



Research article

Are non-steroidal anti-inflammatory drugs exhibiting higher chronic ecological risks? Exploring water quality criteria for ibuprofen in China



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ABSTRACT

The non-steroidal anti-inflammatory drug (NSAID) ibuprofen (IBU), one of the most consumed drugs in the world, is frequently detected in freshwater and seawater. Low doses of IBU are also toxic to aquatic organisms, including endocrine disrupting toxicity, neurotoxicity, reproductive and developmental toxicity, but limited research on water quality criteria (WQC) for IBU hinders its ecological risk assessment. This study aimed to derive freshwater and seawater WQC for IBU in China through the species sensitivity distribution (SSD) method. In addition, a four-level tiered approach was used to assess the ecological risk of aquatic environments. The results showed that the freshwater short-term water quality criteria (SWQC) and long-term water quality criteria (LWQC) for IBU were 1.32 mg/L and 5.33 µg/L, respectively, while the seawater SWQC and LWQC were 6.57 mg/L and 6.33 µg/L, respectively. The risk assessment results indicated that only China's freshwater may face chronic risk, with 12.9 % of water bodies at moderate chronic risk. For global aquatic environment, the assessment concluded that chronic ecological risk of IBU exists in global freshwater and seawater, with more than 20 % of water bodies at moderate to high chronic risk. Additionally, joint probability distribution analysis (JPDA) method warned of potential acute ecological risks in the global marine environment. These findings highlight that NSAIDs may remain a serious concern for aquatic environment in both China and worldwide, requiring urgent attention.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a type of anti-inflammatory drugs without steroid structure providing anti-inflammatory, analgesic, and antipyretic functions, which are one of the most frequently used pharmaceuticals worldwide (Sheikhi et al., 2025). Ibuprofen (IBU), a typical NSAIDs, is safe and effective in clinical applications. IBU not only has significant advantages in antipyretic and analgesic, but also has few adverse side effects and is easy to tolerate, so it is widely used worldwide, with an annual production of more than 15,000 tons (Hu et al., 2025). Currently, China has the largest production of IBU, with a consumption of 2827 tons in 2017, which has been increasing annually (Yan et al., 2021). In particular, IBU is consumed in large quantities during epidemic outbreaks (Yu et al., 2025). For instance, during the COVID-19 pandemic, the average consumption of IBU reached 8070.7 mg/day per 1000 inhabitants, 84 times higher than pre-pandemic levels (Yu et al., 2025; Yan et al., 2021).

IBU plays an important role in the prevention and treatment of human and animal diseases, but their production, use and disposal also

result in significant releases into the aquatic environment (Ma et al., 2024; Adomat and Grischek, 2024; Spataro et al., 2025; Guo et al., 2023). Environmental surveys and monitoring have revealed that IBU concentration in Humber estuary of UK is 6.3 µg/L (Letsinger et al., 2019). A drug research in the Argentina's Uco valley has shown the widespread presence of IBU in freshwater samples, with concentrations up to 1.1 µg/L (Iturburu et al., 2024). However, numerous studies indicated that pharmaceutical residues ranging from ng/L to µg/L may cause adverse effects on aquatic ecosystems (Yu et al., 2025; Barros et al., 2024; Ma et al., 2024; Yang et al., 2024a, 2024b). They pose ecotoxicological risks to aquatic organisms, including neural toxicity (Ma et al., 2024; Islam et al., 2023), reproductive toxicity (Ma et al., 2024; Xie et al., 2022; Islam et al., 2023), endocrine disruption (Godoi et al., 2024; Beitzeder et al., 2025), inhibition of growth and development (Ma et al., 2024; Kropidlowska and Caban, 2023), and causing oxidative damage to organisms (Wang et al., 2020; Sibya et al., 2024; Ma et al., 2024; Martymuk et al., 2022; Zhang et al., 2021; Menicagli et al., 2024). In addition, long-term effects of IBU can lead to slowed heart rate and abnormal morphology in aquatic organisms, and even

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histopathological changes in the gills and kidneys of fish (Li et al., 2016). The danger of IBU to aquatic organisms is significant, highlighting the need to establish WQC for both freshwater and marine environments to safeguard aquatic ecosystems.

Water quality criteria (WQC) define the maximum allowable concentration of a pollutant or hazardous factor in aquatic environments that poses no harm to human health or aquatic ecosystems (MEE of China, 2022a; MEE of China, 2022b). Short-term water quality criteria (SWQC) and long-term water quality criteria (LWQC) are numerical thresholds that reflect safe pollutant concentrations for aquatic organisms under short-term and long-term exposure, respectively. These criteria are widely adopted across different countries (Liu et al., 2024). The studies of WQC on IBU are limited, particularly for seawater, due to the significant lack of toxicity data for marine organisms. And various researchers had employed different methodologies to derive WQC for IBU. In the early stages, researchers such as de Garcia et al. (2014) and Zhu et al. (2013) applied the assessment factor (AF) method to derive freshwater WQC for IBU, yielding LWQC of 13.9 µg/L and 1.65 µg/L, respectively. By 2018, as biotoxicity data of IBU became more comprehensive, researchers (Yang et al., 2024a; Huang et al., 2018) adopted the species sensitivity distribution (SSD) approach to derive freshwater WQC for IBU. However, they still needed to convert acute toxicity values and incorporate nontraditional toxicity data, resulting in LWQC ranging from 0.02 to 13.9 µg/L. In short, research on seawater WQC for IBU remains limited, and freshwater WQC require further refinement of relevant biotoxicity data to establish locally applicable WQC.

Ecological risk assessment (ERA) is a scientific tool essential for balancing economic development and environmental protection (Xu et al., 2024). The risk quotient (HQ) method, the most fundamental approach in ERA, assesses risk at a sampling point by comparing pollutant concentrations to WQC (Lu et al., 2023). However, this single-point estimation method cannot quantify the degree or magnitude of ecological risk (Liu et al., 2024). Therefore, margin of safety at 10 % (MOS₁₀) and the exceedance probability function (EPF), probabilistic methods that construct SSD curves of environmental concentrations for pollutants to quantitatively describe the overall ecological risk of the study area, were applied in this study (Liu et al., 2023, 2024; Luo et al., 2023). Additionally, the more advanced joint probability distribution analysis (JPDA) method was employed to predict the probability of exceeding effect thresholds (Li et al., 2025). By integrating biotoxicity data and environmental exposure concentrations (EEC), JPDA constructs a joint probability distribution function, offering a more precise and comprehensive ecological risk assessment (Li et al., 2025). It can also estimate the probability of risk for different percentage of species affected. Thus, a four-level tiered approach consisting of HQ, MOS₁₀, EPF and JPDA methods provides a robust framework for accurately assessing ecological risks in aquatic environments.

The objectives of this study were: i) to supplement acute and chronic toxicity data by determining half-maximal effective concentration (EC₅₀) or median lethal concentration (LC₅₀) values of six marine organisms and lowest observed effect concentration (LOEC) or no observed effect concentration (NOEC) values of three marine organisms exposed to IBU; ii) to establish freshwater and seawater WQC for IBU in China by fitting SSD curves using four statistical models; iii) to assess the ecological risk of IBU in China's freshwater and seawater by a four-level tiered approach; iv) to compile environmental concentrations of IBU in global freshwater and seawater to predict its ecological risk worldwide.

