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Review

Pharmaceuticals in water as emerging pollutants for river health: A critical review under Indian conditions

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ABSTRACT

The wastewaters from pharmaceutical manufacturing units, hospitals, and domestic sewage contaminated with excretal matters of medicine users are the prime sources of pharmaceutical pollutants (PPs) in natural water bodies. In the present study, PPs have been considered one of the emerging pollutants (EPs) and a cause of concern in river health assessment. Beyond the reported increase in antibiotic-resistant bacteria (ABRB), PPs have been found adversely affecting the biotic diversity in such water environments. Considering Algae, Macroinvertebrates, and Fishes as three distinct trophic level indicators, the present study puts forward a framework for showing River Health Condition (RHC) based on the calculation of a River Health Index (RHI). The RHI is calculated using six Indicator Group Scores (IGS) which individually reflect river health in a defined category of water quality characteristics. While Dissolved Oxygen Related Parameters (DORP), Nutrients (NT), and PPs are taken as causative agents affecting RHCs, scores of Algal-Bacterial (AB) symbiosis, Macroinvertebrates (MI), and Fishes (F) are considered as an effect of such environmental conditions. Current wastewater treatment technologies are also not very effective in the removal of PPs. The objective of the present study is to review the harmful effects of PPs on the aquatic environment, particularly on the chemical and biotic indicators of river health. Based on predicted no-effect concentrations (PNEC) for algae, macroinvertebrates, and fishes in the aquatic environment and measured environmental concentration (MEC) in the river, the estimated risk quotient (RQ) for norfloxacin in the Isakavagu-Nakkavagu stream of river Godavari, Hyderabad is found 293 for algae, 39 for MI, and 335 for fish. Among PPs, in Indian rivers, the presence of caffeine is the most frequent, with algae at the highest level of risk (RQ_{max}= 24.5).

Broadly six PPs, including azithromycin, caffeine, diclofenac, naproxen, norfloxacin, and sulfamethoxazole are found above PNEC values in Indian rivers. The application of IGS and RHI in understanding and presenting the river health condition (RHC) through colored hexagons has been demonstrated for the river Ganga near Varanasi (India) as an example. Identification of critical indicator groups, based on IGS provides a scientific basis for planned intervention for river health restoration to achieve an acceptable category.

1. Introduction

Concerns about emerging pollutants (EPs) were first discussed by Rachel Carson in 1962. The widespread use of dichloro diphenyl trichloroethane (DDT) to get rid of mosquitoes and other pests diclofenac as antibiotics for humans leading to disproportionate death and disappearance of vultures (Sauve, 2014) drew deep attention to scientists and researchers about their long-term effects. The term 'EP' has been used many times in connection with chemicals detected in low concentrations in surface and ground waters. According to the United States Geological Survey, EPs are defined as 'all synthetic or naturally occurring chemicals that are not included in the routine monitoring program but have the potential to enter the environment and cause known or suspected negative ecological, (eco) toxicity, and/or human health effects (USGS, 2017).

Such pollutants have been released into the environment for a long time but are recognized now because of the development of new detection methods. The synthesis of new chemicals or changes in the use and disposal of existing chemicals could create new sources for emerging pollutants (http://www.norman-network.net). Based on sources and

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differing physiochemical characteristics, EPs are categorized into six major classes: (i) Personal Care Products (PCPs), (ii) Endocrine-Disrupting Chemicals (EDCs), (iii) Pharmaceutical Pollutants (PPs), (iv) Persistent Organic Pollutants (POPs), (v) Artificial Sweeteners (ASs), and (vi) Microplastics (MPs) (http://www.norman-network.net).

The consumption of different classes of EPs has increased many times due to population and economic growth. Today more than 700 EPs, their metabolites, and the conversion byproducts are reported in the European aquatic environment (www.norman-network.net).

The detection of EPs in many surface water bodies all over the world has developed as an environmental challenge in recent years (Bolong, 2009; Geissen et al., 2015; Gavrilescu, 2015; Philip et al., 2018; Pena-Guzmán et al., 2019). Although these pollutants have not yet been monitored routinely due to their low concentrations, they are now being examined seriously as they have been found to influence the ecological function of rivers and water bodies (Farré et al., 2008; Poynton and Robinson, 2018; Robinson et al., 2005).

In this study, pharmaceutical pollutants (PPs) have taken a major causative class due to the frequent presence of pharmaceutically active compounds in river water. Among six classes of EPs, PPs contribute to the highest concentrations in the Indian river and affect the ecological diversity of the river environment.

Pharmaceutical Pollutants (PPs) are those substances that are used by an individual for personal health care and products for agribusiness to promote the health or growth of farm animals. PPs include prescription drugs, nonprescription drugs, and veterinary drugs. Bhagat et al. (2018) reported that antibiotics account for 67.3 % of prescription drugs in India. Prescription antibiotics class includes ceftriaxone (69 %), followed by amoxicillin (61 %), ciprofloxacin (16 %), and ofloxacin (7 %). The occurrence of these chemicals in Indian surface waters with concentrations from ng/L to μg/L and their effects on the microbiological consortium have been reported by many researchers (Sharma et al., 2019; Mutiyar et al., 2018, Williams et al., 2019a, Kumar et al., 2019, Fick et al., 2009, Mutiyar et al., 2014, 2018; Mohapatra et al., 2016). It acts as a pseudo-persistent pollutant (Ellis, 2006). Bioaccumulation properties and degradation into toxic compounds have undesirable and unexpected effects on living organisms and the environment (Liu, 2013; Ebele, 2017; Snyder, 2008; de Solla et al., 2016).

In general, conventional wastewater treatment methods are not very effective in removing EPs (Subedi et al., 2015). Thus, hospital wastewater (HWW), if left untreated, could lead to serious outbreaks of communicable diseases, diarrhea and cholera (Gautam et al., 2007). It increases ecotoxicity (Mubedi et al., 2013; Orvos et al., 2002), bioaccumulation (Solla et al., 2016), damages DNA and increases microbial resistance (Krzeminski, 2019). Adsorption using activated carbon and Advanced Oxidation Processes (AOP) using Ozone, Hydrogen Peroxide (H_2O_2), chlorine (Cl_2) or various chlorine compounds, and Ultraviolet (UV) rays irradiation are some of the physicochemical methods of HWW treatment. Conventional Activated Sludge (CAS) process, membrane bioreactor (MBR), Constructed wetlands (CW), and their combinations with ozonation have been used as biological approaches to treat HWW.

The widespread consumption of pharmaceutical-grade pollutants such as antibiotics found in human and veterinary medicinal products has inevitable consequences of Antibiotic Resistance Bacteria (ABRB) in the environment, which are a major problem for both human and animal health (Kümmerer, 2009; Gaskins et al., 2002). ABRB remains alive even after conventional wastewater treatment and ends up in other receiving waters (Rizzo et al., 2013). This poses a potential threat to surface water quality that could also affect the ecosystem and human health as the river is one of the most important water resources in the country. Due to the rapid rise of ABRB, national and international organizations such as the Ministry of Health and Family Welfare (GoI, 2017), the European Antimicrobial Resistance Surveillance Network (EARS-Net) (European Center for Disease Prevention and Control, 2017) and the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) have launched action plans to combat its effects, including the key drug resistance trend.

In India, most sewage treatment plants (STPs) treat the raw wastewater up to secondary levels and discharge their effluents directly or indirectly into the rivers. Total wastewater produced in Class I and II cities in India increased from 7067 MLD in 1978–79–62,000 MLD in 2018–19 (CPCB, 2021). According to Central Pollution Control Board (CPCB, 2015), even after the Environmental (Protection) Amendment Regulations 2015 in the country, except for the conventional pollutant parameters, EPs are not on the list of revised quality standards of treated wastewater for monitoring sewage treatment plants in various industrial sectors. Moving with time, heavy metals and pesticide residue measurements are part of regular river water quality monitoring programs for meeting drinking water quality standards (IS 10500: 2012) in India. However, till now, there is no monitoring of other Emerging Pollutants (EPs) in drinking water and no permissible ambient standards in rivers or effluent standards from STPs have been set. The present study is targeted toward this larger objective taking pharmaceutical pollutants (PPs) as a significant component of it because PPs contribute to the highest concentrations in the river and affect the ecological diversity of the river environment the most. An extensive literature review on the presence of PPs in Indian rivers has been made in the present study. The objective is to suggest limiting concentrations in natural water systems which protects the biotic life and overall river health. Algae, macroinvertebrates, and fish are considered the three distinct trophic levels in natural water systems. The ecological risk on different levels of such aquatic organisms has been assessed to estimate their impact on biotic indicator group scores (IGSs) affecting river health. A framework to calculate a River Health Index (RHI) incorporating the possible effects of PPs in addition to traditionally acknowledged Physico-chemical water quality parameters has been presented and its applicability has been demonstrated. It is observed that the river health condition (RHC) at a site can be presented as a multi-colored hexagon in a pictorial form which gives a visual comparison and comprehensive view of the causes and effects in the aquatic environment. This can ably be used as a scientific tool for prioritizing the areas of action and intervention for river health restoration.

