Aligning Behavioural Ecotoxicology with Real-World Water Concentrations: Current Minimum Tested Levels for Pharmaceuticals Far Exceed Environmental Reality

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Abstract

Behavioural ecotoxicology has rapidly emerged as a key area of research, offering sensitive and ecologically meaningful endpoints for detecting sub-lethal effects of contaminants. Much of this work has focused on pharmaceutical pollutants, now widely recognised as contaminants of emerging concern in aquatic systems. Given the field's rapid growth and the availability of large-scale open-access datasets, we have synthesized across four global databases to evaluate the environmental relevance of tested concentrations—using behavioural ecotoxicology and pharmaceutical pollutants as a case study. We compare exposure data from more than 760 behavioural studies with over 10 million aquatic pharmaceutical occurrence records from global monitoring databases. On average, minimum tested concentrations were 43 times higher than median surface water levels and 10 times higher than median concentrations in treated wastewater. Over half of all tested compounds were never evaluated at concentrations below the highest end of wastewater detections (upper 95% credible interval). Additionally, there was only weak alignment between the pharmaceuticals most frequently tested and those most commonly detected in aquatic environments. These findings reveal a disconnect between experimental design and environmental exposure, potentially limiting the ecological and regulatory relevance of behavioural endpoints in pharmaceutical risk assessment.

Keywords (5-8)

evidence synthesis, sub-lethal toxicity, experimental design, contaminants of emerging concern, ecological risk assessment, environmental monitoring, aquatic toxicology, laboratory field comparison

Synopsis:

We found that pharmaceutical exposures used in behavioural tests often exceed environmentally relevant concentrations, limiting their utility for ecological risk assessment.

Introduction

Behavioural ecotoxicology has emerged as a rapidly expanding field, offering sensitive and ecologically meaningful endpoints for detecting contaminant effects on wildlife [1–3]. Behaviour is the product of sub-organismal molecular and physiological processes that ultimately determines functions essential for survival and reproduction—such as foraging, predator avoidance, and social interaction. Therefore, it is often said to serve as an early warning signal of potential population-level impacts [3–6]. Reflecting this relevance, research in behavioural ecotoxicology has more than tripled over the past two decades [7], with growing interest in integrating behavioural data into environmental risk assessments [8,9].

Much of this work has focused on the effects of pharmaceutical pollutants, which are now widely recognised as contaminants of emerging concern. Over 990 active compounds or their transformation products have been detected in aquatic environments globally [10]. These substances enter waterways via wastewater discharge, agriculture, and pharmaceutical manufacturing, and often persist due to continuous input and resistance to degradation [11]. Designed to act at low concentrations, many pharmaceuticals target conserved biological pathways—making even trace exposures a potential risk to non-target species [2,12,13].

Given the growing interest in behavioural endpoints, particularly regarding pharmaceutical pollutants, and their potential regulatory application, it is critical to assess whether laboratory exposures in this field include environmentally realistic conditions. Specifically, do the concentrations tested align with those observed in aquatic environments? Here, we integrated a global database of behavioural studies—EIPAAB (Evidence of the Impacts of Pharmaceuticals on Aquatic Animal Behaviour), spanning 48 years and 1,739 species–compound combinations [14]—with three major international monitoring datasets that track pharmaceutical occurrence and concentrations in aquatic systems [10,15,16]. Our aims were twofold: (1) to assess whether the concentrations tested in behavioural studies reflect those measured in surface waters and wastewater, and (2) to evaluate whether the pharmaceuticals most frequently studied in behavioural ecotoxicology align with those most commonly detected in the environment.

Materials and Methods

Databases

The databases used for this investigation were: (1) The Evidence of the Impacts of Pharmaceuticals on Aquatic Animal Behaviour (EIPAAB) database [14]; (2) The NORMAN

EMPODAT database for chemical occurrence (accessed on 18/03/2025; [16]); (3) The Umweltbundesamt (UBA, German Environment Agency) Pharmaceuticals in the Environment database (PHARMS-UBA; accessed on 19/12/2024; [10]), and (4) Wilkinson et al. (2022) Pharmaceutical pollution of the world's rivers database [15]. For a numerical summary of the data included from each database, see Table 1.