2. Materials and methods

2.1. Screening of toxicity data

This study aimed to derive WQC values for IBU to protect native freshwater and marine organisms in China. According to Technical Guidelines (MEE of China, 2022a; MEE of China, 2022b), toxicity data of

organisms such as chordates, annelids, arthropods, algae, etc. are required to derive WQC, of which freshwater organisms must meet the requirement of “three phyla and eight families” and marine organisms must meet “five families and eight species”. Toxicity endpoints include death, growth, reproduction, respiration rate, photosynthesis, etc., except for cellular, physiological and biochemical responses, and gene expression. Toxicity data of IBU to aquatic organisms were mainly obtained from ECOTOX database (<http://cfpub.epa.gov/ecotox>), Science Direct online (<https://www.sciencedirect.com/>

), and other open source databases. Eventually, LC₅₀, EC₅₀, EC₁₀ (10 % effect concentration), EC₂₀ (20 % effect concentration), NOEC, LOEC, and MATC (maximum acceptable toxicant concentration) values can be obtained, with LC₅₀ and EC₅₀ acquired from acute toxicity experiments and the others from chronic toxicity experiments (Table S1). Acute toxicity data were not prioritized, and chronic toxicity data were prioritized as EC₁₀ > EC₂₀ > MATC > NOEC > LOEC (MEE of China, 2022a; MEE of China, 2022b). Due to inadequate toxicity data of marine organisms for IBU, additional toxicity experiments must be conducted to complete the derivation of the seawater WQC.

2.2. Test chemicals and organisms

IBU (C₁₃H₁₈O₂, analytical grade, purity ≥95 %) was purchased from Beijing Solaibao Technology Company, China. The compound was dissolved in dimethyl sulfideoxide (DMSO, purchased from Shanghai Acmec Biochemical Co., Ltd.) to make a stock solution. According to *Technical guideline for deriving water quality criteria for marine organisms (on trial)* (MEE of China, 2022b), six marine organisms (*Oryzias melastigma*, *Mytilus galloprovincialis*, *Neomysis awatschensis*, *Artemia salina*, *Skeletonema costatum*, and *Chlorella salina*) were selected for acute toxicity experiments, while three marine organisms (*N. awatschensis*, *S. costatum*, and *C. curisetus*) were used for chronic toxicity experiments, providing toxicity data that met the requirements for WQC derivation using the SSD method. Detailed information of test organisms was provided in Table S2.

2.3. Toxicity tests of Chinese resident marine organisms for IBU

All marine biotoxicity experiments followed the conditions outlined in “Chemicals - Fish Acute Toxicity Test” standard (GB/T 27,861-2011), “Chemicals - Medaka Early Life Stage Toxicity Test” standard (GBT 29764-2013), “Mysid Acute Toxicity Test” standard (USEPA OCSPP 850.1035), “Chemicals - Algae Growth Inhibition Test” standard (GB/T 21,805-2008), “Ecological Effects Test Guidelines OCSPP 850.1055: Bivalve Acute Toxicity Test (Embryo - Larval)”, and “Guidelines on environmental safety assessment for chemical pesticides-Part 21: Macrocrustacean toxicity test”. For example, according to GB/T 27,861-2011, acute toxicity experiments on *O. melastigma* were conducted in 250 mL experimental water, with five concentration groups established based on geometric progression relationship, and each containing 10 fish. The exposure duration was 96 h, with light provided for more than 12 h per day, and no food was administered during the experiment. Table S2 listed the contaminant concentrations in toxicity tests, along with temperature, salinity, and pH during the experiments. Experimental parameters were measured regularly throughout the day to ensure proper water quality, and exposure solutions were changed daily to maintain constant contaminant concentrations. Finally, the acute toxicity endpoints for algae, microcrustacean, and other organisms (shrimp, fish, and molluscs) were determined as 24 h EC₅₀, 48 h LC₅₀, and 96 h LC₅₀, respectively, while the chronic toxicity endpoints for algae and shrimp were 96 h N(L)OEC and 21 d NOEC, respectively. Toxicity data were linearly fitted using Origin 2021 software, with EC₅₀ and LC₅₀ values derived via the Unit Probability method, and L(N)OEC values calculated using SPSS software (ver. 23.0, SPSS Inc., Chicago IL, USA). Additionally, chemical analytical methods for detecting IBU concentrations in exposed solution, as outlined by Guo et al. (2023), were applied in this

study. And the difference between measured and nominal concentrations of IBU analyzed via the LC-MS/MS (Liquid Chromatography-Tandem Mass Spectrometry) instrument was less than 20 %, so nominal concentrations were used to estimate toxicity values in this study.

2.4. The derivation of WQC for IBU

SSD method is widely used in many countries to protect aquatic organisms because it can evaluate the ecotoxicological effects of chemicals (Yang et al., 2024a; Liu et al., 2024; Khan et al., 2025; Blanco-Moreno et al., 2024). And SSD means that the sensitivity of different species to a stressor follows a cumulative probability distribution, with variations in sensitivity across species being describable by probability or empirical distribution functions in a structurally complex ecosystem (Vighi et al., 2006). Different countries use various software for analyzing SSD curve, such as EcoToX (ETX) in the Netherlands (de Groot-Heijtel et al., 2024), Burrlioz in Australia and New Zealand (Golding et al., 2023; Mitchell et al., 2024), and Fortran-based method in the USA (Tan et al., 2022). In this study, SSD curves were generated using EEC-SSD software (National Ecological Environment Criteria Calculation Software - Species Sensitivity Distribution Method), downloaded from Ministry of Ministry of Ecology and Environment of the People's Republic of China website (<https://mee.gov.cn/ywgfz/fgbz/hjjzgl/mxrj>), which is recommended in Technical Guidelines (MEE of China, 2022a; MEE of China, 2022b). Four models (normal, log-normal, logistic and log-logistic models) are available in the EEC-SSD software to fit the biotoxicity data, with the optimal model selected based on p and RMSE (Root-Mean-Square Error) values ($p > 0.05$ and RMSE closest to 0) for deriving WQC. After analyzing SSD curves with the optimal model, HC₅ values (hazardous concentration affecting 5 % of the species) are obtained, and further WQC are obtained based on the ratio of HC₅ to AF, where AF value (2 or 3) is related to the number of available toxicity data (MEE of China, 2022a; MEE of China, 2022b). The number of samples used for each model fit is shown in Fig. 5, which did not exceed 15, so the WQC values were assessed using a factor of 3.

2.5. Ecological risk assessment

The ecological risk of IBU in both freshwater and seawater was analyzed in more detail using a four-level tiered approach (Liu et al., 2024; Sun et al., 2017), outlined as follows:

The first tier of this approach is the HQ method. The HQ value of target chemical is the ratio of MEC to WQC (i.e., HQ = MEC/WQC), where MEC is the measured environmental concentration (Yang et al., 2024a). The ecological risk level for IBU in aquatic environments was categorized as low, medium, or high risk based on HQ values corresponding to $0.01 \leq \text{HQ} < 0.1$, $0.1 \leq \text{HQ} < 1$, and $\text{HQ} \geq 1$, respectively.

The second tier of this approach is the MOS₁₀ method. The MOS₁₀ method involves fitting biotoxicity data and EEC data for targeted pollutant using four models (normal, log-normal, logistic and log-logistic models), plotting the corresponding SSD curves, and determining the MOS₁₀ values by calculating the ratio of the 10th percentile biotoxicity threshold (SSD₁₀) to the 90th percentile EEC level (ECD₉₀) (Liu et al., 2023, 2024). Generally, a MOS₁₀ value below 1 suggests significant ecological risk, while a value above 1 indicates low risk.

The third tier of this approach is the EPF method. The probability that the concentration of target chemical in aquatic environment exceeds WQC values is calculated by EPF method, thus reflecting the level of risk posed to aquatic ecosystem (Liu et al., 2024). This method utilizes SSD curves derived from EEC and applies a logarithmic transformation to WQC values. The exceeding probability value $> 5\%$ indicates a significant ecological risk in the overall aquatic environment, while the value $\leq 5\%$ suggests no significant ecological risk.

The fourth tier of this approach is the JPDA method. JPDA method, an advanced ecological risk assessment method that predicts ecological

risk qualitatively and quantitatively by constructing relationships between EEC and biotoxicity data of target chemical (Xu et al., 2024). The Joint probability curve (JPC), constructed from EEC and biotoxicity data, estimates the risk probability for different percentages of species affected. The enclosed area between the JPC and the axes represents the overall risk probability (ORP), which reflects the overall risk in the study area. Risk levels are classified as negligible (<0.1 %), potential (0.1 % ~ 1 %), and clear ($\geq 1.0\%$).

