Ibuprofen as an Emerging Contaminant of Concern: Occurrence in Southeast Asia Water Environment

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Abstract. Ibuprofen is the third most salable pharmaceutical worldwide even being sold in the absence of prescription. This drug is not thoroughly metabolized and excreted into wastewater as an unchanged molecule and its metabolites. Conventional wastewater treatment plants are insufficient to remove ibuprofen, thus this substance ends up in the effluent of wastewater treatment systems and pollutes water bodies, soil, and other ecosystems. As an emerging contaminant, continuous discharge of ibuprofen has become a threat to the aquatic environment. However, studies of ibuprofen are predominantly concentrated in developed regions. The current status of ibuprofen in developing countries such as Southeast Asia region is unclear. This review aims to inform the current status of ibuprofen research in Southeast Asian countries, particularly focusing on the occurrence in the aquatic environment. This study would fill a considerable knowledge gap on ibuprofen in Southeast Asia and contribute to global knowledge development, including the need for future studies on issues unique to the region.

1 Introduction

The occurrence of micropollutants or emerging contaminants (ECs) in the surface and groundwater has developed into a global concern over the past few decades. ECs comprises of natural or synthetic compounds that infiltrate the environment as consequences of varied anthropogenic activities, manufacturing, farming, or health care facilities. Such activities further encourage the previously occuring problems of freshwater resources sustainability [1-2]. Pharmaceuticals and personal care products (PPCPs), agrochemicals, and other industrial chemicals, such as plasticizers, artificial sweeteners, food additives, etc., are among the broad range of these substances [3]. Although the concentrations of the ECs are remarkably low (ng/L to µg/L) in wastewater or water bodies, their persistence and long-term exposure lead to bio-accumulation in ecosystems and living organisms, increasing comprehension of their potential toxicity [4].

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The ECs are exceptionally persistent in the aqueous environment and the removal efficiency in conventional wastewater treatment plants (WWTPs) is low, ranging from 30 – 90% depends on wastewater characteristics and WWTPs processes applied [5]. The most generally used treatment system in secondary WWTPs is fundamentally designed for the elimination of organic matter and suspended solids to satisfy the minimum effluent standard [6]. Their complex structure and toxicity make them resistant to microbial activity, hence biological treatment methods have repeatedly exhibited their inadequacy to treat ECs. As the results, various ECs and their transformation products end up in the effluent of treatment systems [7]. Continuous discharge and prolonged exposure to these substances may be hazardous to aquatic environment, even at trace levels [8]. For these reasons, collecting of information on the environmental occurrence, source, and potential toxicity of ECs allows systematic evaluation of the environmental risk related with these chemicals.

One of pharmaceuticals frequently found in wastewater and has become a global concern is ibuprofen (2-(4-isobutylphenyl) propionic acid). This substance is a type of nonsteroidal anti-inflammatory drugs (NSAIDs) that is widely used as an analgesic, antipyretic, and anti-inflammatory agent [9]. It is the world’s third most favored, highly prescribed and most profitable over-the-counter medication, even being sold disregarding the prescription [10]. The global production rate of ibuprofen is roughly more than 20,000 tons per year [11]. However, since this drug can be taken over-the-counter or in combination with antibiotics, the amount ingested is overstated. This compound can enter ecosystems through various pathway, including human secretion following the medication use, improper disposal, or even wastewater from the pharmaceutical industry [12]. Continuous discharge of this chemical into the environment accounted for ibuprofen being one of the most frequently detected pharmaceutical in various water bodies.

The therapeutic dose of ibuprofen ranges from 600 to 1200 mg/day and nearly 15% of this value is excreted as unchanged molecules (conjugated with glucuronic acid and thiols) and its metabolites [13]. Meanwhile, the conjugate of this substance will be hydrolyzed in the environment [14]. Furthermore, during the chlorination process, ibuprofen in wastewater will change into intermediate molecules with more toxic properties [15]. Because of its physicochemical characteristics, this molecule is difficult for microbes to degrade in the environment, which might result in bioaccumulation and ecological damages. Therefore, it is necessary to remove ibuprofen from wastewater.

