alone. Our meta-analysis addressed two groups of preregistered research questions and predictions:

1. How does exposure to PPCPs affects the fitness components of freshwater fauna? We predicted that PPCPs overall decrease fitness and increase the variability in fitness among individuals. We further predicted that survival is more strongly affected than reproduction or indirect fitness, and that the magnitude of PPCP effects increases with longer exposure durations. Finally, we evaluated whether different categories of PPCPs have different impacts on fitness, however, without a specific prediction on the direction of this effect.
2. How does the fitness of freshwater fauna to PPCP exposure depend on individual traits and experimental (abiotic) conditions? Specifically, we predicted that early life stages would be more sensitive than later developmental stages, and that responses depend on the taxonomic class and sex (however, without a specific prediction on the direction of these effects). For experimental conditions, we predicted that the effects would be stronger (more negative) when the exposure time is longer, temperature is higher, and

oxygen and food supply are lower than the optimal levels. Such stressful conditions and prolonged exposures likely induce cumulative physiological stress.

An additional aim of our evidence synthesis was to identify gaps in the current knowledge landscape, such as taxonomic biases, the representation of the most common PPCPs in experiments given, or testing of PPCP mixtures at environmentally relevant concentrations, given that freshwater fauna is typically exposed to complex chemical mixtures rather than single compounds (Kidd et al., 2024).

2. Methodology

We preregistered the study protocol prior to literature screening (Tarandek et al., 2025). The Appendix details a few minor deviations from the protocol. We report the systematic review and meta-analysis using PRISMA-Eco Evo (O'Dea et al., 2021) checklist (in the Appendix). The reporting of the methodology followed MeRIT to improve author contributions' accountability (Nakagawa, Ivimey-Cook, et al., 2023). Additional details of the literature search and screening, and model fitting are outlined in the Appendix. Data and code required to repeat the analysis and reproduce the results are provided in (Tarandek et al., 2026).

2.1. Eligibility criteria

We included peer-reviewed experimental studies and published datasets from trusted repositories that were written in English or Croatian (languages spoken by the author team) and published at any time prior to the search (April 2025). They had to meet the following criteria under the Population, Exposure, Control, Outcome (PECO) framework (Foo et al., 2021):

Population: freshwater fauna species that have a full or partial freshwater life cycle, where freshwater has salinity lower than 0.1% NaCl (<1000 mg/L) (Musie & Gonfa, 2023). This includes permanent and semi-permanent freshwater systems, such as lakes, ponds, rivers and streams. Taxa with species that have a partial freshwater life cycle include, but are not restricted to, amphibians and insects with an aquatic life stage.

Exposure: environmentally relevant concentrations in surface waters of PPCPs and their subgroups including but not limited to psychoactive drugs, antibiotics, analgesic and anti-inflammatory drugs (NSAIDs), antiparasitic drugs, cardiovascular drugs, hormones, chemotherapeutic drugs and personal care products (PCPs). Environmentally relevant maximum concentrations could be specifically referenced as such in the study. Otherwise we used two databases: NORMAN database (https://www.norman-network.com/nds/empodat/) that primarily contains monitoring data on PPCPs from European countries and MEC database (Lehmphul, 2016), that contains data on pharmaceuticals (but not on PCPs) from multiple global regions. The exposure concentration had to be maintained at minimum 80% of the initial value through the experiment duration, which could be of any length. Studies that measured solely the effects of mixtures of two or more PPCPs simultaneously, without measuring the effect of each one separately were excluded.

Comparator: for laboratory colonies (e.g., long-term cultures), controls maintained under standard lab conditions without pollutant exposure. For studies using animals collected in the wild, controls maintained in water with the same concentration of the pollutant as in the wild

habitat, to accurately reflect baseline environmental conditions. All other conditions apart from pollutant concentrations should be kept constant between control and experimental groups.

Outcome: components of fitness related to survival, reproduction, and indirect fitness that are strongly linked to survival or reproduction. Each component was represented by several measures. Survival measures comprised adult survival, survival of earlier life stages (e.g. embryo survival, hatching rate, juvenile survival), and combined juvenile & adult survival. Reproductive measures included total offspring production (e.g. total eggs, clutches or offspring) and partial offspring production (e.g. offspring produced per day or per clutch). Indirect fitness measures (fitness proxies) included time to stage (e.g. age at first reproduction, time to hatch) and juvenile size. Studies solely measuring transgenerational effects (exposure of parental line and measuring effects of offspring generations other than the first) were excluded.

We searched Scopus and Web of Science (Core Collection; hereafter WoS) on 02.04.2025 using the search strings (provided in Appendix). They were developed and tested by AT, AC, SH and MV against 10 benchmark papers identified independently of the search process (Bonato et al., 2023; Calma et al., 2018; B. Campos, Piña, Fernández-Sanjuán, et al., 2012; Gayathri et al., 2023; Gilroy et al., 2014; B. Kim et al., 2017; Peltzer et al., 2019; Seyoum & Pradhan, 2019; Tišler & Kožuh Eržen, 2006; Zicarelli et al., 2024). To augment the database search, AT conducted a backward/forward citation search on three relevant reviews already published on the topic (Ebele et al., 2017; Fabbri, 2015; Tijani et al., 2013), using citationchaser (Haddaway et al., 2021).

2.2. Literature screening process

The literature screening process is presented in Figure S1. The search identified 4382 records (Web of Science n = 2200, Scopus n = 2182). After removal of duplicates (using *ASySD* in R, (Hair et al., 2023)), 3055 records entered literature screening, which we conducted using Rayyan (Ouzzani et al., 2016). In the initial screening (abstract, title, keywords), AT, SH, and MV screened the same 100 studies. The agreement rate was 98%. The two conflicts were discussed and resolved. The remaining studies were each screened by one reviewer (AT 84%, SH 3%, MV 13%). Records scored as "Yes" or "Maybe" (n = 227) entered the full-text screening. The full-texts of 117 studies (~50%) were each independently screened by two reviewers. As the agreement rate was nearly perfect, the remaining studies were screened by AT (overall: AT 100%, SH 13%, MV 15%, IS 13%, AC 9%). This resulted in 97 studies that met the eligibility criteria. Studies were excluded at the full-text stage primarily due to unavailable full text (n = 1), language restrictions (n = 6), wrong study design (n = 3), wrong population (n = 1), wrong exposure (n = 107) or wrong outcome (n = 12). Reasons for the exclusion of studies at the full-text screening stage are reported in Table S1. Eight studies met the inclusion criteria but were subsequently excluded because of the lack of quantitative information to calculate effect sizes (see Section 2.4. Data coding and extraction). Backward and forward citation searches of relevant review papers yielded five additional eligible studies.

2.3. Open datasets

On the 24.06.2025, we searched for published (open) datasets on the effects of PPCPs on the fitness of freshwater animals using two aggregators of research data repositories DataCite (https://commons.datacite.org/) and BASE (https://www.base-search.net/) and by direct search in Dryad Digital Repository (https://datadryad.org/). Search terms and search syntax can be found

in the Appendix). AT and AC screened the retrieved datasets against the eligibility criteria and usability (i.e. whether the effect size could be calculated). Searches of DataCite, Dryad and BASE returned 65, 233, and 274 datasets, respectively, of which two datasets met the inclusion criteria.

2.4. Data coding and extraction

Altogether, 96 studies passed the screening and were included in data extraction. For 65% of these, data were independently extracted by two reviewers per study. The agreement between extractions was very high, with only seven discrepancies, all of which were resolved by discussion. None of these discrepancies concerned data used for effect size calculation, but rather other aspects, such as experimental conditions or the inclusion and categorization of certain fitness measures. AT alone extracted data from the remaining 35% of studies (overall contribution: AT 100%, SH 20%, MV 18%, IS 17%, AC 8%).

For each study we extracted 56 variables following the preregistration (Tarandek et al., 2025). We provide descriptions and full definitions of all variables in Table S2. In summary, extracted data belong to four broad categories: (1) study and bibliographic data (e.g. title, publication year); (2) data on the experimental setup (e.g. PPCP identity and category, exposure concentration and duration, temperature, feeding regime, oxygen conditions and experimental design); (3) biological data (e.g. species, taxonomic class, life stage, sex, fitness measured); (4) data to calculate the effect size. Information needed to calculate effect size estimates was extracted from raw data (when available) or summary statistics (means and standard deviations, contingency tables). If results were presented graphically only, we extracted the relevant data using WebPlotDigitizer (https://web.eecs.utk.edu/~dcostine/personal/PowerDeviceLib/DigiTest/index.html). If a study reported more than one environmentally relevant concentration or more than one time point for fitness measures, we extracted data for the highest concentration and the longest exposure duration to ensure consistency.

Some studies used solvents to deliver the main exposure chemical (46 of 96 studies). Of these, 37 included a solvent control, while 9 did not. In studies with solvent controls, most reported no significant differences between solvent and negative controls. Accordingly, we extracted information on the negative controls whenever possible; in studies that only reported solvent controls, we used these instead.