3. Results and discussions

3.1. Acute and chronic toxicity of IBU for marine organisms

The results of acute and chronic toxicity experiments of IBU on marine organisms are presented in Fig. 1. In the acute toxicity tests, *S. costatum* and *C. salina* were tested for 24 h following guideline requirements (MEE of China, 2022b). The 48 h toxicity test was conducted for *A. salina*, as the mortality rate of *A. salina* in the experiment exceeded 20 % after more than 48 h. And other marine organisms were subjected to 96 h acute toxicity tests. From Fig. 1, the inhibition and mortality rates of marine organisms increased significantly with both exposure concentration and time, reaching their maximum values at the longest exposure time and highest concentration. The minimum concentrations of IBU affecting *S. costatum*, *C. salina*, *A. salina*, *M. galloprovincialis*, *O. melastigma*, *N. awatschensis* were 100 mg/L (24 h), 100 mg/L (24 h), 100 mg/L (48 h), 87 mg/L (96 h), 165 mg/L (48 h), 25.6 mg/L (72 h), respectively, with inhibition and mortality rates ranging from 0 % to 20 %, while the maximum concentrations caused inhibition and mortality rates ranging from 70 % to 100 %. Notably, 25.6 mg/L of IBU caused significant mortality (72 and 96 h) in mysid, which was the more sensitive organism among the six marine organisms in this experiment. In contrast, 165 mg/L of IBU caused significant mortality (48, 72 and 96 h) in marine fish, which was the more tolerant organism in the experiment. In the chronic toxicity tests, *S. costatum* and *C. salina* underwent the 96 h toxicity tests, while *N. awatschensis* were exposed to 21 d, as per the guideline (MEE of China, 2022b). Algal growth was significantly inhibited and shrimp mortality was significantly higher in the same concentration group with increasing exposure time, further suggesting that IBU may have a more chronic toxic effect on marine organisms. Therefore, more attention should be given to the chronic toxicity data (Liu et al., 2024). The 96 h-NOEC for *S. costatum* was 23 mg/L, the 96 h-LOEC for *C. salina* was 20 mg/L, and the 21 d-LOEC for *N. awatschensis* was 0.26 mg/L. Thus, the order of chronic toxicity of IBU to these three marine organisms was *N. awatschensis* > *C. salina* > *S. costatum*.

In this study, probability unit method was used to derive the values of acute toxicity indicators for marine organisms (Liu et al., 2023), with the linear fit results shown in Fig. 2. Furthermore, the 24 h-EC₅₀, 24 h-EC₅₀, 48 h-LC₅₀, 96 h-LC₅₀, 96 h-LC₅₀, 96 h-LC₅₀ for *S. costatum*, *C. salina*, *A. salina*, *M. galloprovincialis*, *O. melastigma*, and *N. awatschensis* were deduced from the linear fitting equations, yielding results of 230 mg/L, 194 mg/L, 134 mg/L, 112 mg/L, 185 mg/L, and 40 mg/L, respectively. The data revealed that the acute toxicity rank of IBU to the six marine organisms was *N. awatschensis* > *M. galloprovincialis* > *A. salina* > *O. melastigma* > *C. salina* > *S. costatum*. Among them, *N. awatschensis* was the most sensitive to IBU, while *S. costatum* exhibited the least sensitivity, with a 5.8-fold difference in LC₅₀ (EC₅₀).

The ecotoxicological hazards of IBU were assessed following "The Guidelines for The Hazard Evaluation of New Chemical Substances" (MEP of China, 2004), revealing that IBU posed a medium hazard to *N. awatschensis*, and a low hazard to other tested organisms. Algae had the lowest toxic effect by IBU, with both EC₅₀ values exceeding 190 mg/L. IBU, a nonsteroidal anti-inflammatory drug, primarily inhibits cyclooxygenase (COX) activity and reduces prostaglandin synthesis (Campos et al., 2023). However, algae lack the complex physiological systems and specific drug targets present in other organisms, making it difficult for IBU to exert toxicity through this pathway (Yang et al.,

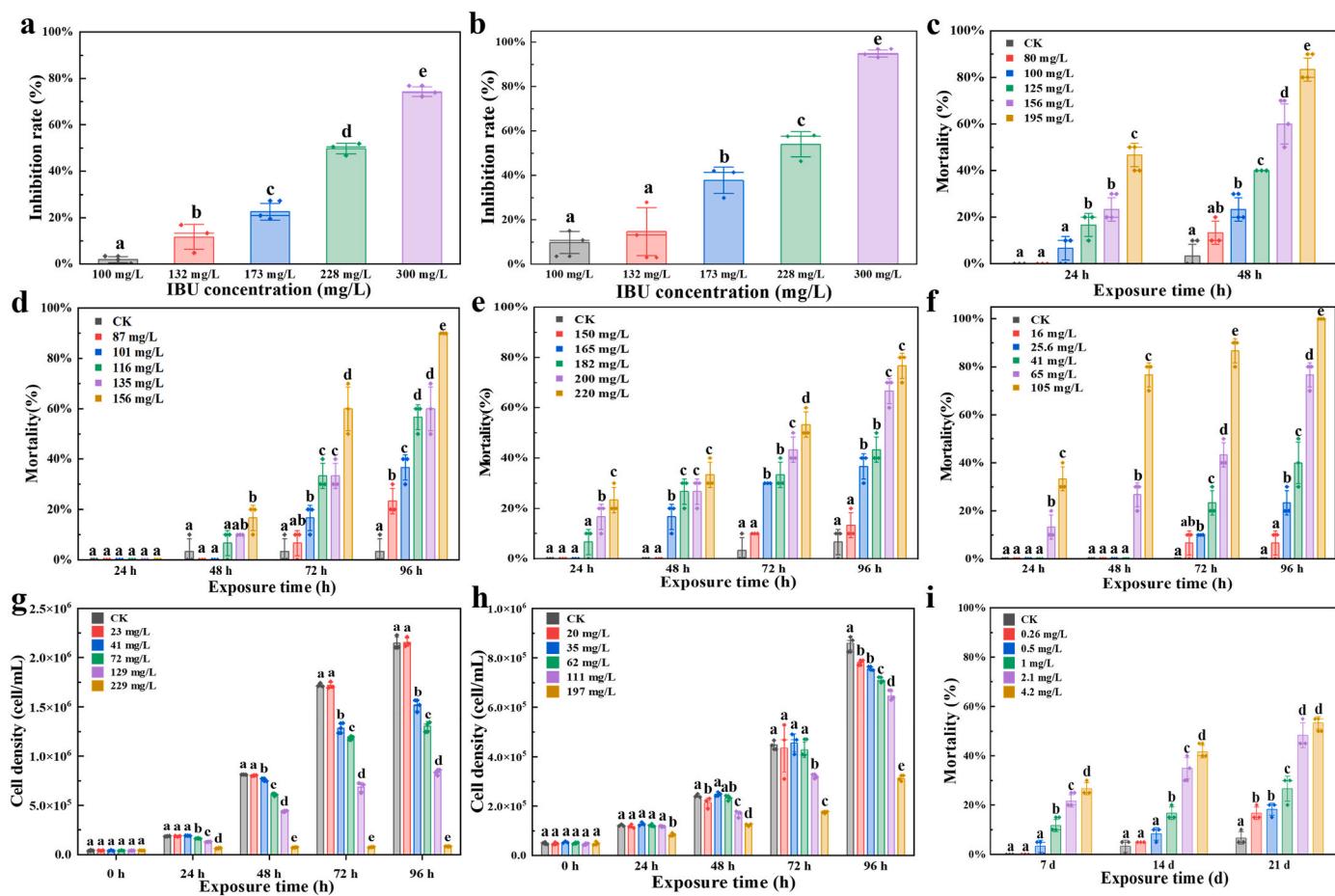


Fig. 1. Experimental results on acute and chronic toxicity of IBU in marine organisms, for which *S. costatum* (a), *C. salina* (b), *A. salina* (c), *M. galloprovincialis* (d), *O. melastigma* (e), *N. awatschensis* (f) were conduct acute toxicity experiments and *S. costatum* (g), *C. salina* (h), *N. awatschensis* (i) were conduct chronic toxicity experiments. The bar indicates the mean \pm standard deviation, and different letters denote statistical significance ($p < 0.05$, $n = 3$).

