Chapter 6

Environmentally Persistent Pharmaceutical Pollutants

CONTENTS

1 Introduction

Presence of Environmentally Persistent Pharmaceutical Pollutants (EPPPs) in groundwater and surface water has become an issue of great concern and numerous incidents of contamination have been documented in developed and developing countries. Several reports are available on the presence of EPPPs in most of the drinking water sources like river, surface and groundwater in India.

Active Pharmaceutical ingredients (APIs) have been used for the benefits of society for treatment, diagnoses, prevention of diseases, etc(WHO, 2012). Large quantities of APIs are identified in the various compartment of the environmental matrix and pose a serious threat to humans, wild, and aquatic life(WHO, 2012). The presence of API in the environment instigating mainly from human consumption pose a potential hazard to the aquatic and terrestrial environments (STOWA, 2003). Migration of pharmaceuticals in water bodies has become an issue of greater concern, and numerous incidents of contamination have been documented in the developed and developing countries. Since 2000, the presence of APIs (concentration ranging from ng/L to µg/L) in the water cycle and their risk have been widely discussed and reported (Mons, M. N., J. van Genderen, 2000; STOWA, 2003).

In 2001, the European Union (EU) implemented that only approved pharmaceuticals should be used and the registration could be done by either the European Medicines Evaluation Agency (EMEA) or respective country (EC, 2001; EC, 2004). Also, a detailed environmental assessment proposed by EMEA "Guideline on the environmental risk assessment of medicinal products for human use," was included in the registration procedure (EMEA, 2018; STOWA, 2003). In the years of 2009-2010, World Health Organization (WHO) constituted the experts' committee and framed the health impacts of APIs residue and drinking water quality(WHO, 2012).

The recent advancement in the analytical methods has shown presence of pharmaceutical residues in aquatic ecosystems and their concentrations were ranging from ng to µg/L (Caldwell et al., 2016; Monteiro and Boxall, 2010). The major sources of APIs reaching the environment are excretion (human and animal excreta) of pharmaceuticals residues or their intermediates/metabolites into sewer/wastewater treatment systems (EMEA, 2018; Tischler et al., 2013). Further, the unsafe disposal of unused or expired medicines, effluent from pharmaceutical manufacturing/formulation units, health-care and veterinary facilities,

biosolids, etc., are the potential sources of pharmaceuticals contamination. The different

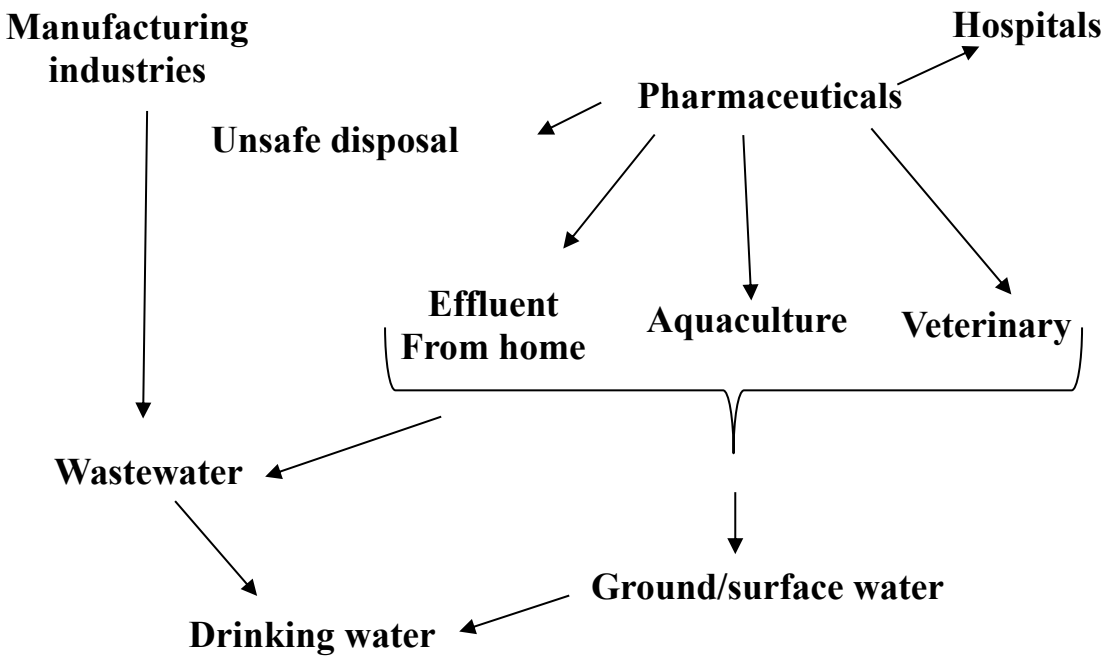

Figure 1.1 Pathways of input and distribution of APIs in the environment.

sources of pharmaceutical contamination in the aquatic environment is given in .

APIs cover a wide range of compounds with different chemical, physicochemical, and biological properties (Klatte et al., 2017). There are 50% of APIs approved for human consumption in Germany that are considered to be bio accumulative, persistent, and toxic to humans (Ebert et al., 2014; Klatte et al., 2017). So far, more than 600 APIs and their transformation products have been identified very often in surface waters and sewage effluent and are reported in 71 different countries (Hamscher et al., 2002; Klatte et al., 2017; Ratsak et al., 2013; Weber et al., 2014). Most commonly identified pharmaceuticals in the environment in 50 different countries are given in Table 1.1.

This report provides an overview of pharmaceutical pollution in India. It discusses about state of EPPPs and Indian pharmaceutical industry. It provides information about occurrences of pharmaceutical contaminants in Indian water bodies such as rivers, lakes, ground water and wastewater treatment plants. The report will also provide information on different sources of pharmaceutical pollution and health effects associated with it. Different existing treatment systems and challenges will be discussed in detail. Finally, detailed recommendations will be provided for management and control of EPPPs in India.

Table 1.1. Most commonly identified pharmaceuticals in the environment in 50 different countries (IWW, 2014)

S. No	Pharmaceuticals	Used for
1	Diclofenac	Pain and inflammation
2	Carbamazepine	Anti-epileptic
3	Ibuprofen	Pain and inflammation
4	Sulphamethazole	Antibiotic
5	Naproxen	Pain and inflammation
6	Trimethoprim	Antibiotic
7	Paracetamol	Pain
8	Clofibric acid	Lipid lowering drug
9	ciprofloxacin	antibiotic
10	ofloxacin	antibiotic
11	norfloxacin	antibiotic
12	acetylsalicylic acid	aspirin, a pain killer
13	estrone, 17β-estradiol	SHAS
14	17α-ethinyl estradiol	SHAS
15	Estriol	SHAS

2 An Overview of Indian Pharmaceutical Industries

The Indian Pharmaceutical industry was valued at USD 33 Billion in 2017 and is expected to grow at a CAGR of 22.4% between 2015- 2020 and achieve a market size of USD 55 Billion, of which the domestic generic market is expected to contribute USD 27.9 Billion (India Brand Equity Foundation, 2019). Indian pharmaceutical industry supplies over 50 per cent of global demand for various vaccines, 40 per cent of generic demand in the US and 25 per cent of all medicine in UK. Annual and quarterly growth of Indian Pharmaceutical market are shown in Figure 2.1and Figure 2.2 respectively.

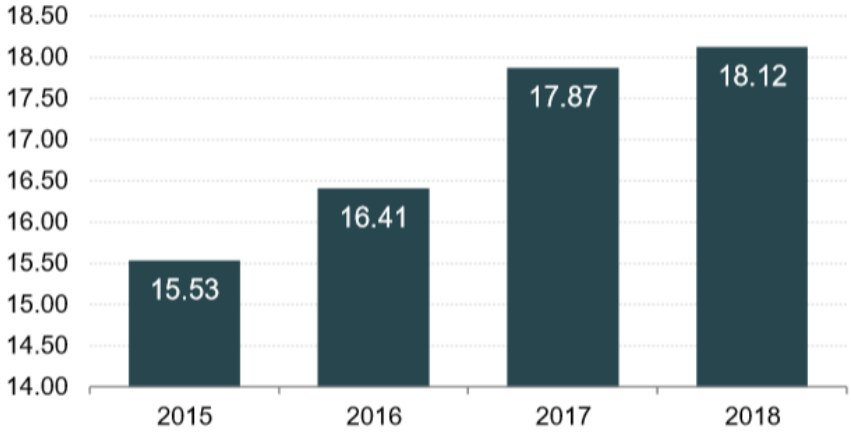

Figure 2.1 Annual Turnover of Indian Pharmaceutical Market (India Brand Equity Foundation, 2019)

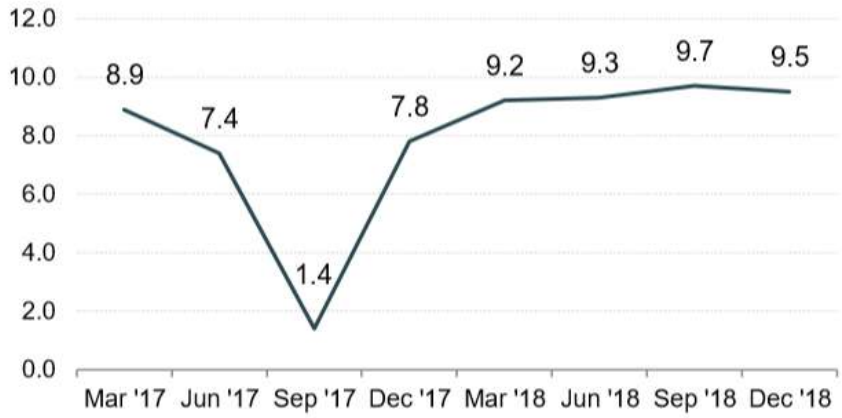

Figure 2.2 Quarterly Growth in Indian Pharma Market(%) (India Brand Equity Foundation, 2019)

India accounts for 20 per cent of global exports in generics. India's pharmaceutical exports stand at US$ 3.1 billion in FY20 (up to June 2019) as compared to US$ 19.14 billion in FY19 (Figure 2.3). The exports are expected to reach US$ 20 billion by 2020. Indian drug manufacturers currently export their products to more than 65 countries worldwide (Figure 2.4). Their largest customer is the U.S., the world's biggest pharmaceutical market.