2. Literature review

2.1. *Common classes of pharmaceutical pollutants*

India has the second-largest share of the pharmaceutical sector, followed by China with a maximum annual turnover accounting for 71 % of the global market. The current market for the pharmaceutical industry is $42 billion and it may reach as much as $120–130 billion by 2030 due to innovative technology, quality research, and cheap production (IBEF, 2021). India is also the world's largest supplier of generic medicines, accounting for 20 % of global exports by volume. Among different pharmaceutical classes antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, and stimulants are used to inhibit the spread of infectious organisms. This group of PPs constitutes around 13.6 % of total production. Antibiotic drug consumption is much higher in India than in other countries all around the world. In terms of concentrations and frequency of occurrence, the presence of antibiotics is the highest, followed by the residue of NSAIDs, anticonvulsants, and stimulants.

2.1.1. *Antibiotics*

India and China are the world-leading countries in antibiotic production. It accounts for 80–90 % of global antibiotic production. Antibiotics are used to treat and prevent bacterial infections in humans and animals (Nathan, 2014). It is also used for the growth of aquaculture farms and animal husbandry (van Boeckel et al., 2017). Different representative chemicals of antibiotics class include norfloxacin, ofloxacin, ciprofloxacin, azithromycin, amoxicillin, ampicillin, sparfloxacin, naproxen, trimethoprim, etc. Antibiotic residues may bioaccumulate in the human body through excess consumption of medication. Studies conducted in Shanghai showed the presence of more than 20 antibiotics in urine samples from children (Wang et al., 2021). The source of 90 % of the antibiotics reported in wastewater is excreted unchanged in the urine and/or feces (Hu et al., 2010; Wang et al., 2020). The highest observed concentration of ampicillin in human feces is 49.52 μg/ kg and in urine, it shows a concentration of more than 40 μg/L (Steinbakk et al., Lienert et al., 2007; Escher et al., 2011). Continuous exposure to antibiotics in the human body intensifies thyotame effects of antibiotic-resistant pathogenic strains (Zhan et al., 2018). An increase in antibiotic resistance bacteria (ABRB) is a cause of concern (Reddy and Dubey, 2019; Voigt et al., 2020). Antibiotic resistance is the ability of bacteria to resist and escape the effect of antibacterial drugs that were once effective in treating the bacteria. Consequently, a high dose of medication is required to cure a disease due to an increase in the resistivity of drugs on the microbial consortium. Almost 7 lakh people worldwide lose their lives to resistant infections each year (Indian Drug Manufactures Association (IDMA (IDMA (2018)). The World Health Organization (WHO) has endorsed a global plan of action to combat ABRB, including the major drug resistance trend. The Government of India has also approved the National Plan of Action to Combat Antibiotic Resistance (Department of Health and Family Welfare, 2017).

In India, the Isakavagu-Nakkavagu stream near Hyderabad, which eventually drains into the river Godavari has been reported to have the highest concentration of antibiotics (ciprofloxacin- 250 μg/L, and norfloxacin- 470 μg/L) (Fick et al., 2009). The study found that the area near pharmaceutical manufacturing facilities is very prone to antibiotic contamination of water bodies, especially when wastewater treatment units are technologically inefficient to remove pollutants.

2.1.2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are widely used around the world that has properties to treat muscle pain, fever, as well as joint inflammation in humans and animals (Parolini et al., 2020). It includes analgesic (for relieving pains) and anti-inflammatory (reducing redness, swelling, and pains) classes of pharmaceutical products. Various NSAIDs are in great demand for both prescription and nonprescription drugs because of their disease-curing properties. Different representative chemicals of analgesic and anti-inflammatory classes include ibuprofen, ketoprofen, acetaminophen, and diclofenac. Among analgesics, acetaminophen is the most widely used nonprescription drug (to treat mild to moderate pain from headaches, toothaches, and backaches, or to reduce fever) in India (Soumya et al., 2016). In natural water systems, the maximum concentration reported in India is for ibuprofen (2.32 μg/L in the Cooun river near Chennai followed by acetaminophen (1.56 μg/L) and ketoprofen (1.07 μg/L) in the river Ganga near Sahibganj, Bihar (Subedi et al., 2015; Sharma et al., 2019). Due to the presence of these pollutants in river water, a moderate to high ecological risk has been reported (Mutiyar et al., 2018).

2.1.3. Anticonvulsants

Anticonvulsants in particular are prescribed to prevent migraines, rapid cycles of mania, and depression (Waszkielewicz et al., 2011). Chemical compounds are used to calm brain hyperactivity as a mood stabilizer in patients with bipolar disorder, neurogenic diabetes, and alcohol withdrawal. Carbamazepine is one such anticonvulsant that is found in various rivers across India. The highest concentration of carbamazepine (1.346 μg/L) is reported in river Yamuna (near Agra) followed by 0.570 μg/L in river Ahar (Udaipur) and 0.008 μg/L in river Brahmaputra (Williams et al., 2019a; Mutiyar et al., 2018). Carbamazepine has a high risk for aquatic organisms, mainly for fish, even at low availability in surface water (Zhou et al., 2019). The highest release of Carbamazepine from STPs is reported in southern states of India ranging between 4.78 and 57.6 mg/d/1000 people (Subedi et al., 2015).

2.1.4. Stimulant

Stimulants are psychoactive chemicals that encourage rational and physical activity. The consumption of caffeine and amphetamines is very high worldwide due to their ability to increase work efficiency and mental concentration (Finnegan, 2002). In India, the beverage is one of the main sources of the presence of stimulants in the environment. The caffeine content in non-alcoholic beverages with a concentration of more than 145 mg/L is labeled as caffeinated (FSSAI 2016). According to Seidi et al. (2011) observed that about 30–62 % of the stimulants are released in the urine within 24 h of ingestion. Amphetamine and caffeine are important stimulants commonly found in high concentrations in surface water. In India, amphetamine (0.984 μg /L) has been reported in the Cooun river, Chennai. A caffeine concentration of 0.11 μg/L (Mutiyar et al., 2018) was found in the river Yamuna (near Agra), 3.68 μg/L (Williams et al., 2019a) in the river Ahar near Udaipur, and 7.43 μg/L in river Ganga (Sharma et al., 2019).

2.2. Treatment technologies for PPs

WHO (2016) reports that treating PPs from wastewater to reduce ABRB in rivers may cost the global economy as much as $ 100 trillion. The main source of PPs in the surface water is hospital wastewater. The concentration of PPs in hospital wastewater is 4–150 times higher than in domestic wastewater (Mesdaghinia et al., 2009) and is only partially treated in conventional wastewater treatment, if at all. Traditional treatment technologies degrade only 18–32 % of the pharmaceutical pollutants (Castiglioni et al., 2006; Lishman et al., 2006 and Paxeus, 2018). Treating PPs at the source is the best option before dilution. Existing WHO guidelines suggest that the disposal of hospital wastewater (HWW) should be regulated to on-site treatment, requiring primary, secondary, and tertiary treatments.

Adsorption using activated carbon (Nguyen et al., 2020) and Advanced Oxidation Process (AOP) using ozone (Gerrity et al., 2011; Tambosi et al., 2009; Khan et al., 2020), and Hydrogen Peroxide (H_2O_2) (Tambosi et al., 2009; Jung et al., 2012) or their combination and UV rays irradiation (Tambosi et al., 2009; Jung et al., 2012) are some of the used physicochemical methods for removal of PPs from hospital wastewaters.

Conventional Activated Sludge (CAS) Process (Fischer and Majewsky, 2014; Sipma et al., 2010), Membrane Bioreactor (MBR) (Vo et al., 2019; Sipma et al., 2010; Tambosi et al., 2009), and Constructed wetlands (Auvinen et al., 2017) are biological methods examined for removal of PPs from HWW.

PPs of high concern for aquatic organisms such as carbamazepine, acetaminophen, diclofenac, and trimethoprim were reported to have a good removal probability above 90 % by advanced oxidation process with a combination of either ozone+ H_2O_2 or H_2O_2 + UV (Rosario -Ortiz et al., 2010; Gerrity et al., 2011).

With activated carbon, the adsorption capacity increases by an increase in the surface area of the porous structure. EPs with properties such as hydrophobic and charged contaminants, especially the non-polar contaminants with Log KOW > 2, are well removed by activated carbon (Wijekoon et al., 2013). Nguyen et al. (2020) reported the removal of PPs such as diclofenac, ibuprofen, carbamazepine, and sulfamethoxazole by 50–80 % using activated carbon at a dose of 50 μg/ L.

Gerrity et al. (2011) examined the ozonation process and reported > 90 % removal of paracetamol, diclofenac, and sulfamethoxazole. The process is effective in removing PPs from HWW by more than 76 % at an ozone dose of 3.5–17.0 mg /L at pH 8 (Khan et al., 2020).

In the biological approach, the removal of PPs, such as sulfamethoxazole and other compounds including ibuprofen, triclosan, etc. through the conventional activated sludge (CAS) process may be enhanced using a combination of different microbial species and specific enzymes (such as monooxygenase and dioxygenases). Also, the increasing sludge retention time (SRT) from 6 days to 54 days was observed to enhance removal efficiency from 30 % to 70 % (Fischer and

Table 1
Concentrations of PPs reported in Indian rivers and PNEC-based risk assessment for biotic indicators.