If the information to calculate the effect size was missing (13 studies), we emailed the authors. If we did not receive the needed information within six weeks, we excluded the effect size (and sometimes the entire study, if the information for all its effect sizes was missing). Missing standard deviations were imputed for 30 effect sizes from 10 studies (see 2.6. Calculation of effect sizes).

In total, 96 studies containing 402 effect sizes were included in the final meta-analysis (n = 89 from database search, two from data search, five from backward/forward search; see PRISMA flow chart Fig. S2). When some values (e.g. duration of the experiment) were reported as ranges, we used the mean value (31 effect sizes from five studies). We calculated nine effect sizes (from three studies) after receiving feedback from the authors, and 16 effect sizes (from three studies) using open data from the corresponding study. Raw data were available for five studies (three from database search, two from data search). The studies included in the meta-analysis were: (Abdullahi et al., 2022; Adamczuk, 2022; Akbar et al., 2020; Alkimin et al., 2020; Alves et al., 2004;

Aulsebrook et al., 2022; Barreto et al., 2022; Bawa-Allah & Ehimiyein, 2022; Berninger et al., 2011; Borgatta et al., 2016; Bouly et al., 2022; Boyd et al., 2021; Bringolf et al., 2010; Brooks et al., 2003; Buchberger et al., 2018; Cahova et al., 2021; B. Campos, Piña, & Barata C, 2012; L. B. Campos et al., 2023; Chaabani et al., 2023; Chen et al., 2019; Cuiping et al., 2023; Da Silva Viana De Souza et al., 2025; Dalla Bona et al., 2014, 2015; Damasceno De Oliveira et al., 2018; Dang et al., 2024; Daniel et al., 2019; De Felice et al., 2019; De Paula et al., 2022; Diogo et al., 2024; Dong et al., 2025; Ferreira et al., 2022; Fuertes et al., 2019; Gong et al., 2013; González-González et al., 2021; Grzesiuk et al., 2018; Gylytė et al., 2023; He et al., 2021; Hossain et al., 2019; Huang et al., 2013; Imiuwa et al., 2024; Jacob et al., 2019; Jobling et al., 2004; Jukosky et al., 2008; Jung Collard et al., 2013; Kamel, 2025; Kawashima et al., 2022; H. Y. Kim et al., 2012; LaLone et al., 2012; Lambert et al., 2021; Lamichhane et al., 2013; Le et al., 2022; Lebreton, Malgouyres, et al., 2021; Lebreton, Sire, et al., 2021; Lee et al., 2019; Leung et al., 2024; Y. Liu et al., 2017; Luna et al., 2013, 2015; Lürling et al., 2006; Mielecki et al., 2023; Minguez et al., 2015; Muambo et al., 2024; Muñiz-González, 2021; Németh et al., 2024; Ng et al., 2020; Nguyen et al., 2021; Ni et al., 2025; Nibamureke et al., 2019; Nkoom et al., 2022; Ohanessian & Billoir, 2025; Omotola et al., 2023; Parrott et al., 2022; Peltzer et al., 2019; Qiao et al., 2022; Ribeiro et al., 2023; P. Rodrigues et al., 2020; S. Rodrigues et al., 2021; Steinkey et al., 2019; Sun et al., 2023; Tian et al., 2019; Tran et al., 2023; Varano et al., 2017; Vo et al., 2018; L. Wang et al., 2016; Y. Wang et al., 2024; Wei et al., 2018; Xu et al., 2019; Yan et al., 2020; Yokota et al., 2016; D. Yuan & Zhang, 2025; L. Yuan et al., 2022; Yuxuan et al., 2018; Zanitti et al., 2023; Y. Zhang et al., 2023; Zhao et al., 2024).

2.5. Calculation of effect sizes

We used Log Response Ratio (*lnRR*) (Lajeunesse, 2015) and Log Variation Ratio (*lnVR*) (Senior et al., 2020) as common effect size metrics to quantify the magnitude and the variability of fitness to PCPPs. *lnRR* quantifies the proportional change in mean fitness outcomes between exposed and control groups, while *lnVR* captures changes in response variability. Analyses based on *lnVR* were restricted to studies reporting continuous outcomes, as variance-based effect sizes cannot be calculated for binary data.

For continuous outcomes, commonly presented as means and standard deviations, we calculated effect sizes and their sampling variances using the *escalc* function from the *metafor* package (Viechtbauer, 2010) with measure = "ROM" for *lnRR* and measure = "VR" for *lnVR*, applying standard formulas (Lajeunesse, 2011; Senior et al., 2020). When standard deviations were equal to zero, they were replaced with a small positive value (0.5) to avoid undefined variances. When information on standard deviation was missing, we imputed them using a weighted coefficient-of-variation approach developed for *lnRR* meta-analyses (Nakagawa, Noble, et al., 2023), which exploits the empirical mean-variance relationship across studies. When SDs were imputed, *lnRR* and its sampling variance were estimated using Taylor-series approximations based on weighted coefficients of variation, following Nakagawa et al. 2023 (Nakagawa, Noble, et al., 2023), allowing inclusion of studies with incomplete variance information while maintaining consistent estimation. For open datasets we calculated means and effect sizes from raw data, and from them the standardized effect sizes as described above.

For studies reporting binary outcomes (e.g., survival, hatching rate), we transformed group means and standard deviations using an arcsine square-root transformation before calculating *lnRR* and its sampling variance via the delta method (Rücker et al., 2009) using *escalc* with

measure = "AS". To ensure consistent interpretation, effect sizes were oriented so that negative *lnRR* values indicate reduced fitness under exposure compared to controls, and positive values indicate increased fitness.

2.6. Meta-analysis models

All statistical modelling was conducted by AT (checked by DŽ). We used multilevel meta-analytic models with a sampling variance-covariance matrix. The t-distribution was used to compute test statistics and confidence intervals for the fixed effects, and restricted maximum likelihood (REML) was used as the model estimator. Effect sizes were weighted by the inverse of their sampling variance and incorporated into the models via the variance-covariance matrix to account for precision differences among estimates.

We fitted separate models for the two effect sizes (*lnRR* and *lnVR*). For each effect size type, we first estimated the global effect size using an intercept-only model that incorporates the random effects. We first fitted a maximal random-effects model including study identity (study_ID), effect size identity (ES_ID), and species as random effects to account for heterogeneity and non-independence at multiple levels. The species-level variance component was negligible based on Akaike's Information Criterion (AIC), so species was excluded from subsequent analyses to improve model performance (see Appendix). Thus, in all the following models, two sources of non-independence were accounted for: study_ID and ES_ID. To test for the influence of different moderators on the effect size, and based on our predictions, we conducted meta-regressions by including each moderator variable as a fixed effect in the main random effect model. Total heterogeneity (the variance not attributable to sampling error) was quantified using I^2. The marginal R^2 was used to quantify the proportion of heterogeneity explained by each moderator (Nakagawa & Schielzeth, 2013).

Data analysis was conducted in the R Statistical Environment version 4.4.0 (*R: The R Project for Statistical Computing*, 2025). The multi-level meta-analysis and meta-regression models were implemented using the *rma.mv* function in the *metafor* package, version 4.6.0 (Viechtbauer, 2010). All visualizations of the models were constructed using *ggplot2*, version 3.5.1 (Wickham, 2016) and *orchaRd*, version 2.0 (Nakagawa, Lagisz, et al., 2023). The data and code to reproduce all the analyses and figures are available at (Tarandek et al., 2026).

2.7. Publication bias, Sensitivity analysis and Risk of Bias

We tested for small-study effects by using a simple extension of Egger's regression (Nakagawa, Yang, et al., 2023), where effect sizes (*lnRR*) were regressed on the square root of their sampling variance. Funnel plots were visually inspected to complement this analysis. To evaluate time-lag bias, we ran a multilevel meta-regression with publication year as moderator.

To assess the robustness of the results, we conducted multiple sensitivity analyses. The first three analyses were restricted to the global *lnRR* model and meta-regression models with two main moderators of interest: fitness component and PPCP category. First, we restricted the dataset to Branchiopoda studies, the most abundant taxon in the dataset. Second, we excluded effect sizes that were based on approximated or imputed data to assess the influence of lower-precision reporting. Third, we considered only effect sizes directly extracted from publications, excluding data obtained via author correspondence or open databases. Additionally, we performed leave-one-out analyses by sequentially removing each study or species to evaluate

their influence only on the global *lnRR* estimate. These analyses ensured that our results were not driven by individual studies, species, or data sources. We did not conduct sensitivity analyses for *lnVR*, because *lnVR* was only calculated for continuous outcomes, preventing robustness checks across the full dataset.