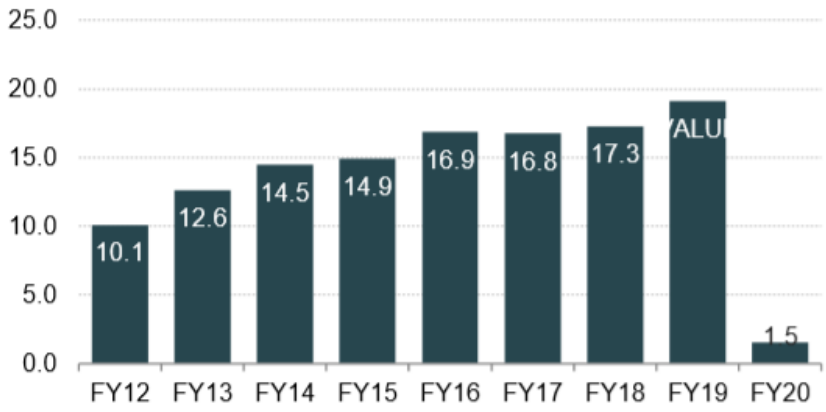

Figure 2.3 Pharmaceutical exports from India(up to June 2019) (India Brand Equity Foundation, 2019)

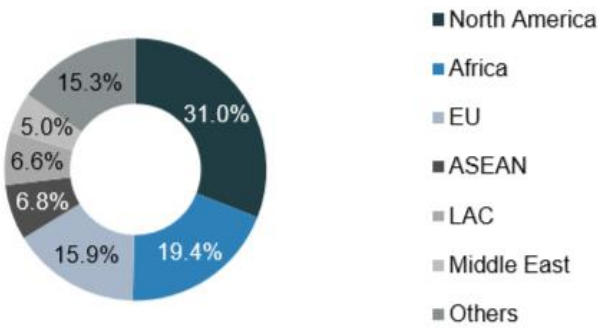

Figure 2.4 Export Destinations in India's Pharma Export in FY 18 (%)(India Brand Equity Foundation, 2019)

EU – European Union, ASEAN - Association of Southeast Asian Nations, LAC - Latin America and the Caribbean

India is the second largest contributor of global biotech and pharmaceutical workforce. The pharmaceutical sector was valued at US$ 33 billion in 2017. Indian healthcare sector, one of the fastest growing sectors, is expected to cross US$ 372 billion by 2022. India has high potential generics market. The domestic generics market is expected to reach US$ 27.9 billion by 2020. India's generics market has immense potential for growth. Indian pharmaceutical companies received record 300 generic drug approvals in USA during 2017 where the generic market is expected to reach US$ 88 billion by 2021. By 2024-25, India's biotech industry is estimated to increase to US$ 100 billion(India Brand Equity Foundation, 2019).

The Government of India unveiled 'Pharma Vision 2020' aimed at making India a global leader in end-to-end drug manufacture. Approval time for new facilities has been reduced to boost investments. Indian pharmaceutical industry is typically involved in four types of businesses- marketing of generic medicines, marketing of branded generic medicines, marketing of innovator medicines, and manufacture and supply of active pharmaceutical ingredients which are used as ingredients in medicines as well as finished formulations. For a global pharmaceutical company seeking to enter Indian pharmaceutical market today, the opportunities are exciting and the potential is tremendous. Several factors attract global pharmaceutical companies to India:

i. Low cost of production due to variety of factors including cheap labour and raw material cost;

ii. Big market not only for life saving drugs but also for lifestyle drugs; Potential for conducting research and development activities in India – India has more than 300 medical colleges, over 20,000 hospitals;

iii. Existing manufacturing capability to produce active pharmaceutical ingredients (APIs) as well as intermediates at lower cost while maintaining quality;

iv. Ease of conducting clinical trials and bio availability and bioequivalence studies due to India's ability to provide speedier and less expensive trials without compromising quality and vast patient pool;

v. India has maximum number of USFDA approved plants outside USA which are over 16910 in number (Figure 2.5);

vi. Product patent regime.

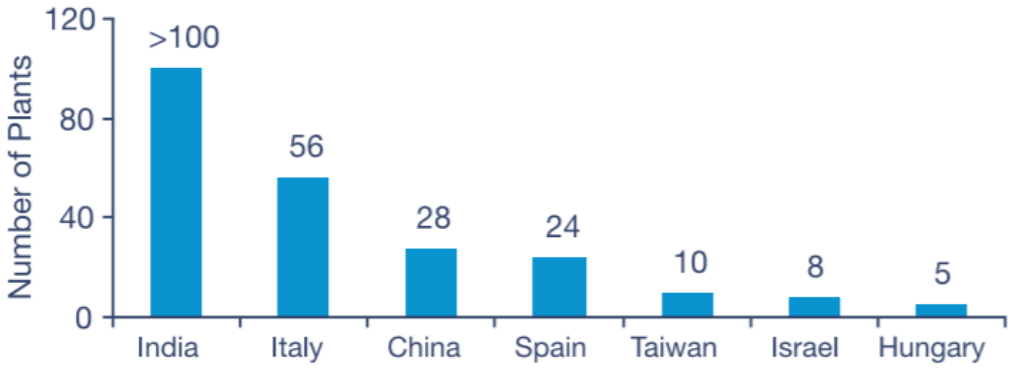

Figure 2.5 Number of USFDA approved plants in different countries (Sciences, 2010)

The "organized" sector of India's pharmaceutical industry consists of 250 to 300 companies, which account for 70 percent of products on the market, with the top 10 firms representing 30 percent. However, the total sector is estimated at nearly 20,000 businesses, some of which are extremely small. Approximately 75 percent of India's demand for medicines is met by local manufacturing. A state wise comparison on number of pharmaceutical industries present in India is given in Figure 2.6.

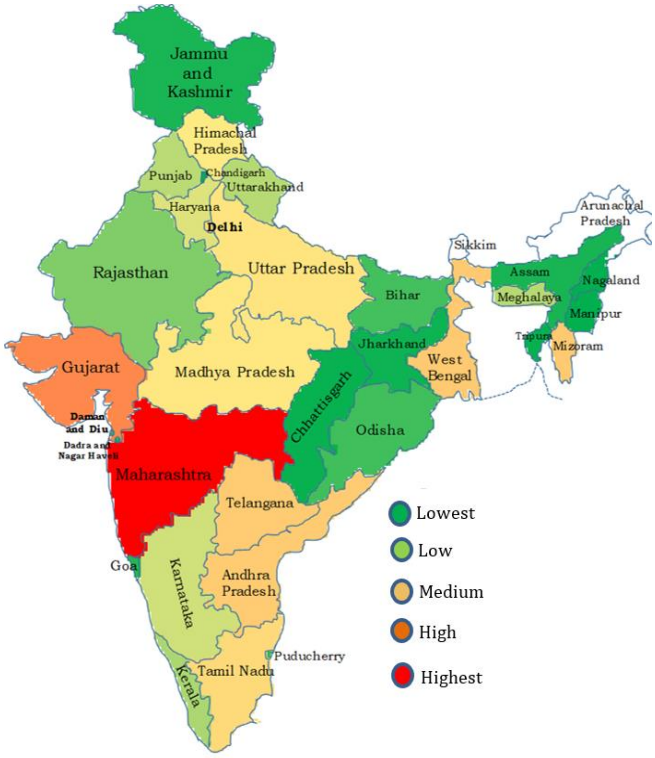

Figure 2.6. Number of pharmaceutical manufacturing units in India

3 Existing Guidelines and Regulations

The research team commenced with a review of documents to get a historical overview of hazardous waste management in the international arena. The UN report titled 'Independent Evaluation of the Strategic Approach from 2006 – 2015 Draft Report' was found particularly useful in understanding the history and the emergence of waste management regime. This UN report provides an overview of the five major international treaties namely Montreal Protocol on Substances that deplete the Ozone Layer (1987), Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposals (1989), the Rotterdam Convention on the prior consent procedure for Certain Hazardous Chemicals and Pesticides in International Trade (1998), Stockholm Convention on Persistent Organic Pollutants (POPs) and Minamata Convention on Mercury (2013). We have documented the salient features of these five treaties.

The research then focused on SAICM and a thorough reading was undertaken of the text titled 'Strategic Approach to International Chemicals Management: SAICM texts and resolutions of the International Conference on Chemicals Management', so as to understand the policy objectives and goals. Our reading shows that although there was an existing framework and global regime to tackle the problem of hazardous waste, in many countries (in India in particular), there has been a proliferation of global chemical industry. and there was also a lack of comprehensive coverage of chemical waste. SAICM was intended to complement the existing conventions on chemical and waste by helping states to reduce the risks of toxic chemicals left unaddressed by the existing global treaties, while also promoting effective implementation. SAICM reflects a collaboration between stakeholders which includes governments, international organisations, industry and civil society organisations. Further, the report titled 'A submission from the Nordic Council of Ministers - Report on the Investigation of elements in support of the global post 2020 framework for chemicals and waste' was discussed which also included certain limitations of SAICM.

The rest of this report is divided into four sections, which directly deal with hazardous chemical waste management and regulatory mechanisms in India

a) Regulations dealing with hazardous chemical waste management in India
b) Regulatory Bodies and Acts dealing with Pharmaceuticals in India
c) Green manufacturing practices in India

d) The way forward

3.1 Regulations dealing with hazardous chemical waste management in India:

The focus of the research was narrowed from international arena to Indian context. The team conducted a preliminary research on the existing legislations in India regarding chemical management. Around forty Acts (including the Indian Ports Act 1908, the Drugs and Cosmetics Act 1940, the Insecticides Rules 1971, Chemical Accidents (Emergency Planning, Preparedness and Response) Rules 1996, the Mines Act 1952) were reviewed. The relevant clauses to chemical waste were identified and compiled for future reference. The article titled 'Environmental Legislations for Chemical Management in India: An agenda for Reforms' provided the groundwork for this research (Balaji et al., 2014). It was observed that the issue of safe chemical management is addressed in various acts but there is lack of a comprehensive regulatory mechanism and guidelines in India.

The second part of research in legislations deals directly with legislations regarding hazardous waste management. Legislations like Hazardous Waste Rules 2016, E- Waste Management Rules 2016, Solid Waste Management rules 2016 etc. were also reviewed. This part of the research was undertaken to create a holistic understanding of the existing overall framework about waste management regime in India

3.2 Regulatory Bodies and Acts dealing with Pharmaceuticals

The team focused its research on the chemical waste generated by pharmaceuticals in India. There are various regulatory mechanisms that deal with the quality, pricing and control of the pharmaceutical sector in India. The major regulatory bodies in pharmaceutical waste are as follows.