The EIPAAB database was developed by Martin et al. (2025) [14] through a systematic review of 5,988 articles using a 'PECO' framework: studies involving aquatic organisms (P) exposed to pharmaceuticals (E), with behavioural outcomes (O) and a control group (C). The search spanned Web of Science, Scopus, and additional sources (e.g., reference lists, social media calls). The final database includes 901 articles published between 1974 and 2022, covering 1,739 species–compound combinations and 426 unique pharmaceutical compounds. For this study, we used metadata on compound names, CAS numbers, minimum exposure concentrations, publication year, and article motivation (e.g., environmental, medical, or basic research).

The NORMAN EMPODAT Chemical Occurrence Database [16] is maintained by the NORMAN Network, an independent consortium of over 80 organisations focused on emerging substances across Europe. Established in 2009. the database contains geo-referenced monitoring and biomonitoring data across water, sediment, biota, soil, sludge, and air, with an emphasis on substances not yet included in routine monitoring programs. As of the latest update, it includes over 96 million data entries covering 4,567 substances from 39 European countries. Data are submitted via a standardised Data Collection Template (DCT) available through the NORMAN website. For this study, we extracted metadata on compound names, CAS numbers, measured concentrations, concentration units, year, environmental matrix, and reporting organisation.

The PHARMS-UBA database, maintained by the German Environment Agency (UBA), was compiled through three systematic literature reviews focused on measured environmental concentrations of pharmaceuticals [17–19]. The initial review [17] covered data from 1987 to 2013 using multiple search strategies across peer-reviewed and grey literature, as well as European Commission databases. The subsequent reviews [18,19] extended the dataset through 2020. Together, these efforts screened over 12,000 articles and compiled 276,895 entries covering 992 pharmaceutical compounds (Version: pharms-uba_v3_2021_0). For this study, we used metadata on compound names, CAS numbers, measured concentrations, concentration units (µg/L), statistical descriptions (aggregate or individual value), and the environmental matrix in which the substance was detected.

The Wilkinson et al. database was produced through a standardised global sampling campaign of pharmaceutical pollution in rivers, spanning 1,052 locations across 104 countries and targeting 258 active pharmaceutical ingredients [15]. The resulting dataset, published as "Database of pharmaceutical concentrations at all the sampling locations monitored in this project" (Dataset S4), provides consistent occurrence data across regions. For this study, we extracted metadata on compound names and measured concentrations.

Database filtering and tidying

To ensure comparability across datasets, all concentration data were filtered to include only values reported in mass per volume of water (e.g., µg/L) for relevant surface water and wastewater samples. For the NORMAN EMPODAT database, we retained entries from eight surface water and four wastewater matrix categories (see Supplementary File 1). As influent and effluent could not be distinguished, both were included. We also restricted entries to compounds listed in the NORMAN Pharmaceuticals Suspect List (PHARMA SusDat), comprising 9,626 compounds and 13,324 unique CAS numbers. For the PHARMS-UBA database, we included six surface water and four effluent categories, covering samples subject to varying levels of treatment (e.g., primary, secondary). Only concentrations reported in mass per volume and as single values or aggregate central tendencies (e.g., mean or median) were retained; minimum and maximum summaries were excluded. Aggregated values made up just 0.33% of the final dataset, and aggregated values represented unique data (i.e. they were not an aggregate of single values already in the database). No filtering was required for the Wilkinson et al. dataset, as all entries represented pharmaceuticals measured in surface water and were consistently reported in µg/L. For the EIPAAB database, we retained only studies with an environmental motivation (as classified in Martin et al., 2025) and exposure concentrations reported in mass per volume units.

To compare the pharmaceuticals used in the behavioural test database (EIPAAB) to those detected in the environment, we combined all environmental occurrence data across the three databases (*n* = 10,010,937; see Table 1 for a database breakdown) and created a compound-level summary (*n* = 1650 compounds). This summary included:

- *Total occurrence* (*i.e. total rows*)
- *Number of samples (which differs from total occurrences because some values were summary values based on aggregated data from multiple samples)*
- *Number of positive detections* (*i.e. above limit of quantification*, n*ot including aggregated values*)
- *Median measured concentration*

- *The upper and lower 95% credible intervals (95% CrIs) of measured concentrations using empirical quantiles*
- *Percentage of positive detections (for compounds with >10 single sample values)*
- *Relative rank occurrence (1–1650)*
- *Relative rank detection frequency (i.e. rank of number of positive detections divided by total occurrence; 1–1424)*

Estimates of median concentration and 95% credible intervals (CrIs) were calculated separately for surface water and wastewater matrices, using only positive detections (i.e., values above zero or above detection limits). This approach was taken for two reasons: (1) we assume that researchers designing exposure studies are simulating contamination scenarios at impacted sites, rather than aiming to replicate a theoretical global average; and (2) excluding non-detections provides a more conservative basis for comparing tested concentrations in behavioural studies with those observed in the environment. When sample size was not reported for aggregate values, we assumed a value two —resulting in likely underestimates of total sample size. Only PHARMS-UBA provided central tendency values; among these, 4,023 entries lacked sample size metadata (<0.05% of all data), making our estimates of sample count very close to actual values. To reduce the influence of extreme outliers on compound-level comparisons, we used the upper bound of the 95% CrI as a more conservative estimate of the maximum concentration rather than the actual maximum observed concentration.