There is no formal tool for assessing the risk of bias of primary studies included in ecological or ecotoxicological meta-analyses. We therefore adapted a structured approach based on (Culina et al., 2025) and evaluated whether experimental units (e.g., individuals or tanks) were randomly assigned to treatments to minimize pre-existing differences between groups and whether observers or analysts were unaware of treatment assignments to prevent conscious or unconscious bias in measurements or data processing. To assess the influence of these two sources of bias on effect size estimates, randomization (yes/no) was included as a categorical moderator in multilevel meta-regression models for *lnRR* and *lnVR*. As none of the studies reported blinding, we could not test for the influence of this moderator.

3. Results

3.1. Summary of the included literature

Our meta-analysis included 402 effect sizes from 96 experimental studies, published between 2003 and 2025, with most studies published in the last decade (Fig. S3). The dataset was dominated by studies conducted in Europe (36 studies) and Asia (33 studies), followed by North America (16 studies), while only a few studies came from South America (6 studies), Africa (3 studies) and Oceania (2 studies; Fig. S4).

The studies were conducted on 28 freshwater species; however, *Daphnia magna* was largely overrepresented (53 studies, 260 effect sizes; Fig. 1). Most species (21/28, 75%) spend their entire life cycle in freshwater, whereas seven (25%) have partially aquatic life cycle.

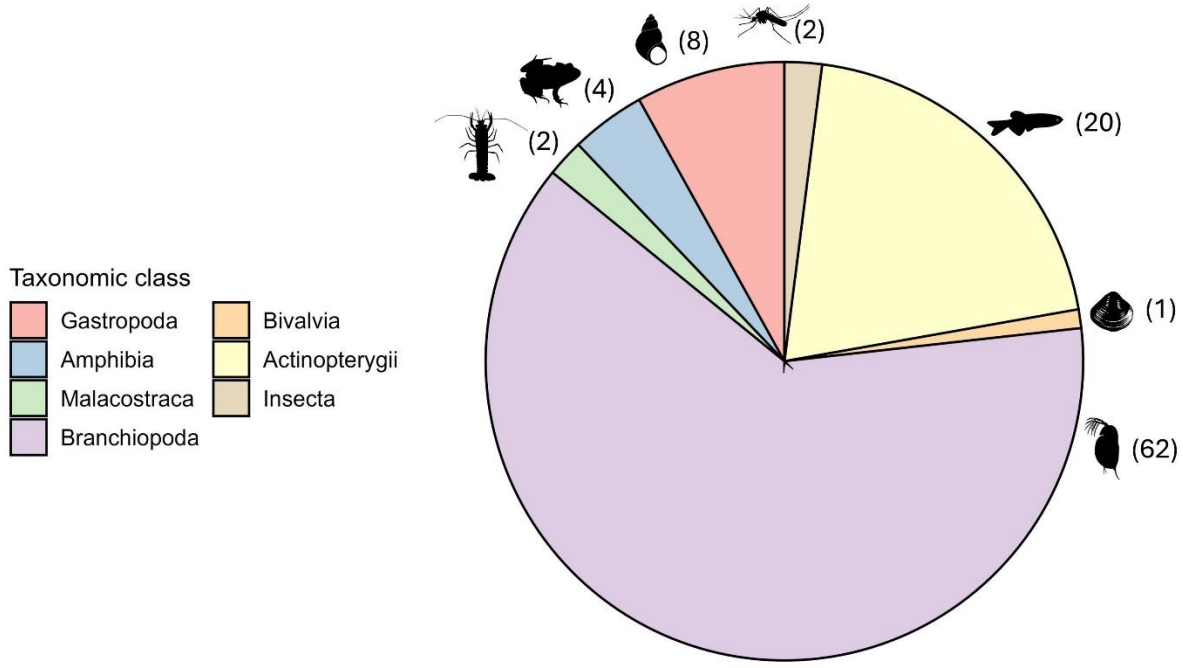

Figure 1. Distribution of taxonomic classes across included studies. Numbers in parentheses indicate the number of unique studies in which each taxonomic class was represented. Silhouettes obtained from PhyloPic (http://phylopic.org; CC0 1.0).

The studies examined the effects of 65 PPCPs, mostly pharmaceuticals (Fig. 2A). The most prevalent pharmaceutical groups (Fig. 2B) were psychoactive drugs (27 studies, 93 effect sizes), analgesic and anti-inflammatory drugs (NSAIDs; 21 studies, 90 effect sizes) and antibiotics (14 studies, 47 effect sizes). The most frequently investigated PPCPs were NSAID diclofenac (9 studies, 37 effect sizes) and PCP octocrylene (5 studies, 17 effect sizes). The studies recorded fitness components (Fig. 2C) as survival (60 studies, 106 effect sizes), reproduction (68 studies, 177 effect sizes), and indirect fitness (54 studies, 119 effect sizes).

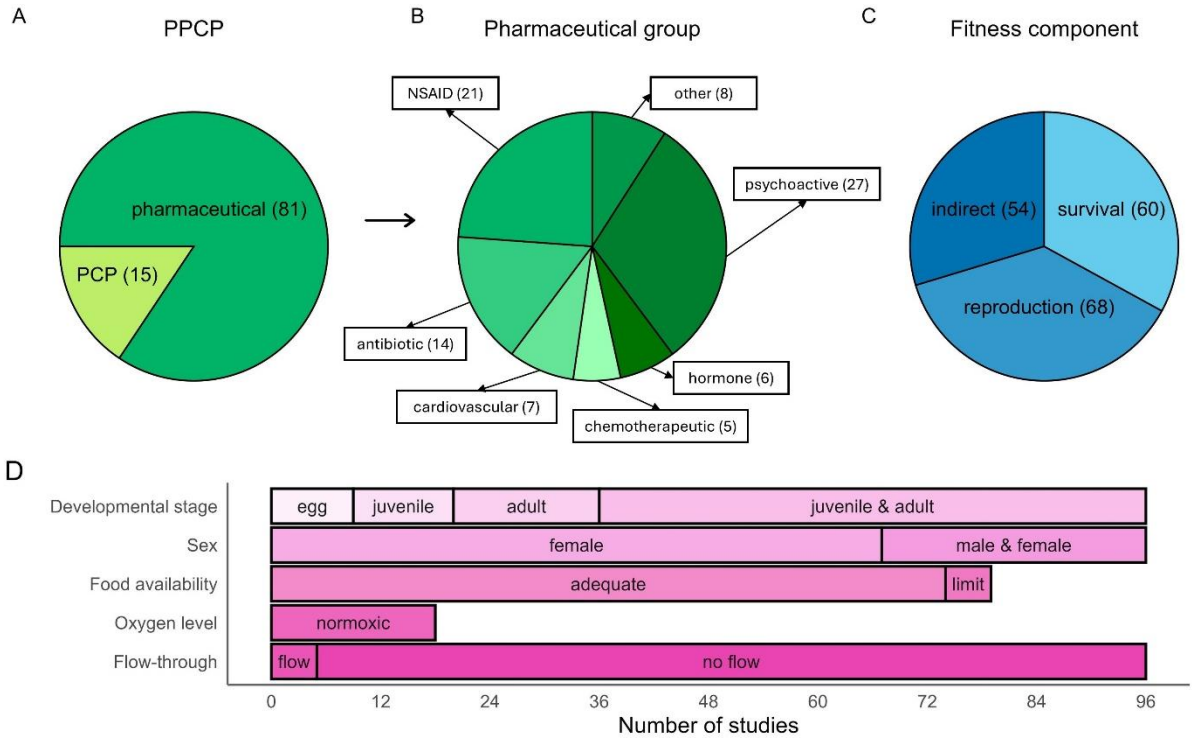

Figure 2. Pie charts represent the number of studies included in the meta-analysis according to: (A) PPCP category, (B) pharmaceutical group and (C) fitness component. The numbers in brackets represent the number of studies. (D) Bar plot showing the number of studies in each category of different biological and experimental conditions: developmental stage, sex, food availability, oxygen level, and flow-through conditions. If a study did not report data on a certain condition, it is not represented in the plot.

Exposure concentrations varied widely, with a median of 3.75 µg/L (first quartile 0.50 µg/L, third quartile 40.00 µg/L, exact concentrations provided in (Tarandek et al., 2026)). Exposure durations also ranged substantially, with a median of 504 hours (first quartile 408 hours, third quartile 528 hours). Only four pharmaceuticals (ciprofloxacin, tetracycline, diclofenac, trimethoprim) and three PCPs (di(n-butyl)phthalate, di(2-ethylhexyl)phthalate, avobenzone) were among 20 pharmaceuticals and 20 PCPs with the highest reported freshwater concentrations, according to our compiled environmental concentration dataset (NORMAN, MEC, and selected publications (Tarandek et al., 2026).

Studies mostly used only females (69 studies, 312 effect sizes; Fig. 2D), some used both sexes (without distinguishing between them), while males were only used in two studies. Studies mostly exposed individuals from juvenile to adult stages (62 studies, 298 effect sizes; Fig. 2D), and less frequently eggs, only juveniles, or only adults. Only three studies (20 effect sizes) used wild-collected animals, while others used laboratory cultures.