3.2.1 Ministry of Health and Family Welfare

- Central Drugs Standard Control Organisation (CDSCO)
- Indian Council of Medical Research (ICMR)
- Indian Pharmacopoeia Commission (IPC)
- National Institute of Biologicals (NIB)

3.2.2 Ministry of Environment and Forest

- The Genetic Engineering Appraisal Committee

- The Review Committee on Genetic Manipulation (RCGM)
- Central Pollution Control Board

3.2.3 Ministry of Chemical and Fertilisers

- Department of Pharmaceuticals (DoP)

The major acts which directly deal with pharmaceuticals (especially in healthcare) are Drugs and Cosmetic Act 1940, The Pharmacy Act 1948, the Drugs and Magic Remedies Act 1954, the Medicinal and Toilet Preparations (Excise Duties) Act 1956, the Narcotics Drugs and Psychotropic Substances Act 1985, the Drug Price Control Order 1995, and Bio medical waste regulations (BMW) 1998. Out of these acts only Bio-medical waste regulations deal directly with chemical waste management in healthcare. According to this Act, the biomedical waste is defined as, "Bio-medical waste means any waste, which is generated during the diagnosis, treatment or immunisation of human beings or animals or in research activities pertaining thereto or in the production or testing of biologicals." The BMW rules were adopted in India in 1998 under the section 6, 8 and 25 of the Environmental Protection Act, 1986. The Bio-medical regulations (1998) lays the basic foundation for regulations of pharmaceutical waste in India. All healthcare facilities in the country are covered under these rules. According to BMW rules 1998, the waste from healthcare waste was divided into ten categories which were further reduced to four categories in 2016 amendment. Figure 1 clarifies the distinction between the four categories. The research team will pursue the wastes in yellow category as it consists of chemical waste and chemical liquid waste. Literature shows that several challenges, like lack of awareness and training, lack of segregation, lack of proper operational strategy, relationship between Health Care Establishments and Common Biomedical Waste Treatment Facilities, continue to remain and need to be addressed.

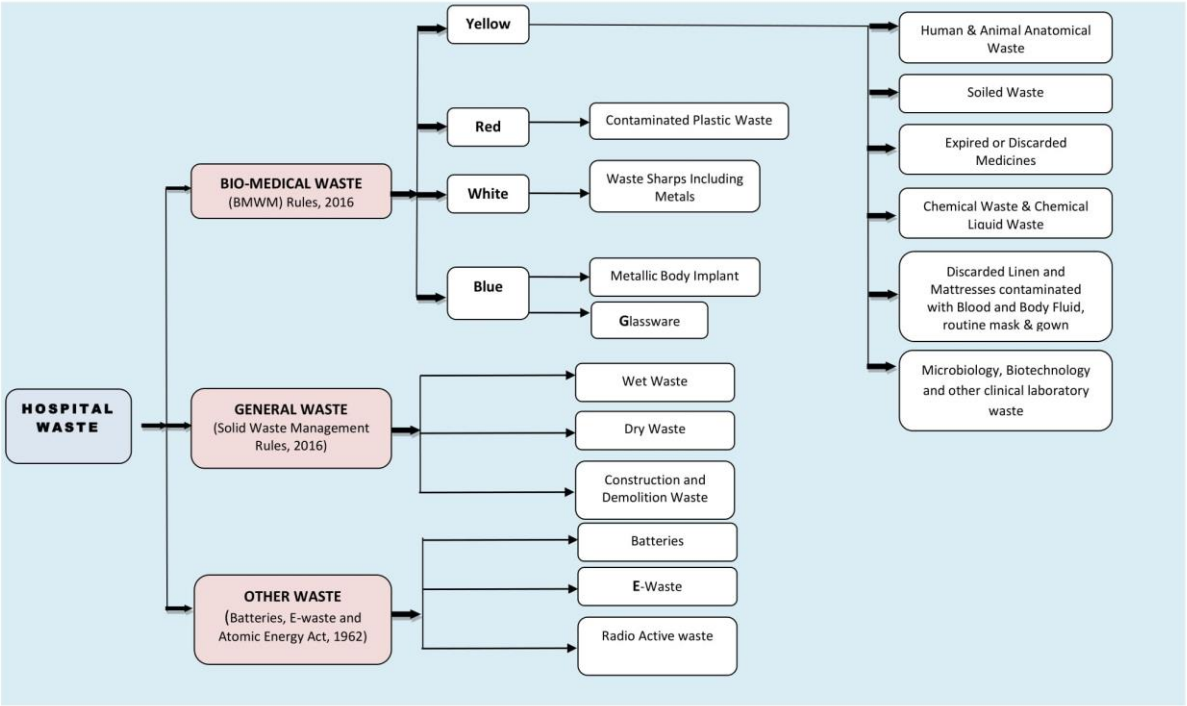

Figure 3.1 Categorisation and Classification of Wastes in Health Care Facilities(Ministry of Health and Family Welfare and Ministry of Environment Forest and Climate Change Delhi).

3.3 Green manufacturing practices in India

According to the report titled 'Green Manufacturing Practices: Energy, Products and Processes' , green manufacturing involves transformation of industrial operations in three ways: (1) using Green energy, (2) developing and selling Green products and (3) employing Green processes in business operations (Bhattacharya et al., 2011). Adoption of green manufacturing practices is relatively new in India but the industries have been receptive to these practices. The adoption of Green practices by manufacturing industries benefit them not only in long–term cost savings, but also in brand enhancement. It also enhances regulatory traction, attracts talent as well as investor interest. The adoption of green manufacturing practices can be highly relevant for pharmaceutical industries which come under the 'red' category of pollution Index. Recently, USV Ltd, a pharmaceutical company at Baddi, Himachal Pradesh received award for adopting green manufacturing practices and deploying sustainability. It is evident that adoption of green manufacturing practices can substantially improve the reduction of harmful chemical waste emitted from these industries. Further

research is being carried out to map the scope of green manufacturing practices in pharmaceuticals. This can emerge as a major policy recommendation and point of discussion for further round table conferences.

3.4 **Way forward**

The team proposes to conduct following research in the coming months in regard to pharmaceuticals.

- Research the scope and adoption of green manufacturing practices in pharmaceuticals and devise recommendations based on it.
- Conduct case study research for certain pharmaceuticals industries located in Hyderabad and Himachal Pradesh to understand the problems in regulatory mechanisms.
- To conduct comparative study of measures adopted by the EU, USA and UK to combat the problem of pharmaceutical chemical waste. The relevant policy measures and practices will be suggested for round table conferences.

We give below the list of key publications consulted so far relevant to the subject

Arindam Bhattacharya, Rahul Jain and Amar Choudhary, *Green Manufacturing: Energy, Products and Processes*, The Boston Consulting Group and Confederation of Indian Industries, March 2011

Balaji, G., Potdar Aditee and Unnikrishnan Seema. "Environmental legislation for chemical management in India: An agenda for reforms." *Journal of Environmental Research and Development* 9, no. 2 (2014): 494-506

Baskut Tuncak, Gretta Goldenman, et al., *Investigation of elements in support of the global post 2020 framework for chemicals and waste*, Swedish Society for Nature Conservation (SSNC), Finnish Society for Nature Conservation (FANC), Norske Naturvernforbundet (Friends of the Earth Norway), and Det Økologiske Råd (Denmark), with co-funding from the Nordic Council of Ministers and the Swedish International Development Cooperation Agency (SIDA), 12 December 2018 (revised 15 March 2019).

Chemicals Road Map, World Health Organization, 2017.

Gore, Andrea C., David Crews, Loretta L. Doan, Michele La Merrill, Heather Patisaul, and Ami Zota. "Introduction to endocrine disrupting chemicals (EDCs)." A Guide for Public Interest Organizations and Policy-Makers; Endocrine Society: Washington, DC, USA (2014).

Government of India, *Guidelines for Management of Healthcare Waste as per Biomedical Wastw Management Rules, 2016*, Ministry of Health and Family Welfare and Ministry of environment, Forest and Climate Change, Delhi.

Greeshma Tony, Naveen Kumar, Brayal Dsouza and sagarika Kamath. “System Analysis of Biomedica; Waste Management Across Healthcare Clinics of Udupi Taluk.” *Journal of Meghe Institute of Medical Sciences University* 13, no.4 (2018): 199-201.

Hyderabad’s Pharmaceutical Pollution Crisis: Heavy Metal and solvent Contamination at factories in a Major Indian drug Manufacture Hub, Nordea and Changing Markets Foundation, 2018.

Mayank Dev Singh and G.D. Thakar, “ Green Manufacturing Practices in SMES of India- A literature Review.” Industrial Engineering Journal XI, no.3 (2018): 37-45.

Options for a Strategic Approach to Pharmaceuticals in the Environment (European Commission, July 2018), prepared by Deloitte, Milieu Ltd, INERIS, Klaus Kummerer.

Piyush Mohapatra, Alka Dubey, Prashant Rajankar, *An investigative Study On Bisphenol- A (BPA) in Baby Feeding Bottles in India*, Toxics Link, 2014.

Robert Nurick, *Independent Evaluation of the Strategic Approach from 2006 – 2015 Draft Report*, SAICM Secretariat, WHO and UNEP, 5 March 2018.

SAICM texts and resolutions of the International Conference on Chemicals Management, SAICM Secretariat, UNEP and WHO, no date available.

N. D. Shrinithivihahshini, D. Mahamuni, and N. Praveen. "Bisphenol A migration study in baby feeding bottles of selected brands available in the Indian market." *Current Science* (2014): 1081-1084.

4 State of EPPPs

Pharmaceutical active compounds are frequently detected in different environmental compartments, owing to their mass production and consumption. The effluents from pharmaceutical manufacturing facilities and domestic sewage may have high levels of Pharmaceutically Active Compounds (PhACs) (Larsson et al., 2007; Mutiyar and Mittal, 2014).

The human body usually does not retain the entire quantity of drug consumed, and a major fraction is excreted in parent form or in the form of active metabolites through urine and faeces (Beaumont et al., 2014). After administration, drugs are transformed to one or more of their metabolites and are excreted as a mixture of metabolites, major drug conjugates, and parent compounds. However, the excretion of drugs are highly compound specific (Lienert et al., 2007). For example, in case of ibuprofen, around 15% of the ingested dose is excreted in form of parent compound, and ~79% is excreted as conjugates (Bruchhausen et al., 1994); but on the other hand, amoxicillin is excreted up to 80–90% as the conjugated parent compound from the human body (Hirsch et al., 1999). Detailed pharmaco-kinetics data revealed that human excretion rates of unchanged drugs exceeded over ~50% and the rest is excreted as metabolites in conjugate forms.

EPPPs are pharmaceutical drugs that are consumed for the treatment of temporary or chronic health conditions in both, humans and animals (Khetan, 2014). EPPPs constitute of organic chemical compounds, transformed metabolites and preservative chemical compounds from pharmaceutical drugs that are persistent in the aquatic environment and have recently gained considerable attention of the scientific world (Daughton, 2004; Daughton and Ternes, 1999). Jjemba (2006) in his study described EPPPs as natural or manufactured chemicals or materials occurring in the environment that are highly biologically active affecting the biochemical and physiological functions of the body. Accordingly, pharmaceutical substances can be defined as ‘Environmentally persistent, biologically active, organic micropollutants derived from anthropogenic sources. EPPPs are broadly classified into five different therapeutic classes as given in

Table 4.1.