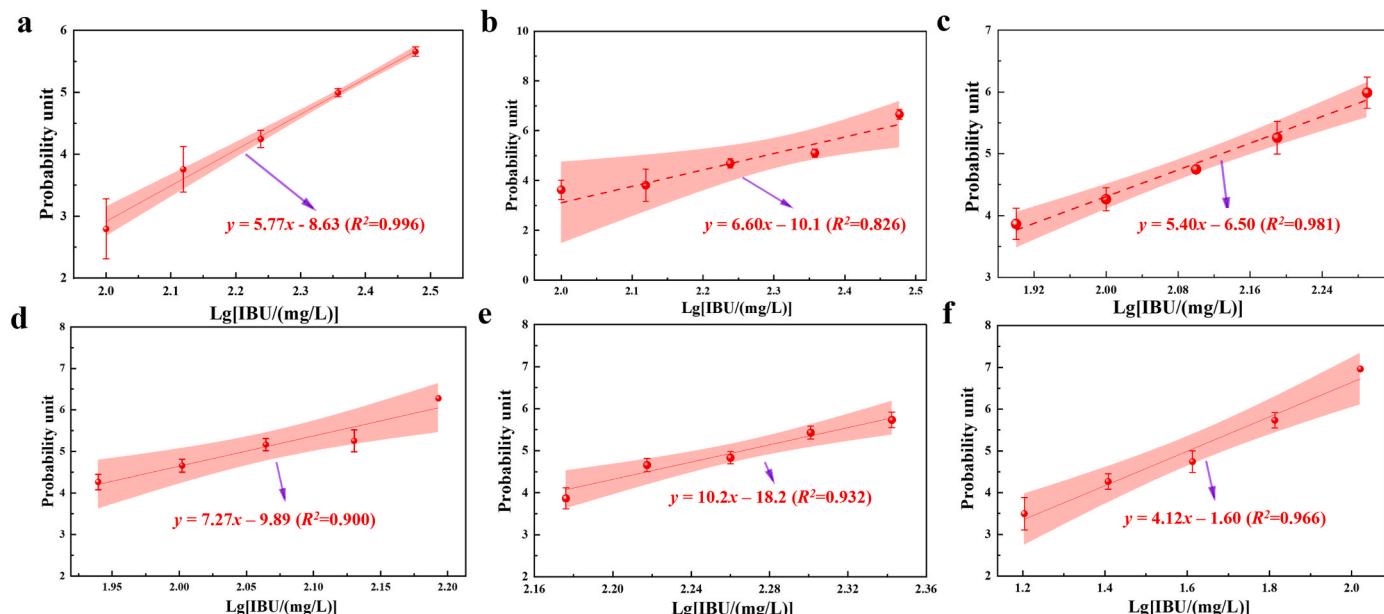


Fig. 2. Linear fitting of toxicity data for marine organisms. *S. costatum* (a), *C. salina* (b), *A. salina* (c), *M. galloprovincialis* (d), *O. melastigma* (e), *N. awatschensis* (f). The pink area represents the 95 % confidence interval of the linear regression equation. The bar indicates the mean \pm standard deviation ($n = 3$).

2024b; Wang et al., 2020). Additionally, the unique cell wall structure of algae, particularly in diatoms with thicker and denser walls made of biogenic silica, can limit IBU entry into the cell, thereby mitigating its toxic effects (Yang et al., 2024b). This explains why the EC₅₀ value for *S. costatum* is higher than that for *C. salina*. The highest toxic effect of IBU in this study was observed in *N. awatschensis*, likely due to their open circulatory system, which allows toxic substances to easily enter their bodies (Do et al., 2025). IBU had lower toxic effects on *O. melastigma*, possibly because it primarily produces neurotoxic and enterotoxic effects (Islam et al., 2023). For instance, Islam et al. (2023) found that zebrafish larvae exposed to 5 µg/L of IBU showed a significant decrease in swimming distance, with a 50 % reduction at 500 µg/L compared to controls. Therefore, it is necessary to consider other more sensitive indicators of toxicity to evaluate the ecotoxicological hazards of IBU in the future.

3.2. Species sensitivity to IBU

A total of 53 toxicity data were collected in this study, including 26 E(L)C₅₀ values and 27 E(L)C₁₀/N(L)OEC/MATC values, focusing on the biotoxicity of IBU in freshwater and seawater (Table S1). The dominant species in the E(L)C₅₀ dataset were mainly fish (26.9 %) and crustaceans (26.9 %), followed by algae (19.2 %), while the dominant species in the chronic toxicity dataset were mainly crustaceans (37 %), followed by fish (25.9 %) and algae (22.2 %). As shown in Fig. 3, there are 16 acute and 18 chronic toxicity data for freshwater and 10 acute and 9 chronic toxicity data for seawater, respectively, of which 9 toxicity data for marine organism were obtained through our supplementary experiments, indicating that seawater toxicity data are more difficult to obtain (Liu et al., 2023). In general, the acute and chronic toxicity data for both freshwater and seawater meet the “three phyla and eight families” and “five families and eight species” criteria outlined in the Guidelines (MEE of China, 2022a; MEE of China, 2022b), allowing for direct derivation of IBU's WQC using the SSD method.

Based on the geometric mean E(L)C₅₀ values of IBU across eight taxonomic groups (Fig. 4(a)), plants were the most sensitive to IBU (EC₅₀ = 4 mg/L), followed by invertebrates (LC₅₀ = 22.4 mg/L), algae (EC₅₀ = 23.2 mg/L), crustaceans (LC₅₀ = 24.9 mg/L), and fish (LC₅₀ = 59.7 mg/L) among freshwater organisms. Worms exhibited the least sensitivity to IBU (Fig. 4(a)). Among marine organisms, invertebrates were the most sensitive to IBU (EC₅₀ = 0.003 mg/L), followed by crustaceans (LC₅₀ = 64.3 mg/L), while molluscs (EC₅₀ = 112 mg/L), algae (EC₅₀ = 149 mg/L), and fish (LC₅₀ = 185 mg/L) were less sensitive. E(L)C₁₀, N(L)OEC, and MATC are indicators of chronic toxicity, reflecting the sensitivity of organisms to a compound under long-term exposure (Fig. 4(b)). Under chronic cycles of IBU exposure, the geometric mean N(L)OEC et al. ranged from 0.1 to 20.4 mg/L and was significantly lower than the E(L)C₅₀. Among them, fish (0.39 mg/L) and plants (0.5 mg/L) in freshwater were the most sensitive to IBU, while molluscs (0.1 mg/L), fish (0.32 mg/L) and crustaceans (0.51 mg/L) in seawater were the most sensitive.