However, the study of ECs quantification including ibuprofen are mostly focused in developed regions, such as Europe and North America, and other developed country in Asia such as China and Japan [16-18]. This is greatly attributed to the enormous resources and financial investment demands required in investigation of ECs. Observing these pollutants in the environment requires the use of scientific and sensitive instrumentation in addition to relevant pretreatment methods. As such, much less is confirmed about emerging contaminant occurrences, i.e. ibuprofen, in developing region such as Southeast Asia.

This literature review aims to present the current status of ibuprofen research in Southeast Asia. The objectives of this study were to identify (i) the occurrence of ibuprofen in wastewater and water environment in Southeast Asian countries, (ii) the source and pathway of ibuprofen in water environment of Southeast Asian countries, and (iii) the potential risks of ibuprofen to the aquatic environment. This study would fill a significant knowledge gap on ibuprofen in Southeast Asia and contribute to global knowledge development, including prospective research topics needed that are definitive to Southeast Asian circumstances.

2 Method

A methodical research was conducted according to Oberg and Leopold [19] and Gaston et al. [20] by using the combination of keywords in the Scopus and Web of Science (Fig. 1).
The criteria for publications to be reviewed consist of: (1) the scope of the research is limited to the issue of emerging contaminants occurrence and quantification in Southeast Asia, particularly ibuprofen; (2) the time span or articles published in the past fifteen years, from 2008 up to November 2023; and (3) they were written in English. By limiting our focus to the past 15 years, the researchers were able to review recent findings on the occurrence of ibuprofen in Southeast Asian water environment.

The phrases "micropollutants" and "emerging contaminants," which are both the most commonly used terminology across the publications, were selected for this review during the preliminary screening. “Pharmaceuticals” was used as the broader categorical term and “ibuprofen” was used as the most comprehensive and relevant database of publications for this review. Management of the compilation of the appointed literature were conducted using EndNote online. Abstracts from more than 3000 publications were meticulously reviewed in the initial screening, and only 534 publications were chosen for the advanced review.

The 534 publications were further reviewed and sorted based on the topic of the journals. Data was compiled by transferring .ris format from EndNote into Ms. Excel spreadsheet, and VOSviewer™ software was used to visualized the inter-topic clustering. To organize and visualize the bibliometric networks between the chosen publications, VOSviewer™ software was utilized. The inclusion criteria for “Grade A” publications resulted from the visualization and used in this study were those that have quantified concentrations of emerging contaminants, particularly ibuprofen, in various environmental matrices, such as wastewater, surface water, groundwater, soil, and sediment. Pilot lab-scale studies, reviews, guidelines, monographs, and research with full text accessibility issues were among the exclusion criteria. Out of 534 publications, only 12 publications that can be categorized as “Grade A” publications. The concluding step was pulling information and synthesizing various things from the chosen literature. Data synthesis's primary goal was to assess different study findings about the prevalence of ibuprofen in Southeast Asian countries. The first section of this paper's framework reports on the prevalence of ibuprofen in various environmental matrices in Southeast Asian countries as reported by information from "Grade A" publications. This is followed by an evaluation of the source of ibuprofen and potential risks it may pose to aquatic environments.

**Scopus and Web of Science Key Search Terms**

<table>
<thead>
<tr>
<th>Step 1: Keyword Search</th>
<th>Step 2: Initial Screening</th>
<th>Step 3: Advanced Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micropollutants OR Emerging Contaminants AND “Country name”</td>
<td>No additional filter criteria</td>
<td>Accepted categories for “Grade A” publications:</td>
</tr>
<tr>
<td></td>
<td>All papers accepted for the next stage of review</td>
<td></td>
</tr>
<tr>
<td>Pharmaceuticals AND Occurrence AND “Country name”</td>
<td>534 publications</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen AND Occurrence AND “Country name”</td>
<td>Key terms desired for the next stage of review: “Wastewater”, “Environmental Monitoring”, “Emerging Contaminant”</td>
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</tr>
</tbody>
</table>

Fig. 1. Flowchart of the selection process for this literature review.
3 Results and Discussion

3.1 Occurrence of ibuprofen in Southeast Asian water environment

The distribution of accepted “Grade A” publications for each country in Southeast Asia resulted in this review is shown in Fig. 2. Vietnam and Indonesia had the most publications out of 11 countries in Southeast Asia that quantified ibuprofen in the environment. Meanwhile, no publications are reported from countries like Laos, Myanmar, Cambodia, Brunei, and East Timor.

