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Hospital Wastewaters

Characteristics, Management, Treatment and Environmental Risks

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Hospital Wastewaters

Characteristics, Management, Treatment and Environmental Risks

Volume Editor: Paola Verlicchi

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Aims and Scope

Since 1980, *The Handbook of Environmental Chemistry* has provided sound and solid knowledge about environmental topics from a chemical perspective. Presenting a wide spectrum of viewpoints and approaches, the series now covers topics such as local and global changes of natural environment and climate; anthropogenic impact on the environment; water, air and soil pollution; remediation and waste characterization; environmental contaminants; biogeochemistry; geoecology; chemical reactions and processes; chemical and biological transformations as well as physical transport of chemicals in the environment; or environmental modeling. A particular focus of the series lies on methodological advances in environmental analytical chemistry.

Series Preface

With remarkable vision, Prof. Otto Hutzinger initiated *The Handbook of Environmental Chemistry* in 1980 and became the founding Editor-in-Chief. At that time, environmental chemistry was an emerging field, aiming at a complete description of the Earth's environment, encompassing the physical, chemical, biological, and geological transformations of chemical substances occurring on a local as well as a global scale. Environmental chemistry was intended to provide an account of the impact of man's activities on the natural environment by describing observed changes.

While a considerable amount of knowledge has been accumulated over the last three decades, as reflected in the more than 70 volumes of *The Handbook of Environmental Chemistry*, there are still many scientific and policy challenges ahead due to the complexity and interdisciplinary nature of the field. The series will therefore continue to provide compilations of current knowledge. Contributions are written by leading experts with practical experience in their fields. *The Handbook of Environmental Chemistry* grows with the increases in our scientific understanding, and provides a valuable source not only for scientists but also for environmental managers and decision-makers. Today, the series covers a broad range of environmental topics from a chemical perspective, including methodological advances in environmental analytical chemistry.

In recent years, there has been a growing tendency to include subject matter of societal relevance in the broad view of environmental chemistry. Topics include life cycle analysis, environmental management, sustainable development, and socio-economic, legal and even political problems, among others. While these topics are of great importance for the development and acceptance of *The Handbook of Environmental Chemistry*, the publisher and Editors-in-Chief have decided to keep the handbook essentially a source of information on "hard sciences" with a particular emphasis on chemistry, but also covering biology, geology, hydrology and engineering as applied to environmental sciences.

The volumes of the series are written at an advanced level, addressing the needs of both researchers and graduate students, as well as of people outside the field of

"pure" chemistry, including those in industry, business, government, research establishments, and public interest groups. It would be very satisfying to see these volumes used as a basis for graduate courses in environmental chemistry. With its high standards of scientific quality and clarity, *The Handbook of Environmental Chemistry* provides a solid basis from which scientists can share their knowledge on the different aspects of environmental problems, presenting a wide spectrum of viewpoints and approaches.

The Handbook of Environmental Chemistry is available both in print and online via www.springerlink.com/content/110354/. Articles are published online as soon as they have been approved for publication. Authors, Volume Editors and Editors-in-Chief are rewarded by the broad acceptance of *The Handbook of Environmental Chemistry* by the scientific community, from whom suggestions for new topics to the Editors-in-Chief are always very welcome.

Damià Barceló
Andrey G. Kostianoy
Editors-in-Chief

Preface

When we think of a hospital, what first comes to mind is a facility that should improve and guarantee the health of patients while carrying out investigations to fight and overcome diseases.

In order to achieve these goals, hospital staff use a wide spectrum of chemicals for therapeutic and diagnostic purposes, room cleaning and equipment disinfection. Unavoidably, residues of these chemicals are present in hospital waste and in particular in hospital effluents. Most of these substances belong to the group of so-called *emerging contaminants*, most of which occur at low concentrations – ng/L or µg/L – in (waste)water and are therefore known as *micropollutants*. Examples are antibiotics, analgesics, anaesthetics, cytostatics and X-ray contrast media.

Although these emerging contaminants are still unregulated compounds in water, their use, consumption and fate in the water cycle represent issues of increasing worldwide concern. In this context, the effluent of health care structures has been the focus of great research and discussion over the last 15 years. Investigations have mainly dealt with: (1) the characteristics of hospital wastewater, exploring its chemical, physical and microbiological composition, (2) the efficiency of conventional treatments in removing targeted micropollutants and the treatment options for improving their removal and (3) the assessment of the environmental risk posed by the residues of pharmaceuticals and other chemicals commonly used in health care structures, still present after the adopted treatments.

It is well known that investigations have dealt with a comparatively low number of compounds, with regard to the thousands of active ingredients used in pharmaceutical preparations. Targeted compounds were generally selected on the basis of the available analytical techniques, consumption data and results from past studies. It is also known that, mainly in the first years of investigations, some compounds were more frequently selected for monitoring programmes and some of them were regularly included in the analyte lists. This prominence was often dictated by the fact that interest given to them in the past generated more attention in the future.

This is the so-called *Matthew Effect*, a psychological phenomenon analysed for the first time by Robert Merton in 1968 [1] and used by Grandjean and colleagues

[2] "to explain the biased path followed by many of the incremental and repetitive findings of environmental science" [3].

In the last few years, attention has also been paid to other emerging contaminants as new analytical techniques have allowed the monitoring of a wider group of substances, and as the scientific community has become more aware that it is necessary to enlarge the spectrum of targeted compounds in order "to reduce biases and uncertainties in the exposure assessment process and in environmental risk assessment" [4].

In addition to compound selection, other issues have been widely discussed: the sampling mode and frequency of the different pharmaceuticals, spatial and temporal variability of concentrations of micropollutants, accuracy of direct measures, uncertainties in predicting concentrations; the reliability and representativeness of measurements and predictions; prioritization of pharmaceuticals; options in the adopted treatment worldwide and promising technologies (on the basis of lab and pilot scale investigations); environmental risk assessment and the release of antibiotic-resistant bacteria and genes.

An attempt to represent the complexity of the problems related to the management and treatment of hospital effluents is made in Fig. 1. Three main fields were identified: composition, management and treatment, and the environmental risk posed by residues in the treated effluent. For each of them, the main subfields are also outlined.

What is known in each field is only the tip of a big iceberg: in Fig. 1 it corresponds to the region above the reference system which separates the space of "*Knowns and Data of absence*" from the space of "*Absence of data and*

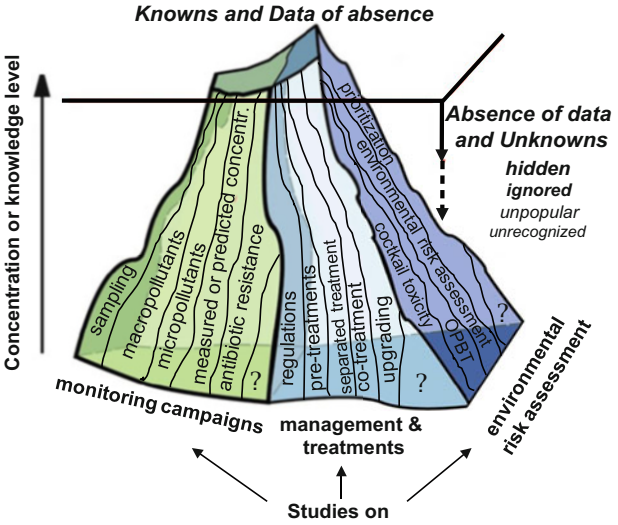

Fig. 1 What is known and what is unknown referring to hospital effluent characterization, treatment and management (adapted from [5])

Unknowns". The "unknowns" include "known-unknowns" that are some things we know we do not know and also "unknown unknowns" that are the ones we don't know we don't know (represented by the three areas with a question mark).

Looking back to past research, this book provides the main findings achieved by different research groups, comments on what is known and what is still unknown and, looking forward, it underlines the perspectives and future needs of the different research issues, promoting investigations in the sphere of known-unknowns and unknown-unknowns.

In brief, it consists of a series of 12 contributions referring to a worldwide overview regarding the regulation of this kind of wastewater (chapter "Hospital Wastewater: Existing Regulations and Current Trends in Management"), a snapshot of the observed range of concentrations of conventional pollutants and micropollutants (pharmaceuticals, heavy metals, microorganisms and viruses) and the ecotoxicity of the effluent (chapters "Occurrence of Common Pollutants and Pharmaceuticals in Hospital Effluents" and "Ecotoxicity of Hospital Effluents"). Then it presents a prioritization of pharmaceuticals on the basis of two approaches: OPBT (Occurrence, Persistence, Bioaccumulation and Toxicity) and assessment of the environmental risk based on calculation of the risk quotient (chapter "Prioritization of Active Pharmaceutical Ingredients in Hospital Wastewater"); a focus on three groups of pharmaceuticals commonly present in hospital effluents (antibiotics, cytostatics and X-ray contrast media) in terms of their occurrence and potential environmental implications (chapter "Occurrence and Risks of Contrast Agents, Cytostatics and Antibiotics in Hospital Effluents") and a discussion of the accuracy and uncertainties in evaluating hospital effluent concentrations and loads by direct measurements and predictive models (chapter "Pharmaceutical Concentrations and Loads in Hospital Effluents: Is a Predictive Model or Direct Measurement the Most Accurate Approach?").

Regarding management and treatment of this kind of wastewater, the book includes an evaluation of the contribution of hospital effluents and urban wastewater to the pharmaceutical load in a catchment area (chapter "Contribution of Hospital Effluents to the Load of Micropollutants in WWTP Influents") and an analysis of the adopted treatments in different countries (chapters "Lessons Learned from European Experiences and Presentation of Case Studies" and "Hospital Wastewater Treatments Adopted in Asia, Africa and Australia").

The following two chapters deal with the description of full-scale plants for the separate treatment of hospital effluents (chapter "Full Scale Plants for Dedicated Treatment of Hospital Effluents") and the most promising technologies aimed at improving the removal of targeted microcontaminants investigated at a lab or on a pilot scale (chapter "Overview on Pilot-Scale Treatments and New and Innovative Technologies for Hospital Effluent"). The conclusions summarize remarks on occurrence, management and treatments of hospital effluent and underline perspectives in future research (chapter "Final Remarks and Perspectives in Management and Treatment of Hospital Effluent").

The book is intended for a broad audience which includes researchers and scientists involved in management and treatment of hospital effluents and wastewater containing micropollutants, administrators and decision-makers who could find strategies adopted in different countries and descriptions of full-scale treatment plants, legislators involved in the authorization and management of health care structure effluents, environmental engineers involved in the design of wastewater treatment plants and also newcomers and students interested in these issues.

Finally, my sincere acknowledgements to all the authors who agreed to take part in this editorial project and who devoted their time to developing their research contribution and, above all, for sharing their knowledge and findings with other readers. A special thanks to Prof. Damia Barceló, HEC Series Editor, who invited me to be the Editor of this book on hospital wastewater and Dr. Andrea Schlitzberger and all her team at Springer Publishers who supported me in every step of its creation.

Ferrara, Italy Paola Verlicchi
May 2017

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Contents

Hospital Wastewater: Existing Regulations and Current Trends in Management

Elisabetta Carraro, Silvia Bonetta, and Sara Bonetta

Abstract Wastewater refers to any water whose quality has been compromised by human activities. It includes liquid waste discharged from domestic homes, agricultural commercial sectors, pharmaceutical sectors, and hospitals. Hospital wastewater (HWW) can contain hazardous substances, such as pharmaceutical residues, chemical hazardous substances, pathogens, and radioisotopes. Due to these substances, hospital wastewater can represent a chemical, biological, and physical risk for public and environmental health. Nevertheless, very frequently there are no legal requirements for hospital effluent treatment prior to its discharge into the municipal collector or directly onto surface water after pretreatment.

In this chapter a brief introduction about the role of hospital wastewater on the environmental contamination was reported. Subsequently the main principles on the hospital wastewater reported in different legislation around the world have been addressed. Moreover the main content reported in the WHO guidelines, EPA guidelines, and guidelines about radionuclide releases to the environment from hospitals was described. A case study of excellence on hospital wastewater management was also illustrated. The chapter ends with some brief final remarks.

Keywords Hospital wastewater, Management, Regulation

Contents

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1 Introduction

Wastewater refers to any water whose quality has been compromised by human activities. It includes liquid waste discharged from domestic homes, agricultural commercial sectors, pharmaceutical sectors, and hospitals. In hospitals, water is consumed in various places such as hospitalization areas, surgery areas, laboratories, administrative units, laundries, and kitchens. In the process, its physical, chemical, and biological quality decreases and is converted to wastewater [1]. Compared to urban wastewaters (UWW), hospital wastewaters (HWW) contain a variety of toxic or persistent substances such as pharmaceuticals, radionuclides, solvents, and disinfectants for medical purposes in a wide range of concentrations [2–4]. In a review, Verlicchi et al. [5] highlighted that concentrations of micropollutants (e.g., antibiotics, analgesics, heavy metals) in HWWs are between 4 and 150 times higher than in UWW. Moreover hospital wastewater is considered one of the major reservoirs of pathogenic bacteria. Wastewater or natural water supplies into which wastewater has been discharged are likely to contain pathogenic organisms mainly coming from human excreta [6]. For example health-care facilities, where the use of antibiotics is more frequent and intensive and where antibiotic resistant bacteria may have a selective advantage over the susceptible counterparts, are regarded as important reservoirs of antibiotic resistance [7].

Considering this information related to the criticality of the wastewater and to the risks associated, very frequently there are no legal requirements for hospital effluent treatment prior to its discharge into the municipal collector or directly onto surface water after pretreatment.

As a matter of fact, in the major part of countries, it is impossible to find specific regulations regarding the management of hospital effluent and not even specific references in this regard within more ample regulations such as those referring to the management of wastewater in general. Therefore, the effective revisions of regulations, in the context of this chapter, have revealed a great difficulty in discovering (at an international level) specific norms, precisely because they are lacking. What is more, if these are present, they are difficult to find because they are in the original language and so difficult to translate with research engines or the Web.

2 Regulations about Hospital Wastewater

The regulations discussed in this paragraph are listed in Table 1. The border between the discipline regarding water and waste is a complex issue and much debated in various productive sectors: often the distinction between the two definitions is not always clearly identified, assumes legal issues and very importantly, management. For this reason, it is necessary to clearly identify the boundary between the waste products identified as wastewater and those identified as liquid waste.

Generally, the waste products of a health facility are considered:

- *Waste*, in the case where the product to be disposed of is a solid, a sludge, or a liquid contained in a container or a liquid absorbed to a solid.
- *Wastewater*, in the case in which the liquid sewage is discharged directly into a sewer.

The two definitions can be confusing when the regulatory parameters of hospital wastewater are reported in the legislation relating to waste management. This occurs, for example, in India, where the characteristics of the effluent produced by hospitals – either connected to sewers without a terminal sewage treatment plant or not connected to public sewers – are described in the regulations on waste management [8]. On the contrary, for discharge into public sewers with terminal

Table 1 Regulations on hospital wastewaters

Nation	Law	Year	Regulation on
UE	European Directive n. 91 of 21 May 1991 on urban wastewater treatment	1991	Wastewater
	Directive 2008/98/EC on hazardous waste	2008	Waste
Spain	Decreto 57/2005, de 30 de junio, por el que se revisan los Anexos de la Ley 10/1993, de 26 de octubre, sobre Vertidos Líquidos Industriales al Sistema Integral de Saneamiento	2005	Wastewater
	Decreto n 26,042-S-MINAE. (1997). Reglamento de Vertido y Aguas Residuales. La Gaeta n. 117, Jueves 19 de junio de 1997	1997	Wastewater
Germany	Wastewater Ordinance (AbwV)	2004	Wastewater
Italy	DPR n. 227/2011 on simplification on environmental law	2011	Wastewater
	DLgs n.152/2006 on environmental protection	2006	Wastewater
India	Environment (Protection) Act	1986	Wastewater
	The Bio Medical Waste Management and Handling Rules S O 630 E 20/7/1998	1998	Waste
China	National Standard of Integrated Water Discharge Standard	1998	Wastewater
Vietnam	Law on environmental protection	2014	Wastewater
	National Technical Regulation on Health Care Wastewater	2010	Wastewater

facilities, the general standards as described under the Environment (Protection) Act, 1986 shall be applicable [9].

A matter of considerable practical relevance to the legal and operational implications arising therefrom is to define if the waters from a particular activity are comparable to domestic wastewater or industrial wastewater. In fact in most of the regulations the wastewater is divided into:

– *Domestic wastewater:* wastewater from residential settlements and services, i.e., water that originates predominantly from the human metabolism and from household activities;
– *Industrial wastewater*: any type of wastewater discharged from premises or facilities in which businesses or production of goods take place, excluding domestic wastewater and by water run-off rain.

In Europe there is no specific directive or guideline for the management of hospital effluents. However, the European Directive n. 91 of 21 May 1991 [10] (91/271/CEE modified from Directive 27 of February 1998 n. 98/15/CE [11]) on urban wastewater treatment aims to protect the environment from the adverse effects of wastewater discharges; it concerns the collection, treatment, and discharge of:

- domestic wastewater
- mixtures of wastewater
- wastewater from certain industrial sectors.