The abiotic experimental conditions were inconsistently reported (Fig. 2D). Temperature was specified in 64 studies (268 effect sizes) and ranged from 11 to 28.5 °C (median 21 °C). Feeding regime was reported in 84 studies, with 80 studies (331 effect sizes) providing adequate food, and only four studies (nine effect sizes) reported limiting food. Only 19 studies (71 effect sizes) reported oxygen levels (all normoxic). Only five studies used flow-through systems (12 effect sizes). Four studies examined combined exposure to two PPCPs at environmentally relevant concentrations. These mostly led to additive reductions in survival and reproduction, while some fitness measures, like reproduction timing or hatching, showed no extra effect beyond individual compounds.

3.2. Global effect and impacts of PPCP categories

Across all studies, exposure to PPCPs significantly reduced the mean of fitness components (i.e. survival, reproduction, and indirect fitness) by 9.55% on average (*lnRR* = −0.1004, 95% CI = [−0.1424, −0.0583], t_{95} = −4.74, $p < 0.0001$; Fig. S5A). The relative heterogeneity associated with *lnRR* was high (I^2_{total} = 99.74%), where 25.60% of heterogeneity originated from differences among studies, and 74.14% from variation among effect sizes within studies. This extremely high heterogeneity indicates that PPCP effects are highly context-dependent, varying substantially across different organisms, exposure conditions and specific compounds.

Variability of the responses (*lnVR,* analyzed only for continuous response variables) was on average 9.02% larger in the exposure group compared to the control, however the 95% CI overlapped zero (*lnVR* = 0.0863, 95% CI = [−0.0224, 0.1951], t_{77} = 1.58, p = 0.1181; Fig. S5B). Heterogeneity for *lnVR* was also high (I^2_{total} = 90.87%), with 19.96% of the variance attributed to differences among studies and 70.91% to variation among effect sizes within studies.

Overall, the category of compound (pharmaceuticals vs PCPs) significantly moderated the mean response of organisms to exposure (*lnRR*: $F_{2, 94}$ = 11.90, $p < 0.0001$, $R^2_{marginal}$ = 0.009; Fig. 3A). On average, exposure to pharmaceutical compounds reduced fitness by 10.48% (*lnRR* = −0.111, 95% CI [−0.1565, −0.0648], $p < 0.0001$), while PCP exposure by 4.61%, with the confidence intervals overlapping zero (*lnRR* = −0.047, 95% CI [−0.1502, 0.0557], p = 0.3647). Variability in responses (*lnVR*: $F_{2, 76}$ = 1.48, p = 0.2333, $R^2_{marginal}$ = 0.004; Fig. 3A) was not significantly moderated by compound category, and the 95% CI overlapped zero for both pharmaceuticals (*lnVR* = 0.0705, 95% CI [−0.0477, 0.1887], p = 0.2386) and PCPs (*lnVR* = 0.1762, 95% CI [−0.1051, 0.4574], p = 0.2160; Fig. S6A).

A meta-regression including pharmaceutical group as a moderator significantly influenced mean fitness (*lnRR*: $F_{7, 74}$ = 4.57, p = 0.0003, $R^2_{marginal}$ = 0.063; Fig. 3B). Antibiotics elicited the strongest reduction in fitness by 22.32% (*lnRR* = −0.2526, 95% CI [−0.3707, −0.1344], $p < 0.0001$), followed by analgesic and anti-inflammatory drugs (NSAIDs) by 10.70% (*lnRR* = −0.1131, 95% CI [−0.2014, −0.0249], p = 0.0122) and psychoactive compounds by 9.90% (*lnRR* = −0.1041, 95% CI [−0.1837, −0.0245], p = 0.0105). Hormones, chemotherapeutics, cardiovascular drugs, and other

pharmaceutics had no significant effects on mean fitness. However, the sample sizes for these were small.

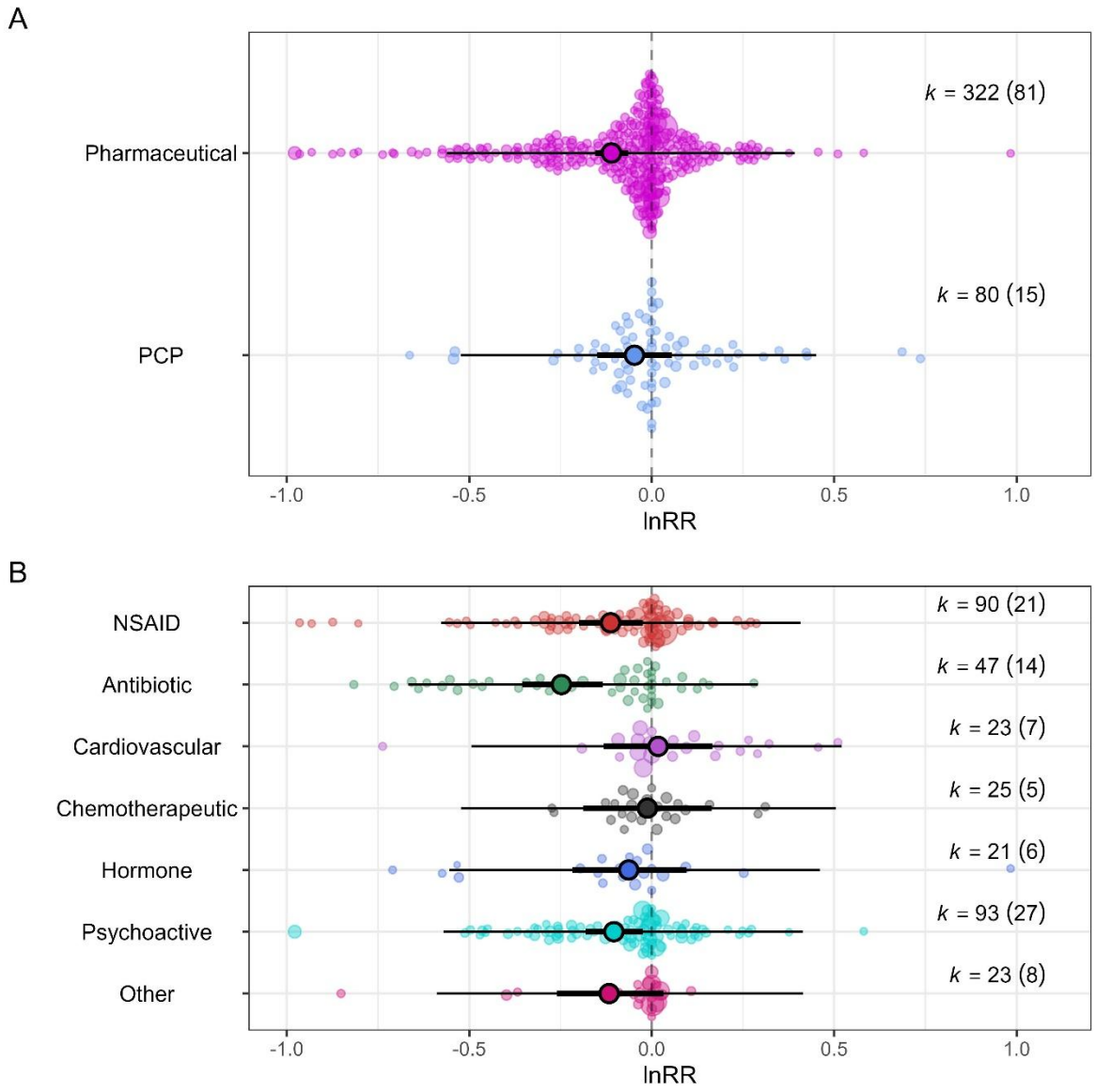

Figure 3. The effect size estimates (*lnRR*) of the impact of PPCPs on the fitness of freshwater fauna shown for (A) PPCP category (pharmaceuticals vs. personal care products) and (B) pharmaceutical group. Figures show the mean difference between control and treatment groups on a logarithmic scale (*lnRR*) as large circles with bold margins, where negative values indicate reduced fitness in exposed organisms. Shorter, thicker whiskers represent 95% confidence intervals, while longer, thinner whiskers indicate 95% prediction intervals. Each circle represents an individual effect size, with circle size scaled according to precision (inverse sampling variance). Values of *k* denote the number of effect sizes, with the corresponding number of studies given in parentheses. The model estimates were obtained using uni-moderator meta-regression models.