Table 4.1. EPPPs of different therapeutic classes

S. No	Pharmaceuticals	Reference
1	Psychiatric drugs	Diazepam, carbamazepine, primidone, lorazepam
2	Lipid regulators	Clofibric acid, bezafibrate, fenofibric acid, etofibrate, gemfibrozil, atorvastatin
3	β- blockers	Atenolol, propranolol, timolol, sotalol, metoprolol
4	Analgesics and anti-inflammatory	Ibuprofen, diclofenac, fenoprofen, acetaminophen, naproxen, acetylsalicylic
5	Antibiotics	Amoxicillin,cefalexin, trimethoprim, erythromycin, lincomycin, chloramphenicol

There are thousands of chemicals that are manufactured in or imported into the India every year. These chemicals are released into the environment and pose a severe threat to the endocrine systems of wildlife and humans by interfering with normal growth and development functions (ATSDR, 2002). These chemicals commonly known as endocrine-disrupting compounds (EDCs) or endocrine disruptors (EDs) are both synthetic and natural compounds in the environment that have the ability to disrupt metabolic pathways by either mimicking or blocking endogenous hormones, or by altering hormone function. Many EDCs are highly carcinogenic and include a variety of chemicals such as pesticides, fungicides, industrial compounds, by-products of industrial processes, and chemicals used in the manufacturing of plastics. Of particular concern are the hormonally active agents that are persistent in the environment, highly lipophilic, readily bio-accumulate and magnify within the food chain (Lyche et al., 2009; Meeker et al., 2009).

Due to increased environmental and health effects, there is an increase on the research focusing EPPPs across the world. Figure 4.1 shows that research and publications on EPPPs are increasing tremendously in the recent decade. Contribution of India towards studies on EPPPs are also increasing as can been seen in Figure 5.2. Beek et al. (2016) discusses about global occurrence of pharmaceuticals in surface waters, ground water or tap/drinking water is shown in

Figure 4.3. There is no data available for occurrence of pharmaceuticals in tap/drinking water and manure/soil in India as can be found from

Figure 4.4 and

Figure 4.5 respectively.

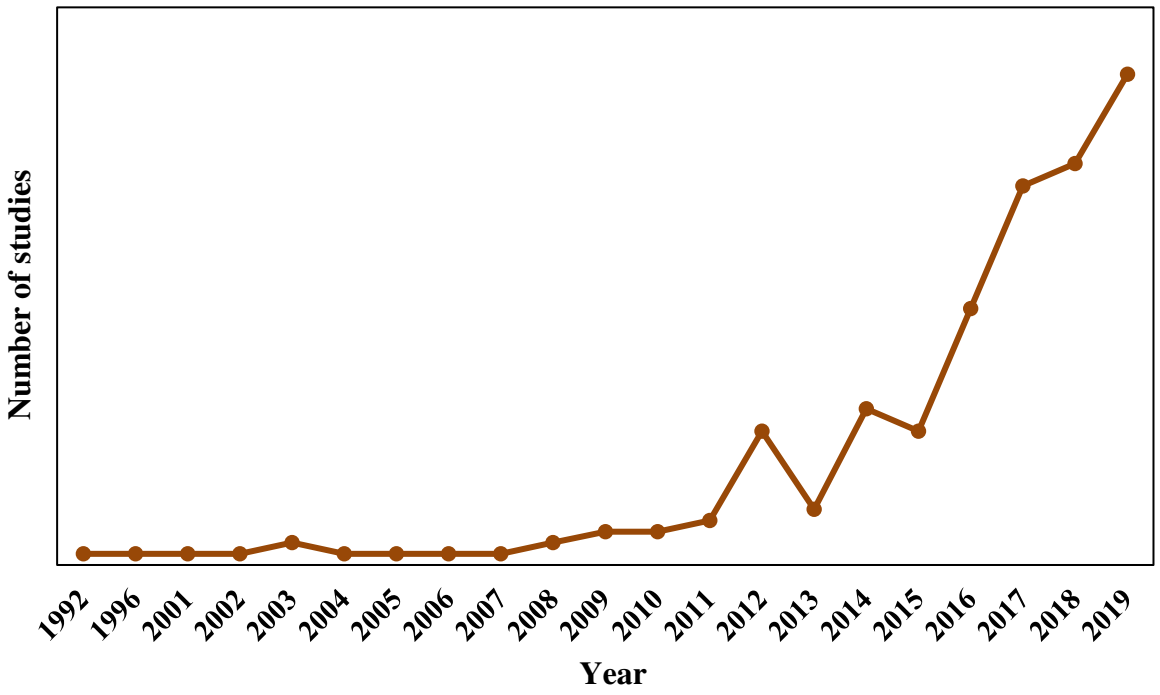

Figure 4.1 Publications on pharmaceutical pollutants

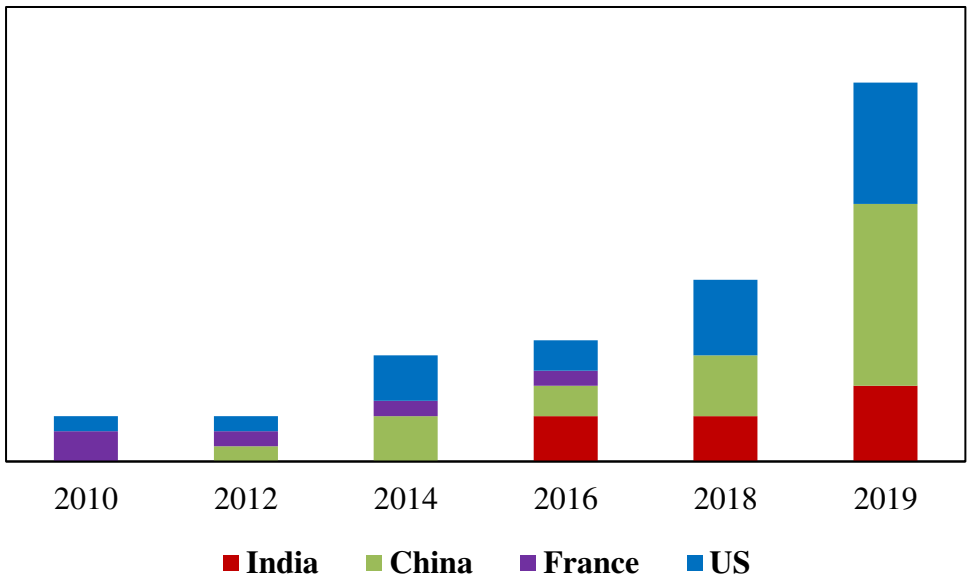

Figure 4.2 Comparison of publications on pharmaceutical pollutants in India, China, France and US

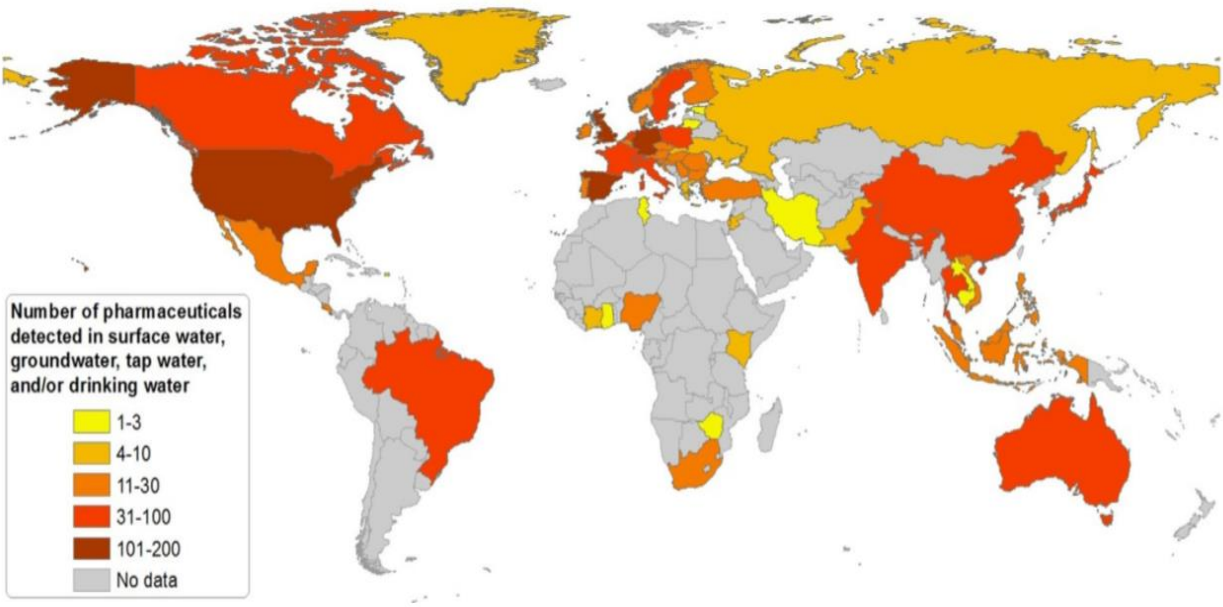

Figure 4.3 Number of pharmaceuticals detected in surface waters, ground water or tap/drinking water (Beek et al., 2016).

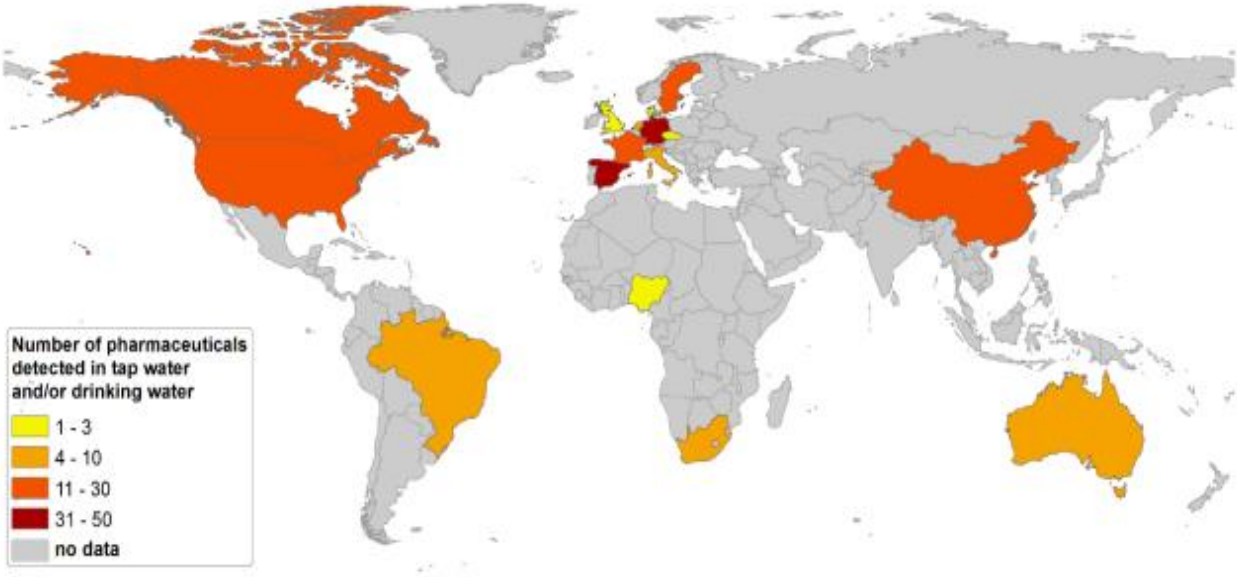

Figure 4.4 Number of pharmaceuticals detected in tap/drinking water (Beek et al., 2016).