S. N.	River	Pharmaceutical Compound	MEC (μg/L)	PNEC (μg/L) *			Remarks
				A	MI	F	
1	River Akravathi (Gopal et al., 2021)	Naproxen*1	4.334	31.80	**2.620**	115.2	RQ= 1.65 for MI due to Naproxen.
		Ibuprofen*1	0.105	4	9.1	170	
		Diclofenac*2	0.041	0.2	20	0.050	
2	River Ganga near Patna (Sharma et al., 2019)	Acetaminophen*2	1.565	13	9.2	38	RQ= 4.95 for A due to Caffeine.
		Caffeine*4	0.743	**0.15**	182	87.5	
		Ketoprofen*2	0.107	160	250	32	
3	River Brahmaputra, Guwahati (Kumar et al., 2019)	Caffeine*4	0.410	**0.15**	182	87.5	RQ= 2.73 for A due to Caffeine.
		Acetaminophen*2	0.060	13	9.2	38	
		Carbamazepine*3	0.008	33.6	13.8	35.4	
4	River Ahar, Udaipur (Williams et al., 2019a)	Caffeine*4	3.680	**0.15**	182	87.5	RQ= 24.5 for A due to Caffeine.
		Ibuprofen*2	1.288	4	9.1	170	RQ= 2.27 for A due to Azithromycin.
		Carbamazepine*3	0.570	33.6	13.8	35.4	
		Azithromycin*1	0.410	**0.18**	0.44	460	
5	River Yamuna, Delhi (Mutiyar et al., 2018)	Carbamazepine*3	1.386	33.6	13.8	35.4	
		Ibuprofen*2	0.808	4	9.1	170	
		Acetaminophen*2	0.333	13	9.2	38	
		Caffeine*4	0.111	0.15	182	87.5	
6	River Cooun, Chennai (Subedi et al., 2015)	Ibuprofen*2	2.320	4	9.1	170	
		Amphetamine*4	0.984	3.803	4.357	37.602	
7	River Yamuna, Agra (Jindal et al., 2015)	Carbamazepine*3	1.850	33.6	13.8	35.4	RQ= 2.71 for A due to Sulfamethoxazole.
		Acetaminophen*2	1.550	13	9.2	38	RQ= 4.97 for A; and 19.88 for F due to Diclofenac
		Sulfamethoxazole*1	0.733	**0.27**	25	506	
		Diclofenac*2	0.994	**0.2**	20	0.050	
		Naproxen*1	0.423	31.80	2.620	115.2	
		Ibuprofen*2	0.133	4	9.1	170	
8	River Yamuna, Delhi (Mutiyar and Mittal, 2014b)	Gatifloxacin*1	4.800	–	–	–	
		Sparfloxacin*1	2.410	–	–	–	
		Cefuroxime*1	1.700	–	–	–	
		Ciprofloxacin*1	1.400	2790	8049	1705	
		Ampicillin*1	1.380	1000	2300	1000	
9	River Yamuna, Delhi (Okhla Water Works) (Mutiyar, 2013)	Amoxicillin*1	8.400	5	182.70	–	
		Ciprofloxacin*1	1.726	2790	8049	1705	
10	River Kaveri (Ramaswamy et al., 2011)	Carbamazepine*3	0.002	33.6	13.8	35.4	
	River Tamiraparani (Ramaswamy et al., 2011)	Carbamazepine*3	0.058	33.6	13.8	35.4	
11	Isakavagu-Nakkavagu Stream of River Godawari, Hyderabad (Fick et al., 2009)	Norfloxacin*1	470.00	**1.6**	**12**	**1.4**	RQ= 293 for A; 39 for MI and 335 for F due to Norfloxacin.
		Ciprofloxacin*1	250.00	2790	8049	1705	
		Trimethoprim*1	4.00	795	120.7	16	
		Ofloxacin*1	1.00	5	31.75	101	

* 1- Antibiotics; * 2- NSAID/ Analgesic; * 3- Anticonvulsant, * 4- Stimulant
(*PNEC Sources: i. **Acetaminophen***2: Calleja et al., 1994; ii. **Ampicillin***1: Park and Choi, 2008/ Kim et al., 2007; iii. **Amoxicillin***1: Eguchi et al., 2004; iv. **Amphetamine***4: Ecological Structure-Activity Relationship (ECOSAR v2.0) (ECOSAR v2.0 USEPA, 2012); v. **Azithromycin***1: Tell et al., 2019; vi. **Caffeine***4: Calleja et al., 1994; vii. **Carbamazepine***3: Kim et al., 2007/Ferrari et al., 2004/ Duan et al., 2008; viii. **Chloramphenicol***1: Zhou et al., 2019/ ECOSAR v2.0 USEPA, 2012; ix. **Ciprofloxacin***1: ECOSAR; x. **Diclofenac***2: Lawrence et al., 2007/ Haap et al., 2008/ Hoeger et al., 2005; xi. **Ibuprofen***2: KNOL/BASF 1995; xii. **Ketoprofen***2: Sanderson et al., 2003a; xiii. **Ofloxacin***1: Isidori et al., 2005/ ECOSAR v2.0 USEPA, 2012; xiv. **Naproxen***1: Isidori et al., 2005/Quinn et al., 2008a / Li et al., 2016; xv. **Norfloxacin***1: Ando et al., 2007 /ECOSAR; xvi. **Sulfamethoxazole***1: Ferrari et al., 2004 /Kim et al., 2007/García-Galán et al., 2012; xvii. **Trimethoprim***1 Kim et al., 2007/ Grung et al., 2008/ Sanderson et al., 2003a)

Majewsky, 2014).

MBR technology efficiently lowers suspended solids (SS), organic pollutants, and pathogens mainly through photodegradation, biodegradation, sorption to sludge, and volatilization. Khan et al. (2020) reported the removal efficiency of 50–90 % for PPs such as diclofenac, ibuprofen, carbamazepine, and ofloxacin by MBR technology. The removal efficiency in MBR technology depends on hydraulic retention time (HRT) and sludge retention time (SRT). Some of the PPs such as ibuprofen and carbamazepine get completely removed by MBR technology (Khan et al., 2020). Tambosi et al. (2009) recommended MBR technology in combination with an AOP (H_2O_2/ UV+O_3) which could remove PPs up to 80–90 % from HWW. Recently Vo et al. (2019) suggested the use of MBR combined with ozonation as a potential technology to remove PPs from wastewater.

2.3. Ecological Risk Assessment due to PPs in Aquatic Environment

The ecological risk of any chemical compound is normally measured through the estimation of risk quotient (RQ) and optimized risk quotient (RQ_f).

2.3.1. Risk Quotient (RQ)

Effects of the pollutants on aquatic organisms are based on the value of measured environmental concentration (MEC) and predicted no-effect concentration (PNEC).

The risk quotient is calculated using the maximum MEC and the PNEC of the pharmaceutical pollutants according to the equation (Sharma et al., 2019; Zhou et al., 2019):

$$RQ = \frac{MEC}{PNEC} \quad (1)$$

Based on the calculated RQ, risk measurement is classified into 3 categories (de Souza et al., 2009; Hernando et al., 2006):

RQ < 0.1, indicates less hazardous effects and thus low risk to the aquatic environment,

0.1 <RQ < 1, considered as moderate risk, and.

Table 2
Summary of PPs found above their respective PNEC values in Indian Rivers.

S. N.	PPs found in river water	Name of River	MEC (μg/L)	PNEC (μg/L)			Remarks
				A	MI	F	
1.	Naproxen*[1]	River Akravathi (Gopal et al., 2021)	4.334	31.80	**2.620**	115.2	RQ= 1.65 for MI due to Naproxen.
2.	Caffeine*[4]	River Ganga near Patna (Sharma et al., 2019)	0.743	**0.15**	182	87.5	RQ= 4.95 for A due to Caffeine.
		River Brahmaputra, Guwahati (Kumar et al., 2019)	0.410	**0.15**	182	87.5	RQ= 2.73 for A due to Caffeine.
		River Ahar, Udaipur (Williams et al., 2019a)	3.680	**0.15**	182	87.5	RQ= 24.5 for A due to Caffeine.
3.	Azithromycin*[1]	River Ahar, Udaipur (Williams et al., 2019a)	0.410	**0.18**	0.44	460	RQ= 2.27 for A due to Azithromycin.
4.	Sulfamethoxazole*[1]	River Yamuna, Agra (Jindal et al., 2015)	0.733	**0.27**	25	506	RQ= 2.71 for A due to Sulfamethoxazole.
5.	Diclofenac*[2]	River Yamuna, Agra (Jindal et al., 2015)	0.994	**0.2**	20	0.050	RQ= 4.97 for A; and 19.88 for F due to Diclofenac
6.	Norfloxacin*[1]	Isakavagu-Nakkavagu Stream of River Godawari, Hyderabad (Fick et al., 2009)	470.00	**1.6**	**12**	**1.4**	RQ= 293 for A; 39 for MI and 335 for F due to Norfloxacin

*[1]- Antibiotics; *[2]- NSAID/ Analgesic; *[3]- Anticonvulsant, *[4]- Stimulant

RQ≥ 1 is considered to pose a high risk to aquatic organisms.

Mutiyar and Mittal (2014a) assessed ecological risks of aquatic organisms based on hazard quotient (HQ). The hazard quotient is the ratio of predicted environmental concentration (PEC) and PNEC. According to Greenhalgh (1987), PEC calculation is difficult in India, due to the high rate of medications being consumed over the counter without prescriptions. It leads to different PEC values than the real environmental concentrations. In such cases, the value of measured environmental concentrations (MEC) is taken as the value of PEC. Thus, the HQ may be the same as RQ, which is the ratio of MEC and PNEC (Mutiyar and Mittal, 2014a).