Compared to other pollutants (e.g. polychlorinated biphenyls, polybrominated diphenyl ethers, polycyclic aromatic hydrocarbons and their derivatives), IBU has lower toxic effects on aquatic organisms (Yang et al., 2024a). However, the toxic effects of IBU on freshwater organisms are significantly greater than those of other NSAIDs, with toxicity levels approximately 20–200 times higher (Yang et al., 2024a). Surprisingly, plants in freshwater ecosystems were the most sensitive to IBU, mainly inhibiting the growth of *Lemna minor* (Pomati et al., 2004). This may be due to the hormones balance in plant was disrupted by IBU, which affected its normal growth, and the induction of ROS in plant by IBU may be another reason (Menicagli et al., 2024; Zhang et al., 2021). In marine ecosystems, larval morphogenesis in *Paracentrotus lividus* was most affected by IBU, as IBU interferes with normal physiological processes during embryo-larval development, impacting key aspects such as cell division, differentiation, and organ formation (Aguirre-Martínez et al., 2015). Crustaceans were commonly used as test organisms due to their high sensitivity, but they are not particularly sensitive to drugs, as

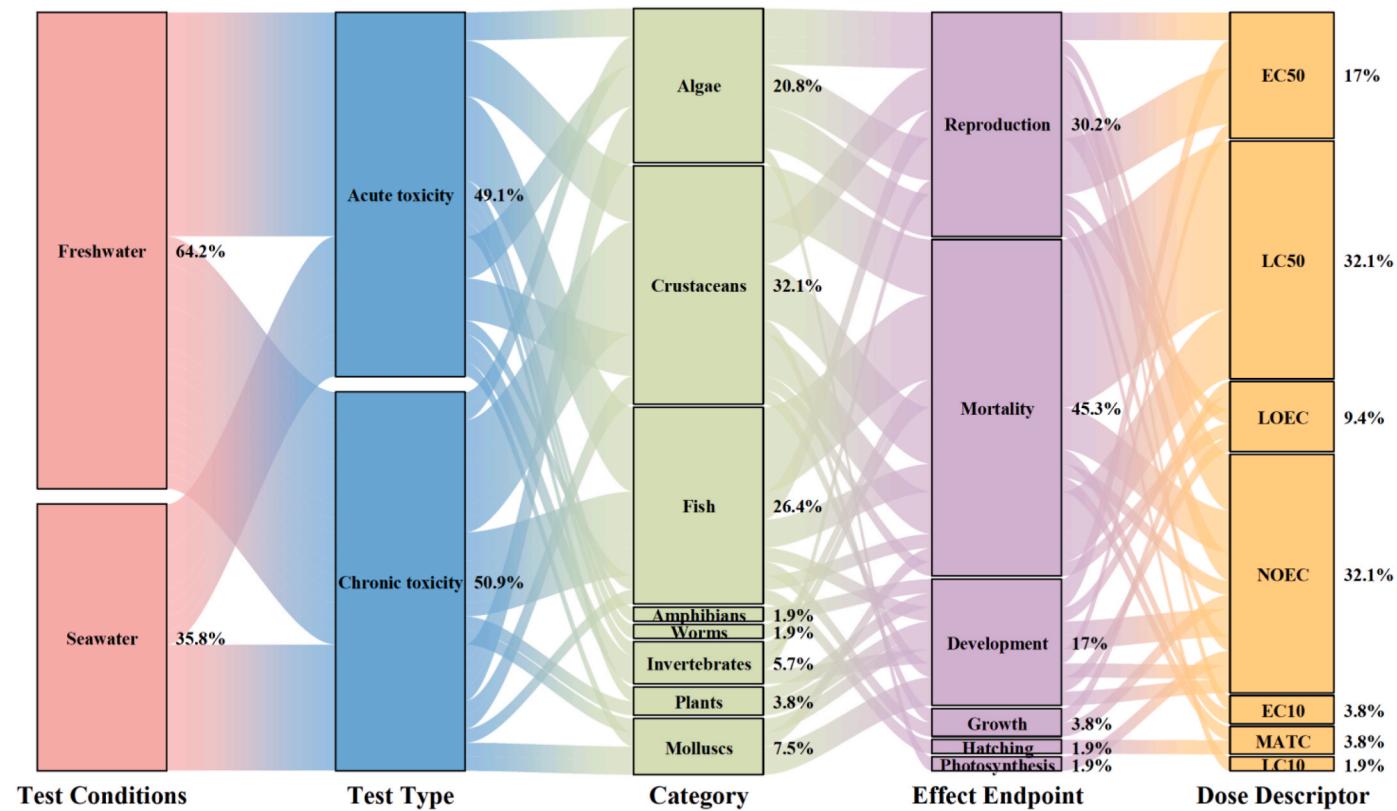


Fig. 3. Profile of the test conditions, test type, category, effect endpoint, and dose descriptor in the full data set (including 53 data).

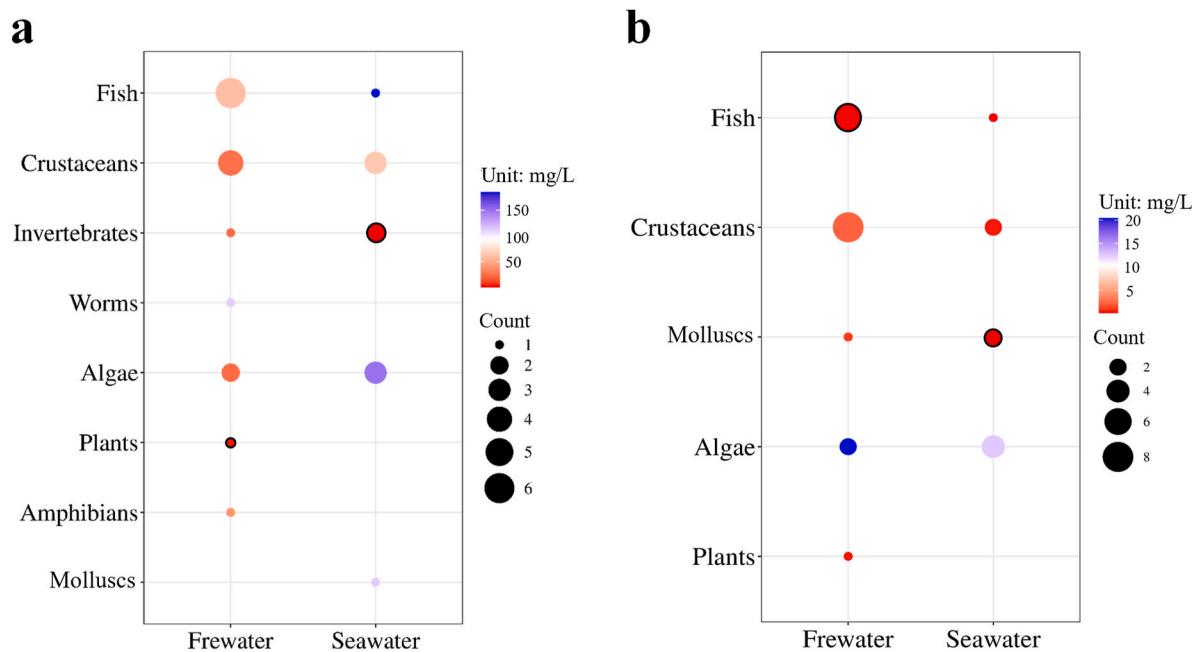


Fig. 4. (a) E(L)C₅₀ and (b) E(L)C₁₀/N(L)OEC/MATC values of freshwater and seawater organisms for IBU are presented by bubble plots. The color represents the toxicity value, the redder the color means the lower toxicity value, the bluer the color means the higher toxicity value. The count represents the number of biological toxicity data, shown by the size of the circle. Bubbles with black circles represent the most sensitive biological group to IBU.

noted in previous studies (Yang et al., 2024a; Kovalakova et al., 2020). IBU was primarily used for human disease treatment, and prolonged exposure in crustaceans may promote the development of their resistance (Liu et al., 2020).

3.3. Derivation of HC₅ and WQC for IBU

In this study, the acute and chronic toxicity data of IBU in freshwater and seawater were fitted using normal, log-normal, logistic and log-logistic models, respectively, and the results of the fits (including *p*, RMSE, HC₅, HC₁₀ and HC₂₅ values) were presented in Fig. 5. Acute toxicity data of seawater could not be fitted by log-logistic model, and chronic toxicity data of freshwater and seawater could not be fitted by log-normal and log-logistic models. The fitting results revealed a range of 0.002–19.7 mg/L for acute HC₅ and 0.008–0.1 mg/L for chronic HC₅. According to the guidelines (MEE of China, 2022a; MEE of China, 2022b), the best model for fitting the freshwater acute toxicity data was

a logistic model, yielding an HC₅ value of 3.97 mg/L. Similarly, the best model for fitting the freshwater chronic toxicity data was also a logistic model, with an HC₅ value of 0.016 mg/L. For seawater, the acute toxicity data were best fitted by a log-normal model, with an HC₅ value of 19.7 mg/L, while the chronic toxicity data were best fitted by a logistic model, yielding an HC₅ value of 0.019 mg/L. A comparison of the acute HC₅ values for freshwater and seawater indicated that freshwater organisms were more sensitive to IBU. Consequently, the freshwater SWQC and LWQC for IBU were 1.32 mg/L and 5.33 µg/L, respectively, while the seawater SWQC and LWQC were 6.57 mg/L and 6.33 µg/L, respectively.