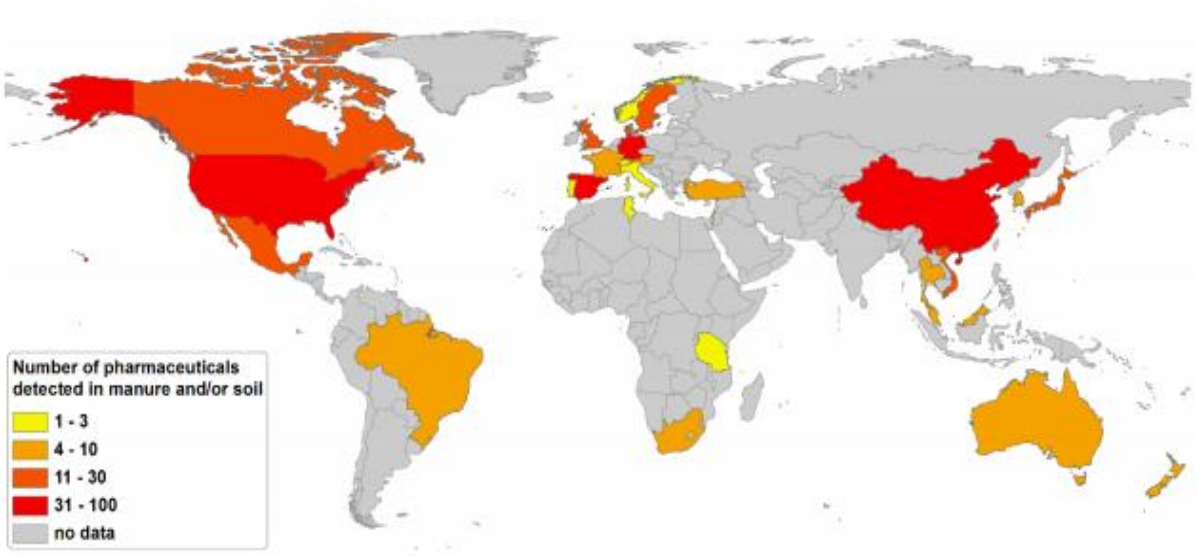

Figure 4.5 Number of pharmaceuticals detected in manure and/or soil per country (Beek et al., 2016).

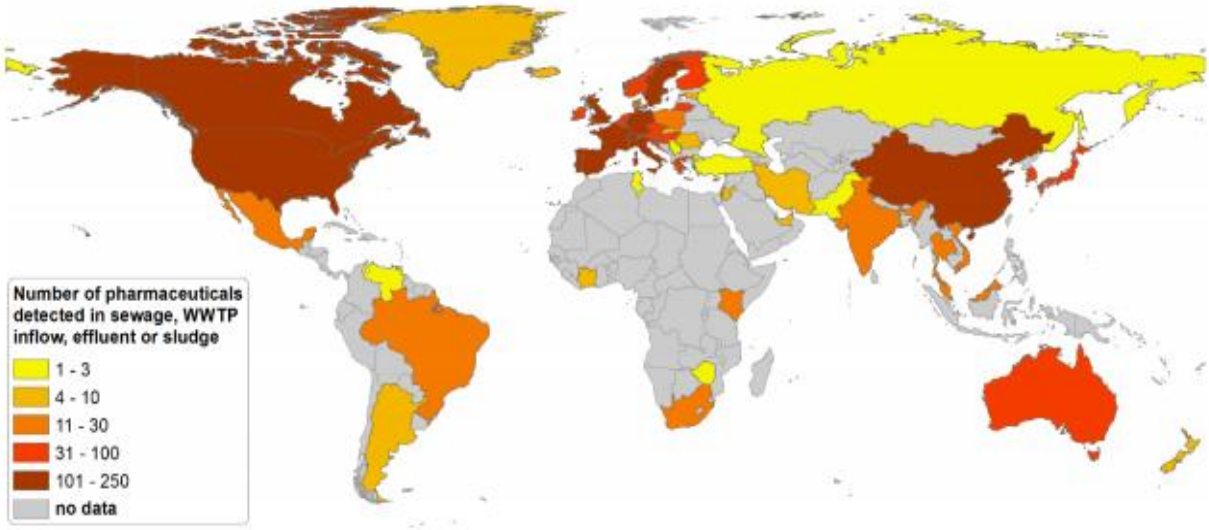

Figure 4.6 Number of pharmaceuticals detected in sewage, water treatment plants inflow/effluent/sludge per country (Beek et al., 2016).

5 Indian Scenario of EPPPs

Pharmaceuticals include active ingredients of prescription and non-prescription drugs for human and veterinary use, illicit drugs, etc. It is reported that 64% of Indians purchase pharmaceuticals without prescription based on peer suggestions and previous experiences (Mutiyar and Mittal, 2013a). During human and veterinary consumption of drugs Active Pharmaceutical Ingredients (APIs) are released into the environment at high amounts, as between 30 and 90% of an oral dose is excreted in urine as an active substance (European Environmental Bureau, 2018). Excretion percentages of different pharmaceuticals are shown in Figure 5.1. The excreted pharmaceuticals reach the wastewater treatment plants (WTPs) and finally discharge raw or treated effluent into the groundwater, rivers, lakes, oceans, and soil.

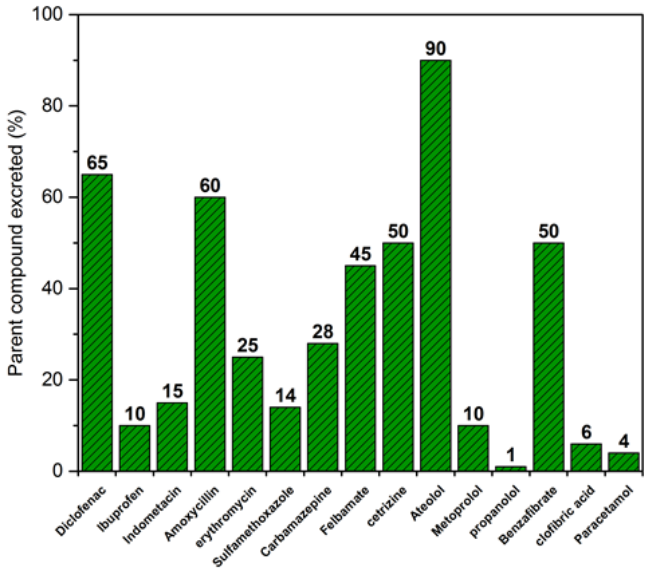

Figure 5.1 Excretion percentage of pharmaceuticals from human body (Surenjan, 2018)

The extent of environmental contamination by EPPPs is presumably significant in developing countries, where the capacity for the treatment of wastewater is far below the quantity of sewage generated by the populations. The treatment capacity of domestic sewage in India is far below the quantity of sewage generated from 1.3 billion people; only 31% of the total sewage produced (~38,254 million liters per day) in 908 cities were treated in 2008 (Subedi et al., 2015).

Apart from human excretion, industrial discharges can contribute to pharmaceutical contamination in the environment (Kurunthachalam, 2012). India is a major hub of

pharmaceutical industries. The organized sector of Indian pharmaceuticals consists of around 250–300 companies and accounts for 70 per cent of products in the market(Morris et al., 2006). Zonal wise comparison of number of pharmaceutical industries in India is shown in . Most of the investigations related to the presence of pharmaceuticals are currently concentrated in the south zone of the country. This is in contrast to the pharmaceutical industrial clusters in the country. Few studies have reported the occurrence of select antibiotics and non-steroidal inflammatory drugs in wastewater (Fick et al., 2009; Larsson et al., 2007; Singh et al., 2014) river water (Mutiyar and Mittal, 2014; Ramaswamy et al., 2011; Shanmugam et al., 2014) and drinking water (Fick et al., 2009) in India. Despite high rates of production and consumption of EPPPs across the country, there is limited management of pharmaceutical pollutants.