2.3.2. *Optimized Risk Quotient (RQ_f)*

The risk quotient approach characterizes the ecological risk of PPs based on the measured environmental concentration (Zhou et al., 2019). But the pharmaceutical pollutants are persistent and show their long-term presence in water bodies thus posing a higher risk to target organisms than the pollutants of non-persistent nature (Desbiolles et al., 2018; Tousova et al., 2017). The optimized risk quotient (RQ_f) (Zhou et al., 2019) is used to calculate the risk to aquatic organisms by pollutants after long-term exposure. The calculation is based on the mean RQ value and the frequency of MECs that exceed PNEC. Variation of the concentration of PPs in river water above PNECs is used to screen the pollutants.

The RQ_f includes all possibilities to recognize worst-case scenarios in comparison to the RQ. RQ_f also encompasses the broad classification of pollutants (high, moderate, tolerable, negligible, and safe) that pose potential risks to aquatic organisms (Zhou et al., 2019).

The RQ_f was calculated by the following equations (Zhou et al., 2019):

$$RQ_f = RQ \times F = \frac{MEC}{PNEC} \times F$$

$$F = \frac{NO1}{NO2} \tag{2}$$

Where F is the Frequency of measured environmental concentrations exceeding predicted no-environmental effect concentration. It is expressed as the ratio of the number of samples with concentrations higher than PNEC (NO_1) and the total number of samples (NO_2). Based on RQ_f estimation, risk measurement is classified into 5 groups (Zhou et al., 2019):

Table 3
Common pharmaceutical classes and their physicochemical properties.

Pharmaceuticals Class	Representatives Chemicals	Chemical Representations	Mol. wt. (g/mol)	pKa	Log Kow	References
1. Antibiotics	Norfloxacin	$C_{16}H_{18}FN_3O_3$	361.37	6.34	0.46	Fick et al. (2009)
	Ofloxacin	$C_{18}H_{20}FN_3O_4$	331.34	5.97	-0.39	Mutiyar et al., 2013
	Ciprofloxacin	$C_{17}H_{10}FN_3O_3$	748.99	6.09	0.28	Williams et al. (2019a)
	Chloramphenicol	$C_{11}H_{12}Cl_2N_2O_{15}$	323.13	5.5	-1.14	Mutiyar et al., 2014
	Azithromycin	$C_{38}H_{76}N_2O_{14}$	785	8.74	4.02	(Choi, 2008)
	Amoxicillin	$C_{38}H_{72}N_2O_{12}$	365.40	3.2	0.87	
	Ampicillin	$C_{16}H_{19}N_3O_5S$	349.40	2.5	1.35	
	Sparfloxacin	$C_{19}H_{22}F_2N_4O_3$	392.41	6.25	0.98	
	Naproxen	$C_{14}H_{14}NaO_3$	252.24	4.19	3.18	
	Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32	7.12	0.91	
	Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.28	5.7	0.89	
	Cefuroxime	$C_{16}H_{16}N_4O_8S$	424.38	3.15	-0.16	
	Gatifloxacin	$C_{19}H_{22}FN_3O_4$	375.4	5.94	-0.83	
2. Non-Steroidal Anti-Inflammatory Drugs	Ibuprofen	$C_{13}H_{18}O_2$	206.28	4.91	3.79	Sharma et al. (2019)
	Ketoprofen	$C_{16}H_{14}O_3$	254.28	4.45	3.12	Williams et al. (2019a)
	Acetaminophen	$C_8H_9NO_2$	151.16	9.9	0.46	Mutiyar et al. (2018)
	Diclofenac	$C_{14}H_{11}Cl_{12}NO_2$				Subedi et al. (2015).
3. Anticonvulsants	Carbamazepine	$C_{15}H_{12}N_{20}$	236.27	13.9	2.45	Kumar et al. (2019) Mutiyar et al. (2018)
4. Stimulant	Caffeine	$C_8H_{10}N_4O_2$	194.194	10.4	-0.07	Sharma et al. (2019)
	Amphetamine	$C_9H_{13}N$	135.21	9.9	2.07	Kumar et al. (2019) Williams et al. (2019a)

i. $RQ_f = 0$: no risk is expected at present (safe).
ii. $RQ_f > 0$, but < 0.01: the effect is quite limited (negligible);
iii. $RQ_f \geq 0.01$, but < 0.10: small-scale adverse effect is expected (endurable);
iv. $RQ_f \geq 0.10$, but < 1: Moderate environmental risk is expected (moderate);
v. $RQ_f \geq 1$: High environmental risk is expected (high).

Table 1 provides a summary of MECs for various PPs reported in Indian rivers and their respective PNEC values for Algae (A), Macroinvertebrates (MI), and Fishes (F).

From Table 1, it is observed that, although researchers have started examining increasing numbers of PPs concentrations in the water environment of Indian rivers, six PPs, namely, i. Azithromycin, ii. Caffeine, iii. Diclofenac, iv. Naproxen, v. Norfloxacin and vi. Sulfamethoxazole has been found above their PNEC values for aquatic organisms. (Table 2).

As concentrations of Sulfamethoxazole[*1] and Diclofenac[*2] much beyond their PNEC values have been observed in river Yamuna near Agra, and Caffeine[*4] in river Ganga near Patna, regular monitoring of these chemicals needs to be emphasized in important locations in Ganga basin.

Table 3 presents some of the properties of common pharmaceutical classes normally found in river waters. These properties are found helpful in understanding their behavior in aquatic environments and devising their control strategies.

The physicochemical properties such as partition coefficient (Log Kow) and ionization constant (pKa) help in determining the persistent nature of organic pollutants and the ability to donate protons of a chemical respectively. Log Kow represents the distribution of a substance in different environmental compartments (water, soil, air, aquatic biota, etc.). High log Kow values tend to absorb more organic matter as their low affinity for water also has the potential for bioconcentration in living organisms. Pollutants with a log Kow value of more than 3.0 show hydrophobic behavior, which can lead to a high potential for the bioaccumulation of these chemicals (Palma et al., 2015). For example, ibuprofen, ketoprofen, azithromycin, and naproxen can persist in the environment for a long time and have high bioaccumulation properties. pKa denotes the acid dissociation constant in an aqueous solution. It represents the strength of the acid and the ability to donate its protons. A lower pKa value indicates a stronger acid and a greater ability to donate its protons. Ampicillin with a pKa = 3.2 represents the strong acid, while carbamazepine with pKa= 13.9 represents a weak acid.

2.4. The Concept of river health and river health assessment methods

River health is a term used to represent the ecological status of a river (Karr, 1997; Barcelo, 2001). A river is considered healthy if different aquatic populations and communities can survive on it (Dos Santos et al., 2021; GRBMP, 2015; Meng et al., 2009; Sargaonkar and Deshpande, 2003; Tan et al., 2015; Czerniawska-Kusza, 2005). The Ganga River Basin Management Plan (GRBMP) under the Government of India, considered the river Ganga from four perspectives: i. Aviral Dhara (continuous flow), ii. Nirmal Dhara (unpolluted river), iii. The geological entity, and iv. Ecological entity (GRBMP, 2015). If the river is considered as an ecological entity, biological parameters become important in its health monitoring. Different biotic species and their distribution in river water establish a relationship to the structure and integrity of aquatic ecosystems(Thompson et al., 2019; Liu et al., 2012; Munyika et al., 2014; Pal Sharma et al., 2015; Singh Yadav et al., 2014b). Algae, macroinvertebrates, and fishes have been accepted as three distinct biotic trophic levels in the aquatic environment. Many Predictive models such as RIVPACS (River Invertebrate Prediction and Classification System) (Wright, 1995), AusRivAS (Australian River Assessment System) (Simpson and Norris, 2000), BEAST (Benthic Assessment of Sediment) (Reynoldson et al., 1997), South African Scoring System (SASS) have been used to understand the biological status of a river. The eco-based index is seen as an instrument for determining the environmental status of rivers (Joshi et al., 2022; Karr, 1997).