WQC for IBU have not been extensively studied, and the methodologies used vary significantly (Lu et al., 2023). The WQC values of IBU derived by different researchers were listed in Table S3. Yang et al. (2024a) derived freshwater WQC for IBU based on all toxicity data, including mortality, growth, behavior, reproduction, cellular, physiological and biochemical responses, which were significantly lower than

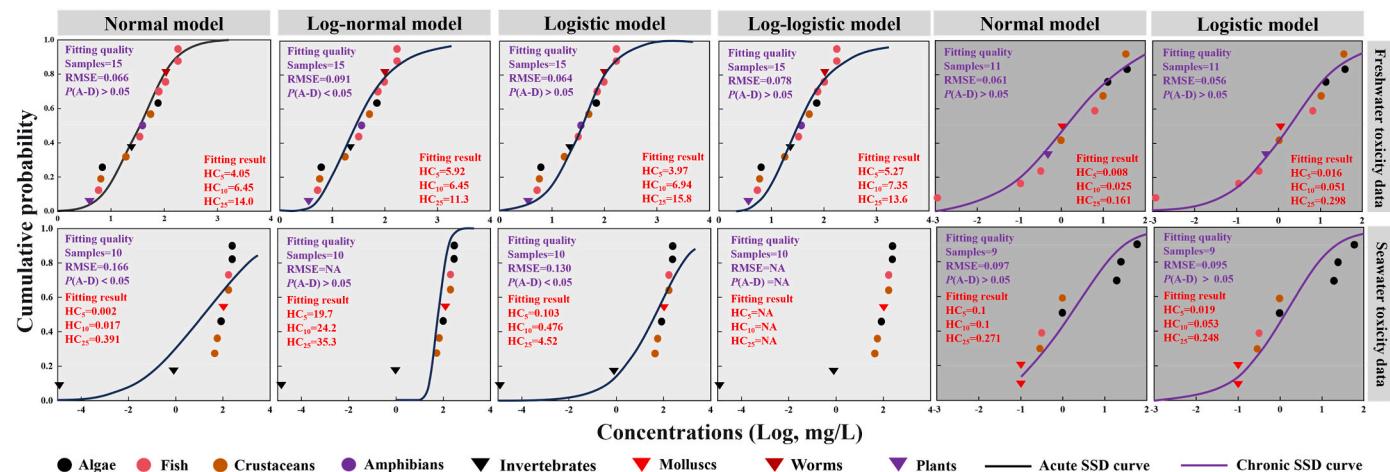


Fig. 5. Species sensitivity distribution curves for biotoxicity data of freshwater and marine organisms. Acute toxicity data of freshwater organisms could not be fitted by log-logistic model, and both chronic toxicity data could not be fitted by log-normal and log-logistic models.

the values derived in this study. Compared to traditional endpoints, low doses of contaminants can induce changes in non-traditional endpoints, such as antioxidant enzyme activity. For instance, while 300 µg/L IBU significantly reduced the cell density of *Phaeodactylum tricornutum*, a much lower dose of IBU (0.8 µg/L) can lead to a significant alteration in its SOD enzyme activity (Silva et al., 2020). Similar conclusions were reached in the experiments of Menicagli et al. (2024) and Ma et al. (2024). Furthermore, Huang et al. (2018) used various toxicity endpoints to derive PNEC (Predicted No-Effect Concentration) for IBU, showing that $PNEC_{mortality} > PNEC_{growth} > PNEC_{reproduction} > PNEC_{biochemical-cellular}$. This finding all suggests that non-traditional toxicity data generally yield lower values than traditional data, and incorporating these data results in a reduction of the WQC value. According to Technical Guidelines of China (MEE of China, 2022a; MEE of China, 2022b), traditional toxicity datasets were required for WQC derivation to enhance their reliability. Moreover, different methods for deriving WQC, including SSD, TPR (toxicity percentile rank), and AF methods, will also yield varying benchmark values. The AF method derives WQC by dividing the lowest biotoxicity value by an assessment factor, creating a strong dependency on extreme toxicity values and potentially leading to “overprotective” or “underprotective” outcomes (Liu et al., 2024; Xu et al., 2024). Toxicity data from four genera with cumulative probabilities close to 0.05 are utilized in the TPR method to derive WQC, but the method may be biased by anomalous toxicity data (Liu et al., 2023). In contrast, the SSD method is widely used to enhance the accuracy of WQC values by incorporating all toxicity data and selecting the optimal model (Liu et al., 2024). De Garcia et al. (2014) and Zhu et al. (2013) reported a significant difference in the PNEC of IBU compared to our study, which may be due to the AF method they employed.

Factors such as salinity, pH, and temperature can cause significant differences in the sensitivity of seawater and freshwater organisms to the

same pollutant (Xu et al., 2024), as demonstrated by the studies mentioned above. However, toxicity data for marine organisms are rarely used to derive seawater WQC for IBU using traditional toxicity datasets, as they are more difficult to obtain (Beiras and Schönemann, 2020). This study supplements marine biotoxicity data and applies the SSD method to fit traditional toxicity data to derive accurate freshwater and seawater WQC, offering comprehensive protection thresholds for aquatic ecosystems.

3.4. Ecological risk assessment for IBU in China

The mean and maximum concentrations of IBU in freshwater and seawater for China were shown in Table S4. The concentrations ranged from ND (not detected) to 1,417 ng/L in freshwater and from 1.49 to 414 ng/L in seawater, with mean values of 189 ng/L and 87 ng/L, respectively. The concentrations of IBU were notably higher in freshwater, indicating a potentially greater risk in freshwater environments.

In order to more accurately assess the ecological risk of IBU in freshwater and seawater for China, the four-level approach of ERA was used in this study. And the maximum concentrations of IBU were used as representative values for risk assessment to fully capture the extent of water pollution. No significant acute ecological risk was observed in either freshwater or marine environments, and the results of the chronic ecological risk assessment were presented in Fig. 6.

The HQ method, which is the most rudimentary ecological risk assessment method to assess the magnitude of ecological risk at each sampling site (Lu et al., 2023), was first used for the preliminary assessment in this study. The results were presented in Fig. 6(a). In China's freshwater environment, all acute HQ values were below 0.1, indicating no significant acute ecological risk. Chronic HQ values ranged from 0 to 0.27, with 12.9 % of water bodies classified as medium risk,