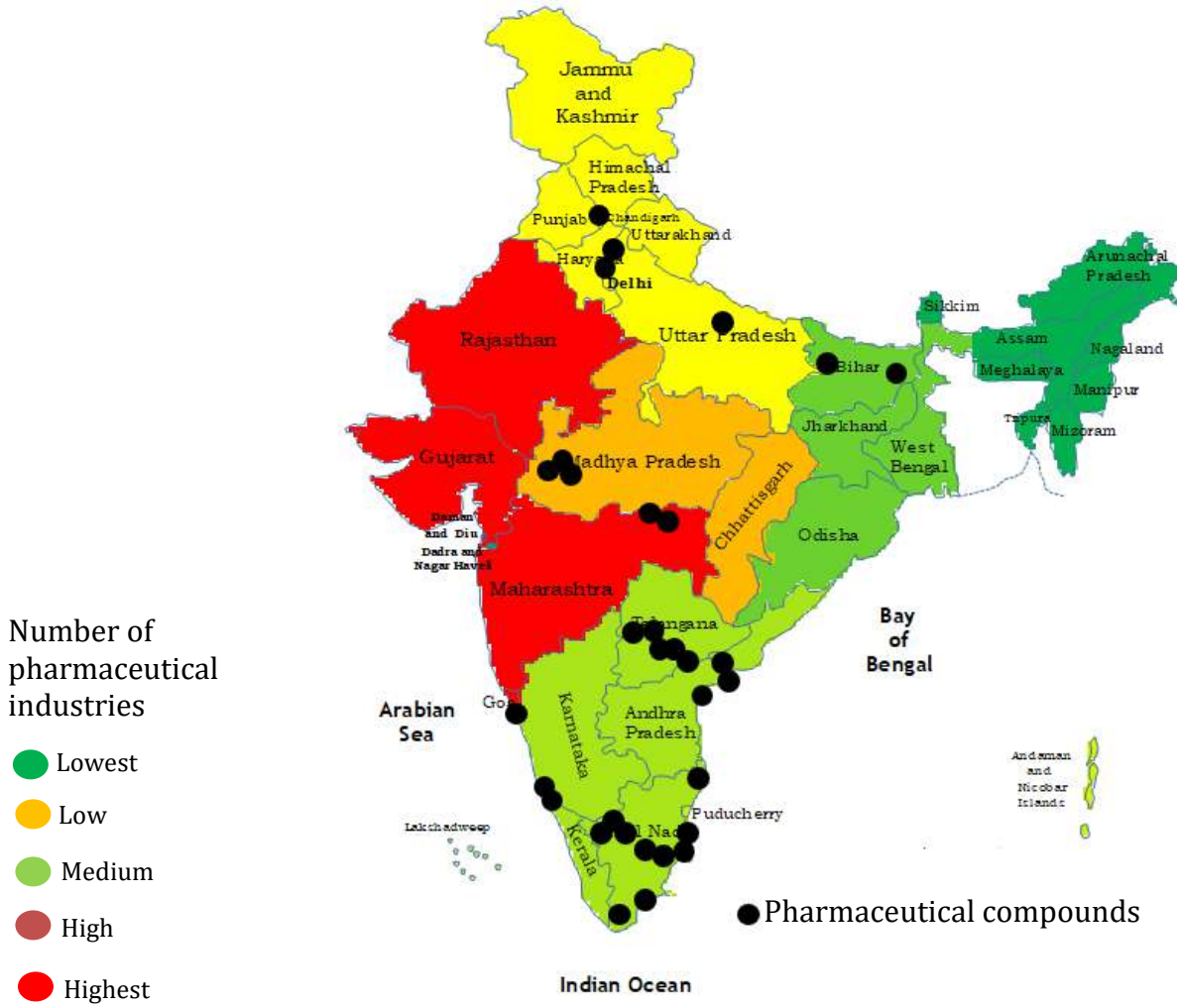

Figure 5.2. Occurrence of pharmaceutical compounds in India

5.1 Occurrence of pharmaceuticals in Indian water bodies

EPPPs are known contaminants of surface and ground water. In some cases, these are persistent organic chemicals which are only partially eliminated during conventional wastewater treatment. They have been detected in the effluent of various Indian wastewater treatment plants. However, there is a growing body of evidence to suggest that discharges from pharmaceutical plants themselves can contribute to the levels of pharmaceuticals in the environment.

High pharmaceutical residue levels are reported in domestic and industrial wastewater, hospital effluent, river water, and groundwater in India(Balakrishna et al., 2017; Mutiyar and Mittal, 2013a; Subedi et al., 2015; Subedi et al., 2017). This section provides a review of occurrences of pharmaceuticals in Indian water bodies.

5.1.1 Wastewater treatment plants

Primary point sources of pharmaceutical contaminants in rivers and oceans are wastewater treatment plants(WTPs) (Daughton and Ternes, 1999). The existing wastewater treatment processes are incapable of removing most of the pharmaceutical contaminants(Mohapatra et al., 2016).

Table 5.1 provides concentrations of pharmaceuticals and their metabolites in wastewater (ng/L) from wastewater treatment plants (WTPs) in India(Akiba et al., 2015; Anumol et al., 2016; Archana et al., 2016; Fick et al., 2009; Larsson et al., 2007; Mohapatra et al., 2016; Mutiyar and Mittal, 2013b; Mutiyar and Mittal, 2014; Prabhasankar et al., 2016; Singh et al., 2014; Subedi et al., 2015; Subedi et al., 2017).

Table 5.1 Mean reported concentrations of pharmaceuticals and their metabolites in wastewater (ng/L) from wastewater treatment plants (WTPs) in India (Balakrishna et al. 2017).

Contaminants	Influent	Effluent
Antischizophrenics		
Quetiapine	38[a], 15[b], 36.8[k], 20.8[l], 24.8[m], 13.8[n], 71.2[o]	20[a], 5.2[b], 6.32[l], 16.6[m], 22.4[o]
Noquetiapine	1.87[k], 6.78[l], 4.70[m], 10.7[n], 16.4[o]	4.04[k], 10.1[m], 1.92[n], 6.50[o]
Aripiprazole	44[a], 29[b], 4.20[l], 14[m]	71[a], 0.4[b]
Dehydroaripiprazole	3.80[k], 0.90[l]	2.20[k]
Sedatives-hypnotics-anxiolytics		
Lorazepam	46[a],26[b], 23.6[n], 19.8[o]	23[a],12[b], 19.1[k], 27.4[l], 24.4[m], 8.26[n], 41.8[o]
Alprazolam	41[a], 10.1[k], 4.20[l], 6.98[o]	33[a], 25[b], 6.94[k], 5.72[l], 2.52[o]
α-hydroxyalprazolam		8.48[k]
Diazepam	23[a], 25[b], 6.80[k], 4.46[l], 6.66[n], 196[o] 140[a], 50 [b], 25.0[m], 13.7[o]	36[a],9.5[b],8.20[k],47.0[l],24.6[n],238[o]
Oxazepam	12[a], 5.9[b], 11.4[k], 5.40[l], 14.5[m], 3.26[n], 12.4[o]	85[a], 50[b], 38.2[m], 17.0[n], 17.0[o]
Nordiazepam	450[a], 550[b], 470[d], 650[e], 580[0]i, 8200[j], 82.2[k], 270[l], 840[m], 22.0[n], 726[o]	85[a], 50[b], 10.5[k], 6.70[l], 8.56[m], 3.08[n], 5.96[o]
Carbamazepine		580[a], 480[b], 88[k], 236[l], 900[m], 147[n], 318[o]
Antidepressants		
Venlafaxine	38[a], 5[b], 30.6[k], 10.3[l], 138[m], 9.30[n], 46.2[o]	15[a],5[b], 6.70[k], 7.96[l], 105[m], 7.26[n], 29.4[o]
Bupropion	19[a], 23 [b]	14[a],5 [b], 3.80[k], 3.42[o]
Sertraline	23[a], 40[b], 5.33[k], 2.53[l], 87.0[m], 10.6[n], 21.8[o]	18[a], 1.7[b], 59.8[m], 10.8[o]
Nosertraline	116[k], 144[l], 386[m]	55.6[k], 57.6[l], 50.0[m]
Citalopram	7.16[l], 16.4[n], 31.8[o]	9.46[m], 14.7[n], 29.8[o]

Antihypertensives		
Propranolol	51[a], 43[b], 17.0[k], 18.5[l], 34.2[m], 14.5[n], 123[o]	43[a],28[b],7.98[k],11.8[l],37.6[m], 11.4[n], 12.3[o]
Atenolol	2900[a],1400[b], 41400[i], 13800[j], 1010[k], 374[l], 2440[m], 192[n], 1910[o]	1500[a],590[b],197[k], 244[l], 2500[m], 16.3[n], 772[o]
Metoprolol	35500[i], 11800[j]	
Diltiazem	55[a], 16[b], 5.64[n], 1.39[o]	5[a], 1.8[b], 1.52[m], 1.53[o]
Desacetyl diltiazem	32[a],6.40[k],1.04[l], 7.62[m], 1.55[n], 44.4[o]	44[a],10[b],3.02[k],1.82[l],8.96[m], 1.51[n], 20.0[o]
Verapamil		2[a], 0.88[l], 1.08[m], 2.64[o]
Norverapamil	36[a], 25 [b], 1.74[k], 0.74[l], 0.61[o] 260[a], 47 [b], 0.88[k], 4.04[m]	4[a], 1.46[m]
Antimicrobial		
Triclocarban	2400[a], 4000[b], 515[k], 933[l], 8880[m], 1150[n], 2100[o]	540[a], 260[b], 22.4[k], 457[l], 5860[m], 48.4[n], 375[o]
Triclosan	4890[f], 450[k], 145[l], 2500[m], 892[n], 2440[o]	3500[f], 2500[m], 202[n]
Antibiotics/fungicides		
Trimethoprim	180[a], 29[b], 4010[d], 210[e],3[h], 4[h],23[h],33.0[k],90.8[l],156[m], 160[n], 35.6[o]	25[b],8[h],1[h],3[h],34.8[k],38.0[l], 103[m], 2080[o]
Sulfamethoxazole	220[a], 100[b],3[h], 66[h],195[k], 288[l], 552[m], 414[n], 2260[o]	260[a], 25[b], 13[h], [27h], 9[h], 70.2[l], 318[m], 228[n], 296[o]
Ampicilin	104.2[c]	12.68[c]
Ciprofloxacin	20.06[c], 12900[f]	8[c], 11670[f]
Erythromycin	12[h]	2[h],1[h],9[h]
Gatifloxacin	2.74[c]	1.22[c]
Levofloxacin	86700[i], 107900[j]	
Nofluoxacin	18200[i]	
Azithromycin	176900[i], 29300[j]	
Sparfloxacin	22.49[c]	0.14[c]
Cefuroxime	3.42[c]	0.22[c]
Ofloxacin		0–212[g]
Clindamycin	210[a], 31[b], 5.16[k], 18.3[l], 27.2[m], 49.6[n], 1870[o]	25[b],48.0[k],6.96[l],17.5[m],63.8[n],952[o]
Lincomycin	730[a], 230[b], 15.2[k], 20.8[l], 226[n], 148[o]	430[a],130[b], 53.0[k], 17.5[l], 3.92[m], 187[n], 43.0[o]
Miconazole	67[a], 42[b], 23.4[k], 65.6[l], 1410[m], 46 [n], 894[o]	8.0[a],25[b],17.8[k],8.92[l],1020[m], 17.0[o]
Tiabendazole	64[a], 123[b]	79[a], 25 [b]