Table 1. Number of pharmaceutical compounds and data entries included from each of the four databases used in this study (EIPAAB, NORMAN, PHARMS-UBA, and Wilkinson). In EIPAAB, each entry represents a distinct pharmaceutical exposure assay (a single article may contain multiple assays across compounds or species). In the environmental databases, each entry corresponds to a single measurement of a compound in a water sample. PHARMS-UBA includes some aggregate entries (e.g., mean or median values), though these account for only 0.33% of the total.

Source	Number of compounds	Data
EIPAAB	184	767
NORMAN*	1,379	9,382,388
PHARMS-UBA	911	564,417
Wilkinson	61	64,132
Total	1,760	10,011,704

***** The NORMAN database was filtered to remove data from the German Environment Agency (UBA), and restricted to 2014-2022, as the PHARMS-UBA also included data from NORMAN prior to 2014; thus, this number is not the true total number of pharmaceutical samples present in the whole NORMAN database.

Analysis

All analyses were conducted in R (v4.2.3) using RStudio (Build 463) [20]. To evaluate whether pharmaceutical concentrations tested in behavioural ecotoxicology studies reflect those found in the environment, we fitted Bayesian linear regression models (via the *brm* function, *brms* package; [21]). Models predicted log-transformed minimum tested concentrations from the EIPAAB database as a function of log-transformed median surface water or wastewater concentrations, with relative publication year (years since 1992) included as a covariate. Both models assumed a Gaussian likelihood.

To assess alignment between the most frequently studied pharmaceuticals in behavioural ecotoxicology and those most commonly detected in the environment, we compared the frequency of behavioural exposure assays per compound with two environmental detection metrics: (1) the total number of positive detections and (2) the percentage of positive detections (i.e., detections relative to total samples). The total number reflects overall monitoring frequency, while the percentage accounts for sampling effort, together providing a more comprehensive view of environmental occurrence. These comparisons were analysed using Bayesian Negative Binomial Regression, appropriate for overdispersed count data.

All models were run with four MCMC chains using default weakly informative priors, each with 8,000 iterations and a 1,000-iteration warm-up. Convergence was confirmed via trace plots and R-hat diagnostics (R-hat = 1.00). Results are presented as posterior means with 95% credible intervals (CrIs), and inference was based on whether CrIs excluded zero.

Results

We compared 767 behavioural exposure assays from the EIPAAB database with 10,009,385 environmental water samples, comprising 9,727,633 surface water and 281,752 wastewater measurements from the NORMAN, PHARMS-UBA, and Wilkinson datasets. Of the 184 pharmaceuticals tested in behavioural studies, 167 (90.8%) had corresponding environmental occurrence data.

Minimum tested concentrations in behavioural studies were not strongly predicted by median surface water concentrations (Bayesian linear regression: $\beta = 0.135$, 95% CrI: –0.123 to 0.393; Fig. 1a). In contrast, there was a positive relationship with median wastewater concentrations ($\beta = 0.665$, 95% CrI: 0.505 to 0.823; Fig. 1b), where a 1% increase in environmental concentration corresponded to an average 0.67% increase in tested concentration, after controlling for publication year. In both models, tested concentrations

declined significantly over time. For surface water and wastewater models, tested concentrations in the behavioural ecotoxicology literature decreased by an average of 10.4% (β = –0.110, 95% CrI: –0.173 to –0.046) and 12.2% (β = –0.130, 95% CrI: –0.189 to –0.070) per year, , respectively (Fig. S2 and S4).