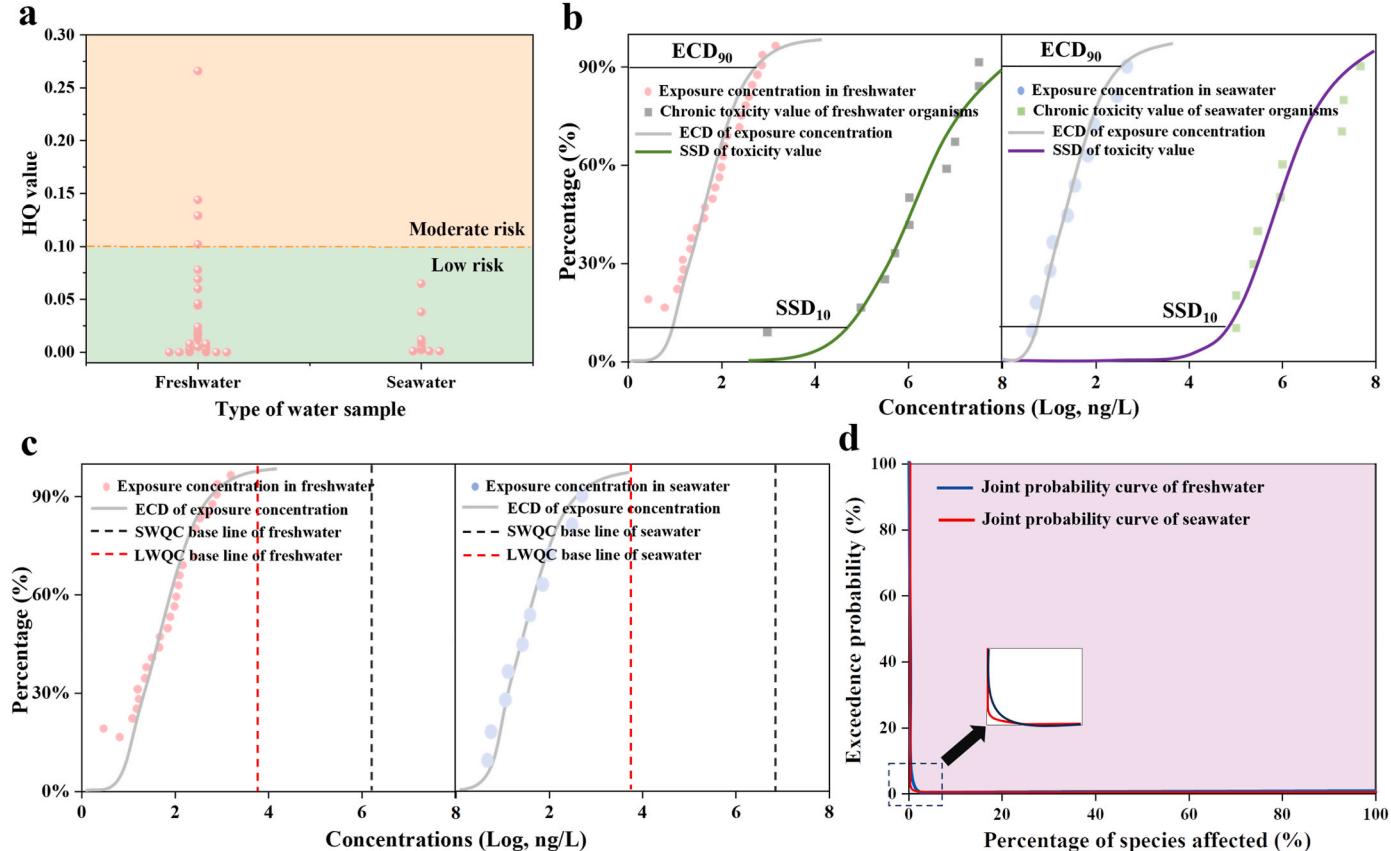


Fig. 6. The chronic ecological risk of IBU in China's freshwater and seawater assessed by a four-level tiered approach. HQ method (a), MOS₁₀ method (b), EPF method (c), and JPDA method (d).

while the rest showed no significant risk. Only Liede stream (Peng et al., 2008), Pearl river (Zhao et al., 2009), and Shijing river (Zhao et al., 2009) showed high concentrations of IBU related to nearby domestic sewage discharges, limited self-cleaning capacity, and seasonal variations in river, posing medium risk. This necessitates a review of pharmaceutical waste disposal and the treatment efficiency of nearby wastewater treatment plants (Zhao et al., 2009). In China's seawater environment, all acute and chronic HQ values were below 0.1, indicating no significant ecological risks. The HQ method, a basic single-point estimation approach (Liu et al., 2024; Lu et al., 2023), cannot provide an overall risk estimate or determine the risk probability for aquatic environment in China. Therefore, the probabilistic approaches were applied for intensive assessment.

The MOS₁₀ method quantified the overall ecological risk in aquatic environment by comparing biotoxicity data with EEC of IBU (Liu et al., 2023; Luo et al., 2023), and the results of the assessment were plotted in Fig. 6(b). The ECD₉₀ values from the SSD curves fitted to EEC were 553 ng/L for freshwater and 306 ng/L for seawater. The SSD₁₀ values from the SSD curves were 6.94 mg/L and 24.2 mg/L based on acute biotoxicity in freshwater and seawater, respectively, and 51 µg/L and 53 µg/L based on chronic biotoxicity. The results revealed that the acute and chronic MOS₁₀ values for both freshwater and seawater were greater than 1, indicating no significant ecological risk in aquatic environment of China. The EPF method can further evaluate the probability of exceeding a specified effect level for IBU in the aquatic environment by comparing the exposure concentration distribution (ECD) curves with the WQC values (Liu et al., 2024), and the results were shown in Fig. 6(c). The results indicated that the acute and chronic exceedance probability values for both freshwater and seawater in China exceed 97 %, indicating no significant risk. Finally, a more comprehensive risk assessment was conducted using JPDA method, an advanced ecological risk assessment method that predicts ecological risk qualitatively and quantitatively by constructing relationships between EEC and biotoxicity data of IBU (Liu et al., 2024; Xu et al., 2024). The

results were provided in Fig. 6(d). The chronic ORP values for China's freshwater and seawater were 0.32 % and 0.0095 %, respectively, indicating no significant ecological risk in seawater but a potential chronic risk in freshwater. While the MOS₁₀ and EPF methods proved no significant acute or chronic ecological risks in freshwater and seawater for China, the HQ and more advanced JPDA methods suggested a potential chronic risk in freshwater, warranting further investigation. Overall, the ecological risk of freshwater remains higher than that of seawater in China.

3.5. Ecological risk assessment of IBU in the global water environment

The ecological impact of NSAIDs in the global aquatic environment remains a concern (Li et al., 2025; Nassri et al., 2023; Lakshmi et al., 2024; Yang et al., 2024a). In this study, global data on the mean and maximum concentrations of IBU in freshwater and seawater were collected (Table S5) to estimate its ecological risk. The IBU concentrations of the world ranged from ND to 15,278 ng/L in freshwater and ND to 8,866 ng/L in seawater, with mean values of 743 ng/L and 755 ng/L, respectively. Notably, the mean concentration of IBU globally was 4–9 times higher than in China, and the maximum concentration was 21 times higher, suggesting a potentially greater ecological risk in other countries.

The ecological risk of IBU in the global aquatic environment was still assessed by the four-level approach of ERA in this study. Similarly, the maximum concentrations of IBU was used as the representative value for risk assessment, ensuring a comprehensive reflection of water pollution. Global acute ecological risk of IBU was not significant as assessed by HQ and MOS₁₀ methods, and this result was not included in Fig. 7. The results of HQ method indicated no significant acute ecological risk globally but revealed a significant chronic ecological risk. In global freshwater, 1.6 % of water bodies were at high chronic risk, while 27.9 % were at moderate chronic risk. In marine environments, 2.4 % of water bodies had high chronic risk, and 19.5 % had moderate chronic