Analgesics		
Ibuprofen	1200[a],1400[b], 2380[d], 1430[e], 1130[k], 686[l], 2140[m], 834[n], 4460[o]	980[a], 630[b], 204[l], 1890[m], 145[n]
Acetaminophen	9000[a], 4500[b], 11500[f], 86800[i], 7100[j]	690[a], 340[b]
Ketoprofen	1080[d], 200[e], 39.6[k], 52.2[l], 9.80[n]	23.4[k], 21.8[l], 5.04[o]
Naproxen	120[d], 59[h], 43[h], 58[h]	
Diclofenac	312[d], 360[e]	11[h], 28[h]
Codeine	160[a], 79[b], 182[k], 80.2[l], 214[m], 62.5[n], 242[o]	82[a], 25[b], 44.2[l], 208[m], 37.2[n], 38.0[o]
Oxycodone	4.0[k], 21.6[n]	
Mefenamic acid	1100[a], 1100[b]	570[a], 440[b]
Antihistamine		
Diphenhydramine	97[a], 44 [b], 83.0[k], 34.8[l], 112[m], 144[n], 130[o]	32[a], 15[b], 35.0[k], 24.6[l], 108[m], 52.4[n], 91.2[o]
DPMA	50.6[n]	32.0[k], 23.2[l], 25.4[o]
Ranitidine	1800[i]	
Antiplatelet		
Clopidogrel	130[a],130[b],34.0[k], 4.78[l], 172[m], 5.08[n], 258[o]	54[b], 2.52[k], 1.95[l], 191[m], 8.84[o]
Clopidogrel carboxylic acid	200[a],300[b], 202[k], 175[l], 658[m], 173[n], 712[o]	430[a],460[b], 149[k], 95.8[l], 1540[m], 84.0[n], 1480[o]
Antihypercholesterolemic		
Atorvastatin	410[a], 380[b]	280[a], 340[b]
UV-filter		
Oxybenzone	5[a], 39 [b], 70.8[n], 85.6[o]	7.0[a], 1.1[b], 41.2[k], 37.0[n]
Benzophenone	3960[f]	1500[f]
Illicit drugs		
Cocaine	32.4[m]	17.0[k], 55.6[m]
Benzoylecgonine	34.2[k],17.8[l],27.8[m],12.5[n], 55.0[o]	33.4[k],14.9[l],33.8[m], 23.2[n], 41.6[o]
Norcocaine	36.4[k], 11.2[l], 15.0[m], 6.44[n], 28.0[o]	34.4[k], 19.0[l], 33.8[m], 29.8[n], 20.0[o]
Morphine	189[k], 148[m], 14[o]	
EDDP	10.4[l], 5.16[m]	10.8[l], 2.58[n]
Methamphetamine	10.9[k],153[l], 42.4[m], 386[n], 10.4[o]	498[k], 304[l], 462[n], 310[o]
Amphetamine	238[k], 286[l], 760[m], 4300[n], 4720[o]	2240[k], 700[l], 558[m], 660[o]
MDA	440[k], 59.2[l], 216[n], 98.0[o]	1150[m], 114[n]
MDMA	23.0[m]	21.8[k]

Stimulant		
Caffeine	61000[a],30000[b],102840[f],29600[i],18400[j], 22.8[k],16.0[l],42500[m],38100[n], 60500[o]	1100[a],3400[b],46700[f],19.0[k],1067[l], 51700[m], 389[o]
Paraxanthine	19000[a], 7400[b]	760[a], 1500[b]

DPMA: 2-(diphenylmethoxy) acetic acid; EDDP: (2-ethylidene-1,5-dimethy-3,3-diphenylpyrrolidine); MDA: (3,4-methylenedioxyamphetamine); MDMA: (3,4-methylenedioxymethamphetamine).

[a] In Udupi WTP, Karnataka, inflow: 7.5 MLD, serve 150,000 people, anaerobic sludge treatment, grab samples, sampled for consecutive seven days in a week (Subedi et al., 2017).

[b] In Mangalore WTP, Karnataka, inflow: 12 MLD, serve 450,000 people, anaerobic sludge treatment and upflow anaerobic sludge blanket digestor, grab samples, sampled for consecutive seven days in a week (Subedi et al., 2017).

[c] In Okhla WTP, Delhi, inflow: 110 MLD, anaerobic sludge treatment, grab samples, sampled for five days (Mutiyar and Mittal, 2014)

[d] In a WTP in Ghaziabad, Northern India, 24 h composite samples (from every 4-h grab samples), sampled once (Singh et al., 2014)

[e] In a WTP in Lucknow, Utter Pradesh, 24 h composite samples (from every 4-h grab samples), sampled once (Singh et al., 2014)

[f] In a WTP in Nagpur, inflow: 80 MLD, primary and secondary anaerobic sludge treatment, grab samples, three sampling events in summer (Archana et al., 2016)

[g] In a WTP in Southern India, inflow:1.7MLD, serve~15,000 people, anaerobic sludge treatment, grab samples, a sampling event in each of three seasons (concentrations were reported in the range) (Akiba et al., 2015)

[h] In a WTP in Southern India, inflow: 2.0 MLD, serve 9000 people, aeration sludge treatment (cost-effective), grab samples, a sampling event in each of three seasons (Prabhasankar et al., 2016)

[i] In a WTP in Western India, inflow: 46 MLD, facultative aerated lagoon based treatment, 24 h composite samples, a sampling event in each of three seasons (Mohapatra et al., 2016)

[j] In a WTP in Western India, inflow: 60 MLD, cyclic anaerobic sludge treatment, 24 h composite samples, a sampling event in each of three seasons (Mohapatra et al., 2016)

[k] In Saidpur WTP in Bihar (Northern India), inflow: 19 MLD, serve 350,000 people, anaerobic sludge treatment, grab samples, sampled once (Subedi et al., 2015)

[l] In Beur WTP in Bihar (Northern India), inflow: 20.9 MLD, serve 275,000 people, anaerobic sludge treatment, grab samples, sampled once (Subedi et al., 2015)

[m] In Coimbatore WTP in Tamil Nadu (Southern India), inflow: 22.5 MLD, serve 350,000 people, anaerobic sludge treatment, grab samples, sampled once (Subedi et al., 2015)

[n] In Udupi WTP in Karnataka, inflow: 2.0 MLD, serve 10,000 people, anaerobic sludge treatment, grab samples, sampled once (Subedi et al., 2015)

[o] In Manipal WTP in Karnataka, inflow: 2.0 MLD, serve 12,000 people, anaerobic sludge treatment, grab samples, sampled once (Subedi et al., 2015)

WTP receiving effluents from pharmaceutical industries

High levels of pharmaceutical contaminants are reported from WTPs that process wastewater from pharmaceutical companies(Fick et al., 2009; Larsson et al., 2007). Highest levels of pharmaceutical contaminants in wastewater reported in the world is from a study conducted at the PETL (Patancheru Enviro Tech Limited) WTP near Hyderabad, that received 1.5 MLD effluents from ~90 bulk drug manufacturers in the vicinity in Patancheru.

The maximum concentrations of ciprofloxacin reported in wastewater were 0.6 µg/L across 6 WTPs in Canada (Guerra et al., 2014) 1.4 µg/L in Holland (Batt et al., 2007), 1.4 µg/L in Portugal (Santos et al., 2013), 3.7 µg/L in Italy (Verlicchi et al., 2012), and 6.9 µg/L in Australia (Pal et al., 2010). The concentration of ciprofloxacin reported by Larsson et al. (2007) was ~4500 times higher than the next highest reported (Australia).

WTP receiving domestic effluents

Indian WTPs that treat predominantly domestic sewage show higher concentrations of carbamazepine (a psychoactive), atenolol (antihypertensive), triclocarban and triclosan (antimicrobials), trimethoprim and sulfamethoxazole (antibacterial), ibuprofen and acetaminophen (analgesics), and caffeine (stimulant). They are the most commonly detected pharmaceutical compounds in WTPs that process wastewater from domestic sewage. Concentration of ciprofloxacin in the outlet at Okhla WTP, Delhi (Mutiyar and Mittal, 2014) is 2.5 times higher than that observed in WTP outlets of Australia (Al-Rifai et al., 2007) 5 times higher than the WTP outlets in Italy (Verlicchi et al., 2012) and at least 15 times higher than the values in the WTP outlets of other countries as shown in given in Figure 5.3. The ciprofloxacin concentration in the discharge of Okhla WTP exceeds the predicted no-effect concentration (PNEC=0.005 µg/L) (Deo and Halden, 2013). Figure 5.3 shows comparison of some commonly detected pharmaceuticals in WTPs across the world.

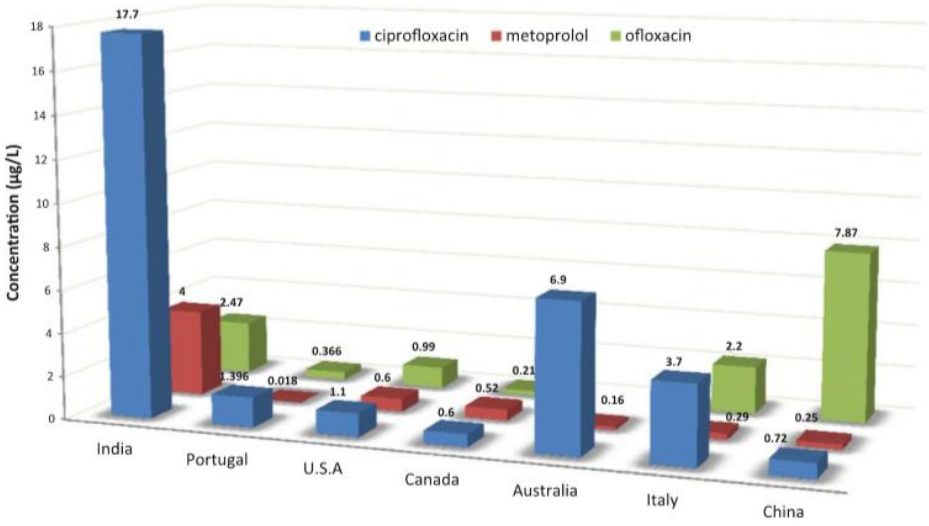

Figure 5.3 Comparison of some commonly detected pharmaceuticals in WTP effluents across the world (Balakrishna et al., 2017)**.**

WTPs receiving hospital effluents

Other point sources of pharmaceutical pollution in the water bodies include hospital effluents. Concentrations of pharmaceuticals in hospital effluents are generally higher than in the domestic WTP effluents (Kovalova et al., 2013). Figure 5.4 shows comparison of pharmaceutical compounds in hospital effluents in India. Concentration of ciprofloxacin in the hospital effluent in India is about 10 times higher than in Italy and five times higher than in Portugal. The concentration of sulfamethoxazole is also about ten times higher than the corresponding concentrations in Italy and Portugal, while that of ofloxacin is found to be almost two times that in Italy and Portugal.