3.3. Impacts of fitness components and organismal traits

The mean response to PPCP exposure was moderated by fitness components (*lnRR*: $F_{3, 399} = 9.04$, $p < 0.0001$, $R^2_{marginal} = 0.012$; Fig. 4A), taxonomic class (*lnRR*: $F_{7, 89} = 3.70$, $p = 0.0015$, $R^2_{marginal} = 0.021$; Fig. S7), sex (*lnRR*: $F_{3, 399} = 7.64$, $p = 0.0001$, $R^2_{marginal} = 0.002$; Fig. 5B), and developmental stage (*lnRR*: $F_{4, 92} = 6.57$, $p < 0.0001$, $R^2_{marginal} = 0.015$; Fig. 5A). The mean survival of exposure group was reduced by 13.73% (*lnRR* = −0.1477, 95% CI [−0.2096, −0.0858], $p < 0.0001$), reproduction by 8.13% (*lnRR* = −0.0847, 95 % CI [−0.1376, −0.0319], $p = 0.0017$), and indirect fitness by 7.40% (*lnRR* = −0.0769, 95% CI [−0.1325, −0.0212], $p = 0.0069$; Fig. 4A).

Fitness of exposed Actinopterygii was reduced by 12.79% (*lnRR* = −0.1368, 95% CI [−0.2364, −0.0372], $p = 0.0072$), of Branchiopoda by 9.69% (*lnRR* = −0.1019, 95% CI [−0.1545, −0.0492], $p = 0.0002$) and Gastropoda showed no significant effect (*lnRR* = 0.0158, 95% CI [−0.1414, 0.1730], $p = 0.8434$). Classes with very few effect sizes were not interpreted due to low precision. Females exhibited a 9.21% reduction in fitness (*lnRR* = −0.0966, 95% CI [−0.1450, −0.0482], $p = 0.0001$) and mixed-sex groups showed a 10.23% reduction (*lnRR* = −0.1079, 95% CI [−0.1838, −0.0319], $p = 0.0055$). Male-only groups were not interpreted due to insufficient effect sizes.

Reduction in fitness was largest for juveniles, by 18.04% (*lnRR* = −0.1990, 95% CI [−0.3173, −0.0807], $p = 0.0010$), and somewhat less (11.84%) for adults (*lnRR* = −0.1260, 95% CI [−0.2345, −0.0174], $p = 0.0230$), and for combined juvenile & adult stages with an 8.15% reduction (*lnRR* = −0.0850, 95% CI [−0.1344, −0.0357], $p = 0.0008$). Effects on eggs were not significant (−5.86%, *lnRR* = −0.0604, 95% CI [−0.2055, 0.0847], $p = 0.4108$).

We fitted separate uni-moderator meta-regression models within each fitness component (survival, reproduction, and indirect fitness) to examine how specific fitness measures respond to PPCP exposure. These models showed that early-life survival (Fig. 4B) had the strongest average reduction of 15.15% (*lnRR* = −0.1643, 95% CI [−0.2563, −0.0722], $p = 0.0006$), while adult survival was slightly less reduced, by 12.42% on average (*lnRR* = −0.1326, 95% CI [−0.2749, 0.0096], $p = 0.0672$) and juvenile & adult survival measured together was reduced by 10.62% (−0.1124, 95% CI [−0.2120, 0.0128], $p = 0.0274$). The total offspring production (measured during the overall period of exposure) was reduced by 9.01% (*lnRR* = −0.0944, 95% CI [−0.1740, −0.0148], $p = 0.0204$; Fig. 4C), while the 95% CI of the estimates for offspring production measured at a certain time point (usually the first reproduction) overlapped zero (*lnRR* = −0.0709, 95% CI [−0.1753, 0.0334], $p = 0.1816$). Of the two indirect fitness measures extracted from the obtained studies, juvenile size was 9.27% lower in treatment group (*lnRR* = −0.0973, 95% CI [−0.1842, −0.0104], $p = 0.0285$, Fig. 4D), but no significant change in time to reach a certain reproductive and developmental stage was detected (*lnRR* = −0.0377, 95% CI [−0.1010, 0.0256], $p = 0.2404$).

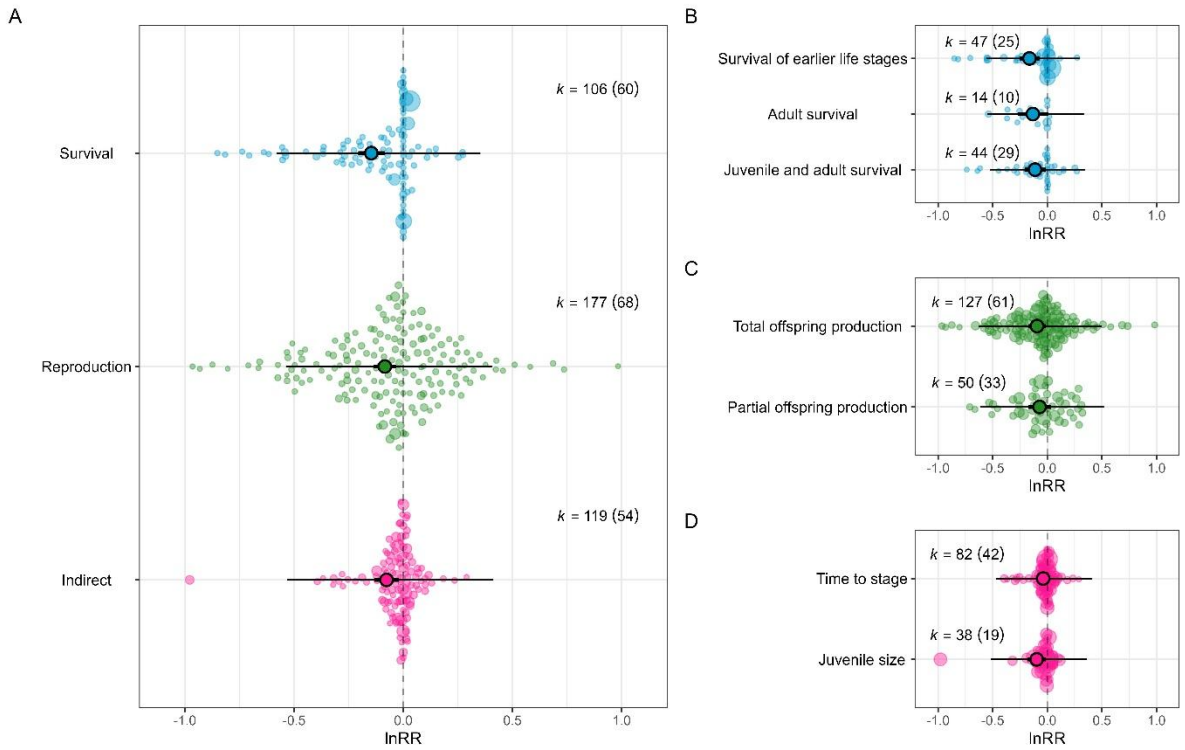

Figure 4. The effect size estimates (*lnRR*) of the impact of PCPPs on fitness of freshwater fauna showed for (A) three main fitness components: survival, reproduction, and traits indirectly related to fitness; (B) survival of different life-stages; (C) reproduction measured during the full experiment or organism life-time or during certain time point (usually the first reproduction), (D) indirect fitness (time required to reach a defined developmental or reproductive milestone) and juvenile size. The figures show the mean difference between control and treatment groups on a logarithmic scale (*lnRR*) as large circles with bold margins, where negative values indicate a reduction in fitness for exposed group. The model estimates were obtained using uni-moderator meta-regression. The remaining details are the same as in Fig. 3.