Specifically the Directive requires: (1) the collection and treatment of wastewater in all agglomerations of >2,000 population equivalents (p.e.); (2) secondary treatment of all discharges from agglomerations of >2,000 p.e., and more advanced treatment for agglomerations >10,000 p.e. in designated sensitive areas and their catchments; (3) a requirement for pre-authorization of all discharges of urban wastewater, of discharges from the food-processing industry, and of industrial discharges into urban wastewater collection systems; (4) monitoring of the performance of treatment plants and receiving waters; and (5) controls for sewage sludge disposal and reuse, and treated wastewater reuse whenever it is appropriate.

As reported previously regarding the treatment of UWW, European regulations require a pre-authorization (if the wastewater is considered to be industrial) before its discharge into UWW collection systems. Moreover, the European Directive n. 98 of 19 November 2008 (2008/98/CEE) [12] about the management of hazardous wastes and the list of hazardous wastes of the European Decision n. 532 of 3 May 2000 (2000/532/CEE) [13] state that some hospital liquid waste (pharmaceutical products, medicines, residues from substances employed as solvents, soaps, non-halogenated organic substance, etc.) must not be discharged into a foul sewer, but must be treated as a waste product and collected and disposed of as such. For the effluents of the hospital foul sewer, there is no specific disposition; so the various member states of the European Union have their own legislation, evaluation, and selection criteria for HWW quality and its management. If a hospital facility is considered, by the legislation of the state, to be industrial or

like a facility that discharges not only domestic wastewater (as in Spain [13] [14]), specific characteristics of the wastewater will be required in order to obtain permission to discharge it into the municipal WWTP; usually a pretreatment is required.

On the other hand, in a country where the HWW is considered to be domestic or communal, neither authorization nor specific characteristics are required (as in Germany, [15]). In other cases, if the HWW complies with the specific characteristics established by the WWTP authority, the wastewater may be considered a domestic effluent and therefore discharged into WWTPs without any permission [16]. For example, in Italy at present, in health facilities with fewer than 50 beds and not provided with analytical and research laboratories, the wastewaters produced by the hospital are treated as domestic wastewater, with the result that these can be discharged without authorization [17]. In all other cases, the discharge of wastewaters produced by health facilities must be authorized according to the Italian Legislative Decree no. 152/2006 [18]. In Italy the authorizing Authority changes from area to area (once were ATO, Ambiti Territoriali Ottimali, and now are provinces or Città Metropolitana), and it usually delegates the integrated water cycle manager. However, the hospital effluents are generally considered of the same pollutant load of domestic ones.

The Chinese normative considers hospitals to be industries [19]. In addition, the number of beds is a determining factor, as in Italy. Specifically, the Chinese normative requires the search for certain indicators (e.g., fecal coliforms) in hospitals with more than 50 beds.

In other countries, the legislation explains specifically how to treat and manage the hospital wastewater. For example, in Vietnam, in the law on environmental protection, there is a specific section on environmental protection regarding hospitals and medical facilities [20]. Article 72 of this law indicates that "Hospitals and medical facilities are obliged to: (a) Collect and treat medical wastewater in accordance with environmental standards." Moreover, unlike what is stated in other regulations, the environmental standards are established considering the use of the water bodies that collect the hospital wastewater. In fact the maximum value of different standards can be calculated using the following formula:

$$C_{\max} = C \times K$$

where C is the value of parameter and it is generally lower when the water resource which collects the wastewater, is used for drinking or for other purposes. K is the coefficient of the size and type of health facility [21]. For example, considering the parameter "total coliforms," the law reports two different values: (1) 3,000 MPN/100 ml if the water resource is used as drinking water supply, and (2) 5,000 MPN/100 ml if the water is not used for drinking water supply. For some parameters (e.g., pH, total coliforms, *Salmonella*, *Shigella*, and *Vibrio colera*) the value of K coefficient is always $=1$.

3 Guidelines for the Management of Hospital Wastewater

The main guidelines on the management of hospital wastewater are reported in Table 2.

3.1 WHO Guidelines

The only existing guidelines concerning hospital effluents were published by the World Health Organization (WHO) in 1999: "Safe Management of Wastes from Health-care Activities" [22] and updated in 2014 [23]. In particular, this document spends a specific chapter on the description of the collection and disposal of hospital wastewater, described in detail subsequently. The guidelines divide the health-care wastewater into three categories:

- *Blackwater* (sewage) is heavily polluted wastewater that contains high concentrations of fecal matter and urine.
- *Greywater* (sullage) contains more dilute residues from washing, bathing, laboratory processes, laundry, and technical processes such as cooling water or the rinsing of X-ray films.
- *Stormwater* is technically not a wastewater itself, but represents the rainfall collected on hospital roofs, grounds, yards, and paved surfaces. This may be lost to drains and watercourses and as groundwater recharge, or used for irrigating hospital grounds, toilet flushing, and other general washing purposes.

Obviously, the wastewater might contain different chemical, physical, and biological contaminants in relationship to the service level and the tasks of the health-care facility. The management of HWW could represent a risk mainly in developing countries, in which the major part of the health-care wastewaters, with no or only partial treatment, are discharged into surface watercourses or risk leaching into underlying groundwater aquifers.

Subsequently, the guidelines report the hazards related to liquid chemicals, pharmaceuticals, and radioactive substances. Moreover, the main wastewater-related diseases are presented. For example, nitrate in the groundwater from untreated wastewater can result in methemoglobinemia, particularly in babies. By disposing of untreated wastewater in the environment the nutrient can increase algal production and algal blooms that will favor potentially hazardous bacteria

Table 2 Guidelines on the management of hospital wastewaters

Guideline	Source	Year	Last revision
Effluent Guidelines and Standards (CFR 40)	EPA	1976	2016
Safe management of wastes from healthcare activities	WHO	1999	2014
Release of patients after radionuclide therapy	IAEA	2009	–
Release of patients after therapy with unsealed radionuclides	ICRP	2004	2013

(e.g. *Cyanobacteria*). Wastewater discharged in an uncontrolled manner into the environment can lead to several waterborne diseases that are a threat to human life, especially in developing countries. A specific section presents a selection of these diseases found widely in the world (e.g. campylobacteriosis, cholera, hepatitis A and E). After a brief evaluation of the amount of wastewater produced in high-income countries and primary health-care clinics, there follows an interesting description of the composition of wastewater produced by different sources in health-care facilities (e.g., kitchen, hemodialysis, dental department).

Whereas segregation, minimization, and safe storage of hazardous materials are just as important for liquid wastes as they are for solid wastes, a specific section is dedicated to the management of liquid health-care waste. In particular, the set-up of sewerage systems for health-care facilities and the kind of pre-treatment of hazardous liquids (e.g., blood, stool) are described in detail.

The main topic of the following paragraphs is the management of the discharge of hospital wastewater. In particular, discharge into the municipal sewage system is recommended if the municipal sewage-treatment plant fulfils the local regulatory requirements and satisfies some minimum requirements such as a treatment that ensures at least a 95% removal of bacteria or a plant that has primary, secondary, and tertiary treatment. If these requirements cannot be met, the wastewater should be treated in an onsite wastewater system or managed applying a minimum approach. The most efficient onsite plant for treating the hospital wastewater – divided by kind of treatment (primary, secondary, and tertiary) – is described. The text goes into detail about the disinfection of wastewater, the disposal of sludge, and the possible reuse of wastewater and sludge, including the application of emerging technologies (e.g., membrane biological reactor, anaerobic treatment) for hospital wastewater treatment.

Typical problems in the operation of wastewater are subsequently reported. Considering that the disposal of liquid hazardous waste via the sink is still practiced daily and commonly, the first indication of a problem is the large wastewater losses between the entry points (sinks, toilets, drains) and the arrival at an onsite treatment plant or tank or discharge point into a municipal sewerage system. Moreover the operation of wastewater-system monitoring is described, considering control of the sewerage system and the effluent quality: the most common parameters to be used for the evaluation of the effluent quality are listed (e.g., temperature, BOD_5, presence, and concentration of *Escherichia coli*).

After the description of the best practices for management of the HWW, the WHO document treats the minimum approach necessary to manage the HWW. In particular, considering that in many health-care facilities in developing countries patients have no access to sewer-based sanitation facilities, human sanitation is often by pit latrines or something similar, and, at worst, by open defecation in the grounds of the health-care facility or nearby, the WHO guidelines underline the prime importance of providing access to adequate sanitation in every health-care facility by providing sufficient toilets. Moreover when no other way for hazardous liquid waste disposal is available, the text describes the management of the main liquid waste using the appropriate Personal Protective Equipment (PPE). For

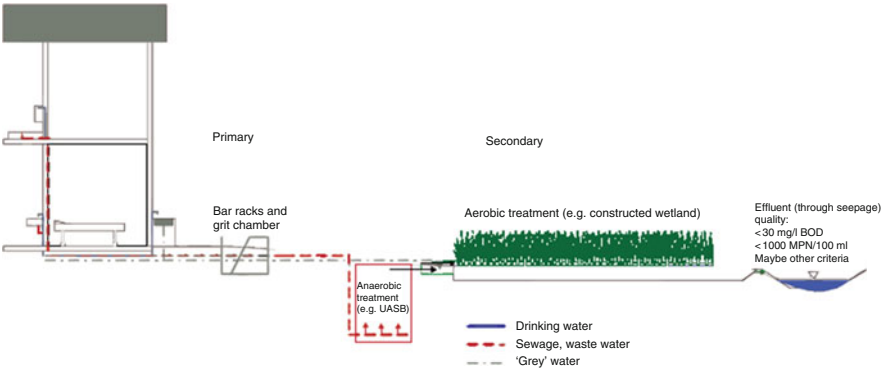

Fig. 1 Basic hospital wastewater-treatment system with two treatment stages [23]. *BOD* biological oxygen demand, *MPN* most probable number, *UASB* upflow anaerobic sludge blanket

example stool, vomit, and mucus from highly infectious patients (e.g., cholera patients) should be collected separately and thermally treated before disposal (e.g., by an autoclave reserved for waste treatment). Lime milk (calcium oxide) can be used during emergencies and if no autoclave or appropriate disinfectants are available. The WHO Guidelines report a useful scheme of a basic hospital wastewater-treatment system consisting of a primary and secondary treatment stage, which is considered as the minimum treatment for primary and secondary level rural hospitals (Fig. 1).

Finally the WHO Guidelines indicate desirable improvements to the minimum approach, divided into enhancements to the minimum (e.g., set up a budget line to cover wastewater-treatment costs; enforce liquid hazardous waste management; segregate and pretreat hazardous waste, etc.) and enhancements for intermediate approaches (e.g., disinfect the wastewater by UV or change to chlorine dioxide or ozone; regularly inspect the sewerage system and repair whenever necessary). In conclusion a table that lists the key points to remember is presented (Table 3).

3.2 EPA Guidelines

In the USA, the major environmental law governing surface water discharges is the Clean Water Act (CWA) [24]. The EPA, states, and local city pretreatment programs implement the CWA through publication of specific regulations and discharge permits for point sources of wastewater pollution. Each discharge to the surface waters or municipal wastewater treatment plants (called publicly owned treatment works, POTWs) must comply with the more stringent of the technology-based standards ("effluent guidelines") and local-site specific effluent limitations ("local limits").

Table 3 Key points to remember [23]

Untreated wastewater from health-care facilities may result in waterborne diseases and environmental problems, and can pollute drinking-water resources
A separate financial budget, a routine maintenance system, and a working management system for liquid hazardous waste are key elements in developing and operating an efficient wastewater-management system
Basic systems can reduce the risk of waterborne diseases drastically if appropriately planned and implemented; more advanced systems reduce the risk further
Pharmaceuticals and other hazardous liquid wastes in wastewater may form a serious future problem and must be carefully observed and minimized. This includes reducing to an absolute minimum the presence of antibiotics and pharmaceutical residues in wastewater
Low-cost and low-maintenance systems, such as anaerobic treatment and reed bed systems, are available
A good, well-maintained sewerage system is as important as an efficient wastewater-treatment plant

Effluent limitation guidelines and standards (ELGs) are an essential element of the nation's clean water program, which was established by the 1972 amendments to the CWA. ELGs are technology-based regulations used to control industrial wastewater discharges. The EPA issues ELGs for new and existing sources that discharge directly to surface waters, as well as those that discharge to POTWs (indirect dischargers). ELGs are applied in discharge permits as limits to the pollutants that facilities may discharge. To date, the EPA has established ELGs to regulate wastewater discharges from 58 categories of point-sources. This regulatory program substantially reduces industrial wastewater pollution and continues to be a critical aspect of the effort to clean the nation's waters. In addition to developing new ELGs, the CWA requires EPA to revise existing ELGs when appropriate. Over the years, the EPA has revised ELGs in response to developments such as advances in treatment technology and changes in industry processes. To continue its efforts to reduce industrial wastewater pollution and fulfill CWA requirements, the EPA conducts an annual review and effluent guidelines planning process. The annual review and planning process has three main objectives: (1) to review existing ELGs to identify candidates for revision, (2) to identify new categories of direct dischargers for possible development of ELGs, and (3) to identify new categories of indirect dischargers for possible development of pretreatment standards [25].

A typical health-care facility has a wide variety of wastewater sources, such as lavatories, sinks, showers, laboratories, photo processing labs, washing machines and dishwashers, boilers, and maintenance shops. The facility will fall under one of two sets of regulations, depending on where the water goes next. Facilities that discharge their wastewater into a municipal sewer system are referred to as indirect dischargers, while those that discharge directly to streams or rivers are considered direct dischargers.

The vast majority of health-care facilities are indirect dischargers. Such facilities are subjected to regulations by their local sewer authority, which are in turn regulated by the CWA. Typically, indirect dischargers must obtain a permit

(defined as an *industrial user permit*), and are required to comply with the specific rules stated in the permit. CWA regulations expressly prohibit any indirect discharger from releasing any of the following into the sewer:

- fire or explosion hazards
- corrosive discharges (pH < 5.0)
- solid or viscous pollutants; heat (in amounts that cause the treatment plant influent to exceed 104 °F)
- pollutants that cause toxic gases, fumes, or vapors
- any other pollutant (including oil and grease from a cafeteria) that will interfere with or pass through the municipal treatment plant.

Beyond that, the local sewer authority will establish rules and limits for the facility that take into account local conditions, and the requirements of the authority's own permit.

Some hospitals, primarily larger ones located in smaller communities, may be designated by their sewer authority as a *significant industrial user*. This designation is usually associated with manufacturing facilities, but a sewer authority can apply the designation if a facility has a "reasonable potential for adversely affecting" the operation of the sewage treatment plant. A hospital designated as a significant industrial user must sample and analyze its wastewater and submit reports to the sewer authority twice a year.

In addition to the specific rules discussed above, the CWA provides municipalities with regulatory flexibility so that they can meet their specific needs. Many municipalities have chosen to establish local rules that apply specifically to medical waste discharges. Examples range from blanket prohibitions on "all medical waste" to more specific prohibitions regarding items such as recognizable body parts or radioactive compounds.

For hospitals that are direct dischargers, the EPA has established national discharge standards, which are numerical limitations for certain specific pollutants. These standards are much more difficult to meet than the limitations for indirect dischargers, which is understandable, given that the wastewater from direct discharge hospitals flows directly into a stream or river, without having been treated or monitored by a municipal system. To meet the direct discharge limitations, a hospital would have to obtain a permit from its state environmental agency or the EPA (depending on the status of the state agency) and install a complex wastewater treatment plant.

3.3 Guidelines about Radionuclide Releases to the Environment from Hospitals

Nuclear medicine involves the use of unsealed radionuclides. This critical issue regards the exposure of the treated patient to radionuclides, but also the release of

the radionuclides to the environment from the hospital laboratories and through the disposal of the excreta of hospital patients. Radioactive iodine treatment is the main source of exposure to the public and relatives from patients who have received unsealed radionuclides. Other radionuclides traditionally used in therapy are usually pure beta emitters (e.g., 32P, 89Sr, and 90Y) that pose much less risk to others. Recently, a number of new therapeutic methods have come into clinical use like 177Luoctreotate, 68Ga-octreotate, and 90Y-SIRS particles [26]. In this context some guidelines regarding the release of patients after radionuclide therapy were produced. The guidelines produced by the International Atomic Energy Agency [27] underline that the predominant issue regards how the patients could represent a risk through their radioactive excreta (urine and feces). Much of the activity initially administered is eventually discharged to sewers. Table 4 shows the proportion for some therapeutic radionuclides typically discharged by this route.

As reported in this table the main radionuclide discharged into the environment following radionuclide therapy is radioiodine (I131). Owing to its half-life of 8 days, I131 can be detected in the general environment after medical use. However, the degree of dilution and dispersion caused by mixing with normal waste, and the length of time required for any contamination to be returned to the ecosystem, reduces the environmental impact to a level that is below that suggested in all available guidelines.