![Fig. 2. Distribution of ibuprofen studies in Southeast Asian countries.](image)

Table 1. Ibuprofen occurrence in Southeast Asia water environment.

<table>
<thead>
<tr>
<th>Country</th>
<th>Concentration (ng/L)</th>
<th>Matrices</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>2,315 ± 17</td>
<td>Wastewater</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.0 – 22</td>
<td>Surface seawater</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>30 – 1,700</td>
<td>Surface seawater</td>
<td>[23]</td>
</tr>
<tr>
<td>Malaysia</td>
<td>7,400 – 15,100 (STP1)</td>
<td>Wastewater</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>2,400 – 8,300 (STP2)</td>
<td>Wastewater</td>
<td></td>
</tr>
<tr>
<td></td>
<td>344 ± 138</td>
<td>Wastewater</td>
<td>[25]</td>
</tr>
<tr>
<td>Singapore</td>
<td>&lt; MQL – 2,445</td>
<td>Wastewater</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>&lt; MQL – 111</td>
<td>Surface water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; MQL</td>
<td>Groundwater</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29,075 – 55,975</td>
<td>Wastewater</td>
<td>[27]</td>
</tr>
<tr>
<td>Philippines</td>
<td>max of 276 ± 15 to</td>
<td>Surface water</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>838 ± 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>385 – 1,260</td>
<td>Wastewater</td>
<td>[29]</td>
</tr>
<tr>
<td>Vietnam</td>
<td>210 – 1,500 (S1)</td>
<td>Wastewater</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>340 – 950 (S2)</td>
<td>Wastewater</td>
<td></td>
</tr>
<tr>
<td></td>
<td>350 – 1,850 (S3)</td>
<td>Wastewater</td>
<td></td>
</tr>
<tr>
<td></td>
<td>260 – 580 (S1)</td>
<td>Lake water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 – 1,100 (S2)</td>
<td>Lake water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210 – 950 (S3)</td>
<td>Lake water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>780 – 1,120 (WWTP A)</td>
<td>Wastewater</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>160 – 1,700 (WWTP B)</td>
<td>Wastewater</td>
<td></td>
</tr>
<tr>
<td></td>
<td>max of 39,100</td>
<td>Surface water</td>
<td>[32]</td>
</tr>
</tbody>
</table>
Ibuprofen have been detected in different matrices of Southeast Asia water environment at varied concentrations. The summary of ibuprofen occurrence in Southeast Asia reviewed in this study is presented in Table 1. The highest concentration of ibuprofen has been reported by Tran and Gin [27] at the maximum of 55,975 ng/L detected in raw influent of water reclamation plant in Singapore. The ibuprofen concentrations in South East Asian water environment were comparable to ibuprofen recorded in influent found in most of developing countries, such as Kenya (30,000 ng/L) [33] and South Africa (84,600 ng/L) [34].

Meanwhile, different concentrations were reported in another regions, i.e. Europe, North America and other developed Asian countries. Kodom et al. [35] reported ibuprofen with concentration of 13,100 ng/L in the influent of WWTPs in Finland. Ibuprofen was also detected in the concentration range of 381 – 1130 ng/L in Japan’s wastewater [36]. A relative significant concentration of ibuprofen (4374 ng/L) was also observed by Carmona et al. [37]. The occurrence of this compound in the influent of WWTPs is primarily influenced by consumption patterns in each country, population density, climatic conditions, water consumption, etc., hence, the significance of different exposure pathways also varies geographically.