Leigh et al. (2012) in their report entitled "Assessment of River Health in the Liao River Basin (Taizi Sub-catchment)" grouped the entire range of indicators into five categories: i. Water Quality, ii. Nutrients, iii. Algae, iv. Macroinvertebrates, and v. Fish. Among water quality indicators pH, dissolved oxygen (DO), electrical conductivity (EC), suspended solids (SS), total dissolved solids (TDS), anions and cations (K, Ca, Na, Mg, Cl), alkalinity; oxygen demand variables (BOD_5, CODCr, CODMn), nutrients (NH_4, TN, NO_2, NO_3, PO_4, TP), phenols; and fecal coliforms (E. coli) were considered. Based on analyses, they recommended DO, EC, SS, TN, NH_4, and TP (6 parameters) for high lands; DO, EC, SS, TN, NH_4, TP, and phenols (7 parameters) for midlands; and DO, EC, BOD_5, CODMn, TN, NH_4, TP and phenols (8 parameters) for lowlands river health assessment. The authors noted that E. coli could be included as an indicator if the program monitored and assessed the river from a human health perspective. In addition to water quality parameters, they included benthic algae, aquatic macroinvertebrates, and freshwater fish as groups of indicators for the assessment of ecosystem health. For benthic algae, two indices- Index of biotic integrity (ABI), and Algae Berger-Parker (ABP) index, were used. For macroinvertebrates, four indices: total number of taxa (MS), Biological Monitoring Working Party (MBMWP) index, Family level richness of EPT taxa (MEPTS), and Berger-Parker (MBP) index; and for fish, Number of individuals (FN), Species-level richness (FS), Fish index of biotic integrity (FBI), Fish Berger-Parker index (FBP) were estimated. Based on "target" (the guideline representing good health, score 1)" and "critical threshold" (some level of unacceptable health, score 0), site indicator scores (SIS) and indicator group scores (IGS) were calculated. The overall Ecosystem Health Score was calculated as:

$$\text{Ecosystem health score} = (\text{Physical and chemical score x } 2/15) + (\text{Nutrients score x } 2/15) + (\text{Algae score x } 3/15) + (\text{Macroinvertebrates score x } 4/15) + (\text{Fish score x } 4/15) \quad (3)$$

The Ecosystem health score may range between 0 and 1.0. The ecosystem health was classified as critical (EH score < 0.2), poor (≤ 0.4), fair (≤0.6), good (≤ 0.8), and excellent (>0.8). The ecosystem health is schematically presented as a colored pentagon, each of whose five sectors represents the indicator group health score. Red indicates a score of 0–0.2, while green indicates a score of 0.6–1.0 (Leigh et al., 2012).

Following a similar analogy, Singh and Saxena (2018) proposed a scheme of river health assessment based on the calculation of the river health index (RHI) on a 0–100 increasing scale. Along with Physico-chemical (P&C) and nutrients (NT) parameters, biotic indicators for three trophic levels in aquatic environments, such as algae, macroinvertebrates, and fish were considered for the assessment of river health.

The RHI was calculated using the following equation:

$$RHI= [(P\&C \times w_1) + (NT \times w_2) + (A \times w_3) + (MI \times w_4) + (F \times w_5)] \times 100 \quad (4)$$

Where P&C: Physical and Chemical group score, NT: Nutrient indicator group score, A: Algal indicator group score, MI: Macroinvertebrate indicator group score, F = Fish indicator group score, and w_1 to w_5 are their respective weightage.

Saxena and Singh (2020) further refined the approach and used a normalization scheme for selected parameters/indices on a 0–5 scale based on a critical threshold (score 0) and target values (score 5) to calculate the RHI. River Health Condition (RHC) is presented through a colored circumscribed pentagon each of whose sectors through the center represents one of five indicator groups: i. Organo-electrolytic-bacterial (OEB) qualities. ii. Nutrients, iii. Algae, iv.

Macroinvertebrates, and v. Fish. The color of each sector of the pentagon reflects the health score of the concerned indicator group and that of the circumscribing pentagon gives the overall river health condition (RHC) at a given location.

2.5. Including effects of pharmaceutical pollutants in river health assessment

An overview of available literature clearly indicates that PPs have shown their presence in an aquatic environment all across the world, including many rivers in India. Considering rivers as ecological entities, several approaches have been developed to assess river health using physico- chemical water quality parameters and biotic indicators present in it. Although many researchers have shown that the presence of emerging pollutants (Sengar and Vijayanandan, 2022; Singh and Suthar, 2021; Steinbakk et al., 1992) in general, and pharmaceutical pollutants, in particular, have serious implications on the biotic component of the aquatic environment, there is very little information available on acceptable levels and the critical concentrations with respect to algae, macroinvertebrates, and fishes whose species density and distribution reflect overall river health. One of the major objectives of the present study is to suggest limits of acceptable and critical threshold values for pharmaceutical pollutants in river water. The effect of increasing levels of such pollutants on the three biotic indicator groups and overall river health has been examined and possible strategies to improve the river health condition in such cases have been discussed.

2.6. Critical threshold concentrations of PPs causing ecological imbalances in the aquatic environment

The physical interpretation of RQ (Eq. 1) suggests that when the MEC is less than the PNEC, RQ is less than 1, which indicates that there is no ecological risk in the aquatic environment. Even if MEC is equal to the PNEC, RQ= 1, and by definition of PNEC, there is no environmental risk. Environmental risk starts only when MEC> PNEC, giving RQ= MEC/PNEC> 1. However, the estimation of RQ beyond 1 does not evaluate the quantum of risk involved.

Optimized Risk Quotient (as given by Eq. 2) can be equal to 0, when, either MEC is 0, or F is 0. This simply means that when the measured environmental concentration of the PP is zero, or MEC never exceeds PNEC, the environmental risk is likely to be zero.

When RQ $\geq$ 1, that is, MEC $\geq$ PNEC, there is some possible risk to the aquatic environment. Based on the frequency of occurrence (F) and thus the optimized risk quotient, the whole domain of risk evaluation has been divided into four categories: negligible, endurable, moderate, and high (Zhou et al., 2019).

When MEC > PNEC and the frequency of such occurrence is less than 1 % (that means less than 1 sample out of every 100 samples), (thus $RQ_f > 0$, but < 0.01), although there is some risk, it is negligibly small.

When MEC > PNEC and the frequency of such occurrence is greater than 1 %, but, less than 10 %, (i.e., less than 10 samples out of every 100 samples shows MEC > PNEC), ($RQ_f \geq 0.01$, but < 0.10), the risk is said to be 'endurable'.

When the frequency of occurrences of MEC> PNEC is between 10 % to say, 99 %, ($RQ_f \geq 0.10$, but < 1) the risk is said to be 'moderate' and when 100 % of samples show MEC> PNEC, ($RQ_f \geq 1$) there is 'high risk'.

However, as the maximum value of F is 1 (i.e., 100 %), $RQ_f \geq 1$ does not indicate any upper quantitative limit of MEC when the high-risk conditions become critical for biotic indicators.

PNEC values are calculated by dividing the lowest NOEC (no observed effect concentration), LOEC (lowest observed effect concentration), or E(L)C50 (expected lowest concentration to kill 50 % of the test population) values of the most sensitive species by an appropriate assessment factor (AF). This AF is used to overcome the uncertainty related to the raw toxicity data and to derive the PNEC (Vryzas et al., 2011). According to the EU guidelines (European Commission, 2003), (i) an assessment factor (AF) of 1000 is used in the cases where at least one short-term E(L)C50 from each of the three evaluated trophic levels is available; (ii) an AF of 100 is used when one long-term assay is available for either algae, crustaceans or fish; (iii) an AF of 50 is used in the case of existing two long-term assays in two different trophic levels; and (iv) an AF of 10 is used when three long-term assays in three different trophic levels are available.

Hence, MEC/PNEC = 10 may be taken as the critical threshold to define ecologically 'high risk' conditions, beyond which river health may be considered endangered due to severe imbalances in the aquatic environment. This limit has been decided and used in the present study on river health risk assessment.

3. Methodology for the present study

3.1. Framework for calculation of River Health Index (RHI)

In the present study, a framework to calculate the river health index (RHI) including the effects of Emerging Pollutants (EPs) on the water environment has been developed. Beyond the models reported by Leigh et al. (2012), Singh and Saxena (2018), and Saxena and Singh (2020) all of which used five groups of indicators, an additional group named EPs, has been included to calculate RHI. Accordingly, the six indicator groups include: i Dissolved Oxygen Related Parameters (DORPs), ii. Nutrients (NTs), iii. Emerging Pollutants (EPs), iv. Algal Bacterial (AB) Group v. Macroinvertebrates (MI) and, vi. Fish (F). The first three may be broadly considered as causes, whereas the latter three represent biotic responses or effects in the aquatic environment. The expression for calculating RHI can be written as:

$$RHI= [(DORPs \times w_1) + (NTs \times w_2) + (EPs\times w_3) + [(AB\times w_4) + (MI \times w_5) + (F \times w_6)] \times 100 \quad (5)$$

Where, DORPs = Dissolved oxygen-related parameters group score, NTs = Nutrient indicator group score, EPs= Emerging Pollutants group score, AB= Algal Bacterial indicator group score, MI = Macroinvertebrate indicator group score, and F = Fish indicator group score, and w_1, w_2, w_3, w_4, w_5, and w_6 are weights assigned to these respective parameters/ indicator groups.

For illustrative purpose, the DORP group of indicators include four parameters: DO, BOD, COD, and EC. The NT group includes three characteristics of water: NH_3-N, TN, and TP. Caffeine (CAFN), diclofenac (DIC), and Sulfamethoxazole (SMZ) have been included amongst Pharmaceutical Pollutants (PPs) as part constituting EPs. Among the biotic indicators, fecal coliform (FC) count and APPI have been considered in the AB group, as there is a symbiotic relationship between algae and bacteria. Family level Species richness index (FR) and Shannon Weiner Diversity index (FSW) have been considered for Fish in an aquatic environment.

The individual values of all parameters have been normalized on a 0–5 scale, based on being within acceptable/ or target limits (score 5) and beyond the critical threshold (score 0). The arithmetic mean of normalized scores of all parameters/ indices within an indicator group has been converted on a 0–100 scale to indicate the indicator group score of river health at a given location.