Also the International Commission on Radiological Protection (ICRP) published a guideline for the release of patients after therapy with unsealed radionuclides [28, 29]. This document reported that Technetium-99m dominates discharges to the environment from the excreta of nuclear medicine patients, but its short half-life limits its importance. The second largest discharge, iodine-131, can be detected in the environment after medical uses but with no measurable environmental impact. Radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public dose limits. In this context it is important to highlight that the ICRP recommendations do not explicitly require that patients are hospitalized for radionuclide therapy. On the other hand, guidance from the IAEA of 1992 indicated that in radioiodine therapy for cancer: “it is not

Table 4 Proportion of administered activity discharges to sewers [27]

Nuclide and form	Disease or condition treated	Amount of activity discharged to sewers (%)
Au-198 colloid	Malignant disease	0
I-131	Hyperthyroidism	54
I-131	Thyroid carcinoma	84–90
I-131 MIBG[a]	Phaeochromocytoma	89
P-32 phosphate	Polycythemia, etc.	42
Sr-89 chloride	Bone metastases	92
Y-90 colloid	Arthritic joints	0
Y-90 antibody	Malignancy	12
Er-169 colloid	Arthritic joints	0

[a]*MIBG* meta-iodobenzylguanidine

recommended to let the patient return home immediately. Instead, he or she should be kept at the hospital for a period of between some hours and several days." Moreover in the more recent guidelines of 2009 it is reported that the major advantage of retaining a patient in hospital is that, with good practice, the environment and the associated risks are controlled.

4 Case Study

The management of HWW as described above is therefore not easy, but the growing emphasis on the possible role of the hospital effluents as microbial and chemical contamination sources has provided the stimulus for the creation of case studies of excellence. An example is the creation of the pilot site Bellecombe, born of necessity in 2009, by the municipal grouping of Bellecombe (SIB), to provide for extension work of its wastewater treatment plant due, in particular, to the construction of a new hospital on its territory. Located in the Haute-Savoie "department," near the border with Switzerland, the pilot site consists of: the Geneva Hospital Alps (CHAL) commissioned in February 2012, with a 450-bed capacity of the plant; the wastewater treatment plant (WWTP) of Bellecombe, with two separated processing lines for isolating the hospital effluents; an acceptor: the Arve River, which provides a portion of water intended for human consumption. An important feature of the system is the possibility of treating hospital wastes separately or mixing them with domestic effluent and distributing all effluent on three lines, with a total capacity of 26,600 population equivalent as reported in Fig. 2 [30].

A first meeting in March 2010, which brought together the founding members and partners, allowed the establishment of the project basis SIPIBEL (Pilot Site Bellecombe), which aims to define the characterization, treatability, and impacts of hospital waste in the urban sewage treatment plant. SIPIBEL was created with local actors (e.g., Sanitation managers, hospital), public research laboratories, industrial designers, and institutional partners. To get an initial reference before the opening of the hospital in February 2012, a monitoring program was created in 2011. The observatory has been working routinely since February 2012. 2013 saw the beginning of the Franco-Swiss Interreg IRMISE project, which placed the SIPIBEL in a broader context and made it cross-border. SIPIBEL is an observation and research institution consisting of:

- the *Observatory*, which aims to monitor the effluents and their impact on the receiver environment
- implementation of *research programs* in support of SIPIBEL
- a development and *communication center*.

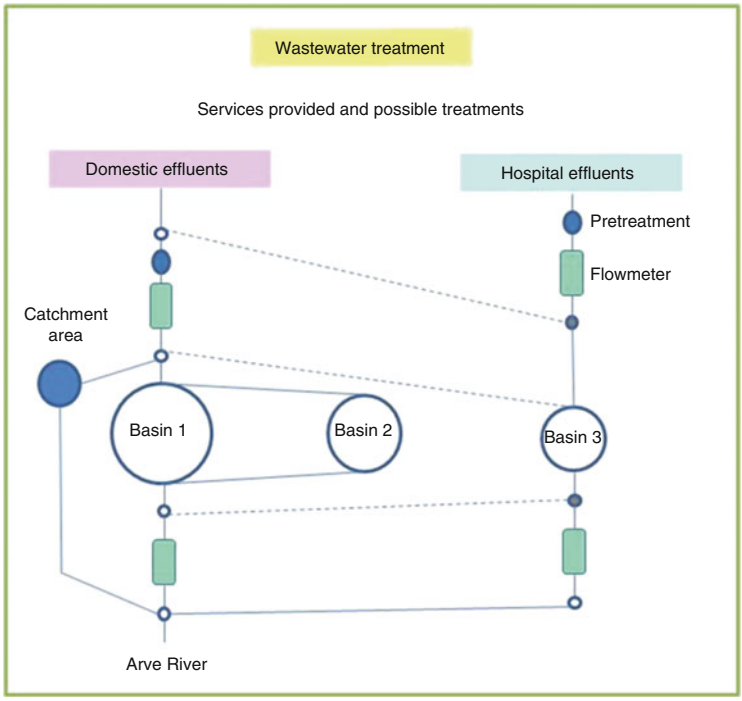

Fig. 2 Scheme of wastewater treatment in the Bellecombe site (adapted from [30])

The *Observatory's purposes* are:

- the definition and management of measurement campaigns with scientists and field workers: the monitoring of the physico-chemical and ecotoxicological quality effluent, but also the monitoring of sociological elements of the territory
- capitalization of data through an online data management system with national and European approaches
- valuation analysis after the results of validation and interpretation: disseminating analytical reports to partners, communication via the website, the organization of knowledge transfer activities (conferences, joint publications), associated research programs.

The *research programs* in the SIPIBEL framework have been specifically developed to address the major issues of knowledge and strategies identified in the various national and regional plans being implemented.

An enhancement and *communication center* whose purpose is to ensure:

- the integration between observation and research
- their inclusion in national and European standardization process plans

– the combination of broader approaches to territorial policies and the exchange of experiences (contractual health facilities, civic initiatives, the management of non-domestic effluent).

The coexistence of diverse realities in the Bellecombe site demonstrates the need and the utility of a multidisciplinary approach to the management of hospital wastes, both from the scientific point of view and that of communication. It is important to underline that SIPIBEL was created prior to the opening of the hospital, thereby highlighting a correct preventive approach to the management of hospital wastes. Such an approach is to be hoped for in other realities as well.

In the previous years also other projects were funded on the study of the spread of pharmaceutical residues in the environment (NoPills project) and on the role of hospital wastewater in this context (SIPIBEL RILACT project).

In the 2012 started the "NoPills" project funded by European Interred IVb Programme. This project aimed to provide further information on the fate of pharmaceutical residues in the aquatic environment, and provide practical experience on the identification of potential and actually implemented technical and social intervention points across the medicinal product chain with a focus on consumer behavior, wastewater treatment, and multi-stakeholder engagement [32].

The SIPIBEL RILACT project financed by French national funds in 2014, currently still in progress (will be completed in 2018), is the natural continuation of the SIPIBEL project and has several key objectives:

– developing methods for the identification and quantification of drugs, detergents, and biocides and of their metabolites and degradation products
– characterizing the sources of drugs and their dynamics in hospital and municipal wastewater
– contributing to the environmental risk assessment for the evaluation of the biological effects
– developing research and a sociological study
– enhancing and transferring gained results and knowledge [31].

5 Final Remarks

The consideration of what has been written here means that certain critical points emerge. A fundamental aspect is the dishomogeneity of hospital waste management legislations amongst different countries, which makes comparison quite difficult. In many countries there are not even specific legislations for the management of these wastes, which are in some cases considered domestic and in others industrial. In regard to the guidelines available at present, there emerges the need to furnish not only specific indications for the management of hospital wastes, but also to provide indications as to the parameters for quality and control of this type of waste.

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Occurrence of Common Pollutants and Pharmaceuticals in Hospital Effluents

Tiago S. Oliveira, Mustafa Al Aukidy, and Paola Verlicchi

Abstract This chapter summarizes the current knowledge on the occurrence of common pollutants and pharmaceuticals in hospital effluents. These common pollutants include a myriad of biological, inorganic and organic pollutants. Daily and weekly concentration variability is presented for many of the covered pollutants. Particular attention is given to heavy metals (gadolinium and platinum) and pharmaceuticals commonly used in hospitals. For pharmaceuticals, the prevalent therapeutic categories are presented and are found to be dependent on the type of healthcare facility – general hospital, specialized hospitals, wards, and units.

Keywords Common pollutants, Heavy metals, Hospital effluent, Microbiological indicators, Pharmaceuticals

Contents

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1 Introduction

Hospital activities have an important role in the population well-being and healthcare research advancements. During these activities, unwanted generated by-products are treated following country-specific regulations and by using, in most cases, established management systems.

In the last decades, the scientific community has been focusing on the characterization of hospital effluents in terms of their biological, physical, and chemical properties to assess potential risks associated with discharges into aquatic ecosystems.

Pollutants such as coliforms (total and fecal), chemical residues (e.g., detergents), pathogens (e.g., *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella* and *Vibrion*), pharmaceutical residues, radioelements (e.g., ^{131}I), and other heavy metals and toxic chemical compounds (e.g., Cd, Cu, cyanide, Fe, Gd, Hg, Ni, Pb, Pt, Zn, phenol, etc.) have been quantified in hospital effluents [1, 2]. Many of these pollutants are commonly classified based on their detected concentrations as micropollutants (10^{-6}–10^{-3} mg L^{-1}) or macropollutants ($>10^{-3}$ mg L^{-1}) and the majority has no regulatory status.

Hospital activities generate variable quantities of effluent, being dependent on numerous factors (e.g., number of beds; facility age and maintenance practices; existent general services – kitchen, laundry, temperature control systems; number and type of wards and units; number of inpatients and outpatients; institution management policies, geographic location, hour of the day and season) [1, 3–5].

The water demand typically observed in hospitals has been estimated between 200 and 1,200 L bed^{-1} day^{-1} with the highest values reported from industrialized countries and the lowest from developing countries (200–400 L bed^{-1} day^{-1}) [1, 5, 6]. In industrialized countries, estimates of total effluents produced from hospitals range between 250 and 570 m^3 day^{-1} and the percentage of hospital effluent flow rate of the total discharge treated in municipal WWTP ranges between 0.2 and 65% [1, 6, 36].

The removal efficiency of common pollutants originated in hospital effluents is compound specific (being dependent on biodegradability and physicochemical properties – water solubility, adsorption, and volatilization) and is dependent on the WWTP characteristics (primary, secondary, and tertiary treatments), operational conditions (hydraulic and sludge retention time, pH, temperature), reactor type and its configuration (mainly conventional activated sludge system, membrane biological reactor, sequencing batch reactor), and environmental characteristics (irradiation, precipitation, temperature) [7–9]. Most municipal WWTPs have been designed to remove easily or moderately biodegradable carbon, nitrogen and

phosphorous compounds, and microbiological organisms but not micropollutants such as pharmaceutical residues and other chemical residues [8].

The assessment of pharmaceutical residues presence in hospital effluents has been performed either by using predicted concentrations or measured concentrations [37]. The calculation of predicted concentrations is based on parameters such as active ingredient consumption, water consumption per bed, and excretion percentage. Measured concentrations are determined by sample collection and subsequent analysis with analytical instrumentation in a laboratory setting. Predicted and measured concentrations of pharmaceuticals in hospital effluents might present different results. These differences can be partially attributed to the time scales considered. While predicted concentrations are extrapolated in most cases by using yearly pharmaceutical consumption data, measured concentrations are determined at a certain point in time and for a limited period of time. Measured concentrations may present higher variability than predicted concentrations, depending on the compound [9, 37]. Some authors consider predicted concentrations a better option to determine discharge of pharmaceuticals over longer time periods [9]. Each approach has merits and shortfalls and should be considered when developing a source characterization effort, as discussed in another chapter of this book. Ultimately the defining factors to use one or the other are dependent on cost, access to consumption information, and/or access to sewage systems and research goals. Predicted and measured concentrations are used in this chapter to illustrate the significance of these analytes in hospital effluents.

In most instances research groups not only intend to characterize effluent sources but also assess their impact in WWTP performance [3, 4, 6–8, 10]. As there are thousands of pharmaceuticals commercially available and many can be found in the environment in their parent form and as conjugates, prioritization strategies have been developed. These prioritization strategies take into consideration different criteria (e.g., consumption/sales, physico-chemical properties, (eco)toxicity, risk, degradability/persistence, resistance to treatment) [3, 12].

To date over 300 pharmaceutical residues, conjugates, and other chemical residues have been screened in hospital effluents and the latest investigations have been incorporating an increasing number of compounds for assessment due to the commercial availability of more analytical standards and the improvement of analytical instrumentations. These pollutants are of particular concern due to the mounting evidence of potential impact to aquatic organisms (e.g., genetic lesions, organ and reproductive abnormalities, behavioral changes) and the production of antibiotic-resistant bacteria and genes once released into the environment [13–18].

This chapter intends to summarize the current knowledge on the occurrence of common pollutants and pharmaceuticals in hospital effluent.

2 Hospital Effluent Characterization

Hospital effluents have been characterized in different geographic regions for conventional and non-conventional parameters by several research groups. A summary of the ranges of concentrations measured for several chemical, biological, and microbiological parameters is presented in Table 1.

2.1 Physico-Chemical Characterization

The physico-chemical characterization of hospital effluents includes the assessment of different parameters. Among these parameters, the most routinely used to assess the presence and loads of inorganic/organic matter in the effluent are electric conductivity (EC), biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), and total nitrogen. The concentration ranges for these parameters measured in hospital effluents collected in different countries over a 20-year span are summarized in Table 1. The concentration ranges measured demonstrate the relevance of hospital effluents as a source of inorganic/organic matter loads particularly when compared with municipal effluents (whose variability intervals usually observed are: BOD_5 between 100 and 400 mg L^{-1}, COD between 43 and 270 mg L^{-1}, TSS between 150 and 500 mg L^{-1}, and total N between 30 and 100 mg L^{-1}) [2]. Verlicchi et al. [5] indicate that hospital effluents typically present BOD_5, COD, and TSS 2–3 times higher than in municipal effluents corresponding to specific contributions of 160 g BOD_5 patient^{-1} day^{-1}, 260–300 g COD patient^{-1} day^{-1}, and 120–150 g TSS patient^{-1} day^{-1}.

2.2 Bacteriological Characterization

The bacteriological characterization of hospital effluents typically includes the assessment of indicators of fecal contamination and pathogens.

Fecal coliforms are typically determined by analyzing *E. coli* since they represent 80 to 90% of detected thermo-tolerant coliforms [2]. *E coli*. are a facultative anaerobic bacteria species predominant in the gut and feces. The presence of these bacteria in wastewater is regarded as an indication of fecal contamination and therefore the presence of pathogenic fecal micro-organisms. Other less commonly analyzed parameters in hospital effluent include: a) bacteria such as spores of sulfite-reducing anaerobes, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella*; and b) pathogenic virus such as enterovirus, norovirus, adenovirus, rotavirus, and hepatitis A virus [1, 2].

Fecal contamination (total and fecal coliforms) load is generally more relevant in municipal effluents than hospital effluents. This is resultant of the higher dilution

Table 1 Hospital effluent characterization parameters

Parameter (unit of measure)	Concentration(s)
Electrical conductivity (μS cm^{-1})	300–2,700
pH	6–9
Redox potential (mV)	850–950
Fat and oil (mg L^{-1})	50–210
Chlorides (mg L^{-1})	80–400
Total N (mg N L^{-1})	60–230
NH_4 (mg NH_4 L^{-1})	10–68
Nitrite (mg NO_2 L^{-1})	0.1–0.6
Nitrate (mg NO_3 L^{-1})	1–2
Phosphate (mg P-PO_4 L^{-1})	6–19
Total suspended solids (mg L^{-1})	116–3,260
COD (mg L^{-1})	39–7,764
Dissolved COD (mg L^{-1})	380–700
DOC (mg L^{-1})	120–130
TOC (mg L^{-1})	31–180
BOD_5 (mg L^{-1})	16–2,575
BOD_5/COD	0.3–0.4
AOX (μg L^{-1})	550–10,000
E. coli (MPN 100 mL^{-1})	10^3–10^6
Enterococci (MPN 100 mL^{-1})	10^3–10^6
Fecal coliform (MPN 100 mL^{-1})	10^3–10^4
Total coliform (MPN 100 mL^{-1})	10^4–10^7
EC_{50} (Daphnia) (TU)	9.8–117
Total surfactants (mg L^{-1})	4–8
Total disinfectants (mg L^{-1})	2–200
Norovirus (genomic copies L^{-1})	2.4×10^6
Adenovirus (genomic copies L^{-1})	2.8×10^6
Rotavirus	1.9×10^6
Hepatitis A virus	10^4
Gd (μg L^{-1})	<1–300
Hg (μg L^{-1})	0.3–8
Pt (μg L^{-1})	0.01–289
Hg (μg L^{-1})	0.04–5
Ag (μg L^{-1})	$150–437 \times 10^3$
As (μg L^{-1})	0.8–11
Cu (μg L^{-1})	50–230
Ni (μg L^{-1})	7–71
Pb (μg L^{-1})	3–19
Zn (μg L^{-1})	70–670

Adapted from [1, 2, 5, 20, 22–26, 33]

of the hospital effluent due to significant water consumption per bed [1]. The opposite has been reported for enterovirus concentration being 2–3 times higher in hospital effluent than in municipal effluent [1].