Not only in wastewater, ibuprofen was also observed in water bodies, such as surface water and ground water, as well as soil, e.g. irrigation land and sludge in WWTPs. Ibuprofen was observed pollutes surface water in Taiwan with concentrations in the range of 5 – 280 ng/L [38]. Surface water in China is also polluted by ibuprofen with concentrations reaching 1417 ng/L [39]. Ibuprofen with maximum concentration of 385 ng/L was also reported to pollute groundwater in Europe [40]. Furthermore, Ashfaq et al. [41] reported that as much as 321 – 610 µg/kg of ibuprofen was detected in soil in Pakistan. Soil irrigation in Spain was also found to contain 213 ng/L ibuprofen [42]. Ibuprofen was also observed in sediment samples along Cao River in Vietnam with concentration of less than 10 µg/kg [43]. This compound is a moderate hydrophobic substance according to its log K_ow value (3.97) [44], thus ibuprofen will have moderate adsorption potential. Substances with this value of log K_ow have a low affinity with water and tend to adsorbed on soils or sediments. This explains the reason why ibuprofen was also observed in soils and sediment. However, even though ibuprofen was detected at very low levels in the effluent of WWTPs, the potential risks caused by the presence of ibuprofen in the environment cannot be ruled out.

### 3.2 Sources of ibuprofen

The presence of ibuprofen is attributed to anthropogenic activities including discharge of pharmaceutical industry, treated effluents from household and hospital WWTPs, sewer leaking, sewer overflow and surface runoff (Fig. 3). Ibuprofen is not thoroughly metabolized and roughly 15% of ingested ibuprofen gets excreted after consumed by human and animals, as unchanged molecule and its metabolites [13]. After the excretion, both ibuprofen and its metabolites discharged into WWTPs, STPs, even river, lake, oceans, soil, groundwater etc. The wastewater treatment system at WWTPs is designed to eliminate organic matters (such as BOD) and suspended solids to generate effluent within the standard quality. However, conventional wastewater treatment systems are unable to eliminate ibuprofen completely and other emerging contaminants because their complex structure and toxicity make these compounds resistant to microorganism activity. As the results, ibuprofen and the transformation products of this pollutant ends up in the effluent of wastewater treatment systems and pollute water bodies, soil and other ecosystems [45].

As the world’s third most salable drug, ibuprofen become the most consumed medicine worldwide even being sold without prescription [46]. In Malaysia, 14.2% of the adults consume NSAIDs drugs and 4.2% of them are frequent user [47]. Ibuprofen consumption rate in Sleman, one of the regions in Indonesia, averaged 156,236 DDD (defined daily dose)
per 1000 population [48]. It means that 157 people out of 1000 will consume this medicine. Meanwhile, average of 3.6 – 4.6 g/1000 people of ibuprofen was consumed daily in Vietnam [49]. Thus, ibuprofen contained in human excretion-based wastewater further contributing to the concentration of ibuprofen detected in wastewater.

Fig. 3. Ibuprofen sources of occurrence.

### 3.3 Potential risks of ibuprofen

Although no adverse human health has been reported, exposure to ibuprofen through wastewater, surface water, and groundwater may pose potential risks to some aquatic organisms. This substance will give adverse effect on aquatic organisms due to cytotoxic and genotoxic damage, high oxidative cell stress, and unfavorable effects on growth and reproduction as shown in Fig. 4.

Many researchers have assessed the potential risks of ibuprofen at different dosages on invertebrates, mainly mollusks and crustaceans, and vertebrates, including specific species of fish. Studies on daphnia (crustacean water fleas) and fish have examined the acute (up to 24 hours of exposure) and chronic (repeated exposure) toxic responses to ibuprofen. Long-term exposure will bring about an imbalance in cell oxidation followed by damage to cells, proteins and DNA [50]. Exposure to a sub-chronic environmental ibuprofen concentration (0.8 µg/L) for 14 days decreased the protein carbonyl concentration and lysosomal integrity in the digestive glands of bivalve molluscs (Unio tumidus, typically used as bioindicators of freshwater quality). Additionally, the exposure induced cholinesterase [51]. It also has been observed that ibuprofen decreases fish sperm and egg production while simultaneously increasing the number of eggs Oryzias latipes, a type of medaka fish [52]. Furthermore, ibuprofen exposure has also been linked to membrane damage in the digestive glands and elevated levels of lipid oxidation in shellfish [53]. Ibuprofen was also observed instigating substantial destructive impact on Chrinomus riparius (harlequin fly) metabolism. This substance will prevent insects from synthesizing prostaglandin. Even at trace levels, ibuprofen disrupts physiology, immunity, and reproduction because prostaglandins play critical roles in these processes [54].