Assuming justifiable weights for different groups of indicators, an overall river health index (RHI) is calculated using Eq. 6. The river health condition is classified into two broad categories: Acceptable (RHI> 60), and Poor (RHI<60). The acceptable river health condition may further be classified into three categories: Good (RHI: 60–70), Very Good (RHI: 70–80), and Excellent (RHI>80). Similarly, Poor River health conditions may be subdivided into four suboptimal categories: Stressed (RHI: 60–50), Over Stressed (RHI: 50–40), Critical (RHI: 40–20), and Sick/Dead (RHI<20).

The river health condition has been presented as a colored circumscribed hexagon, each of whose six sectors represents the river health

Table 4
Application of Indicator Groups Scores (IGS) in ecosystem health classification.

	Source: Leigh et al. (2012)					Source: Saxena and Singh (2020)					Present Study					
Indicator Group	**P&C**	**NT**	**A**	**MI**	**F**	**OEB**	**NT**	**A**	**MI**	**F**	**DORPs**	**NTs**	**EPs**	**AB**	**MI**	**F**
Weightage	0.14 (w_1)	0.14 (w_2)	0.20 (w_3)	0.26 (w_4)	0.26 (w_5)	0.15 (w_1)	0.15 (w_2)	0.20 (w_3)	0.25 (w_4)	0.25 (w_5)	0.10 (w_1)	0.20 (w_2)	0.20 (w_3)	0.20 (w_4)	0.20 (w_5)	0.10 (w_6)
Parameters Considered	DO BOD_5 CODMn EC Phenols	TN TP NH_4	ABI2, ABP	MS, MBMWP, MEPTS MBP	FN, FS, FBI, FBP	EC DO BOD COD FC	NH_3-N TN TP	APPI	MSW MBMWP	FS FSW	EC, DO, BOD, COD	NH_3-N, TN TP	CAFN, DIC, SMZ	APPI, FC	MSW MBMWP	FS FSW
Normalization Scale of Parameters	0–1	0–1	0–1	0–1	0–1	0–5	0–5	0–5	0–5	0–5	0–5	0–5	0–5	0–5	0–5	0–5
Nomenclature used	Ecosystem Health Score Scale: 0–1.0		Ecosystem health score: > 0.8: Excellent > 0.6 ≤ 0.8: Good ≤ 0.6: Fair ≤ 0.4: Poor < 0.2: Critical			River Health Index (RHI) Scale: 0–100	River health condition classification: **Acceptable:** > 80: Excellent 70–80: Very Good 60–70: Good **Poor:** 50–60: Stressed 40–50: Over Stressed 20–40: Critical ≤ 20: Sick/Dead				River Health Index (RHI): 0–100		River health condition classification: **Acceptable:** > 80: Excellent 70–80: Very Good 60–70: Good **Poor:** 50–60: Stressed 40–50: Over Stressed 20–40: Critical ≤ 20: Sick/Dead			

Causative Indicators:
P&C: Physico- chemical, **NT**: Nutrients, **OEB**: Organo- Electrolytic- Bacterial
Emerging pollutants (EPs); Caffeine (CAFN), Diclofenac (DIC), and Sulfamethoxazole (SMZ)
Effect Indicators:
Algae (A): Index of Biotic Integrity (ABI2), Berger Parker Index (ABP); Genus level Algal Palmer Pollution Index (APPI)
Macroinvertebrate (MI): Total no. of taxa (MS); BMWP index (MBMWP); Family Level Richness of EPT taxa (MEPTS); Berger-Parker Index (MBP); Shannon Weiner Diversity index (MSW); Macroinvertebrate BMWP score (MBMWP)
Fish (F): Number of Individual (FN); Fish Index of Biotic Integrity (FBI); Berger-Parker Index (FBP); Family level Fish Species richness index (FR); Shannon Weiner Diversity index (FSW)

Table 5
Scheme of color presentation for Indicator Group / River Health Condition based on IGS or RHI.

River Health Category	IGS or RHI	IGC or RHC	Color Scheme
Acceptable	> 80	Excellent	Blue
	70–80	Very Good	Green
	60–70	Good	Yellow
Poor	50–60	Stressed	Orange
	40–50	Over Stressed	Grey
	20–40	Critical	Red
	≤ 20	Sick/ Dead	

(Source: Saxena and Singh, 2020)

with respect to one of the indicator groups selected, and its color reflects its indicator group condition at the given site. The color of circumscribing hexagon represents the overall river health condition.

Salient features of parameters/ indicators selected in the earlier studies (e.g., Leigh et al., 2012, Saxena and Singh, 2020) and the present study have been summarized in Table 4.

3.2. Normalization scheme for quality parameters and indices

In addition to five indicator groups considered for river health assessment under Indian conditions by Saxena and Singh (2020), the present study attempts to incorporate EPs as an additional causative group for the purpose. (Table 5).

Table 6 presents the parameters normalization scheme for IGS calculation used by Saxena and Singh (2020). Based on PNEC as the target value and critical value being ten times the PNEC, Table 7 gives a scoring scheme for pharmaceutical pollutants under the EPs category.

3.3. Validation of the framework

In order to check the applicability of the framework for calculating RHI and classification of river health conditions, the water quality data for river Ganga upstream of Varanasi city (India) during the spring season (March 2018) (Saxena, 2020) has been used. In addition, as emerging pollutants in the river, concentrations of PPs reported in the river Ganga by Jindal et al. (2015) and Sharma et al. (2019) have been used to understand their possible impacts, assuming their presence on the same level at the time of monitoring of other parameters near Varanasi. Table 8 presents the set of water quality characteristics data used for the purpose of demonstrating the applicability of the framework developed in the present study. The weightage of different indicator groups has been assigned judiciously with 50 % for water quality parameters and 50 % for biotic indicators in rivers. While DORP is considered quickly changing and very unstable, and fish are at the top of the trophic level to be minimally affected, their weightage has been kept relatively lower (0.10) than other groups (0.20), such as NT, EP, AB, and MI.

4. Results and discussion

4.1. Presence of PPs in Indian rivers above PNEC

The observations and analyses reveal that there are several PPs, such as azithromycin and caffeine (Williams et al., 2019a), diclofenac and sulfamethoxazole (Jindal et al., 2015), naproxen (Gopal et al., 2020), and norfloxacin (Fick et al., 2009) whose concentrations in Indian river waters have been found above their respective PNEC for aquatic organisms considered in the present study. Table 9 presents a summary of such chemicals. The RQ values range from 1.65 to 335. RQ≥ 1 is considered to pose an increased risk to aquatic organisms. Classifying RQ = 1–3 as 'moderately high'; 3–5: 'significantly high'; 5–8: 'critically high'; 8–10: 'severely high'; and > 10 as 'fatally high', the reported concentrations of PPs show the river conditions as shown in Table 9.

4.2. Calculation of RHI in river Ganga near Varanasi including the effects of PPs

Based on water quality characteristics reported for river Ganga upstream of Varanasi city (India), the normalized scores of parameters, the indicator group scores, and RHI have been calculated, as summarized in Table 10.

Fig. 1 shows the colored pictorial representation of river health

Table 6
Normalization scheme on 0–5 scale for water quality parameters and biotic Indices, (5 for within Target Value, 0 for beyond critical threshold value).

Indicator Group	Parameters included	Normalized Score (0–5 scale)						Reference
		5	4	3	2	1	0	
1. Dissolved Oxygen Related Parameters (DORPs)	i. EC (μmhos/cm)	**≤ 400**	**400–750**	**750–1000**	**1000–1250**	**1250–1500**	**> 1500**	EHMP (2010); Anon (2000)
	i. DO (mg/L)	**≥ 7**	**6–7**	**5–6**	**4–5**	**3–4**	**< 3**	UNECE (1994)
	i. BOD (mg/L)	**≤ 3**	**3.0–4.0**	**4.0–5.0**	**5.0–6.5**	**6.5–8**	**> 8**	UNECE (1994);CPCB (2015, 2002)
	i. COD (mg/L)	**≤ 30**	**30–40**	**40–50**	**50–65**	**65–80**	**> 80**	**Singh and Saxena (2020)**
	a. FC (MPN/ 100 mL)	**≤ 500**	**500–1000**	**1000–1500**	**1500–2000**	**2000–2500**	**> 2500**	CPCB (2015)
2. Nutrients (NTs)	i. NH_3-N (mg/L)	**≤ 0.3**	**0.3–0.6**	**0.6–0.9**	**0.9–1.2**	**1.2–1.5**	**> 1.5**	CPCB (2002);MEP (2008)
	i. TN (mg/L)	**≤ 0.5**	**0.5–0.8**	**0.8–1.2**	**1.2–1.6**	**1.6–2.0**	**> 2**	Anon (2000); MEP (2008)
	i. TP (mg/L)	**≤ 0.1**	**0.1–0.15**	**0.15–0.2**	**0.2–0.25**	**0.25–0.3**	**> 0.3**	CPCB (2002)
3. Algal Bacterial (AB)	i. APPI	**≤ 10**	**11–12**	**13–14**	**15–17**	**18–20**	**> 20**	Palmer (1969)
	i. FC (MPN/ 100 mL)	**≤ 500**	**500–1000**	**1000–1500**	**1500–2000**	**2000–2500**	**> 2500**	CPCB (2015)
4. Macroinvertebrates (MI)	i. MSW	**> 3.5**	**3.0–3.5**	**2.0–3.0**	**1.0–2.0**	**0–1.0**	**0**	Kerkhoff (2010)
	i. MBMWP	**> 7**	**5.5–7.0**	**4.0–5.5**	**2.0–4.0**	**0–2.0**	**0**	CPCB (2015)
5. Fish (F)	i. FS	**≥ 75**	**55–75**	**35–55**	**15–35**	**1–15**	**0**	Das et al. (2013)
	i. FSW	**> 3.5**	**2.5–3.5**	**1.5–2.5**	**0.75–1.5**	**0–0.75**	**0**	Das et al. (2013)

Table 7
Normalization scheme for PPs based on concentration and RQ for different aquatic organisms.