2.3 *Heavy Metals and Other Toxic Chemical Compounds Characterization*

The main heavy metals found in hospital effluents are gadolinium (Gd), mercury (Hg), and platinum (Pt) [5, 20]. Other heavy metals such as Cd, Cu, Fe, Ni, Pb, and Zn typically present similar concentrations as the reported in municipal effluent [20].

Gadolinium containing substances (e.g., gadodiamide, gadopentetic acid, Gd-diethylenetriamine pentaacetate) are applied (orally or intravenously) during magnetic resonance imaging (MRI) because of its high magnetic moment imaging of the digestive tract, brain, and spine.

The contrast media are excreted non-metabolized into hospital sewage within a few hours after application. With a residence time of 70 min and with an excretion of 85–98% within 24 h, it is estimated that approximately 90% of Gd is excreted during the patient hospital stay [5, 21].

Kümmerer and Helmers measured Gd in effluent originated in Freiburg University Hospital (Germany) with three MRI systems serving 15–25 patients per day. The Gd concentrations measured ranged between <1 and 55 μg L^{-1} and presented low concentrations overnight with a noticeable increase in the morning (around 10 a.m.) and also exhibited two peaks later in the day(6 p.m. and 10 p.m.). Daouk et al. [22] assessed Gd temporal variability during 1 week in the Geneva University Hospital main building (741 beds – Switzerland) and reported a noticeable increase at the end of the week (Friday). They measured Gd concentrations within the range $<$ 1–300 μg L^{-1}.

Mercury is usually found in diagnostic agents, active ingredients of disinfectants and diuretic agents. Hg concentrations in hospital effluent range between 0.3 and 7.5 μg L^{-1} [23, 24]. Since the early 2000s, there has been an effort in industrialized countries to reduce Hg contamination by using diagnostic agents without this heavy metal and by implementing better waste management practices.

Platinum containing substances (e.g., carboplatin and cisplatin) have been used as antineoplastics for oncological treatment since the mid-1970s. After being administered, these antineoplastics are excreted at different rates (patient dependent). Carboplatin is excreted at a rate of 50–75% within the first 24 h after being administered. Cisplatin is excreted at a rate of 31–85% within the first 51 days after being administered. The biological half-lives for the two long-term phases of renal platinum excretion are 160 and 720 days. It is estimated that 70% of the administered Pt is excreted into the hospital effluents [25].

Kümmerer et al. [25] measured Pt in five European hospitals of different size (from 174 to 2,514 beds). They found concentrations varying between <0.01 and 3.5 μg L^{-1}. They also analyzed Pt concentration variation in the Freiburg University Hospital (Germany) during a 24-h period and found two concentration peaks, at 4 a.m. and 10 a.m. Daouk et al. [22] assessed Pt temporal variability during 1 week in the Geneva University Hospital main building (741 beds – Switzerland) and reported a noticeable increase at the end of the week (on Thursdays). They measured Pt concentrations within the range <0.01–2 μg L^{-1}. Lenz et al. [26] measured Pt in an oncological in-patient treatment ward in Vienna (Austria) and reported concentrations ranging between 2.0 and 289 μg L^{-1}. They conducted Pt speciation analysis and identified carboplatin as the main contributor to Pt loads.

2.4 Pharmaceuticals Residues Characterization

The consumption of pharmaceuticals is variable among healthcare facilities [9, 27]. As an example, in Germany the total pharmaceutical consumption has been estimated for a psychiatric hospital, a nursing home, and a general hospital. The total pharmaceutical consumption ranged between 32 (psychiatric hospital) and 1,263 kg $year^{-1}$ (general hospital) with annual average consumption of individual pharmaceuticals ranging between 0.1 and 1,000 g bed^{-1} [9]. In general, the main therapeutic categories consumed in hospitals are contrast media, laxatives, analgesics, anti-inflammatories, antibiotics, and cytostatic drugs [6, 22]. Once consumed, the pharmaceuticals are excreted mainly via urine (55–80%) and at a lower rate via feces (4–30%), as non-metabolized substances, metabolites, or conjugated with inactivating substances [1, 38].

The concentration of pharmaceutical residues in hospital effluents are the result of the combination of three main factors: administered quantity, excreted percentage, and chemical characteristics (mainly stability and biodegradability) of the specific compounds [5]. Hospital effluents have been screened for pharmaceutical residues in different geographic regions (e.g., Asia – [28]; Europe – [4, 11, 29]; North-America – [6, 39, 40]).

The total load of pharmaceuticals in the effluents of the hospitals in these geographic regions ranged between 78 μg L^{-1} [28] and 5 mg L^{-1} [29] with 12 therapeutic categories being regularly measured (Table 2). These therapeutic categories comprise ≥94% of the total concentrations measured.

The therapeutic categories percentage distribution is very dependent on the analytes targeted for analysis. Within the therapeutic categories regularly measured in hospital effluents, contrast media agents, cytostatics, analgesics, and antibacterials and anti-infectives are the most relevant. When prevailing, these categories can individually reach >40% of the total concentration measured [4, 11, 28, 29]. Other relevant therapeutic categories include anti-epileptic, anti-inflammatory, psychoanaleptic, and β-blocker drugs reaching a maximum of 20% of the total concentration measured [4, 6, 28].

Table 2 Therapeutic classes and range of concentration measured in healthcare facilities effluents

Therapeutic class	Investigated compounds	Concentration(s) μg L^{-1}
Analgesics/anti-inflammatories	Codeine	0.02–50
	Diclofenac	0.24–15
	Ibuprofen	0.07–43
	Naproxen	10–11
	Paracetamol	5–1,368
	Salicylic acid	23–70
Antibiotics	Ciprofloxacin	0.03–125
	Clarithromycin	0.20–3
	Coprofloxacin	0.85–2
	Doxycycline	0.1–7
	Erythromycin	27–83
	Lincomycin	0.3–2
	Metronidazole	0.1–90
	Norfloxacin	0.03–44
	Ofloxacin	0.35–35
	Oxytetracycline	0.01–4
	Penicillin G	0.85–5
	Sulfamethoxazole	0.04–83
	Tetracycline	0.01–4
	Trimethoprim	0.01–15
Psychiatric drugs	Carbamazepine	0.54–2
Anti-hypertensives	Diltiazem	0.71–2
Beta-blockers	Metoprolol	0.42–25
Hormones	17β-estradiol, E2	0.03–0.04
	Estriol, E3	0.35–0.50
	Estrone, E1	0.02–0.03
	Ethinylestradiol, EE2	0.02–0.02
Contrast media	Iopromide	0.2–2,500
	Iomeprol	0.01–1,392
Anti-diabetics	Glibenclamide	0.05–0.11
Anti-viral	Aciclovir	0.02–0.60
	Famciclovir	N.D.-0.11
	Penciclovir	N.D.-0.01
	Valaciclovir	N.D.-0.01
Anti-cancerdrugs	4-Hydroxy tamoxifen	N.D.-0.01
	5-fluorouracil	5–124
	Azathioprine Bicalutamide	blq-0.09 N.D.-0.08
	Capecitabine	N.D.-0.05
	Cyclophosphamide	0.008–2
	Docetaxel	blq-0.08
	Doxifluridine	N.D.-0.08
	Etoposide	blq-0.7

(continued)

Table 2 (continued)

Therapeutic class	Investigated compounds	Concentration(s) μg L^{-1}
	Ifosfamide	0.01–2
	Methotrexate	blq-0.02
	Paclitaxel	blq-0.10
	Tamoxifen	0.004–0.17
	Tegafur	N.D.-0.09

Adapted from [22, 33, 34]
Note: country-specific prescription habits influence the compounds present in the effluent
N.D. not detected, *blq* below limit of quantification

Most pharmaceuticals screened in hospital effluents present maximum concentrations <10 μg L^{-1}. Higher concentrations are typically measured for specific compounds some of which are presented in Table 2 (e.g., acetaminophen, caffeine, ciprofloxacin, gabapentin, ibuprofen, iomeprol, iopamidol, iopromide, metformin, theobromine) reaching concentrations within the low mg L^{-1} range for several contrast media agents [4, 6, 11, 28, 29].

Daouk et al. [22] investigated pharmaceuticals belonging to different categories in effluents originated in the Geneva University Hospital main building (741 beds – Switzerland) and calculated mean daily loads for 15 pharmaceuticals ranging mainly between 0.1 and 14 g day^{-1}, except for acetaminophen (143 g day^{-1}), piperacillin (0.08 g day^{-1}), and diclofenac (0.04 g day^{-1}). The weekly variability of these pharmaceuticals was assessed and the daily load remained with the 50–150% of the average for compounds which are widely consumed on a regular basis such as acetaminophen, morphine, and ibuprofen.

Pharmaceuticals consumed at lower extent such as the analgesics diclofenac, mefenamic acid or the anti-epileptics gabapentin and carbamazepine presented on the contrary a higher variability, up to 400% of the average value with the highest concentrations being measured throughout the week. For the investigated antibiotics, a higher variability was observed for metronidazole than for sulfamethoxazole and ciprofloxacin. Metronidazole presented highest concentrations earlier in the week.

Specialized hospitals and wards (e.g., oncologic in-patient care, intensive care, geriatric care, psychiatric care) use a different range of drugs than general hospitals. The effluents originated by an oncological in-patient care ward (18 beds) in Vienna University Hospital (Austria) have been characterized for antimetabolites and anthracyclines [26, 30]. The antimetabolite 5-fluorouracil is administered in the treatment of breast, skin, bladder, and lung cancer in dosages ranging from 200 to 1,000 mg m^{-2} body surface [30]. Approximately 2–35% of the administered drug is excreted un-metabolized via urine within 24 h [30]. The anthracyclines doxorubicin, epirubicin, and daunorubicin are frequently used in the treatment of hematological and solid neoplasms, including acute leukemia, high grade lymphoma, breast cancer, and bladder cancer in dosages ranging from 15 to 120 mg m^{-2}

body surface. Approximately 3.5–5.7% of administered doxorubicin, 11% of epirubicin, and 13–15% of daunorubicin are excreted un-metabolized via urine within 24 h. [30]. Of the administered cytostatics, 5-fluorouracil and doxorubicin have been measured in the effluent at <8.6–124 μg L^{-1} and <0.26–1.35 μg L^{-1}, respectively [30]. In total, 0.5–4.5% of the administered amount of 5-fluorouracil and 0.1–0.2% of the administered amount of doxorubicin were found in the effluent of the oncological in-patient treatment ward [26].

Lopes de Souza et al. [31] investigated intravenous antibiotics consumed in an intensive care unit (16 beds) in a Brazilian hospital, calculated the predicted environmental concentration (PEC), and performed an environmental risk assessment. The consumption of these antibiotics in the intensive care unit was identified as being relevant since this unit with only 10% of the total number of beds available in the hospital used 25% of the total antibiotic consumption. Several intravenous antibiotic classes were used and the highest consumption was identified for the antibiotics ceftriaxone, meropenem, cefazolin, clindamycin, piperacillin, cefepime, ampicillin, vancomycin, trimethoprim, sulbactam, and ceftazidime [31]. The highest consumption was identified for ceftriaxone with 3.13 g $year^{-1}$. These authors calculated PECs factoring in dilution of effluent by surface water flow (10 times). If the dilution factor is not considered, the predicted concentrations released by the intensive care unit range between 1.15 μg L^{-1} for quinolones and 701 μg L^{-1} for cephalosporins. Within cephalosporins, the highest predicted concentrations were calculated for cefazolin (280 μg L^{-1}) and ceftriaxone (320 μg L^{-1}). Other classes with significant predicted concentrations include carbapens and penicillins with 229 μg L^{-1} and 262 μg L^{-1}, respectively. Within these two classes, the highest predicted concentrations were calculated for meropenem (220 μg L^{-1}) and ampicillin (222 μg L^{-1}). Lopez de Souza and colleagues [31] indicate that most of the intravenous antibiotics investigated present a high risk to the environment. Some of the risks associated with the release of antibiotics is related with the high potential to generate antibiotic-resistant bacteria [1, 13–19].

Herrmann et al. [9] investigated the pharmaceutical contributions by a psychiatric hospital (146 beds) and a nursing home (286 beds) in Germany. In these facilities, most of the pharmaceuticals consumed act on the nervous system and include anti-epileptics, psycholeptics, and psychoanaleptics. Anti-epileptics are commonly used to treat epilepsy, but some substances in this therapeutic category, such as gabapentin, pregabalin and valproic acid, are also used to treat bipolar disorders or neuropathic pain, hence their relevance in the psychiatric hospital and the nursing home. Valproic acid was identified as the pharmaceutical with the highest consumption in the psychiatric hospital with 33.1 ± 4.8 g bed^{-1} $year^{-1}$. In the psychiatric hospital, psycholeptics (antipsychotics, tranquilizers, and hypnotics) were consumed more frequently than psychoanaleptics (antidepressants) because individuals suffering from depression are, in general, treated more often as outpatients [9]. The antipsychotic quetiapine was found to be consumed in high quantities in either facility (e.g., psychiatric hospital – 25.8 ± 3.6 g bed^{-1} $year^{-1}$). Other relevant pharmaceuticals included two analgesics/anti-inflammatories (ibuprofen

– 22.6 ± 1.1 g bed^{-1} year^{-1} and metamizole – 24.7 ± 2.4 g bed^{-1} year^{-1}) and the antidiabetic metformin −12.3 ± 4.5 g bed^{-1} year^{-1} [9].

Santos et al. [11] screened 78 pharmaceuticals and other chemical residues in Portuguese hospitals and estimated total mass loads ranging between 1.5 g day^{-1} (Maternity hospital with 96 beds) and 306 g day^{-1} (University hospital with 1,456 beds) and Oliveira et al. [6] screened 185 pharmaceuticals and other chemical residues in the US hospitals and estimated total mass loads ranging between 180 and 310 g day^{-1} for general hospitals (250 to 600 beds).

Besides the number and size of the healthcare facilities, the impact of healthcare facilities pharmaceuticals and chemical residues loads into WWTP is related with the size of the sewer network. Sewer networks treating effluent volumes originating from different sources result in increased dilution of the loads originating from healthcare facilities. Oliveira and co-authors [6] investigated sewer networks with variable number of hospitals (1–2) and inflows (1,300–103,000 m^3 day^{-1}) and estimated that the pharmaceuticals and other chemical residues loads originating from 6 general hospitals at the WWTPs influents ranged between 1 and 59%. Additionally, estimates of individual pharmaceuticals contributions from healthcare facilities at WWTP influent indicate that higher inflows ($\geq$10,000 m^3 day^{-1}) result in a lower individual pharmaceutical contribution from healthcare facilities ($<$15%) [6, 32] and that lower inflows ($<$10,000 m^3 day^{-1}) individual pharmaceutical can reach $>$80% [6].

High concentrations of some anti-cancer drugs were found in HWWs than the influent of a WWTP in Girona, Spain [33], highlighting the importance of applying decentralized solutions to treat hospital effluent *on-site* before being discharged into the urban sewage collection system to reduce the environmental risks posed by pharmaceuticals [33, 35].

3 Hospital Effluent Treatment Guidelines and Regulatory Efforts

Guidelines for the management of hospital effluents have been set forth by international organizations (e.g., World Health Organization, WHO [41]).These guidelines have been summarized by Carraro et al. [1] and also discussed in a chapter in this book. In general, the WHO guidelines recommend pre-treatment of effluents originated from specific departments (e.g., medical laboratories, dental) and indicate the minimum requirements for the discharge of hospital effluent into municipal sewer systems. These requirements include the existence of a WWTP with tertiary treatment with the treated effluent bacterial removal rate $\geq$95% and anaerobically produced digested sludge with no more than one helminth egg per liter. In addition, the waste management system of the healthcare facilities should ensure that only low quantities of toxic chemicals, pharmaceuticals, radionuclides, cytostatic drugs, and antibiotics are present in the discharged sewage.

The WHO guidelines also recommend monitoring the sewer system and the effluent quality. Effluent quality is recommended to be assessed by monitoring common parameters such as temperature, pH, BOD_5, COD, nitrate, total phosphorus, total suspended solids, presence and concentration of *E. coli*. In general, many countries have the infrastructures recommended and their legislation requires the assessment of these same effluent quality parameters.

For effluents originated by specific sources such as healthcare facilities the legislation might require the measurement of additional parameters such as adsorbable organic halogens (AOX), total and free chlorine, detergents, disinfectants, surfactants, oil and grease, sulfates, cyanides, organophosphates, total nitrogen, heavy metals, microbiological parameters (total coliform), and toxicity.

The research contributions identifying micropollutants (pharmaceuticals and other chemical residues) sources, their predicted and measured concentrations in effluents and the environment, and risk assessment have had an important contribution to have regulatory institutions considering the need to investigate some of these organic compounds.