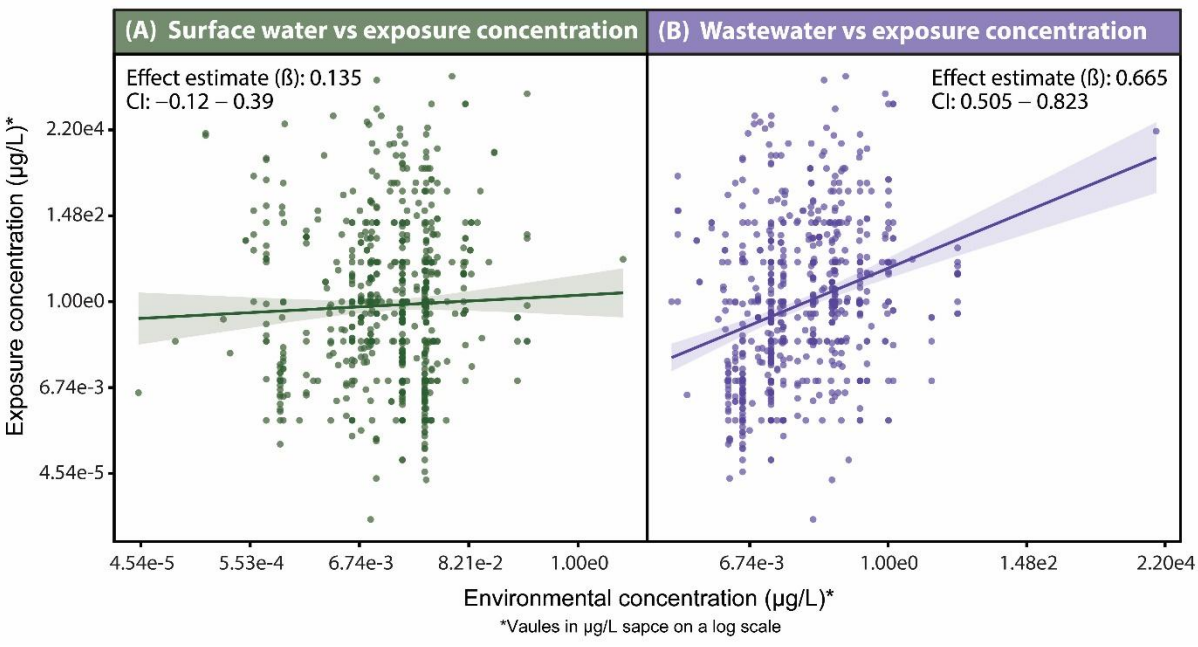

Figure 1. Relationship between environmental concentrations and tested concentrations in behavioural studies. **(A)** Median surface water concentrations vs. minimum tested concentrations in behavioural ecotoxicology; **(B)** median wastewater concentrations vs. minimum tested concentrations in behavioural ecotoxicology. All concentrations are reported in micrograms per litre (µg/L) and plotted on a log scale for interpretability. Lines represent Bayesian log–log linear regression estimates.

Across 706 compounds with both behavioural and surface water data, only 19% of behavioural studies used concentrations below the median environmental level, and 38% fell below the upper 95% credible interval (CrI; Table S2). For wastewater (714 matched cases), just 23.4% of behavioural studies used concentrations below the median, and 53.1% were below the upper 95% CrI. On average, concentrations used in behavioural studies were 43 times higher than median surface water levels (Fig. 2) and 10 times higher than median wastewater levels (Fig. S5). Overall, 50.4% of compounds (70 of 139) were never tested at concentrations below the high end of surface water levels, and 44.6% (66 of 148) were never tested below the high end of typical wastewater levels (defined as the upper 95% CrI).