Ibuprofen undergoes oxidative and photolytic breakdown into a variety of degradation metabolite chemicals. These metabolite chemicals may have effects that are more harmful than the original compound [55]. For example, ibuprofen conjugated with diacylglycerol discouraged cell division and the nondisjunction of several chromosome pairs [56]. As illustrated in Fig. 5, ibuprofen's metabolism consists of conjugation with glucuronic acid and oxidation, producing two major products: hydroxyibuprofen (OH-IBU) and carboxyibuprofen (CX-IBU). In activated sludge, OH-IBU was formed in an aerobic environment, whereas CX-IBU was produced in an anoxic environment [57]. Ibuprofen
metabolites were also detected in photo-based processes, i.e. photolysis in the presence UV light, photo-H₂O₂ oxidation with UV light and photo-Fenton oxidation with visible light radiation [58]. Up to 15 different metabolite types were found during the advanced oxidation processes (AOPs)-mediated breakdown of ibuprofen. The toxic intermediate in the form of 4-isobutylacetophenone was only found in the photolysis process via decarboxylation or hydroxylation reactions. Ferrando-Climent et al. [59] investigated the presence of ibuprofen and its main metabolites in a batch activated sludge system. While CX-IBU disappeared more quickly than hydroxylated metabolites, 1-hydroxylated ibuprofen (1-OH-IBU) and 2-hydroxylated ibuprofen (2-OH-IBU) were shown to remain in the system after degradation. These metabolites were also detected in water bodies. The effect of ibuprofen and its metabolites on wastewater treatment was investigated by Jia et al. [60]. The results showed that in an aerobic sequencing batch reactor (SBR) system ibuprofen underwent biotransformation into 1-OH-IBU and 2-OH-IBU as well as CX-IBU. Increasing ibuprofen concentration in the influent was followed by decreasing of COD removal suggesting inhibitory effect of ibuprofen on aerobic microorganism. However, no significant effect was found on nitrogen removal.

Fig. 4. Ibuprofen adverse effect on ecosystem.

Fig. 5. Major metabolic pathway of ibuprofen.

Even while WWTPs are able to remove over 80% of ibuprofen from raw influent, a considerable quantity still remains in the effluent, which may have a negative impact on the receiving environment [61]. Repeated use of sewage sludge and reclaimed water for irrigation may result in ibuprofen accumulation in agricultural soil. Abiotic stress due to contaminated environment is being held responsible for morphological and physiological changes on plants [62]. Wijaya et al. [63] investigated the effects of ibuprofen on vegetative stage of Vigna unguiculata (cowpea). Significant abatement of chlorophyll (chl) a, chl b, total chlorophyll, and total carotenoid contents in cowpea leaves were inevitable following ibuprofen uptake by the plant. These pigments are compulsory for photosynthesis process.
This result is in accordance with those investigated by Iori et al. [64] who investigated ibuprofen effects on Salix alba (willow). Utilization of treated wastewater effluent from WWTPs that contain ibuprofen was also investigated by Picó et al. [65]. It was reported that 46 metabolites of ibuprofen, including 1-OH and 2-OH-IBU, were confirmed in Vigna unguiculata. High solubility and intermediate hydrophobicity properties are proclaimed to encourage its mobility in wastewater and potential uptake by plants.

4 Conclusion

The present study provides literature overview on the current state of knowledge on the exposure of pharmaceuticals in aquatic environment. Through this review it was found that the research about ibuprofen quantification, one of the most salable pharmaceuticals, in Southeast Asia is hardly any. Among 534 publications about emerging contaminants in this region, only 12 publications that focusing on this topic while it’s still barely any in countries such Laos, Myanmar, Cambodia, Brunei, and East Timor. However, available publications displayed the presence of ibuprofen in wastewater and water bodies in Southeast Asia regions. Considering the potential adverse effects due to prolonged exposure to ibuprofen demonstrated in publications from other regions, the risks caused by the presence of this contaminants in the aquatic environment cannot be ruled out. Therefore, in order to guarantee the safety and security of water resources in the future, it will eventually be necessary to develop local ability on identifying emerging contaminant pollution and then completely remove this source of contamination.

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