In addition, some of these substances (erythromycin, clarithromycin, azithromycin, 17-α-ethinylestradiol (EE2), 17-β-estradiol (E2), estrone (E1), diclofenac) have been included in the European watch list and in the US contaminant candidate list (erythromycin, 17-α-ethinylestradiol, 17β-estradiol, 17-α-estradiol, equilenin, equilin, estriol, estrone, mestranol, and norethindrone) that concerns new substances for priority action. Priority action involves additional research to determine the risk associated with the release into the environment and the potential need to set regulatory limits on these pharmaceuticals.

4 Conclusions

Hospital effluents have been characterized in different geographic regions. These involved monitoring physico-chemical parameters, biological pollutants, inorganic pollutants, and organic pollutants.

Healthcare facilities effluents physico-chemical parameters demonstrate the relevance of these facilities as a source of organic/inorganic loads when compared with municipal effluents. Some authors reported that healthcare facilities effluents typically present physico-chemical parameters such as BOD_5, COD, and TSS 2–3 times higher than municipal effluents.

Bacteriological characterization in hospital effluents is frequently performed by determining fecal contamination (e.g., *E. coli*) and less commonly by analyzing other bacteria and viruses (e.g., enterovirus). As healthcare facilities consume considerable amounts of water (200–1,200 L bed^{-1} day^{-1}), fecal contamination is normally less relevant than in municipal effluents due to higher dilution. The opposite has been reported for enterovirus with the concentration being 2–3 times higher in hospital effluents.

Heavy metal characterization in hospital effluents demonstrates the relevance of gadolinium (Gd) and platinum (Pt) with concentrations reaching $\leq$300 μg L^{-1}.

Pharmaceutical residues characterization demonstrates their presence in effluents originated in general hospitals operating in different geographic regions and the relevance of 12 therapeutic categories. Within these therapeutic categories the highest total percentage has been measured for analgesics, anti-bacterials, and anti-infectives, contrast media and cytostatics (>40%). Other relevant therapeutic categories include anti-epileptics, anti-inflammatories, psychoanaleptics, and β-blockers ($\leq$20%). With some exceptions, most pharmaceuticals quantified in healthcare facilities effluents present maximum concentrations <10 μg L^{-1}.

Specialized hospitals and wards effluent characterization/consumption patterns demonstrate the relevance of a different range of pharmaceuticals between different hospitals.

Total mass loads for pharmaceutical and other chemical residues have been estimated for hospitals with varying sizes and types of treatment in different geographic regions. The total mass loads reported ranged between 1.5 and 310 g day^{-1}. Besides the healthcare facilities characteristics their potential presence at the WWTP influent is also related with the size of the sewer network and the presence of other discharging sources. The investigation of sewer networks with variable number of hospitals and inflows estimated that pharmaceuticals and other chemical residues loads originating from general hospitals at the WWTP influents can reach up to 65%. Additionally, estimates of pharmaceutical individual contributions originating from healthcare facilities at WWTP influent indicate that at lower flows they can reach >80%.

Healthcare facilities are a source of an array of pollutants which can reach the WWTP influent, resist treatment, and enter the environment with potential effects on aquatic organisms and water quality. To minimize these effects, it is recommended to implement effluent treatment prior to their release, when the sewer system is dimensioned to treat <10,000 m^3 day^{-1} inflow, has multiple healthcare facilities connected to the system and the WWTP is performing secondary treatment. Additionally, further research is required for the: (a) characterization of effluents originated from specific wards and specialized hospitals; (b) assessment of concentration variability during larger periods of time (monthly, yearly); and (c) risk assessment of many of the pollutants already measured in the effluents for potential inclusion in priority/candidate lists and subsequent inclusion in specific source regulations.

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Ecotoxicity of Hospital Wastewater

Yves Perrodin and Frédéric Orias

Abstract During the last 10 years, characterizing the ecotoxicity of hospital wastewater (HWW) has focused on different aspects. Initially, it mainly consisted in collecting information on ecotoxic substances used in hospitals (disinfectants, detergents, pharmaceuticals, etc.). Thereafter, experimental measurements of ecotoxicity on whole effluent were carried out in different hospitals. These data have shown the generally high ecotoxicity of this effluent, and its considerable evolution during a single day and a full year of activity. In addition, the bioaccumulation of certain pharmaceuticals in organisms and trophic chains has been demonstrated, which contributes to increasing the risk of these molecules. The interactions between the molecules present in HWW have also been the subject of studies. The collection of all these data have enabled researchers and managers to carry out the first ecotoxicological risk assessment studies in different hospitals around the world. It is now necessary to complete these works, in order to refine the characterization of HWW ecotoxicity and consolidate the methodologies of ecotoxicological risk assessment formulated.

Keywords Ecological risk assessment, Ecotoxicity, HWW, Pharmaceuticals, Pollutants

Contents

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1 Introduction

Studies on the characterization of hospital wastewater ecotoxicity have undergone considerable development over the last 10 years.

Initially, they mainly consisted in collecting information on ecotoxic substances used in hospitals (disinfectants, detergents, pharmaceuticals, etc.) which can be found in their effluents, or in measuring their concentrations directly in the effluents, aided by progress in analytical chemistry.

Subsequently, experimental measurements of ecotoxicity on the whole effluent were performed in different hospitals around the world. These measurements were carried out using a wide variety of bioassays (or ecotoxicity tests). They have led to better knowledge of the general level of ecotoxicity of these effluents, and made it possible to assess their evolution during a single day and a full year of activity. They have also allowed characterizing the effectiveness of different treatments of such effluents.

Finally, combining the exposure concentrations of aquatic organisms living in rivers into which HWW has been discharged with the toxic effect concentrations of these substances has led to the implementation of ecotoxicological risk assessments for various scenarios and provided operational tools for the management of these effluents.

All these works are presented in detail in this chapter.

2 Ecotoxicity of Substances Present in HWW

2.1 Identification and Ecotoxicity of the Substances

In a review article published in 2013, Orias et al. [1] grouped all the concentration values measured in HWW available in the literature (30 publications between 1990 and 2013), and all the ecotoxicity data available in international databases and publications on substances detected in HWW.

The synthesis of this work showed that 297 molecules, including 240 Pharmaceutical Residues (PR) belonging to almost all the therapeutic groups (Table 1), were searched at least once in these effluents. Among the molecules sought, 190 were detected at least once in HWW by analytical laboratories. The range of concentrations in these effluents was extremely wide: one tenth of an ng/L to 10 mg/L). Regarding PR, the concentration range was also very wide, although slightly more restricted: one tenth of an ng/L (e.g., tamoxifen, finasteride) to a few mg/L (e.g., iobitridol, iopamidol).

Regarding the ecotoxicity of substances in HWW, the data collected led to the establishment of 261 PNEC (Predicted No Effect Concentration): 204 values on the basis of experimental data from international databases (e.g., EPA ECOTOX [3], Wikipharma [4]) and from the scientific literature, and 61 values based on a theoretical approach (ECOSAR method [5]).

This synthesis showed the considerable variability of the ecotoxicity values of the substances concerned: minimum PNEC close to 0.01 pg/L and maximum PNEC close to 1 mg/L.

The updating of this work with new ecotoxicity data in 2016 concerns seven molecules. Of these seven molecules, it is possible to calculate only one new PNEC

Table 1 Classes and codes of anatomical and therapeutic classification systems, data from [2] (the groups in which no compound was sought are in *bold type*)

ATC class	Therapeutic groups
A	Alimentary tract and metabolism
B	**Blood and blood forming organs**
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	**Systemic hormonal preparations, excl. sex hormones, and insulins**
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	**Antiparasitic products, insecticides, and repellents**
R	Respiratory system
S	**Sensory organs**
V	Various

(Table 2). This PNEC was calculated using the same rules as those established by Orias and Perrodin in 2013 [1].

In order to identify the substances contributing most to the ecotoxicity of HWW, Orias and Perrodin [6] proposed the calculation of an ecotoxicological hazard quotient (HQ) for each substance, taking into account both its ecotoxicity (via PNEC) and maximum concentration measured in HWW (MEC_{max}):

$$HQ = MEC_{max}/PNEC$$

They were thus able to determine which RPs present in hospital effluents were the most hazardous. 127 HQ could be calculated. Of these, 50 had an HQ lower than 1 and 62 had an HQ between 1 and 1,000. The 15 most hazardous RPs, i.e., those with an HQ higher than 1,000, and estimated on the basis of existing ecotoxicological data, are presented in Table 3.

2.2 Involvement of PRs from Various Therapeutic Groups in HWW Ecotoxicity

According to Orias and Perrodin [1], the therapeutic groups of PRs present in HWW are almost all represented, but antibiotics are those detected most (Fig. 1). Indeed, of the 162 PRs detected one third are antibiotics. Drugs used for the nervous system and for the cardiovascular system take second and third positions of the groups detected most, with respectively 15 and 13% of the RPs detected.

After characterizing the representation of each of the therapeutic groups regarding the PRs found in HWW, Orias and Perrodin [6] studied which therapeutic groups contained the largest number of dangerous PRs. The objective was to determine whether a small number of therapeutic groups contained most of the dangerous RPs. However, they observed a very similar representation of RPs with an HQ higher than 1, but with a significant increase in the proportion of PRs related to the nervous system.

Nonetheless, when looking at the distribution of the most dangerous RPs ($HQ > 1{,}000$) by pharmaceutical group (Fig. 2), we observe that the distribution is globally the same, with "J" and "N" taking up the largest shares of the distribution. We note, however, the disappearance of the cardiovascular group and the very strong representation of hormones in relation to the number of molecules of this group found in HWW.

Table 2 Updating of ecotoxicity data of substances present in HWW since 2013

ATC class	N° CAS	Compound	MEC_{max} (µg/L)	Endpoint		Organism	Value	Reference	Extrapolation factor	PNEC (µg/L)
D	86386-73-4	Fluconazole	*3.445*	LOEC	Population growth	*P. subcapitata*	3.06 mg/L	US EPA	*1,000*	*0.306*
				LC50	Immobilization	*T. platyurus*	>100,000 µg/L			
				LC25	Mortality	*D. rerio*	>306 mg/L			
				LOEL	Teratogenicity		306 µg/L			
				LC50	Mortality	*O. latipes*	>100,000 µg/L			
N	93413-69-5	Venlafaxine	*0.811*	LOEC	Crawling speed	*U. cinerea*	31.3 µg/L	Wikipharma	*NA*	*NA*
				LOEC	Detachment of foot	*N. ostrina*	1.57 mg/L			
				EC50 48 h	Immobilization	*D. magna*	141 µg/L			
				LOEC	Detachment of foot	*C. funebralis*	157 µg/L			
J	63527-52-6	Cefotaxim	*0.413*	LC25	Mortality	*D. rerio*	486 µM	US EPA	*NA*	*NA*
				LOEL	Development		1,000 µM			
N	76-74-4	Pentobarbital	*0.15*	LC50	Mortality	*D. rerio*	>10 mM	US EPA	*NA*	*NA*
J	196618-13-0	Oseltamivir	*0.025*	EC50	Mortality	*Quinquelaophonte* sp.	>2.5 mg/L	Wikipharma	*NA*	*NA*
V	737-31-5	Diatrizoate	*348.7*	NOEC	Population growth	Ciliate	0.001 M	US EPA	*NA*	*NA*
C	137862-53-4	Valsartan	*3.032*	NOEC 72 h	Growth inhibition	*D. subspicatus*	85 mg/L	US EPA	*NA*	*NA*

Table 3 HQs of the most dangerous pharmaceuticals in HWW (data from [6])

ATC class	Pharmaceutical	HQ
N	Propyphenazone	1,162
N	Sulpiride	1,353
J	Ofloxacine	2,000
J	Sulfapyridine	2,057
J	Trimethoprim	2,585
G	Estrone	2,593
N	Lidocaine	3,499
M	Diclofenac	3,500
N	Chlorpromazine	4,136
G	17α-Ethynilestradiol	10,800
J	Norfloxacin	27,500
G	17β-estradiol	28,750
L	5-Fluorouracil	122,000
D	Clotrimazole	220,000
J	Ampicillin	508,000

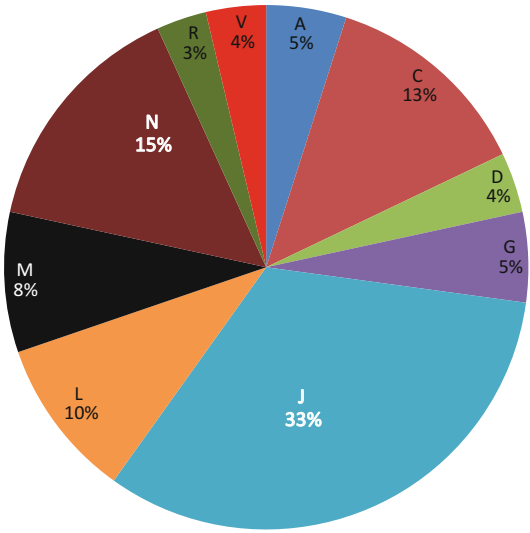

Fig. 1 Distribution of PRs detected in HWW according to therapeutic group (ATC) ($n = 162$)

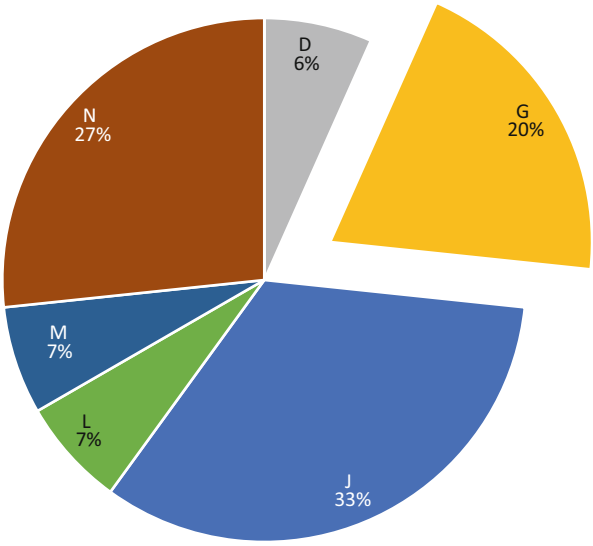

Fig. 2 Distribution of RPs (HQ > 1,000) detected in HWW according to therapeutic group (ATC classification) ($n = 15$)

3 Experimental Measurement of HWW Ecotoxicity

3.1 Synthesis of Experimental Measurements Performed

In their review of 2013, in addition to the "substance" approach, Orias et al. [1] brought together all the available data concerning the "holistic" approach to ecotoxicity. They collected all the studies that focused on the direct measure of effluent ecotoxicity by exposing the organisms tested to increasing concentrations of HWW.

This work showed that to date few studies have implemented this approach. Indeed, data on experimental ecotoxicity are available for only 12 HWW, and concern only 25 ecotoxicity tests. Moreover, the variety of organisms tested is very limited and almost half of these tests focused on the crustacean *Daphnia magna*. Regarding ecotoxicity values, they were highly variable as a function of the organisms tested for the same effluent. Thus some effluents were not toxic at all for a given organism, whereas they were toxic at several tenths of percent for other biological models.

This approach is interesting because it takes into account the global ecotoxicity of an effluent. In particular it presents an advantage for studying the reduction of the ecotoxicity of HWW by a Wastewater Treatment Plant (WWTP), and monitoring the evolution of ecotoxicity over time (see the following paragraphs).

3.2 Variability of HWW Ecotoxicity in Relation to the Bioassays Used and the Filtration of Samples

The ecotoxicological characterization studies carried out on HWW show that the responses are in general very different with regard to the bioassays used [7–10].

For example, the works by Boillot et al. [11] on the effluent of a hospital in Lyon showed an EC20 (Efficient Concentration on 20% of organisms) situated between 0.7% (reproduction of *Brachionus calyciflorus*) and 100% (growth of duckweed *Lemna minor*).

In addition, the implementation of bioassays which can be used on both untreated and filtered samples (*Daphnia magna* and *Lemna minor*) revealed the strong ecotoxicity of the particular phase of the effluents studied [11]. This implied the need to include tests that do not require filtration in the batteries of bioassays used to characterize the ecotoxicological nature of HWW.

3.3 Temporal Variability of HWW Ecotoxicity

3.3.1 Variability During a Normal Day of Activity

To characterize the evolution of ecotoxicity of HWW during a normal day of activity, a study was conducted on effluents from a hospital in the city of Lyon in France [11].

The sampling procedure adopted for the characterization of these effluents during a campaign carried out in 2006 was the following: collection of five "periodic" samples corresponding to five periods of the day at the following times: 1–5 p.m., 5–11 p.m., 11 p.m.–5 a.m., 5–9 a.m., and 9 a.m.–1 p.m.

The organisms included in the battery of bioassays were the microcrustacean *Daphnia magna* (inhibition of mobility in 48 h), the bacterium *Vibrio fischeri* (inhibition of luminescence in 30 min), and the algae *Pseudokirchneriella subcapitata* (growth inhibition in 72 h).