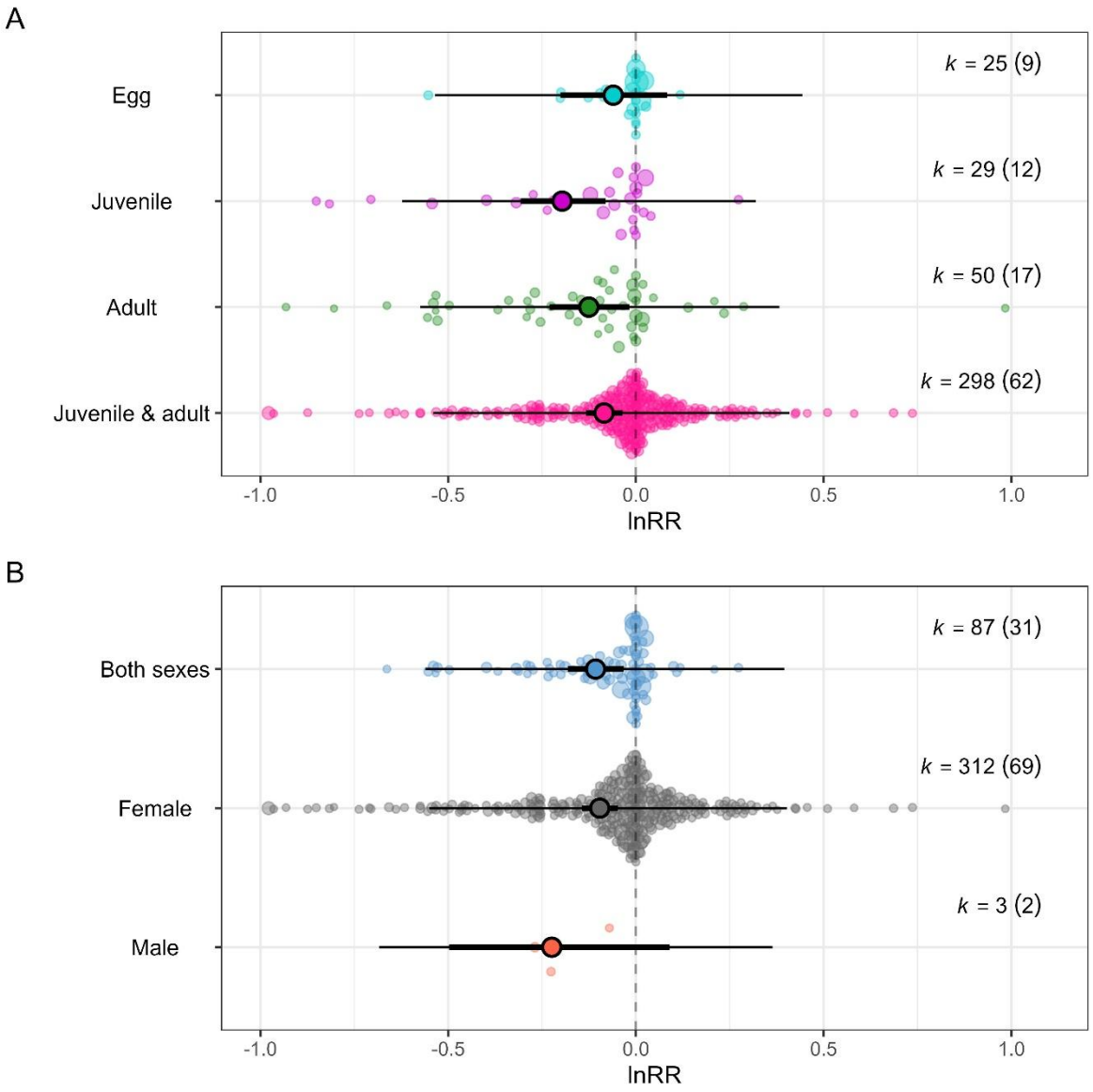

Figure 5. The effect size estimates (*lnRR*) of the impact of PPCP exposure on the fitness of freshwater fauna shown for (A) developmental stage and (B) sex. Figures show the mean difference between control and treatment groups on a logarithmic scale (*lnRR*) as large circles with bold margins, where negative values indicate reduced fitness in exposed organisms. Model estimates were obtained using uni-moderator meta-regression models. The remaining details are the same as in Fig. 3.

The variability of response to PPCP exposure was only partially moderated by fitness components (*lnVR*: $F_{3, 300} = 1.58$, $p = 0.1944$, $R^2_{marginal} = 0.008$; Fig. S6B). Variability of survival (*lnVR*) was higher (33.04%) in exposed individuals compared to the control group (*lnVR* = 0.2885, 95% CI [0.0024, 0.5685], $p = 0.0481$, Fig S6B), while the variability of reproduction and indirect fitness was similar between the groups (reproduction: *lnVR* = 0.0608, 95% CI [−0.0655, 0.1870], $p = 0.345$); indirect fitness: *lnVR* =0.0774, 95% CI [−0.0654, 0.2202], $p = 0.2872$).

3.4. Impacts of experimental conditions

The mean response to the exposure was significantly moderated by PPCP concentration (*lnRR*: $t_{(401)} = -4.32$, $p < 0.0001$, $R^2_{marginal} = 0.076$; Fig. 6A), exposure duration (*lnRR*: $t_{(387)} = -4.22$, $p < 0.0001$, $R^2_{marginal} = 0.002$; Fig. 6B) and temperature (*lnRR*: $t_{(267)} = -4.27$, $p < 0.0001$, $R^2_{marginal} = 0.002$; Fig. 6C). The mean fitness decreased by 5.63%, per unit increase in log concentration (*lnRR* = −0.0580, 95% CI [−0.0844, −0.0316]), and by 3.16% (*lnRR* = −0.0321, 95% CI [−0.0470, −0.0171]) with each unit increase in log-transformed duration. The effect of temperature was smaller with an estimated 0.44% reduction in fitness for each 1 °C increase (*lnRR* = −0.0044, 95% CI [−0.0065, −0.0024]). We could not assess the influence of feeding regime, oxygen, nor flow-through conditions, as these variables were inconsistently reported or poorly represented in the dataset: only five studies used flow-through systems, limited feeding was applied in only four studies, and all studies reporting oxygen concentration maintained normoxic.

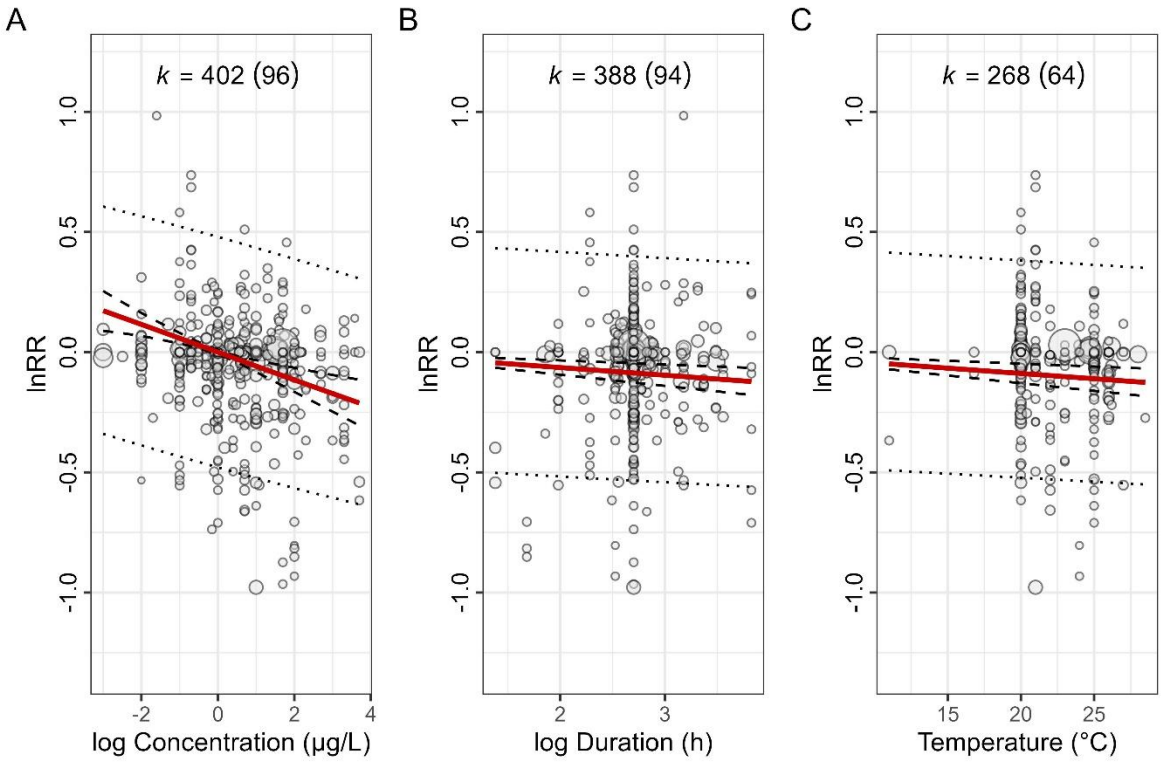

Figure 6. The effect size estimates (*lnRR*) of the impact of PPCP exposure on fitness of freshwater fauna as a function of (A) log PPCP concentration, (B) log exposure duration and (C) temperature. Each circle represents a separate effect size estimate (i.e. the mean difference between control and treatment groups on a logarithmic scale. Negative values indicate a reduction in fitness in the exposed group. The model estimates were obtained using uni-moderator meta-regression. The remaining details are the same as in Fig. 3.

3.5. Publication bias, sensitivity analysis, and Risk of Bias

We found no statistical evidence of publication bias (i.e., no bias towards the publication of larger effects). This was supported by visual inspection of the funnel plot (Fig. S8) and Egger's regression (*lnRR* = −0.2128, 95% CI [−0.6228, 0.1972], $t_{(400)} = -1.02$, $p = 0.3082$; Fig. S9A). Time-lag bias was

also absent, with effect sizes showing no systematic change over publication year (*lnRR* = −0.0205, 95% CI [−0.0615, 0.0204], $t_{(400)}$ = −0.99, p = 0.3242; Fig. S9B).