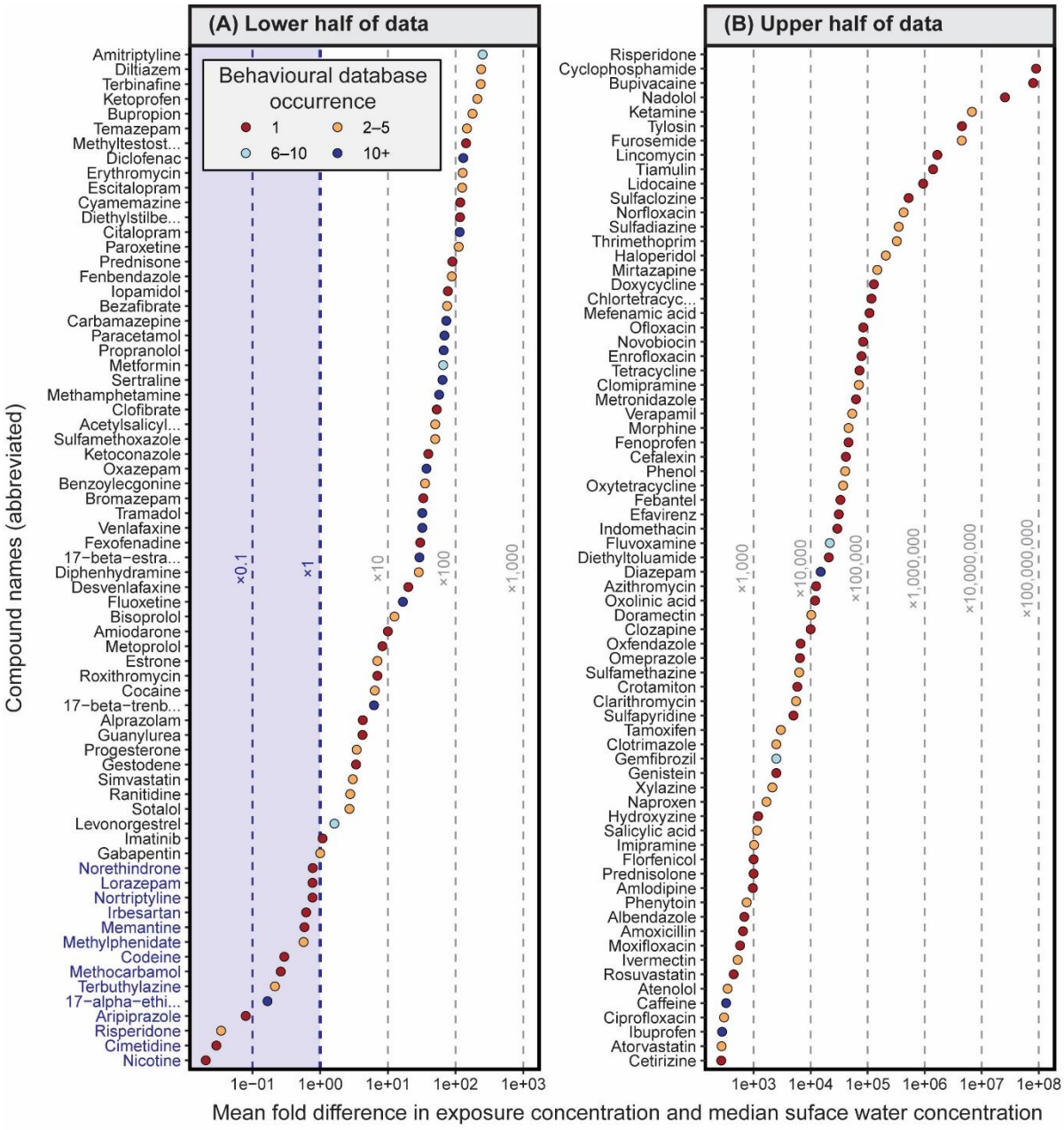

Figure 2. Fold difference between tested concentrations and median surface water concentrations for 139 pharmaceutical compounds. **(A)** Compounds in the lower half of fold differences; **(B)** compounds in the upper half. Blue shading in (A) highlights compounds with mean exposure concentrations in behavioural ecotoxicology studies equal to or below environmental levels (i.e. fold difference ≤ 1). Point colour indicates compound frequency in the behavioural database.

There was a weak positive relationship between the number of behavioural exposure assays per compound (EIPAAB) and the total number of environmental detections (i.e., samples above detection limits) across the environmental databases (Bayesian Negative Binomial

Regression: $\beta = 1.11 \times 10^{-4}$, 95% CrI: 4.24×10^{-5} to 1.90×10^{-4}; Fig. 3a). Each additional environmental detection increased the expected number of behavioural assays by just 0.01% (Fig. S10). A similarly small positive effect was observed for the percentage of environmental samples testing positive ($\beta = 0.011$, 95% CrI: 0.001 to 0.022), where each 1% increase in detection frequency corresponded to a 1.15% increase in EIPAAB assay count (Fig. S11). These results are further discussed in Supplementary File 1.

Discussion

With pharmaceutical pollution as a case study, we evaluated whether the concentrations and compounds tested in behavioural ecotoxicology align with those most commonly found in aquatic environments. By integrating over 10 million global environmental concentration records with 767 behavioural exposure assays, we reveal a substantial disconnect between tested concentrations and environmental reality, with the minimum tested concentrations in behavioural studies being, on average, 43 times higher than median surface water concentrations and 10 times higher than median wastewater concentrations. Over half of all compounds were never tested at concentrations below the upper 95% credible interval (i.e., likely maximum value) for their concentrations in wastewater.