The results (Table 4) show that the samples collected overnight are less ecotoxic than the samples collected during the day, and that the sample corresponding to the period of activity from 9 a.m. to 1 p.m. is the most ecotoxic.

Table 4 Daily evolution of the ecotoxicity of HWW in Lyon (France). Data from [11]

Periods of activity	1–5 p.m.	5–11 p.m.	11 p.m.–5 a.m.	5–9 a.m.	9 a.m.–1 p.m.
EC 20 *Daphnia magna* 48 h (% HWW)	14	45	>100	48	**5**
EC 20 *P. subcapitata* 30 min (% HWW)	22	25	65	21	**4**
EC 20 *Vibrio fischeri* 72 h (% HWW)	17	38	95	25	**7**

3.3.2 Variability During a Year

The considerable evolution of ecotoxicity of effluents from a hospital over 1 year has been demonstrated by various authors [12–14]. For example, Fig. 3 corresponds to the monitoring of HWW ecotoxicity at the "SIPIBEL" pilot site in France [15]. It shows the high ecotoxicity of the effluent during sampling campaigns in January 2013 and in November 2013, and the low ecotoxicity of the effluent during the campaigns of February 2013, with intermediate situations for other sampling dates.

4 Interaction Between Ecotoxic Substances from HWW

The characterization of ecotoxicity of hospital effluents using a "substance" approach does not take into account the "cocktail effect" linked to the presence in these effluents of molecules which can interact with each other, leading to synergistic or antagonistic phenomena.

To identify these potential impacts and better understand their origin, works have been performed by various authors.

Boillot [16] studied the interaction phenomena present in binary mixtures of disinfectants and surfactants with respect to mobility inhibition in *Daphnia magna*. In particular, she studied compounds from the following substances very present in

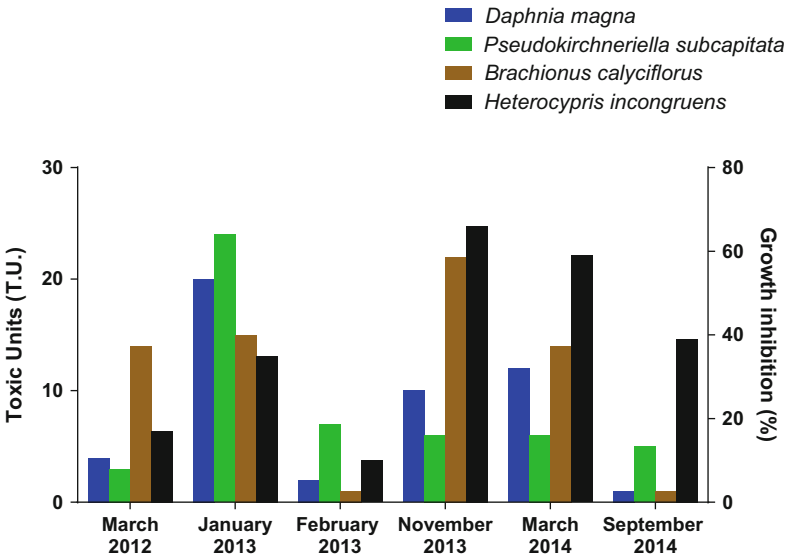

Fig. 3 Annual monitoring of ecotoxicity of the HWW from the SIPIBEL pilot site in France. *Toxic units*: *Daphnia*, *Pseudokirchneriella* and *Brachionus*. *Growth inhibition*: *Heterocypris*. Data from [15]

hospital effluents: (1) disinfectants: glutaraldehyde and sodium hypochlorite; (2) surfactants: sodium dodecyl sulfate (anionic), Triton X-100 (non-ionic), and hexadecyltrimethylammonium bromide (cationic). The results showed that these mixtures have no major antagonistic or synergistic effect on the mobility of *Daphnia magna*.

Furthermore, Panoullières et al. [17] studied the potential interactions in binary mixtures composed of acetic acid (a disinfectant increasingly used in hospitals to replace sodium hypochlorite) and of the same detergents as above.

The results showed that there was no significant antagonistic or synergistic effect between the molecules present in these mixtures on the mobility of *Daphnia magna*.

This lack of significant synergistic or antagonistic phenomena is in agreement with the results often obtained by authors who have worked on interactions in mixtures of hazardous substances [18–22].

5 Role of Bioaccumulation in HWW Ecotoxicity

Some pharmaceutical compounds have the property of accumulating in organisms and trophic chains. This phenomenon can ultimately lead to internal concentrations high enough to be toxic.

5.1 Identification and Prioritization of Bioaccumulative Pharmaceuticals in HWW

In order to identify and prioritize bioaccumulative pharmaceuticals present in HWW, Jean et al. [23] listed all the drugs used in the hospitals of the city of Lyon, France. Then, they searched those of them that were the most bioaccumulative among the 966 pharmaceuticals used in these hospitals. An initial list of 70 particularly bioaccumulative molecules was established on the basis of their modeled bioaccumulation factor (BCF). This list was later reduced to 14 pharmaceuticals considered to represent the greatest risk to aquatic ecosystems, taking into account additional criteria (consumption, low biodegradability, etc.).

All the therapeutic classes were present in this list of priority pharmaceuticals, in particular widely used pharmaceuticals, such as those used for the cardiac system (nicardipine and amiodarone), and with antibiotic power (telithromycin). Other pharmaceuticals, consumed less but with high potential impact, such as sex hormones (ethinyl estradiol and norgestimate), and pharmaceuticals used to treat cancer (mitotane or tamoxifen), were also selected [23].

5.2 Experimental Characterization of the Bioaccumulation of Pharmaceuticals from HWW

So far, very few studies have focused on the experimental bioaccumulation of PR, given the complexity, arduousness, and cost of such works. Among the 14 priority molecules identified above [23], Orias et al. chose to work on tamoxifen in order to initiate the process [24–26].

This choice was made according to several criteria: (1) the considerable theoretical bioaccumulation of this substance, (2) the existence of an analytical protocol for monitoring the substance in organisms, and (3) the will to work on a substance that had already been found in the environment.

With a theoretical BCF equal to 370,000, the existence of analytical protocols for detecting concentrations of tamoxifen close to 1 μg/L in water, and concentrations of several 100 μg already found in the environment, tamoxifen well satisfied these criteria.

These works first focused on the bioconcentration of tamoxifen in three model organisms belonging to three different trophic levels: (1) the unicellular alga (*Pseudokirchneriella subcapitata*) as a primary producer, (2) the invertebrate (*Daphnia magna*) as a primary consumer, and (3) the vertebrate (*Brachydanio rerio*) as a secondary consumer. The authors also investigated whether tamoxifen could bioaccumulate via food, by exposing the first two links of the experimental trophic chain formed by these organisms to contaminated food.

The results of these studies confirmed the very high power of tamoxifen bioconcentration in all the organisms studied (algae, daphnia, and fish) [24–26]. Furthermore, the bioaccumulation factor was shown to be significantly higher when *Daphnia magna* was exposed to contaminated food as well as being immersed in contaminated water [26]. What is more, it was demonstrated with *Brachydanio rerio* that tamoxifen concentrated differently in different fish organs. Thus the gonads were seen to be the organs that bioconcentrated tamoxifen most in *Brachydanio rerio* [25].

All these works showed the accentuation of the potential impact on aquatic ecosystems of tamoxifen (and other bioaccumulative molecules) linked to its bioaccumulation in organisms and trophic chains. In the particular case of tamoxifen, it should be noted that it is an endocrine disruptor well known to ecotoxicologists. Thus the question arises regarding the long-term effect of this type of substance on fish populations, even at very low concentrations: the highest concentrations to which these vertebrates were exposed in the laboratory were almost 40 times lower than certain concentrations observed in the environment.

6 Ecotoxicological Risk Assessment of HWW

6.1 PEC/PNEC Approach

The ecotoxicological risk assessments of HWW listed in the international literature are usually based on the "PEC/PNEC" (Predicted Environmental Concentration/ Predicted No Effect Concentration) approach. This ratio, calculated for a given hospital located in a given context (scenario), concludes a significant risk when the PEC/PNEC quotient is higher than 1. The higher the quotient is over 1, the greater the risk.

The results of studies based on this approach show contrasting situations at the international level, depending on the capacity of the hospital, the nature of the detergents, disinfectants and pharmaceuticals used, and also the conditions of discharging HWW into the natural environment (efficiency of sewage treatment, low water flow of the receiving stream, etc.) [7, 10, 13, 27–30].

6.2 Approach Taking Bioaccumulation into Account

One of the first studies in this area was conducted by Brackers de Hugo et al. [31] in 2013 on mitotane, a substance with a very high BCF (BCF = 7,330).

In order to study the toxicity of this pharmaceutical on a representative animal model of the aquatic ecosystem, an in vitro approach based on the use of fish cell lineages was implemented. These cells were used as a model of the internal medium of the fish, which was exposed to concentrations reflecting the internal level to which the animal is exposed once the pharmaceuticals concentrated in its tissues.

Two endpoints were chosen: cytotoxicity (via cell death) and genotoxicity (via the measurement of primary DNA damage).

The critical values for cytotoxicity (CL10 = 6 mg/L for the gill cell lineage "RTG W1," and CL10 = 18 g/L for the "PLHC" cell lineage taken from a hepatocellular carcinoma) were well above the concentrations that can be observed in the aquatic environment.

Based on this parameter, the risk to fish exposed to environmental levels of mitotane may appear limited. However, the results for genotoxicity showed much weaker effect concentrations, close to environmental reality. Finally, the authors concluded on the need to consider bioaccumulation for assessing ecotoxicological risks associated with pharmaceutical molecules.

7 Conclusion

These works have first shown the strong ecotoxicity of hospital effluents (in general). This ecotoxicity is on average higher than that of urban effluents. It is linked to the presence of toxic molecules whose PNEC is very low (PNEC <1 ng/L for the most ecotoxic). These ecotoxic molecules belong to numerous chemical families, including disinfectants (active chlorine, glutaraldehyde, etc.), detergents (especially cationic and non-ionic detergents), and certain pharmaceutical residues (ecotoxic molecules present in most therapeutic groups).

The global ecotoxicity of the effluent is the result of a cocktail effect between different substances which interact with each other and can lead to phenomena of additivity, synergy, or antagonism. Moreover, the bioaccumulation of some of these substances has been demonstrated, which increases the risk associated with these substances.

All these data have enabled researchers and managers to carry out the first ecotoxicological risk assessments in different hospitals around the world. It is now necessary to complete these works in order to consolidate the methodologies formulated for ecotoxicological risk assessment. The main fields of this research concern: (1) the interactions between substances present in HWW and the resulting cocktail effect; (2) the bioaccumulation of certain pharmaceuticals in organisms and trophic chains and the resulting impact on aquatic ecosystems.

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Prioritization of Active Pharmaceutical Ingredients in Hospital Wastewater

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Abstract A large amount of residues from active pharmaceutical ingredients (API) that are currently in use are known to reach aquatic ecosystems and have potentially adverse effects on living organisms. Prioritization methods are useful tools for both regulation and surveillance purposes in the environmental policy of APIs. Their use has largely increased over the last decade, and the different existing methodologies can lead to large discrepancies between the highlighted substances. This chapter aims at discussing studies conducted in the context of hospitals. Perhaps more important than the results themselves, the methodologies with the set of selected criteria are discussed, as well as their advantages and associated uncertainties. A case study of API prioritization applied to a Swiss university hospital is presented with two different approaches: a ranking-based OPBT approach (Occurrence, Persistence, Bioaccumulation, and Toxicity) and an environmental risk assessment (ERA), with the calculation of risk quotient (RQ). The ERA results combined with those of other studies dealing with ERA-based API prioritization in hospitals highlighted several compounds presenting high risks for the aquatic ecosystems

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(RQ > 1): antibiotics (ciprofloxacin, amoxicillin, piperacillin, azithromycin), anti-inflammatory drugs (diclofenac, mesalazine), as well as the hormone estradiol and the antidiabetic metformin. Nevertheless, only the antibiotic ciprofloxacin was commonly determined as problematic. Finally, the most critical issues for API prioritization in hospitals were identified from the literature overview and the results of the presented case study: handling of the consumption data, involvement of expert judgment, uncertainties linked with the predicted environmental concentration (PEC) calculation, and quality of the hazard evaluation. Although prioritization procedures applied to hospitals can be burdensome to apply in practice and many associated uncertainties remain, they represent essential tools to establish lists of priority molecules to follow via monitoring programs and allow their theoretical risk assessment.

Keywords Environmental risk assessment, Hospital effluents, Pharmaceuticals, Predicted environmental concentrations, Prioritization

Contents

1 Introduction

A large amount of the many active pharmaceutical ingredients (APIs) currently in use reaches aquatic ecosystems and generates potentially adverse effects for living organisms [1–3]. Once in the environment, API residues can indeed cause some adverse effects to wildlife, such as the feminization of male fish from synthetic hormones [3, 4] or the impairment of organs by the nonsteroidal anti-inflammatory drug diclofenac in trout [5].

Sources of APIs in surface water are diverse: they may come from human and animal use, waste disposal, and/or manufacturing [2, 6]. Generally, urban wastewater treatment plants (WWTPs) are the main contributors of API residues into aquatic ecosystems through human consumption in households [7, 8]. Urban wastewater was shown to have contained pharmaceutical residues for decades [9]. Recently, however, increasing attention was paid to hospitals and healthcare facilities as a source of environmental pollution through their effluents [10–12]. They

differentiate themselves from domestic sources by the nature of the administered molecules [10, 13]. Hospitals represent only a small proportion of the urban API load source found at the watershed outlet on average: <10% [2], <15% [11], and 20–25% [12]. Nevertheless, this fraction can vary from 3 to 74% according to the compound type and the hospital bed/inhabitant ratio of the watershed [14]. An in-depth analysis is developed in the chapter by Chonova et al., in this book.

All APIs currently in use, which vary between 3,000 and 5,000 [15–17], cannot be measured in monitoring campaigns or be assessed for environmental risk. Prioritization methods are thus necessary because they allow the establishment of priority lists of molecules to be monitored, based on a set of selected criteria. Prioritization was thus identified by a panel of 40 international experts as the second most important question in the area of ecotoxicology and environmental risks of pharmaceuticals [15]. The use of prioritization methodologies for APIs increased in the past 15 years, but some methodological discrepancies are largely observed between studies due to different objectives. Indeed, they were implemented with different emphases: spatial variability [18, 19]; some specific types of drugs, such as veterinary drugs [20, 21] or anticancer drugs [18, 22]; and hospital effluents [23, 48].

This chapter aims at presenting, first, an overview of the different prioritization methodologies currently used, both in a broader context and for hospital wastewater. Second, these approaches are illustrated with a case study from a major hospital in Switzerland. The priority list obtained is detailed and compared with other studies. Finally, the most important parameters when applying API prioritization in hospitals are identified and discussed.

2 API Prioritization Approaches

2.1 Method Overview

In general, API prioritization methods are based on consumption data and on a simplified risk assessment for the environment and/or human health [11, 24, 25]. The parameters considered are environmental persistence, the bioaccumulation potential, and the effects [26–29]. The elaboration of a priority list of pharmaceuticals thus strongly depends on the quantity and the quality of the available data for these three parameters [13, 30]. Some studies also consider the mode of action [31] or the analytical feasibility in the procedure [7]. Therefore, the relevance of the chosen criteria is of great importance and may lead to important methodological discrepancies from one study to another and can also induce many uncertainties in the results [30, 32].

One commonly used method for prioritizing is the persistence, bioaccumulation, and toxicity (PBT) approach proposed in Europe in the framework of the registration, evaluation, authorization, and restriction of chemicals (REACH). Specific

studies dealing with pharmaceuticals were also applied in this approach, which consists of calculating a ranking of concern according to the PBT properties of the substances [28, 33, 34]. For example, the national approach developed in Sweden established a ranking from 1 to 3 for each parameter, with a maximum global rank of 9.[1] Unfortunately, the experimental data are still scarce, inducing a lack of realistic information regarding the PBT properties and the behavior of pharmaceuticals in the environment [34].

This leads researchers to use computational tools such as Quantitative Structure Activity Relationship (QSAR) models to predict the missing values [35]. However, computed values cannot replace experimental ones [27, 36, 37]. Nevertheless, the use of two different QSAR models for the prioritization of more than 1,200 APIs was shown to be in agreement with each other's models (86%) [34]. More importantly, several priority compounds that were highlighted, such as clotrimazole, sertraline, loratadine, or miconazole, were in line with previous studies and have already been detected in the environment [28, 36].

Another method for prioritizing pharmaceuticals is proposed by the European Medicines Agency in the preapproval phase for the authorization of new medicinal products for human use [25]. The EMEA guidelines require an environmental risk assessment for the new compounds introduced into the European market since 2006 [25]. It is worth stressing that the environmental risks for APIs registered before that date are therefore not properly assessed or are not assessed at all [34]. This ERA consists of a tier-based environmental risk assessment procedure for APIs, which comprises two phases: the estimation of exposure (Phase I) and the environmental fate and effects analysis (Phase II). This procedure has been adopted by several authors and is adapted according to the study's specific needs [13, 26, 29].