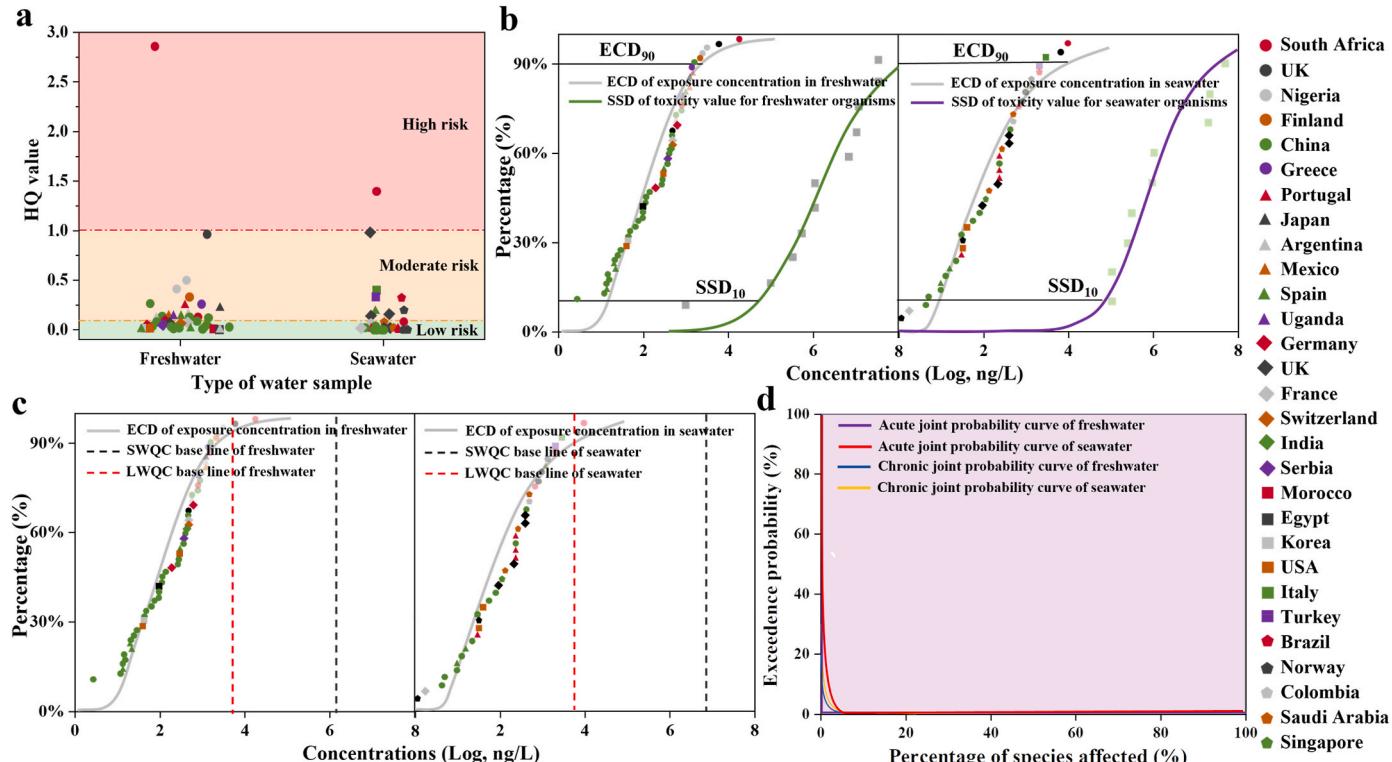


Fig. 7. The ecological risk of IBU in global freshwater and seawater assessed by a four-level tiered approach. HQ method (a), MOS₁₀ method (b), EPF method (c), and JPDA method (d). Various graphical symbols or colors representing EEC for different countries are displayed on the right side of the figure.

risk. Overall, more than 20 % of global water bodies were at moderate to high chronic risk, significantly exceeding the risk level in China, which warrants greater attention. The highest HQ values were observed in the Umgeni River and Blue Lagoon Beach in South Africa, both at high chronic risk (Ngubane et al., 2019). This may be due to the proximity of the sewage treatment plant outfall upstream of the Umgeni River to the sampling site, allowing pollutants to be transported downstream to Blue Lagoon Beach, resulting in elevated concentrations of IBU (Ngubane et al., 2019). To estimate the overall global ecological risk, the MOS₁₀ method was applied. From the SSD curves fitted to global EEC (Fig. 7(b)), ECD₉₀ values of 2.1 µg/L for freshwater and 5.9 µg/L for seawater were derived. Since both acute and chronic MOS₁₀ values were greater than 1, no significant ecological risk was indicated for global aquatic environment. However, the EPF method results indicated no significant acute ecological risk for global freshwater and seawater, while 6 % of freshwater bodies and 10 % of seawater bodies exhibited chronic ecological risk (Fig. 7(c)), contradicting the findings from ecological risk assessment in China. This suggests that both global freshwater and seawater probably suffers from more severe environmental issues for IBU, which is further supported by JPDA method calculations. The JPDA method, a more advanced ecological risk assessment approach, can accurately estimates the probability of organisms being threatened in global aquatic environment (Liu et al., 2024). As shown in Fig. 7(d), the acute and chronic ORP values for global freshwater are 0.0006 % and 0.64 %, respectively, and for global seawater, they are 0.35 % and 0.49 %, respectively. These results suggested possible ecological risk in all cases except for acute ecological risk in global freshwater, which was not significant. In brief, all HQ, EPF and JPDA methods concluded that chronic ecological risk of IBU exists in global freshwater and seawater, with more than 20 % of water bodies at moderate to high chronic risk according to HQ method. Additionally, the JPDA method indicated the potential for acute ecological risk in global seawater environments, warranting further attention.

The four-level approach of ERA can provide accurate predictions of ecological risk levels for pollutants in the world, but there are other uncertainties that influence the assessment in this study. First, the bio-toxicity data used in this study are from China, making it uncertain whether different ecosystems could influence these values to change WQC. Second, the data only consider inhibition and death, excluding indicators like neurological damage, tissue lesions, or behavioral abnormalities etc. that may reduce toxicity values (Yang et al., 2024a), especially for pharmaceuticals. Finally, limited and outdated EEC data of IBU may compromise the accuracy and timeliness of assessments, potentially delaying effective treatments. However, there are still many water bodies in China and around the world where pollutant concentrations have not been measured, so we need to collect more water samples in a timely manner to fill in the gaps of concentration values in the global aquatic environment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jenvman.2025.126724>.

Abbreviations

AF	assessment factor	LOEC	lowest observed effect concentration
COX	cyclooxygenase	LWQC	long-term water quality criteria
EC ₁₀	10 % effect concentration	MATC	maximum acceptable toxicant concentration
EC ₂₀	20 % effect concentration	MEC	measured environmental concentration
EC ₅₀	half-maximal effective concentration	MOS ₁₀	margin of safety at 10 %
ECD	exposure concentration distribution	ND	not detected
ECD ₉₀	90th percentile environmental concentration level	NOEC	no observed effect concentration
EEC	environmental exposure concentrations	NSAIDs	non-steroidal anti-inflammatory drugs
EPF	exceedance probability function	ORP	overall risk probability
ERA	ecological risk assessment	PNEC	predicted no-effect concentration

4. Conclusion

This study aims to establish WQC of IBU in freshwater and seawater for China and to conduct a comprehensive risk assessment for aquatic environment in China and globally. Analysis of supplemental and collected toxicity data revealed that plants and invertebrates were the most sensitive organisms to IBU in freshwater and marine environments, respectively. The SWQC and LWQC of IBU were derived using the SSD method, resulting in values of 1.32 mg/L and 5.33 µg/L for freshwater, and 6.57 mg/L and 6.33 µg/L for seawater. The four-level tiered ERA results indicated no significant risk for seawater in China but identified a potential chronic ecological risk for freshwater, with 12.9 % of water bodies at moderate chronic risk. At the global scale, only seawater exhibited potential acute ecological risk. And all HQ, EPF and JPDA methods concluded that chronic ecological risk of IBU exists in global freshwater and seawater, with more than 20 % of water bodies at moderate to high chronic risk according to HQ method. Overall, the impact of IBU on aquatic ecosystems in China and globally is severe, necessitating increased attention to NSAIDs like IBU.

This study refines the establishment of freshwater and seawater WQC, providing a scientific basis for exploring water quality standards for IBU in different water environments. The multilayered, in-depth ERA method of this study more accurately determines the ecological risk of IBU from China to global scale, revealing trends in pollutant risks worldwide. It provides valuable insights for refined and regionalized risk management of IBU, overcoming the limitations of traditional single-scale assessments.

CRediT authorship contribution statement

Shuai Liu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Yuxuan Wang:** Data curation. **Yuxuan Huang:** Data curation. **Yongyu Li:** Supervision. **Xinhong Wang:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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HQ	risk quotient	RMSE	root-mean-square error
IBU	ibuprofen	SSD	species sensitivity distribution
JPC	joint probability curve	SSD ₁₀	10th percentile biotoxicity threshold
JPDA	joint probability distribution analysis	SWQC	short-term water quality criteria
LC ₅₀	median lethal concentration	TPR	toxicity percentile rank
LC-MS/MS	liquid chromatography-tandem mass spectrometry	WQC	water quality criteria

Data availability

Data will be made available on request.

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