We conducted multiple sensitivity analyses to evaluate the robustness of the main *lnRR* results. First, we restricted the analysis to Branchiopoda studies, which yielded effect sizes consistent with the global model (*lnRR* = −0.0990, 95% CI [−0.1529, −0.0450]; Fig. S10). Furthermore, we assessed the influence of lower-precision reporting by excluding effect sizes based on approximated or imputed data (*lnRR* = −0.1090, 95% CI [−0.1589, −0.0592]; Fig. S11) as well as those obtained via sources other than the original publication, i.e. open data or author correspondence (*lnRR* = −0.1063, 95% CI [−0.1516, −0.0609]; Fig. S12). These analyses produced results consistent with the global model. The estimates of the meta-regression sensitivity analyses using fitness components, or PPCP category were also consistent with the estimates of the general analyses (Table S3-5, Fig. S10-S12). Finally, the leave-one-out analyses, sequentially excluding each study or species, indicated that no single study or species substantially influenced the overall results (Fig. S13-S14). Removing each study resulted in *lnRR* estimates ranging from −0.1055 to −0.0874, while removing individual species produced *lnRR* estimates from −0.1147 to −0.0942.

Studies included in our meta-analysis show a high risk of bias for randomization and blinding. Of the 96 included studies, only 46 reported random allocation of experimental units to treatments, while 50 did not specify whether randomization was applied (which equates to a high risk of bias). None of the included studies reported the use of blinding during outcome assessment or data analysis (i.e. high risk of bias). Meta-regression with randomization (yes/no) as a moderator indicated that effect sizes differed between studies that reported randomization and those that did not. The estimates were slightly more negative for studies reporting randomization (*lnRR* = −0.1127, 95% CI [−0.1729, −0.0526], $t_{(94)}$ = −3.72, p = 0.0003) than for those not reporting it (*lnRR* = −0.089, 95% CI [−0.1483, −0.0291], $t_{(94)}$ = −2.95, p = 0.0040). For *lnVR*, the estimates were higher for non-randomized studies (*lnVR* = 0.2026, 95% CI [0.0514, 0.3537], $t_{(76)}$ = 2.67, p = 0.0093), than for randomized studies (*lnVR* = −0.0273, 95% CI [−0.1760, 0.1215], $t_{(76)}$ = −0.36, p = 0.7162).

4. Discussion

We conducted the first meta-analysis on the effects of pharmaceuticals and personal care products (PPCPs) on the fitness of freshwater fauna. Based on the results from 96 experimental studies conducted across 28 freshwater species and 65 compounds, our meta-analysis demonstrates that exposure to PPCPs at environmentally relevant concentrations is associated with consistent negative effects on freshwater fauna. Across taxa, life stages, and experimental conditions, PPCP exposure reduced mean fitness, including survival, reproduction, and several indirect fitness measures (Feckler et al., 2025; Wilkinson et al., 2016). In contrast, effects on response variability were less clear, with increased variability detected for some fitness components but not consistently across fitness or compound categories. The overall patterns were robust across multiple sensitivity analyses and showed little evidence of publication bias, suggesting that the observed effects are not driven by specific studies, effect sizes, or data sources. At the same time, substantial heterogeneity among effect sizes highlights strong context dependence in PPCP effects, consistent with differences in experimental conditions (e.g. compound identity, exposure duration), exact fitness measures that were measured, and traits of the exposed organisms. Worryingly, existing experimental evidence covers only a small fraction

of the PPCPs frequently detected in freshwater systems and is largely limited to a narrow set of species, representing ~0.02% of all described freshwater species (Balian et al., 2008). These major gaps in the current evidence base limit generalization and the potential for the application to the real-world exposure scenarios.

4.1. PPCP exposure and fitness

Across all included studies, exposure to PPCPs to environmentally relevant concentrations resulted in an average fitness decline of approximately 10% relative to controls. This overall negative effect was accompanied by a high heterogeneity, indicating that its magnitude and even direction varies substantially across and within studies, consistent with heterogeneity commonly found in ecological meta-analysis (Senior et al., 2016). We could attribute some of this heterogeneity to the differences in experimental conditions, and in studied organisms. Our results indicate that pharmaceuticals are dominant drivers of PPCP-related fitness decline, while the effects of PCPs remain less consistent. This finding likely reflects the fundamental differences in PPCP chemical design and biological activity (Tijani et al., 2013). Pharmaceuticals are explicitly developed to interact with conserved molecular targets at low concentrations, and many retain biological activity in non-target organisms, even at environmentally relevant exposure levels (Ebele et al., 2017). As a result, pharmaceutical compounds can elicit more pronounced effects on survival and reproduction across diverse freshwater taxa (Cardoso, 2022; Chakraborty et al., 2023).

Effect sizes also varied among pharmaceutical groups, further indicating compound-specific mechanisms. Antibiotics, bioactive agents designed to be active against microorganisms and highly toxic to non-target organisms (Välitalo et al., 2017), led to the strongest reductions in fitness, while the effects of analgesic and anti-inflammatory compounds and psychoactive compounds were less strong. Consequently, the combination of their negative effect on fitness and high environmental prevalence suggests that these three pharmaceutical groups may contribute substantially to cumulative fitness impacts in natural populations (N. Liu et al., 2025; Świacka et al., 2022). Other pharmaceutical groups, including hormones, chemotherapeutic and cardiovascular drugs, showed no detectable effects on mean fitness. However, these estimates were of lower precision and based on fewer studies. The absence of a significant mean effect for PCPs can reflect a combination of factors. PCPs represent a broad, chemically heterogeneous group and their coverage at environmentally relevant concentrations is limited, reducing power to detect consistent effects (Adeleye et al., 2022; Brausch & Rand, 2011; Katsikaros & Chrysikopoulos, 2021).

Our analysis identified that survival is slightly more sensitive to PPCPs compared to reproduction or indirect fitness. This might reflect the composition of our dataset, where most of the survival data refer to survival of early life stages (e.g. Amphibia, Insecta) and survival of Branchiopoda that were exposed to PPCPs from juvenile to adult stage. Early life stages typically exhibit higher mass-specific metabolic rates, underdeveloped detoxification capacity, and smaller body size, all of which increase susceptibility to chemical exposure (Calow, 1991; Fabbri, 2015; Sibly & Calow, 1989). Thus, their exposure is expected to lead to stronger reduction in survival compared to adults (Beckerman et al., 2002; Houde, 1987; Werner & Gilliam, 1984). Related to this, we also detected that juvenile size was significantly reduced in exposed group compared to controls, reduced juvenile size likely reflects slowed growth or metabolic stress under PPCP exposure.

Smaller juveniles have increased mortality risk, reduced competitive ability, and lower probability of reaching reproductive maturity in aquatic organisms (Beckerman et al., 2002; Houde, 1987; Werner & Gilliam, 1984). Reduced survival early in life could have important consequences as it limits the recruitment to the breeding population, thereby constraining population growth even when adult survival is only moderately affected. Such early-life bottlenecks are widely recognized as key drivers of population dynamics in aquatic organisms (Beckerman et al., 2002; Houde, 1987; Werner & Gilliam, 1984). Interestingly, survival of exposed eggs was generally not reduced, likely because protective membranes and lower metabolic activity can buffer embryos against PPCP uptake and delay toxic effects until later developmental stages, a pattern commonly observed for aquatic contaminants (Pechenik, 2006; Samson et al., 2001).

Our results suggests that exposed organisms may initially compensate for chemical stress but experience cumulative reproductive costs under prolonged exposure. Namely, our analysis showed that early or partial reproductive output (e.g. first clutch or short-term fecundity) provided little evidence of reduction, whereas reduction in total offspring production over the experimental period was larger. Such delayed effects are consistent with energetic trade-offs, where resources are temporarily reallocated to maintain reproduction at the expense of somatic maintenance, ultimately reducing lifetime reproductive output (Boxall et al., 2012; Calow & Sibly, 1990; Cardoso, 2022). Endocrine disruption and chronic physiological stress may further exacerbate these long-term reproductive costs (Fabbri, 2015; Feckler et al., 2025).

Sex did not emerge as a clear determinant of sensitivity to PPCP exposure. However, this likely reflects limitations of studies included in our dataset rather than true equivalence between sexes, as sex-specific responses to contaminants have been documented in multiple taxa (Guillante et al., 2023; Madenjian et al., 2016; Polverino et al., 2023). Only two studies in our dataset evaluated the effect on males, while other used females, or did not separate between the sexes. Our results highlight the need for future experiment to explicitly test sex as a factor, consistent with previous recommendations (Morrison et al., 2025; Rehberger et al., 2017).

Our meta-analysis showed that PPCP effects are not uniform across freshwater fauna. Actinopterygii exhibited the strongest average reductions in fitness, followed by Branchiopoda, whereas Gastropoda showed no detectable effects. Other classes were underrepresented for a meaningful analysis. Although all the taxa included in this synthesis share high reproductive output characteristics, differences in physiology and development can generate taxon-specific responses even among species with broadly similar reproductive strategies (Sibly & Calow, 1989). However, the observed taxonomic differences should be interpreted cautiously, as the experimental conditions also largely differed between taxa. For example, comparative ecotoxicological research demonstrates that sensitivity frequently differs among major aquatic taxa, but these patterns are highly compound-specific (Coleman & Edmands, 2024; von der Ohe & Liess, 2004; Xin et al., 2015; L. Zhang et al., 2023).