Phase I comprises a PBT approach and the calculation of the predicted environmental concentrations (PEC) in receiving surface water (PEC_{SW}), which are calculated as follows:

$$PEC_{sw} = \frac{DOSE_{ai} \times F_{pen}}{WW_{inhab} \times DIL} \quad (1)$$

with $DOSE_{ai}$ being the maximum daily dose consumed per inhabitant, F_{pen} as the fraction of the market penetration, WW_{inhab} as the amount of wastewater per inhabitant per day, and DIL as a dilution factor, which represents the dilution of wastewater in surface water. Thus, PEC_{sw} does not consider degradation or retention in WWTP, nor patient metabolism. Moreover, the default values of 0.01 for F_{pen}, 200 L inh^{-1} d^{-1} for $WW_{inhab,}$ and 10 for DIL are proposed in the EMEA guidelines.

[1] http://www.janusinfo.se/Beslutsstod/Environment-and-Pharmaceuticals/Dokument/Classification/.

F_{pen} may also be calculated according to the consumption data and defined daily dose[2] (DDD) values proposed by the World Health Organization (WHO). Thus, by using PBT properties derived from QSAR modeling and PEC_{sw} generated with a number of default values, the procedures following the guidelines are likely unrealistic. Nevertheless, if the results of Phase I show that the active ingredient in question has a bioaccumulation tendency (Log $K_{ow} > 4.5$) or exhibits a PEC above 10 ng/L, then Phase II is needed.

Phase II addresses the calculation of the environmental risk quotient (RQ) as the ratio between exposure (PEC) and effects (PNEC):

$$\mathrm{RQ} = \frac{\mathrm{PEC}}{\mathrm{PNEC}} \tag{2}$$

PNEC is defined as a predicted non-effect concentration and is calculated by applying an assessment factor (AF) to the non-observed effect concentration (NOEC), which is calculated based on ecotoxicological tests performed on several species. AF can vary between 10 and 1,000 according to the number of tested species [38].

In 2008, Besse and Garric [26] reviewed studies from eight different countries that prioritized and identified the most problematic pharmaceutical compounds for the environment in Europe and the USA between 2000 and 2008. They noted that despite similar methods used to determine the exposure, i.e., the PEC calculation, there were some important discrepancies in the methodologies used to assess PNEC values, making a proper comparison of the results difficult. For example, PNEC values can be associated with either acute or chronic toxicity tests, and it has been shown that the acute risks linked with API were rather negligible, whereas chronic risks could not be ruled out because of the scarcity of the ecotoxicological data [36]. Thus, ERA studies based on acute toxicity tests do not reflect the risks of long-term exposure to subacute levels.

More recently, Mansour et al. [39] identified 33 studies in a broader context and discussed the different criteria used: sale values, exposure data (measured environmental concentrations, MEC, or PEC values), toxicity data, pharmacological data, physicochemical properties, wastewater treatment plant removal efficiencies, and other criteria. They pointed out that almost all of the prioritization studies were performed in North America, Europe, and China, and that priority lists in other regions of the world may be different due to other types of pharmaceuticals consumed, other wastewater treatment systems, and/or other climatic conditions. They applied prioritization approaches to the most commonly consumed APIs in Lebanon, and these international concerns will probably follow an increasing trend.

In Europe, prioritization studies are used to develop monitoring strategies from a regulatory perspective [40], and several pharmaceuticals were recently proposed to

[2]DDD "is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs only give a rough estimate of consumption and not an exact picture of actual use" (Source: www.whocc.no).

be placed on a watch list with ten high-priority compounds [41]. The highlighted APIs were the NSAID[3] diclofenac, the hormones estrone (E1), 17-β-estradiol (E2), and 17-α-ethinyl estradiol (EE2), as well as the macrolide antibiotics erythromycin, azithromycin, and clarithromycin. Indeed, the clearly established deleterious effect of diclofenac on trout kidneys [5] and the endocrine-disrupting problems observed in fish [3, 4] were already mentioned. Due to their antimicrobial properties and their role in the propagation of resistance, antibiotics are considered one of the most hazardous pharmaceutical classes for the aquatic environment [42]. Although diclofenac and hormones are not likely to be found in high concentrations in hospital wastewater, antibiotics residues have proven to be a major driver in the propagation of resistance in the environment [43, 44].

2.2 *Prioritization Studies Applied to Hospital Wastewater*

Prioritization methods can also be applied to hospital wastewater but need to be adjusted. The PBT approach is readily transposable to the consumed APIs in hospitals, but when performing an environmental risk assessment, some slightly different parameters are often considered while calculating predicted concentrations or risk quotients.

Predicted concentrations in hospital wastewater (PEC_{HWW}) are obtained by dividing the excreted mass – i.e., the consumed mass (M) multiplied by the excretion factor (F_{excr}) – by the volume of wastewater (V) [13, 29, 36, 38]:

$$PEC = \frac{M \times F_{excr}}{V} \tag{3}$$

Often, the volume of consumed water is used instead of the volume of wastewater, which is not easy to assess. Excretion factors are considered the sum of excretion in urine and feces as unchanged drugs but do not take into account metabolites. Some authors assume that the glucuronide conjugates are cleaved in the environment and should therefore be taken into account in the calculation [45]. However, glucuronide bonds are known to be unstable, and their behavior in aquatic environment is unknown. The glucuronide conjugates of some compounds were already detected in the surface water [46].

The predicted concentrations in receiving surface water (PEC_{SW}) are calculated by considering the removal efficiencies in WWTP (R) and the dilution (DIL) that hospital effluents undergo in the watershed [13, 29, 36]:

$$PEC_{sw} = \frac{M \times F_{excr} \times (1 - R)}{V \times DIL} \tag{4}$$

[3]Nonsteroidal anti-inflammatory drug.

The dilution factor (DIL) is usually fixed at 10 for pharmaceuticals in WWTPs, according to the European guidelines [25]. However, this factor accounts for the dilution of municipal wastewater into the receiving aquatic ecosystem but not for hospital effluents, which are first diluted in the urban sewer network. Kümmerer [42] suggests that the dilution of hospital effluents in municipal wastewater is more important than the dilution of the latter into rivers or lakes and proposes a dilution factor of 100, which is close to reality when calculated [36].

It is not realistic to calculate the risk for hospital effluents, because the exposure of living organisms is null in hospital sewers; thus the calculation of hazard quotient (HQ) has been suggested [47]. HQ is thus calculated for hospital wastewater (HQ_{HWW}) and risk quotient for surface water (RQ_{SW}) while considering the dilution in the aquatic environment. Generally, a $RQ_{SW} \geq 1$ means that the considered API poses a high risk for the aquatic ecosystems, with $0.1 \leq RQ_{SW} < 1$ denoting medium risk and $RQ_{SW} < 0.1$ denoting low risk [48]. $HQ_{HWW} \geq 1$ would only mean that the considered API contributes significantly to the environmental hazard of the hospital effluents.

To our knowledge, only a few studies applied prioritization methods to the hospital-based consumption of APIs (Table 1). The prioritization is always realized with a subset of substances, varying from 15 to 250 according to the limiting factors defined through expert judgment. Expert judgment is indeed very often applied for the inclusion/exclusion of APIs, either before or after the prioritization, and chosen criteria are very diverse: previously highlighted compounds, reported measured environmental concentrations (MEC), or a focus on drugs with bioaccumulation potential [27] or anticancer drugs [22]. Other criteria considered for the prioritization are human metabolism through the excreted fraction (F_{excr}), the environmental behavior according to drug properties (pK_a, K_{oc}, K_{ow}, etc.), the removal efficiencies in the wastewater treatment plants, as well as the potential effects on living organisms through PNEC values.

Hereafter, we will present the results of our prioritization study, which were generated in a major hospital in Switzerland and were previously published [23]. The results will be compared to those of other studies, and the discrepancies observed in terms of the methodologies and criteria used will be discussed.

3 Geneva University Hospitals: A Swiss Case Study

3.1 Setting and Consumption Data Collection

The Geneva University Hospitals (HUG) are some of the most important hospitals of Switzerland. They comprise eight different hospitals (general, pediatric, psychiatric, maternity, etc.) and approximately 40 other healthcare facilities, providing both primary and tertiary care. In 2012, 8,443.2 full-time equivalent collaborators and a total of 671,709 days of hospitalization were registered for 1,908 beds, 48,112

Table 1 Non-exhaustive list of studies dealing with API prioritization in hospitals with a brief description of the different parameters used (*X* considered; – not considered)

Reference	Country	Hospital(s)	No. of drugs	Type of drugs	Criteria	Expert judgment criteria used for compounds inclusion/ exclusion	F_{excr}	PEC	Toxicity	Physical-chemical properties	WWTP removal
					Consumption data source						
Booker et al. [22]	UK	31	65	Anticancer drugs	NW England hospital survey	– MEC	X	X	–	K_{ow}, K_{oc}	X
Daouk et al. [23]	CH	1	71	All	Geneva University Hospitals pharmacy	– API consumption >1 kg/year – PNEC values availability	X	X	PNEC	K_{ow}	X
Helwig et al. [12]	D, NL, CH, L, UK, FR	7	15	All	Annual prescription data from the different hospitals	– Highly consumed – Identified by several partners – Previous lists – Already detected	–	MEC	PNEC	K_d, biodegradation	–
Jean et al. [27]	FR	1	70	Bioaccumulable	Hospices Civils de Lyon pharmacies	– Potentially bioaccumulable	X	–	–	BCF, biodegradation	–

Helwig et al. [54]	UK	Not only	250 (41 only hospitals)	All except X-ray contrast media	Scottish National Health Service (NHS) and Hospital Medicines Utilization Data	– Exclusion	X	X	PNEC	–	X
Guo et al. [40]	UK	Not only	146 (20 only hospitals)		Prescription cost data from England, Scotland, and Wales and data from British Generic Manufacturers Association	– Exclusion of 12 compounds out of scope – Inclusion of 23 compounds over the counter	X	X	PNEC	K_{oc}, K_{ow}, K_d, pK_a, BCF, FssPC	X

F_{excr} excretion factor, *PEC* predicted environmental concentrations, *MEC* measured environmental concentrations, *PNEC* predicted no effect concentration, *BCF* bioconcentration factor, K_{ow} octanol water partition coefficient, K_{oc} organic carbon partition coefficient, pK_a acid constant dissociation, *FssPC* steady state concentration in fish plasma, *WWTP* wastewater treatment plants

inpatients, and over 860,000 outpatient consultations. The average daily water consumption was approximately 760 m^3.

The aggregated data for drugs dispensed in both the inpatient and outpatient settings in 2012 were first obtained from the hospital pharmacy database using the "Business Object®" software. These data correspond to the drugs ordered by the different medical units to the pharmacy to treat their patients – as well as the returns (stock and delivery errors, discharged or deceased patients, etc.). The data give an approximation of the yearly inpatient consumption of APIs by transforming the overall unit doses (UD) in grams of active ingredients while considering their dosages [27]. Moreover, the pharmacy data are delivery data, which can differ from real consumption in the service due to lack of patient compliance, outside consumption, or other reasons [27]. All confidential health information was removed to create anonymous analytic datasets in conformity with Swiss data protection regulations.

According to the consumption data, 4,301 kg of APIs were delivered in 2012. Given the hypothesis that 100% of the administered drugs is consumed in the hospitals, this results in a ratio of 90 g/patient. However, while taking into account outpatient consultations, a much more realistic ratio of 4.8 g/patient is obtained. Thus, it is important to consider outpatient consumption, which can represent an important fraction of the consumption depending on the nature of the compounds. Indeed, outpatient treatments have increased significantly with, in some cases, only 20% of the drugs prescribed to outpatients excreted on-site [49]. Weissbrodt et al. [50] showed that 50% of iodinated X-ray contrast media and 70% of antineoplastic agents prescribed in the studied hospital were excreted at home. Concerning systemic antiviral drugs, they are specifically prescribed and delivered in the HUG as in a city pharmacy, but they are likely to be excreted at home by outpatients [11, 51].

In general, antibiotic drugs are the most commonly consumed class of drugs in hospitals [10, 11], but in our case, analgesics were more important (31.3%) than antibiotics (11.4%), followed by antiviral (6.4%) and anti-inflammatory (4.9%) drugs. While taking the excretion rate into account, antiviral and antibiotic drugs are excreted at a higher proportion compared to another Swiss hospital, whereas a lower fraction of iodinated X-ray contrast media and laxatives is excreted [36, 51]. This is probably due to the size difference between the two hospitals (338 vs. 1,908 beds) and the difference in prescriptions and activities between a cantonal hospital and a university hospital.

3.2 Prioritization

3.2.1 PBT Approach

The prioritization procedure applied to active pharmaceutical ingredients (APIs) consumed in the Geneva University Hospitals was adapted from previous studies

[26, 27, 29]. Among the approximately 1,000 APIs delivered by the hospital pharmacy in 2012, only 150 APIs with more than 10,000 unit doses (UD) were first retained. After the conversion from UD to grams of API, only 84 APIs, for which more than 1 kg were sold in 2012, were kept. The objective was to obtain a list of priority compounds to monitor; thus, the less consumed APIs were thought to be undetectable in hospital wastewater. Nevertheless, antineoplastic and immunomodulant drugs (Code L, according to the Anatomical Therapeutic Classification, ATC) with more than 10,000 UD were added to these 84 APIs due to their inherent toxicity, resulting in a total of approximately 100 APIs for the prioritization. Each API has been given 4 rankings, from 1 to 5, based on 4 criteria: Occurrence (O), Persistence (P), Bioaccumulation (B), and Environmental Toxicity (T). A final ranking was then obtained by the addition of the ranks of the four criteria, which are weighted according to the data quality. Indeed, to take into account the data quality, the ranks of the different criteria were multiplied by a quality factor: this factor is equal to 1 if no data were available, 2 if the PNEC or the Log K_{ow} were modeled with a QSAR approach, and 3 if the experimental values were available.

Among most of the priority compounds highlighted were NSAIDs (ibuprofen, diclofenac, and mefenamic acid), antiviral drugs (ritonavir, raltegravir), the antidepressant sertraline, anesthetics and analgesics (lidocaine, gabapentin, propofol), as well as antibiotics (sulfamethoxazole, trimethoprim, ciprofloxacin, and metronidazole), drugs for the cardiovascular system (metoprolol, oxazepam), and antineoplastic drugs (paclitaxel). Ritonavir was previously identified as a problematic hospital compound [36], and sertraline shows adverse effects in aquatic organisms [3] and is considered a priority compound by several authors [26, 28]. Note that 55% of the compounds were present in the top 20 list when taking into account data quality. This means that weighting according to the data quality changes the order of importance for about half of the compounds. More details can be found in Daouk et al. [23].

3.2.2 Environmental Risk Assessment

Among the 20 APIs with the highest PEC_{HWW}, 8 antibiotics and 5 antiviral drugs were identified. Note that PEC_{HWW} were calculated assuming that 100% of drug consumption occurs on site, and thus they are certainly over-evaluated due to the fractions excreted by outpatients [11]. Moreover, the volume of wastewater (V) was assumed to be equal to the known volume of consumed water (760 m^3). In our case, the predicted loads of the most frequently consumed APIs (paracetamol, ibuprofen, and the antibiotics metronidazole, ciprofloxacin, and sulfamethoxazole) were in agreement with the measured loads, but over- and underestimations are observed for other APIs (Fig. 1).

In general, overestimations of PEC are commonly observed when compared to measured concentrations (MEC) [11, 28]. They are mostly due to uncertainties linked with wastewater volume measurements and excretion factors [52]. Other

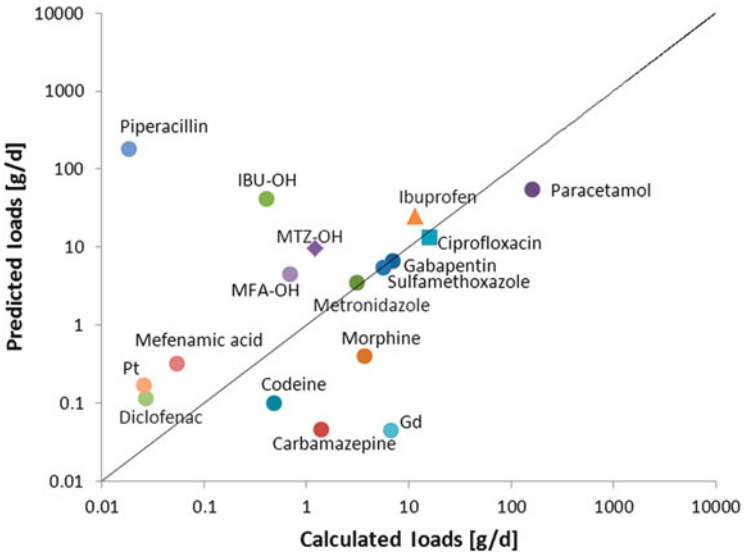

Fig. 1 Comparison of the loads calculated according to the effluent flow measurements with those predicted based on water consumption. Note the logarithmic scales. *IBU-OH* ibuprofen-hydroxyl, *MFA-OH* mefenamic acid-hydroxyl, *MTZ-OH* metronidazole-hydroxyl, *Gd* gadolinium, *Pt* platinum

parameters can also influence the observed overestimations, such as the retention or degradation processes. Indeed, although the excreted fractions of hydroxyl metabolites were considered to predict concentrations and loads, the latter were overestimated compared to the measured fractions. One possible explanation would be a rapid transformation in wastewater due to a chemical instability or biodegradation tendency. This was probably also the case for the antibiotic piperacillin, which was rarely detected and only in trace concentrations [53], although it was identified as a problematic compound in another study [54]. Unfortunately, no information was found in the literature.