We propose that the misalignment between tested and observed concentrations may, in part, be a result of temporal shifts in the availability of relevant environmental concentration data and the precision with which we can measure these types of compounds. Improvements in analytical chemistry have lowered detection limits and enabled broader contaminant screening capabilities [22], while inclusion of select pharmaceuticals on regulatory monitoring lists, such as the EU Watch List (starting in 2015 with the Commission Implementing Decision (EU) 2015/495) and NORMAN Network Suspect & Monitoring Lists (starting 2007, with formal use by the European Commission form 2015), has also increased monitoring efforts—resulting in a clear picture of which pharmaceuticals are present in surface waters, and at what concentrations. This is generally supported by annual trends observed in the PHARMS-UBA database—the database for which we have the best temporal distribution—for both total sampling effort (Figure S10) and the cumulative number of pharmaceuticals reported (Figure S11). Thus, we acknowledge that older behavioural studies may have been designed with limited reference points for environmental relevance. Indeed, we found that tested concentrations have been reducing by approximately 10% annually, reflecting a broad movement towards more environmentally realistic exposures.

With this said, when controlling for study year, we detected a positive association between the minimum test concentrations in behavioural studies and median observed wastewater concentrations. However, there was no strong support for an association between test concentrations and surface water concentrations. This may reflect the desire of researchers to replicate the more extreme scenarios of environmental pollution—such as effluent-dominated systems—as a basis for study design, either by using direct effluent concentrations or selecting more extreme concentrations from surface water reports as their minimum dose.

To our knowledge, our study is the first to perform a cross-database quantitative comparison of tested to field-observed concentration on this scale. We are aware of only a few other attempts to compare tested concentrations with environmental observation concentrations in ecotoxicology, but for those that do exist, our findings seem to align [23,24]. For instance, Wolf and Segner (2023) [23] reviewed 50 ecotoxicology studies spanning various chemicals (e.g. pesticides, heavy metals, pharmaceuticals) and showed that the majority of toxicologically tested concentrations far exceeded those found in nature, with little justification for their selection. Similarly, Mills et al. (2023) [24] reported that rodent toxicology studies on microplastics used doses hundreds of thousands of times higher than those found in terrestrial soils. Although studies like these are few, the patterns suggest a potentially widespread trend across ecotoxicology: a tendency to prioritise proof-of-concept effects over environmentally realistic scenarios.

Failing to incorporate environmentally realistic doses is particularly pressing for studies assessing sublethal endpoints, such as behaviour, which can be highly sensitive to very low concentrations of contaminants [3,6]. Unlike traditional apical endpoints (e.g. survival or growth), behavioural traits often respond to subtle (neuro)physiological or hormonal disruptions that can occur well below concentrations typically associated with overt toxicity [4]. In such cases, omitting low, environmentally relevant doses may obscure real-world risks. Furthermore, many pharmaceuticals—including endocrine disruptors, anxiolytics, and antidepressants—exhibit non-monotonic dose–response relationships, where the effect size does not consistently increase with concentration [25,26]. In such scenarios, key biological effects may only emerge at low or intermediate doses, while higher doses may produce diminished or qualitatively different effects. Failure to include environmentally realistic concentrations in the experimental design may therefore miss ecologically relevant responses or lead to misleading conclusions about a compound’s potency or mode of action.

More broadly, the absence of low-dose testing hinders the field’s ability to inform ecologically meaningful thresholds, complicates the derivation of risk-based benchmarks, and

limits the use of behavioural data in regulatory contexts, where environmental realism is a growing expectation. In summary, we recognise that it is still important to include doses that exceed typical environmental doses to identify thresholds for effects used in chemical risk assessment (e.g. predicted no effect concentrations [PNEC], effective concentrations [EC]), to reveal potential dose-response relationships, and to include procedural treatments like positive controls. With that said, we advocate for future studies assessing the effects of pharmaceuticals on animal behaviour—and ecotoxicological studies more broadly—to leverage the large quantity of environmental concentration data now available and include a median environmental concentration within the tested dosage range.

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Data and code availability

All R scripts used for data cleaning, filtering, and analysis are available on the corresponding author's GitHub repository: https://github.com/JakeMartinResearch/field-vs-lab-doses. A rendered HTML version of the full analysis workflow is accessible at: https://jakemartinresearch.github.io/field-vs-lab-doses/. All datasets used in this study are openly available on the Open Science Framework (OSF) under the DOI: 10.17605/OSF.IO/H6CDE.

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