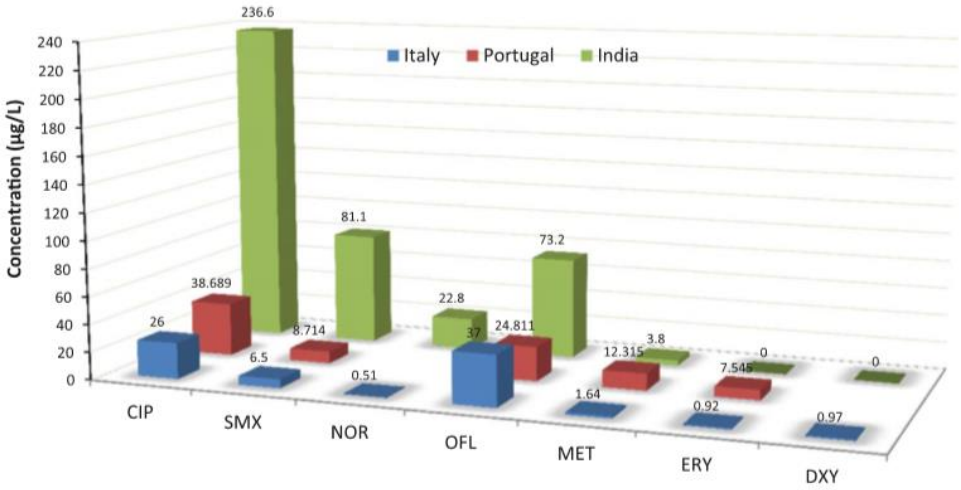

Figure 5.4 Comparison of EPPPs in hospital effluents in India (Balakrishna et al., 2017)**.**

Abbreviations: CIP, ciprofloxacin; SMX, sulfamethoxazole; NOR, norfloxacin; OFL, ofloxacin; MET, metronidazole; ERY, erythromycin; DXY, doxycycline.

5.1.2 Rivers and Lakes

Sewage originating from the WTPs, agricultural discharges and direct discharges are the major source of pharmaceuticals in natural water bodies (Li et al., 2014). The studies carried out so far to identify the pharmaceutical concentrations in Indian rivers have confirmed the presence of pharmaceuticals in the concerned rivers (Archana et al., 2016; Fick et al., 2009; Kristiansson et al., 2011; Mutiyar and Mittal, 2014; Ramaswamy et al., 2011; Shanmugam et al., 2014; Subedi et al., 2015).

5.1.3 Groundwater

A considerable amount of data exists on pharmaceutical wastes in surface water; yet, literature demonstrating the pharmaceutical contamination of groundwater is relatively less (Wolf et al., 2012). Direct pathways of pharmaceutical contamination to the groundwater include disposal of sewage effluents on land, sewer leakage, landfill leachates, and sewage overflow during monsoon(Jones et al., 2002). The maximum concentration of ciprofloxacin in ground water from India (Fick et al., 2009) was 90 and 43 times higher than in China (Ma et al., 2015) and Spain (Cabeza et al., 2012), respectively.

5.2 Pharmaceuticals, an unregulated industry in India

Pharmaceutical industry in India currently faces many challenges due to improper regulations and guidelines. There are insufficient monitoring requirements and no specific emission limits in place for API releases from manufacturing plants in India. Good Manufacturing Practices do not take into account the risks that medicinal products may pose to the environment and human health at the manufacturing stage. There are no limits in place for the content of pharmaceuticals in drinking water, in surface water, or waste water, not even from hospitals' effluents. Although pharmaceuticals contain hazardous substances, there are no specific regulations for the management of most human and veterinary medicinal products waste. There is no obligation to monitor or regulate medicinal pharmaceuticals present in sewage sludge or in manure used in agriculture.

Priority list and standards for compounds in the priority list must be made in India. Australia has provided guidelines for pharmaceuticals in drinking water(Patel et al., 2019). Table 5.2 shows the standards given for different compounds.

Table 5.2 Standards for pharmaceuticals in drinking water in Australia

Compound	ADI (µg/kg/d)	DW guideline (µg/L)
Ibuprofen	11.4	400
Naproxen	6.3	220
Carbamazepine	2.8	100
Gemfibrozil	17	600
Ciprofloxacin	7.1	250
Diclofenac	0.5	1.8
Aspirin	8.3	29
Ketoprofen	1	3.5
Acetaminophen	50	175
Amoxycillin	0.43	1.5
Sulfamethazole	10	35

A priority list of compounds can be made based on most occurring compounds and toxicity. Acute and chronic toxicity of different EPPPs are shown in Figure 5.5. Causes of occurrence of pharmaceutical compounds in the environment are human excretion or industrial discharge. To identify compounds of high priority due to human excretion, most prescribed compounds in India with high excretion percentage should be identified. Most prescribed compounds given by a survey conducted in India (Mohapatra et al., 2016) and excretion percentage of different compounds are given

Figure 5.6 and Figure 5.1 respectively. Scaling criteria of different factors for preparation of the priority list is given in

Table 5.3.

Table 5.4 shows the priority list made on these factors. Similarly, a priority list must be made based on industrial discharges of EPPPs in India. Most manufactured EPPPs in India should be identified and a priority list can be made based on this data and toxicity as discussed for the cause, human excretion.

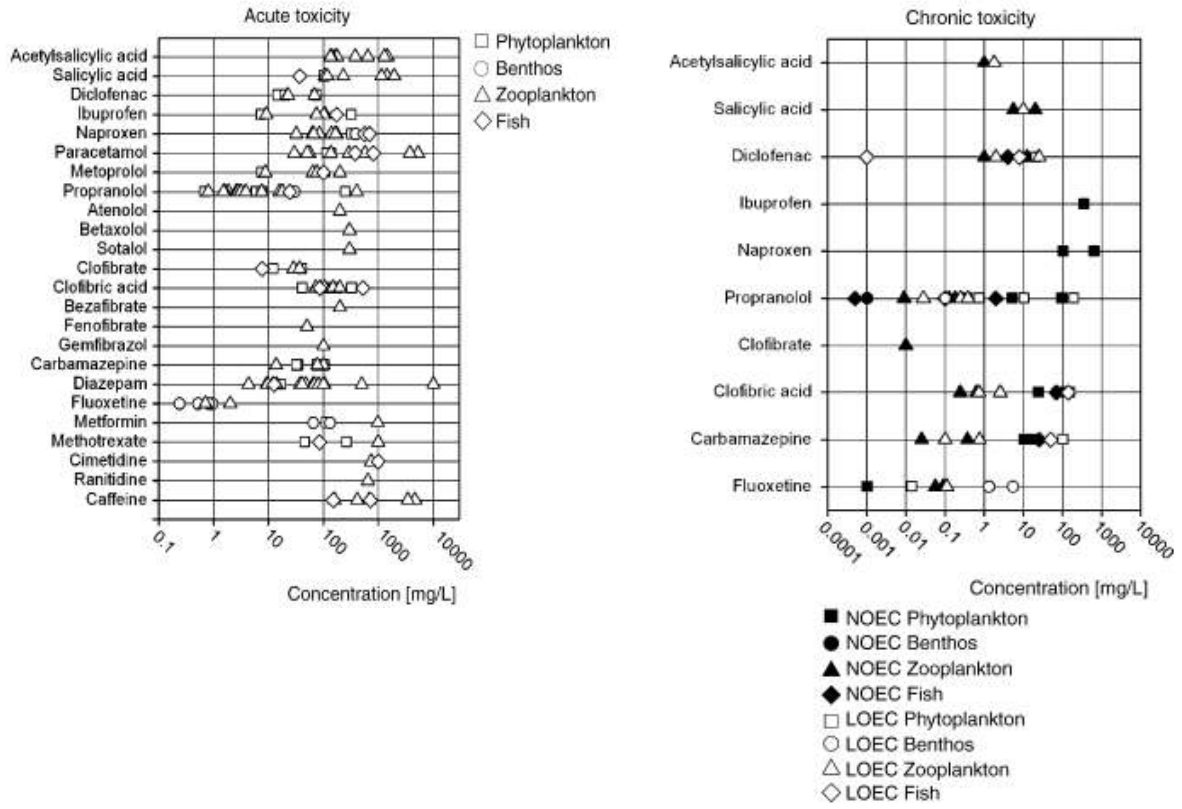

Figure 5.5 Acute and chronic toxicity on different organisms (Fent et al., 2006)

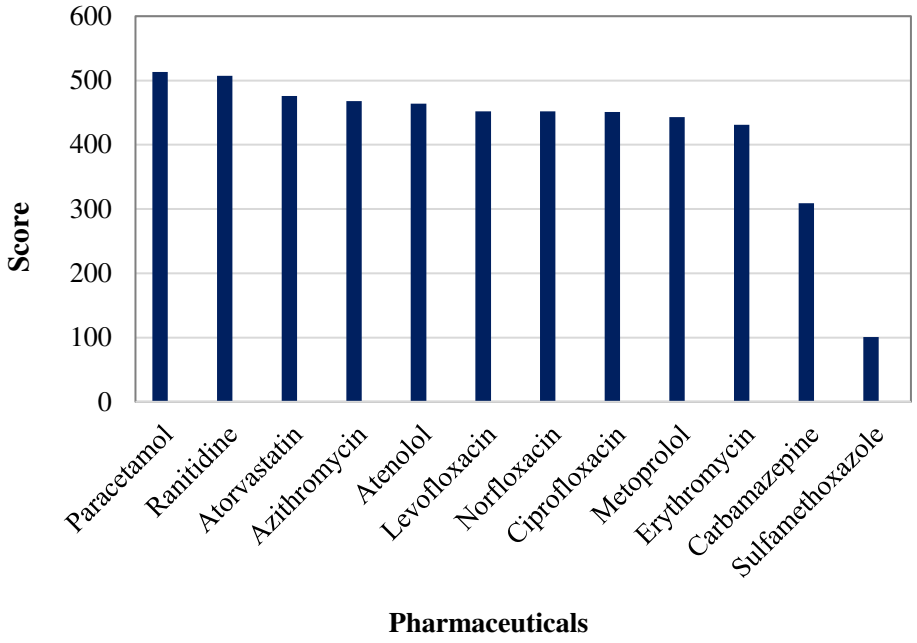

Figure 5.6 Obtained score from the Survey conducted in India.

Table 5.3 Scaling criteria of different factors

Factor	Weighting criteria	Score
Prescription (based on obtained score from Indian survey)	100-200 201-300 301-400 401-500 >500	1 2 3 4 5
Excretion Percentage	0-20 21-40 41-60 61-80 81-100	1 2 3 4 5
Acute Toxicity (conc. in mg/l)	>100 100-1000 10-100 1-10 0-1	1 2 3 4 5

Table 5.4 Priority list based on occurrence due to human excretion

Compound	Prescription	Excretion%	Acute Toxicity	Total Score
Atenolol	4	5	2	11
Paracetamol	5	1	3	9
Metoprolol	4	1	4	9
Carbamazepine	3	2	3	8
Erythromycin	4	2	1	7
Sulfamethoxazole	1	1	3	4

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