Chemicals	Biotic Trophic Level	Normalized score (0–5)					
		5 (RQ < 1)	4 (3 >RQ ≥1)	3 (5 >RQ≥ 3)	2 (8 >RQ≥ 5)	1 (10 > RQ≥ 8)	0 (RQ >10)
		Concentration ranges of PPs (μg/L)					
1. Acetaminophen	Algae	< 13	38–13	64–39	103–65	129–104	> 130
	Macroinvertebrates	< 9.2	9	45–27	72–46	91–73	> 92
	Fish	< 38	113–38	189–114	303–190	379–304	> 380
2. Ampicillin	Algae	< 1000	2999–1000	4999–3000	7999–5000	9999–8000	> 10,000
	Macroinvertebrates	< 2300	6599–2300	11499–6900	18399–11500	22999–18400	> 23,000
	Fish	< 1000	2999–1000	4999–3000	7999–5000	9999–8000	> 10,000
3. Amoxicillin	Algae	< 5	14–5	24–15	39–25	49–40	> 50
	Fish	< 183	547–183	913–548	1461–914	1826–1462	> 1827
4. Amphetamine	Algae	< 4	10–4	18–11	29–19	37–30	> 38
	Macroinvertebrates	< 4	12–4	21–13	34–22	43–35	> 44
	Fish	< 38	112–38	187–113	300–188	375–301	> 376
5. Azithromycin	Algae	< 0.18	0.53–0.18	0.89–0.54	1.43–0.9	1.79–1.44	> 1.8
	Macroinvertebrates	< 0.44	1.31–0.44	2.1–1.32	3.51–2.2	4.39–3.52	> 4.4
	Fish	< 460	1379–460	2299–1380	3679–2300	4599–3680	> 4600
6. Caffeine	Algae	< 0.15	0.44–0.15	0.74–0.45	1.99–0.75	1.49–1.2	> 1.5
	Macroinvertebrates	< 182	545–182	909–546	1455–910	1819–1456	> 1820
	Fish	< 88	262–88	437–262.5	699–437.5	874–700	> 875
7. Carbamazepine	Algae	< 33.6	100–33.6	167–100.8	268–168	335–268.8	> 336
	Macroinvertebrates	< 13.8	41–13.8	68.5–41.4	110–69	137–110.4	> 138
	Fish	< 35.4	106–35.4	176–106.2	283–177	353–283.2	> 354
8. Chloramphenicol	Algae	< 1259	3776–1259	6294–3777	10,071–6295	12,589–10072	> 12,590
	Macroinvertebrates	< 1000	2999–1000	4999–3000	7999–5000	9999–8000	> 10,000
	Fish	< 1900	5699–1900	9499–5700	15,199–9500	18,999–15200	> 19,000
9. Ciprofloxacin	Algae	< 2790	8369–2790	13,949–8370	22,319–13950	27,899–22320	> 27,900
	Macroinvertebrates	< 8049	24,146–8049	40,244–24147	64,391–40245	80,489–64392	> 80,490
	Fish	< 1705	5114–1705	8524–5115	13,639–8525	17,049–13640	> 17,050
10. Diclofenac	Algae	< 0.2	0.59–0.2	0.9–0.6	1.5–1	1.9–1.6	> 2.0
	Macroinvertebrates	< 20	59–20	99–60	159–100	199–160	> 200
	Fish	< 0.05	0.14–0.05	0.24–0.15	0.39–0.25	0.49–0.4	> 0.5
11. Ibuprofen	Algae	< 4	11–4	19–12	31–20	39–32	> 40
	Macroinvertebrates	< 9.1	27–9.1	45–27.3	72–45.5	90.9–72.8	> 91
	Fish	< 170	509–170	849–510	1359–850	1699–1360	> 1700
12. Ketoprofen	Algae	< 160	479–160	799–480	1279–800	1599–1280	> 1600
	Macroinvertebrates	< 250	749–250	1249–750	1999–1250	2499–2000	> 2500
	Fish	< 32	95–32	159–96	255–160	319–256	> 320
13. Ofloxacin	Algae	< 5	14–5	24–15	39–25	49–40	> 50
	Macroinvertebrates	< 31.75	95–31.75	158–95.25	253–158.75	317–254	> 317.5
	Fish	< 101	302–101	504–303	807–505	1009–808	> 1010
14. Naproxen	Algae	< 31.8	95–31.8	158–95.4	254–159	317–254.4	> 318
	Macroinvertebrates	< 2.62	7.7–2.62	13–7.86	20–13.1	26–20.96	> 26.2
	Fish	< 115.2	345–115.2	575–345.6	921–576	1151–921.6	> 1152
15. Norfloxacin	Algae	< 1.6	4.7–1.6	7.9–4.8	12–8	15.9–12.8	> 16
	Macroinvertebrates	< 12	35–12	59–36	95–60	119–96	> 120
	Fish	< 1.4	4–1.4	6.9–4.2	11–7	13.9–11.2	> 14
16. Sulfamethoxazole	Algae	< 0.27	0.80–0.27	1.34–0.81	2.1–1.35	2.69–2.16	> 2.7
	Macroinvertebrates	< 25	74–25	124–75	199–125	249–200	> 250
	Fish	< 560	1679–560	2799–1680	4479–2800	5599–4480	> 5600
17. Trimethoprim	Algae	< 795	2384–795	3974–2385	6359–3975	7949–6360	> 7950
	Macroinvertebrates	< 120.7	362–120.7	603–362.1	965–603.5	1206–965.6	> 1207
	Fish	< 16	47–16	79–48	127–80	159–128	> 160

conditions based on IGSs and overall RHI calculated for the river Ganga at Varanasi (India).

It is observed that based on RHI, the RHC is indicated as 'Good' in the river Ganga near Varanasi, when possible, concentrations of PPs are not considered. Once the presence of PPs is considered to coexist with other measured physio-chemical and biological parameters, the RHC is found under the 'Stressed' condition. The obvious reason for the decrease in RHI from 65 (indicating 'Good' river health condition) to 58 (indicating 'Stressed' condition) appears the inclusion of those chemicals under the PPs category, whose concentrations have been reported above PNEC for aquatic organisms in the river environment. The Algal- Bacterial (AB) and the Macroinvertebrate (MI) groups are the worst affected biotic indicators affecting river health. This clearly establishes that appropriate treatment and management of PPs before their mixing with river water should be the first priority for river health restoration at this site of study.

5. Conclusions

Among EPs in an aquatic environment, the presence of PPs is observed to be a serious challenge in Indian rivers. Pharmaceutical compounds are structurally designed to pose maximum effect on cells of organisms at very low concentrations. Accordingly, pollutants show significant adverse impacts on biotic indicators of the aquatic environment also. The present study has focused on the presence and impacts of PPs on river health by developing a framework to calculate the River Health Index (RHI) and classification of River Health Condition (RHC) as 'acceptable' or 'poor' based on RHI. The results of the study can be summarized as follows:

- Among a number of PPs examined for their presence in Indian rivers, azithromycin, caffeine, diclofenac, naproxen, norfloxacin, and sulfamethoxazole are found in concentrations much above their

Table 8
Water quality characteristics of river Ganga near Varanasi city (India).

S. N.	Indicator Group	Weightage for the Group	Parameters	Measured Environmental Concentrations (MEC)	Source
1.	Dissolved oxygen-related parameters (DORPss)	$w_1 = 0.10$	i. EC (μmhos/cm) ii. DO (mg/L) iii. BOD (mg/L) i. COD (mg/L)	332 6.3 4.0 52	Saxena and Singh (2020)
2.	Nutrients (NTs)	$w_2 = 0.20$	i. NH_3-N (mg/L) ii. TN (mg/L) iii. TP (mg/L)	0.31 0.78 0.125	
3.	Emerging Pollutants (EPs)	$w_3 = 0.20$	i. Caffeine (μg/L) ii. Diclofenac (μg/L) iii. Sulfamethoxazole (μg/L)	0.743 0.994 0.773	Sharma et al. (2019) Jindal et al. (2015) for river Yamuna at Agra in Ganga Basin
4.	Algal Bacterial (AB)	$w_4 = 0.20$	i. APPI i. FC (MPN/100 mL)	13 1200	Saxena and Singh (2020)
5.	Macroinvertebrate (MI)	$w_5 = 0.20$	i. MSW ii. MBMWP	1.65 4.8	
6.	Fish (F)	$w_6 = 0.10$	i. FS ii. FSW	70 2.23	

Table 9
Critical compounds of PPs reported in Indian Rivers and their biotic significance.