We expected PPCP exposure to increase variability in fitness, as environmental stressors often amplify inter-individual differences by revealing hidden variation and heterogeneous sensitivities among individuals in populations (Cockrem, 2022; Medina et al., 2007; Shahmohamadloo et al., 2024). Such stress-induced increases in variability have been proposed as indicators of ecological disturbance. However, increased variability in our analysis was only observed for survival and was not consistently detected across fitness components or compound categories.

This may reflect the generally short duration of many experiments, potentially limiting the expression of delayed or condition-dependent responses that would increase variance over time. Additionally, experimental designs mostly relied on genetically uniform laboratory populations or clonal species, which may inherently constrain observable variability.

4.2. Impacts of experimental conditions

PPCP concentration was the strongest experimental moderator of the effect size. This pattern indicates that even relatively small increases in PPCP concentration within realistic environmental ranges are associated with additional reductions in fitness (Wang et al., 2021). Consequently, spatial and temporal fluctuations in PPCP concentrations, such as those near effluent sources or during seasonal peaks, may have significant impacts on organismal fitness (Adeleye et al., 2022; Fabbri, 2015; Wilkinson et al., 2016). Episodic contamination events could further increase these effects beyond the levels examined.

While longer exposure times were also associated with moderately larger negative effects, most of the experiments in our dataset were short-term (≤21 days). Fitness endpoints often integrate cumulative sublethal stress over time. Therefore, such short-term experiments may underestimate the ecological consequences of PPCPs by failing to capture delayed effects that manifest only after prolonged exposure (Boxall et al., 2012; Fent et al., 2006). The generally short duration of many studies in the dataset underscores the need for longer-term experiments that better reflect chronic exposure scenarios typical of natural freshwater systems (Boxall & Brooks, 2024; Cardoso, 2022; Vestel et al., 2016).

Temperature influenced PPCP effects, with warmer conditions inducing modest fitness reductions, however, as with the duration, most of the experiments were conducted within 20 – 25 °C range. Elevated temperatures can increase chemical uptake rates, alter biotransformation processes and reduce the energy available for maintenance, growth, and reproduction, thereby amplifying contaminant effects (Fabbri, 2015; Patra et al., 2015; Wang et al., 2019). These findings align with evidence showing that chemical stressors and warming interact additively or synergistically, raising concern that PPCP impacts may intensify under ongoing climate change (Bethke et al., 2023). Future studies should also examine variable temperature regimes, including short-term thermal extremes, to better reflect climate-change conditions (Folguera et al., 2011). Several potentially important experimental conditions could not be robustly evaluated due to limited or inconsistent reporting. Feeding regime and oxygen conditions were rarely manipulated, which restricts conclusions about how PPCP effects interact with common environmental stressors (Holmstrup et al., 2010; Wang, 2018). This underscores the need for more comprehensive experimental designs that incorporate multiple, realistic conditions.

4.3. Limitations, gaps and future directions

This meta-analysis provides the first large-scale synthesis of the fitness impacts of PPCPs on freshwater fauna. However, our study has several limitations and highlights important priorities for future research. The main issue of the published literature, and thus the dataset we have obtained, is that it is heavily unbalanced in several aspects, and likely does not provide a strong base to make conclusions that would be applicable to the real-world scenarios.

First, the included studies assessed only a small fraction of the most frequently detected PPCPs in freshwater environments. Specifically, only four of the 20 most prevalent pharmaceuticals and

three of the 20 most prevalent personal care products have been tested for effects on fitness, meaning that our results are based on a narrow subset of compounds that may not fully reflect the diversity of PPCPs encountered in the environment (Meyer et al., 2019). This limitation is compounded by geographic biases in environmental concentration data. For pharmaceuticals, data were obtained from both NORMAN and MEC databases, providing relatively broad geographic coverage. In contrast, personal care product data were only available from NORMAN, which is largely Europe-focused, resulting in a dataset that is more strongly biased toward European monitoring and may not represent conditions elsewhere.

Second, although PPCPs typically occur as complex mixtures, most experiments investigated single compounds, and our meta-analysis concentrated on these studies. Studies examining mixtures suggest additive effects on survival and reproduction, although some endpoints, such as hatching timing or reproduction, showed no additional effects. The scarcity of mixture studies at environmentally relevant concentrations limits understanding of the effects under real-world exposure scenarios (Kidd et al., 2024). In addition, a subset of studies applied solvents without corresponding solvent controls, thus minor solvent-related effects could go undetected. Solvents can confound biological endpoints if present at sufficient concentrations, so when used, they should be applied at low, likely biologically inert concentrations and verified not to affect measured responses (Bertram et al., 2024; Green & Wheeler, 2013; Hutchinson et al., 2006).

Third, taxonomic coverage also remains narrow, and more than half of the studies were conducted on *Daphnia spp*. Expanding experimental research across a broader range of freshwater taxa will be essential for improving generalization and strengthening ecological risk assessments of PPCPs, particularly beyond commonly studied invertebrates (Boxall et al., 2012; Ebele et al., 2017). Related to this, many of the studies included were short-term experiments which may inadequately represent the chronic, low-level exposures characteristic of natural freshwater systems, and especially for longer-lived organisms. Long-term experiments would improve ecological relevance and help resolve delayed or cumulative effects on fitness (Boxall & Brooks, 2024; Cardoso, 2022; Vestel et al., 2016).

Fourth, studies were mostly conducted on females and often did not separate the effects on different life stages. Males were almost not studied, although sex-specific sensitivity may influence population-level outcomes and has been repeatedly recommended in the literature (Morrison et al., 2025; Rehberger et al., 2017). Similarly, understanding life-stage specific effects remains challenging in the current dataset, as most studies assessed juveniles and adults together without separating responses by stage. Similar limitations have been noted in other ecotoxicological syntheses and highlight the need for experimental designs that explicitly isolate stage-specific responses (Cardoso, 2022; Saaristo et al., 2018).

Importantly, experimental studies in our dataset have a high risk of bias for randomization and blinding. Fewer than half of the studies reported randomization, and none reported blinding. Non blinded studies in ecology generally show higher effect than blinded studies (Holman et al., 2015; Kardish et al., 2015). The results of these studies, and therefore of our meta-analysis, should be considered within this limitation. Finally, methodological reporting and study design further constrained our synthesis. While most studies described basic experimental setups, key details such as exposure duration, sample size or statistical variance were often incompletely reported.

In addition, the application of core design features (e.g. exposure duration) was inconsistent. Incomplete reporting and limited use of bias-reducing practices increase uncertainty and highlight ongoing challenges in experimental standardization within ecotoxicology (Hitchcock et al., 2018; Morrison et al., 2025; Wang, 2018).

5. Conclusions and broader implications

Overall, our synthesis demonstrates that PPCPs consistently reduce fitness in freshwater fauna, even at environmentally relevant concentrations. Our results indicate that antibiotics may exert relatively strong negative effects, highlighting the potential ecological risk posed by this pharmaceutical class. However, current experimental coverage is limited, leaving substantial gaps. The heterogeneity of observed effects underscores the need for more standardized experimental designs to improve comparability across studies. Future research should prioritize expanding chemical coverage to better reflect environmental exposure profiles, focusing on PPCPs that are frequently detected but remain largely untested in experimental studies. Studies should examine mixtures of PPCPs at environmentally realistic concentrations and incorporate multiple environmental stressors, such as altered temperature, reduced food availability, hypoxia, or modified flow regimes to reflect natural conditions. Use of under-represented taxa, and wild-caught organisms, rather than exclusively laboratory-cultured populations, would improve representation of natural variability. Further, studies should be conducted over longer time periods and explore life stage and sex-specific responses, as sensitivity to PPCPs can vary across developmental stages and between sexes. Finally, improving reporting standards remains essential. Transparent reporting of sample sizes, exposure durations, variance estimates and raw data availability would enhance reproducibility and enable stronger integration of fitness-based evidence into risk assessment and regulatory decision-making.

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Author contributions (CRediT)

Anita Tarandek: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation**,** visualization, writing – original draft preparation, writing – review & editing. **Sandra Hudina:** conceptualization, investigation, methodology, writing – review & editing. **Marina Veseli:** conceptualization, investigation, methodology, writing – review & editing. **Ivan Senta:** investigation, methodology, writing – review & editing. **Danijela Žanko:** formal analysis, software, writing – review & editing. **Antonia Smolić:** conceptualization, methodology, writing – review & editing. **Jelena Bujan:** conceptualization, methodology, writing – review & editing. **Ana Previšić:** conceptualization, methodology, writing – review & editing. **Antica Čulina:** conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, writing – review & editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data and code availability

The data and code needed to reproduce the analyses have been deposited at Zenodo repository under the DOI 10.5281/zenodo.18671409

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