S. N.	River	Critical compound	RQ	Biotic significance
1.	River Akravathi (Gopal et al., 2021)	Naproxen[*1]	1.65 for MI	Macroinvertebrates are under the '**moderately high-risk**' category.
2.	River Ganga near Patna (Sharma et al., 2019)	Caffeine[*4]	4.95 for A	Algal species in '**significantly high risk**' conditions.
3.	River Brahmaputra, Guwahati (Kumar et al., 2019)	Caffeine[*4]	2.73 for A	Algal species in '**moderately high risk**' conditions.
4.	River Ahar, Udaipur (Williams et al., 2019a)	Caffeine[*4]	24.5 for A	Algal species in '**fatally high risk**' conditions.
		Azithromycin[*1]	2.27 for A	Algal species in '**moderately high risk**' conditions.
5.	River Yamuna, Agra (Jindal et al., 2015)	Sulfamethoxazole[*1]	2.71 for A	Algal species in '**moderately high risk**' conditions.
		Diclofenac[*2]	4.97 for A; and 19.88 for F	Algal species in '**moderately high risk**' and Fish in '**fatally high risk**' conditions.
6.	Isakavagu-Nakkavagu Stream of River Godavari, Hyderabad (Fick et al., 2009)	Norfloxacin[*1]	293 for A; 39 for MI, and 335 for F	All three biotic trophic levels are in '**fatally high risk**' conditions.

As can be seen from Table 9, algae are the most vulnerable biotic level due to PPs followed by macroinvertebrates and fishes. Such high-risk conditions are reflected in poor river health at the given site.

predicted no-effect concentration (PNEC) values for algae, macroinvertebrates, and fishes in the aquatic environment.

- At present, the available literature on the subject does not clearly provide the classification of risks on aquatic organisms based on PNEC and risk quotient (RQ). Based on analyses, this study proposed an assessment factor (AF) of 10 over PNEC to define the critical threshold concentration of any polluting chemical in a river environment. Accordingly, the risks to aquatic organisms have been classified into five categories: moderately high, significantly high, critically high, severely high, and fatally high based on RQ values 1–3, 3–5, 5–8, 8–10, and > 10 respectively.
- Based on concentrations of PPs reported in rivers in India, the risk quotient (RQ) ranges from a modest value of 1.65 with naproxen on macroinvertebrates in river Akaravathi (Bangaluru) to more than 300 with norfloxacin on fish in a stream Isakavagu-Nakkavagu, a tributary of river Godavari, near Hyderabad. The concentrations reported indicated 'moderately high' to 'fatally high' risk conditions for these biotic indicators.
- A framework to access RHC based on six categories of water quality parameters has been developed and demonstrated in the present study. Three physico-chemical indicator groups: Dissolved Oxygen Related Parameters (DORPs), Nutrients (NTs), and Emerging Pollutants (EPs) were considered as causes, and three biotic groups: Algal Bacterial (AB), Macroinvertebrates (MI) and, Fish (F) indicators were considered as the response in calculating the RHI.
- In addition to the normally monitored physico-chemical characteristics of the river Ganga upstream of Varanasi city and including the effect of PPs with them, based on calculated RHI value, the health condition of the river is found under "stressed" condition. The indicator group score (IGS) for PPs is found under the "critical" category.
- Any river health restoration and improvement plan must prioritize reduction in concentrations of PPs in order to achieve Good river health conditions in the Acceptable category.
- Azithromycin, caffeine, diclofenac, naproxen, norfloxacin, and sulfamethoxazole are the major pharmaceutical chemicals whose concentrations are found much higher than the PNEC values for aquatic organisms.
- Pictorial representation of river health conditions based on RHI including the status of different indicator groups measured through respective IGSs gives a clear indication of priority actions for intervention and improvements.

6. Future Scopes

Photodegradation, biodegradation, and bioremediation are the preferred methods for the removal or reduction of PPs concentrations in the aquatic environment. Among biological approaches, membrane bioreactor (MBR) coupled with Constructed Wetlands (CW) or ozonation has been suggested for mitigating conventional and pharmaceutical pollutants. Effective management of PPs to keep their concentrations within PNEC values appears as the first step in the endeavor to achieve acceptable river health conditions. Planning and implementation of such a strategy remain the vital next step toward the objectives of river health restoration.

Table 10
Parametric normalized scores, Indicator Group Scores, and RHC of the river Ganga near Varanasi.

S. No.	Indicator Group	Parameters	Normalized score (0–5)	IGS (0–100)	Indicator Group/ River Health Condition
1.	Dissolved oxygen-related parameters (DORPs) (w_1 = 0.10)	i. EC (μmhos/cm)	5	75	Very Good
		i. DO (mg/L)	4		
		i. BOD (mg/L)	4		
		i. COD (mg/L)	2		
		∑ Normalized score	15		
		No of the parameters considered	4		
2.	Nutrients (NTs) (w_2 =0.20)	NH_3-N (mg/L)	4	80	Very Good
		TN (mg/L)	4		
		TP (mg/L)	4		
		∑ Normalized score	12		
		No of the parameters considered	3		
3.	Emerging Pollutants (EPs) (w_3 =0.20)	Caffeine	0	27	Critical
		Diclofenac	0		
		Sulfamethoxazole	4		
		∑ Normalized score	4		
		No of the parameters considered	3		
4.	Algal Bacterial (AB) (w_4 =0.20)	APPI	3	60	Stressed
		FC (MPN/ 100 mL)	3		
		∑ Normalized score	6		
		No of the parameters considered	2		
5.	Macroinvertebrates (MI) (w_5 =0.20)	MSW	2	50	Over Stressed
		MBMWP	3		
		∑ Normalized score	5		
		No of the parameters considered	2		
6.	Fish (F) (w_6 =0.10)	FS	4	70	Good
		FSW	3		
		∑ Normalized score	7		
		No of the parameters considered	2		
			RHI (0–100)	58	**Stressed**

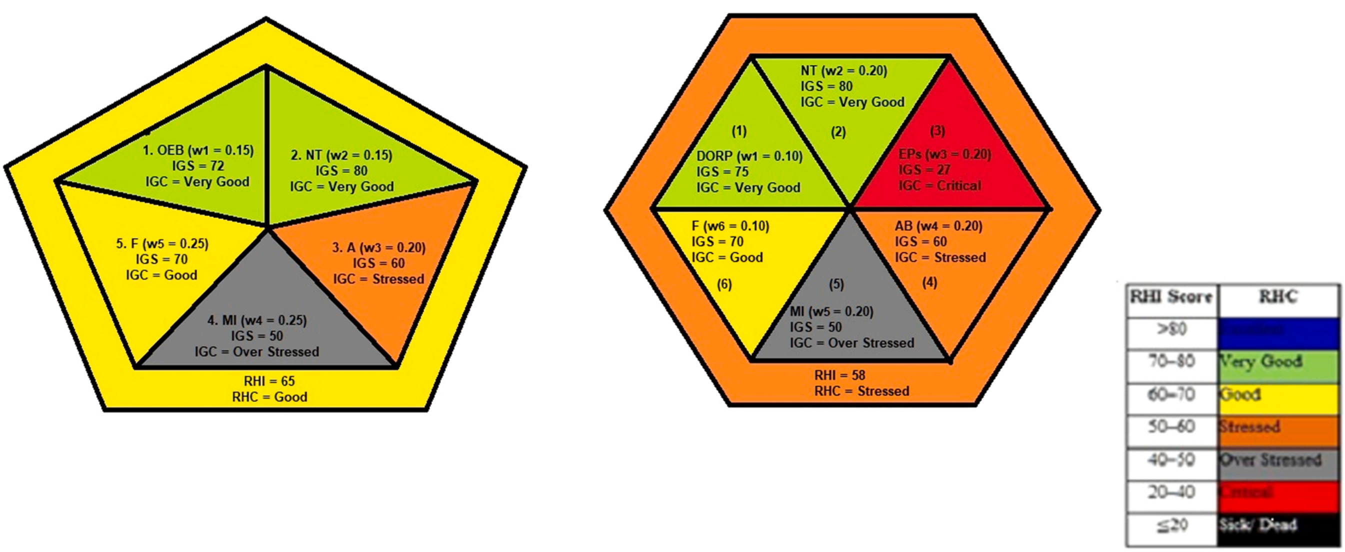

Fig. 1. (a): 'Good' River Health Condition (RHC) of the river Ganga at upstream of Varanasi city (India), as reported by Saxena and Singh (2020) without considering the presence or effect of PPs., Pentagonal shape reflects five Indicator groups considered in calculating RHI, Colour of each sector reflect river health condition with respect to that indicator group., Color of circumscribing pentagon reflects overall River Health Condition based on RHI., (b): 'Stressed' River Health Condition (RHC) of the river Ganga at upstream of Varanasi city (India), considering the presence of PPs as reported by Jindal et al. (2015) and Sharma et al. (2019) in rivers of Ganga basin in addition to water quality characteristics reported by Saxena and Singh (2020) at Varanasi., Hexagonal shape indicates six groups of indicators considered in formulation of RHI., Colour of each sector inside hexagon reflects river health condition with respect to that indicator group., Color of circumscribing hexagon reflects overall River Health Condition based on RHI.

CRediT authorship contribution statement

Mr. Nitin Ranjan: Conceptualization, Investigation, Methodology, Data analysis, Writing – original draft. **Prabhat Kumar Singh:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Nityanand Singh Maurya:** Supervision, Validation, Review.

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.

Data Availability

Data will be made available on request.

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