Underestimations were also observed for the analgesics morphine and codeine, as well as for the antiepileptic carbamazepine and gadolinium (Gd). Some possible explanations, such as private consumption outside the hospital and excretion within the hospital, are depicted in more detail in Daouk et al. [53]. Nevertheless, overestimation is more frequent than underestimation [52].

In our case, a dilution factor of 296 was used for the dilution of hospital wastewater in the urban network (obtained by dividing the volume of hospital water consumption by the volume of urban wastewater for the year 2012), and a factor of 10 was applied to the second dilution in receiving water (DIL = 2,960). Thus, the PEC_{SW} are only representative of the hospital contribution and do not take into account domestic consumption. PEC_{SW} highlighted the high probability of finding the antibiotic drugs piperacillin (69 ng/L) and amoxicillin (33 ng/L) and the

antidiabetic metformin (32 ng/L) in the freshwater environment. In our case, PEC_{SW} were lower than MEC in the grab surface water samples of the downstream river [55]. This is easily explained by the fact that the predicted values only consider hospital consumption (and not domestic consumption) and were thus only representative of the API hospital fraction.

The hazard quotient calculated for hospital wastewater (HQ_{HWW}) varies widely (from 10^{-3} to 10^{3}), and for the 71 calculated HQ_{HWW}, 32 were above 1 (45%). The ten most hazardous compounds were ciprofloxacin, amoxicillin, trimethoprim, 5-fluorouracil, ibuprofen, lidocaine, sulfamethoxazole, paracetamol, ritonavir, and lopinavir (Table 2). These results are consistent with previous studies [47, 56]. Although the prescribed drugs can differ between hospitals, heavily consumed APIs, such as the latter, are likely to participate in generating

Table 2 Twenty priority compounds highlighted in several studies dealing with environmental risk assessment of APIs in hospitals

#	Daouk et al. [23]	Helwig et al. [54]	Guo et al. [40]	Guo et al. [40]
Remarks	Chronic PNEC/all trophic levels with appropriate AF	Chronic PNEC/all trophic levels with appropriate AF	Acute PNEC/ low trophic levels	Chronic PNEC/low trophic levels
1	Ciprofloxacin*	Amoxicillin*	Amoxicillin*	Diclofenac*
2	Amoxicillin	Piperacillin*	Clarithromycin*	Atorvastatin*
3	Trimethoprim	Flucloxacillin*	Ciprofloxacin*	Estradiol*
4	Fluorouracile/ capecitabine	Penicillin V*	Azithromycin*	Mesalazine*
5	Sulfamethoxazole	Tazobactam*	Metformin*	Omeprazole*
6	Ritonavir	Erythromycin*	Mesalazine*	Paracetamol
7	Ibuprofen	Ketoconazole*	Paracetamol	Mebeverine
8	Lidocaine	Ciprofloxacin*	Phenytoin	Sulfasalazine
9	Gabapentin	Oxytetracycline*	*N*-Acetyl-5-aminosalicylic acid	Codeine
10	Lopinavir	Propranolol	Omeprazole	Fluoxetine
11	Propofol	Clotrimazole	Iminoquinone	Azithromycin
12	Ifosfamide	Naproxen	Mycophenolic acid	Diltiazem
13	Oxazepam	Amlodipine	Norsertraline	Mefenamic acid
14	Clozapine	Venlafaxine	Sulfasalazine	Ranitidine
15	Raltegravir	Metformin	Ranitidine	Clarithromycin
16	Citalopram	Ethinyl estradiol	Oxytetracycline	Terbinafine
17	Piperacillin	Povidone-iodine	Homovanillic acid	Metformin
18	Mycophenolic acid	Ferrous sulfate	Carbocisteine	Etodolac
19	Diclofenac	Allopurinol	Mebeverine	Carbocisteine
20	Efavirenz	Fluoxetine	Propanolol	Atenolol

Compounds with RQ > 1 are highlighted with an asterisk (*)

environmental hazards. HQ_{HWW} can thus help hospital managers and local authorities to identify priority compounds and develop strategies to reduce their input into aquatic ecosystems.

The environmental risk quotient calculated for surface water (RQ_{SW}) revealed that a priori only the hospital fraction of ciprofloxacin was likely to pose a high risk to aquatic ecosystems ($RQ_{SW} > 1$). This was further confirmed with measurements [53] and confirms previous results obtained in another Swiss hospital [57]. The antibiotics amoxicillin, trimethoprim, sulfamethoxazole, the cytostatic fluorouracil, and the antiviral ritonavir were shown to pose a medium risk ($RQ_{SW} > 0.1$).

The 20 highest priority compounds were consistent with other studies (see Table 2). Sulfamethoxazole, ciprofloxacin, and ibuprofen were indeed identified as high-priority pharmaceuticals for the water cycle by de Voogt et al. [58]. Ritonavir was identified as a risky hospital compound by Escher et al. [36], and lidocaine, amoxicillin, ciprofloxacin, and sulfamethoxazole were selected as typical hospital compounds for monitoring by Helwig et al. [12] and are likely to pose problems when reaching the aquatic ecosystem [47, 59, 60].

Trimethoprim is generally administered in combination with sulfamethoxazole, and it has also been identified as problematic by Valcarcel et al. [59]. Fluorouracil (5-FU) and capecitabine were predicted as having low concentrations in European surface water [61], but they were not considered together by the latter authors. Capecitabine is a prodrug that is enzymatically transformed into 5-FU in the body and thus should be considered together with 5-FU. Although capecitabine was not among the priority compounds according to the OPBT approach because it is not excreted in high amounts, it contributes to the environmental risk to aquatic species ($RQ_{SW} = 0.2$).

3.3 Sensitivity Analysis

A sensitivity analysis was performed for 34 APIs to assess the variability of the predicted risk quotients associated with the different parameters taken into account for prediction: consumption, excretions factors (F_{excr}), removal efficiencies in WWTP, hospital water consumption, and PNEC values [23]. In general, the excretion rates (F_{excr}) and the ecotoxicological data (PNEC values) are likely to influence most of the final RQ values, while API consumption (M) and removal efficiencies (R) have moderate consequences, and the water consumption pattern has a small impact. Indeed, RQ values varied up to one order of magnitude according to changes in the excretion rates and up to three orders of magnitude with the uncertainties associated with the PNEC values [23]. In our case, the excretion rates of cytostatic and antiviral drugs were highly uncertain, as well as the PNEC values of cytostatics and antibiotics. The influence of the monthly variability of API consumption on RQ values is mass dependent: highly consumed APIs such as anti-inflammatory (ibuprofen) or analgesic drugs (paracetamol) exhibited much lower variations than the least commonly consumed cytostatic drugs (methotrexate,

epirubicin). In the end, according to the worst-case scenario (maximum values for M and F_{excr} and minimum values for V, R, and PNEC), 5 compounds exhibited high risk and 4 moderate risk compared to 1 and 5, respectively, according to the mean scenario.

3.4 Discussion

3.4.1 Methodologies Comparison

The comparison of the highest priority compounds resulting from the different approaches applied to the API consumption of the Geneva University Hospitals – the ERA and the PBT with and without weighting – highlighted that 8 drugs were revealed by the 3 methodologies (40%) and 12 by at least 2 different methodologies (60%). The ERA highlighted more antibiotics (4 in the top 5), whereas PBT ranked more NSAIDs (3 in the top 5). This difference can be explained by the fact that the ERA does not take into account the bioaccumulation potential (Log K_{ow}). Furthermore, PNEC values were not available for 27 molecules, and, thus, the latter were not taken into account with the ERA. According to our point of view, both approaches are complementary, and combined evaluations should therefore be considered. One possibility of doing so includes adding the ranks of both OPBT and ERA approaches. In our study, the NSAID ibuprofen becomes the highest priority compound, and diclofenac, mefenamic acid, the antidepressant sertraline, and the antibiotic sulfamethoxazole are in the top 5 [23]. Antiviral drugs (ritonavir and raltegravir), analgesics (lidocaine and propofol), and antibiotics (trimethoprim, amoxicillin, ciprofloxacin, and metronidazole) were also highlighted in the top 20 with the rank combination of both methods. Nine compounds (ibuprofen, paracetamol, diclofenac, ciprofloxacin, sulfamethoxazole, trimethoprim, metronidazole, metoprolol, and carbamazepine) were previously highlighted as priority compounds in at least two different studies as reported by Al Aukidy et al. [48].

It is worth stressing that these prioritizations have some drawbacks: they deal only with the most consumed drugs (>1 kg/year); many PNEC and Log K_{ow} values are obtained by QSAR models, and the excretion factors were fixed to mean values. Nevertheless, and despite being a theoretical approach, the highlighted priority compounds – NSAIDs, antiviral drugs, the antidepressant sertraline, the sedative propofol, and/or the antibiotics sulfamethoxazole, trimethoprim, ciprofloxacin, and amoxicillin – are consistent with results of previous studies [11, 14, 26, 36].

3.4.2 Comparison with Other Studies

Hereafter, the prioritized compounds according to ERA are compared to the results of other prioritization studies dealing with ERA in hospitals (Table 2). To summarize, we obtained consumption data from the central pharmacy of the Geneva

University Hospitals, and 32 APIs showed a hazard quotient (HQ_{HWW}) above 1 [23]. However, by taking into account dilution in the surface water, only the antibiotic ciprofloxacin had a risk quotient above 1. Nevertheless, when considering both urban and hospital consumptions, 7 APIs out of the 15 measured had RQ above 1: ciprofloxacin, ibuprofen, piperacillin, mefenamic acid, diclofenac, gabapentin, and sulfamethoxazole [53].

Helwig et al. [54] obtained consumption data from both Scottish hospitals and community pharmacies. While considering both urban and hospital consumptions, 9 antibiotics had RQs >1: amoxicillin, piperacillin, flucloxacillin, penicillin V, tazobactam, erythromycin, ketoconazole, ciprofloxacin, and oxytetracycline (Table 2). This is not really surprising as low PNEC values were determined for antibacterial drugs during the last decade [54]. Furthermore, they observed that half of the API with risk quotients above 1 had high hospital contributions.

Guo et al. [40] analyzed 146 APIs that are used in the community or in hospital settings in the UK (England, Scotland, and Wales). The risk scores were calculated as the ratio between exposure in the different environmental compartments (PEC) and the hazard toward living organisms from different trophic levels (PNEC). Forty international experts were also solicited to identify compounds with low use and of potential high concern. Expert judgment was used to exclude 12 substances with high usage but falling outside the scope of the project, such as calcium carbonate or ferrous sulfate (see Table 1). They identified 13 compounds with risk quotients above 1 for the aquatic ecosystem. The highlighted compounds were antibiotics (amoxicillin, clarithromycin, ciprofloxacin, azithromycin), anti-inflammatory drugs (diclofenac, mesalazine), an antidiabetic (metformin), an antidepressant (amitriptyline), atorvastatin and its metabolites, omeprazole, and the hormone estradiol (Table 2).

Although this comparison should be considered with precaution because of the differences in the parameters used, it allows the complementary identification of priority APIs: antibiotics (ciprofloxacin, amoxicillin, piperacillin, azithromycin), anti-inflammatory drugs (diclofenac, mesalazine), hormone estradiol, and the antidiabetic metformin. However, ciprofloxacin is the only compound identified as highly problematic in the three studies.

4 Conclusions and Perspectives

Though differences are commonly observed between countries and hospitals, we were able to identify five key issues for the prioritization of pharmaceuticals in hospitals based on a literature review and our Geneva case study:

(1) *Access to consumption data*. Although the availability and quality of consumption data improved in the last few years, many uncertainties remain due to the tediousness of data handling and conversion [54]. Note that hospitals are not likely giving their consumption data, the availability of which is often limited

by their costs. Moreover, many different drug prescription systems exist, and thus the list of prescribed drugs may differ in each hospital. Indeed, a commission of experts often evaluates the list of medicines and chooses the allowed candidates, at least in Switzerland.

(2) *Quality and handling of the consumption data*. Tedious and time-consuming manipulation is required to extract usable data for API prioritization and/or environmental risk assessment. Indeed, pharmaceutical dataset are not readily suitable for environmental assessment needs, and the transformation into grams of active ingredient per time unit is not easily performed.

(3) *Expert judgment*. Criteria used by experts for the inclusion-exclusion of compounds, either before or after the prioritization, are highly variable (previously highlighted compounds, reported measured concentrations (MEC), etc.) and induce some large discrepancies in established lists of priority compounds.

(4) *Uncertainties associated with the PEC model*. The PEC model, when applied to both hospital wastewater and surface water, can be of help during the selection process for monitoring campaigns and allow the calculation of risk quotients, but they include strong limitations or associated uncertainties:

   a. *100% consumption hypothesis* – the assumption of the complete consumption of the delivery data is a source of uncertainty. Moreover, the seasonal variation of the consumption is difficult to take into account and can, for some compounds such as antibiotics, strongly influence the resulting concentrations [62].
   b. *Wastewater volume* – as we discussed, water consumption is often considered equal to the volume of wastewater, which is not always the case. Moreover, when the volume of wastewater is measured, high uncertainties are associated with the measurement techniques [52, 53].
   c. *Excretion factors* – human metabolism is highly variable, and the elimination of APIs by the human body is not reproducible from one patient to another. Therefore, when considered, the excretion factor values are average values with high intrinsic uncertainties. Excretion factors were indeed identified as major sources of uncertainties by Verlicchi and Zambello [52], as well as by the sensitivity analysis of the presented case study.
   d. *Local dilution factors* – from both hospital effluents to urban wastewater and from urban wastewater to surface water, as well as the associated uncertainties for ERA, the dilution rates used are often not properly calculated for local hydrological conditions.
   e. *Degradation* – the often considered conservative mass transfer of substances during their transport through the urban wastewater network and surface water and the huge variability linked with the few available WWTP removal data are both sources of uncertainties.

(5) *Quality of the hazard/risk evaluation*. Although the availability and quality of ecotoxicological data improved in the last few years, many shortcomings remain, leading to major uncertainties in the PNEC calculation. Indeed, PNEC values are likely to be highly variable due to the way in which they

are calculated, and the uncertainties associated to the calculated risk quotients are highly dependent to these PNEC values. This was stressed by the sensitivity analysis of the presented case study.

Therefore, prioritization procedures applied to hospitals can be burdensome to apply in practice, and many uncertainties are linked with the different issues detailed above. Nevertheless, prioritization approaches represent essential procedures when dealing with the very high number of API currently in use. They indeed allow for the theoretical identification of the degree of environmental threat for each pharmaceutical product, as well as establishing lists of priority molecules to follow for monitoring programs. Prioritization methods thus represent helpful tools for creating the environmental policy of APIs, for both regulation and surveillance purposes.

There will certainly be an increasing use of prioritization methods for APIs consumed in hospitals in the future. Nevertheless, ecopharmacovigilance is a relatively new domain of investigation, and methodological adaptations to the new challenges for the water quality monitoring are somehow necessary. Environmental risk assessment studies of API residues must indeed consider the risks of long-term exposure to subacute levels, as well as the risks of mixtures of pollutants in the aquatic ecosystems. Moreover, the emphasis is widely placed on parent compounds and the risks toward aquatic organisms, whereas metabolites and soil or sediment compartments are scarcely considered. The recent development of pharmaceutical drugs based on biotechnologies (monoclonal antibodies and vaccines) will certainly induce some methodological adjustments to take them into account. Thus, along with the development of green pharmacy, an update of the European guidelines proposed by the EMEA will be necessary in the future.

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Occurrence and Risks of Contrast Agents, Cytostatics, and Antibiotics in Hospital Effluents

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Abstract During the past 20 years, the presence of pharmaceutical active compounds (PhACs) in the water bodies has been gaining increasing attention and nowadays there is a broad acknowledgment on their consideration as an emerging environmental problem. As a response to this threat, regulatory agencies and the European Commission have implemented a regulatory framework for environmental risk assessment (ERA) of PhACs. One of the main sources of pharmaceuticals in the environment is connected to the hospital discharge into the urban system including the antibiotic resistances and large number of pathogens. Despite wastewater is normally collected and delivered to wastewater treatment plants, it has been demonstrated that the regular treatments applied in such facilities are not completely effective through a variety of pharmaceuticals that are subsequently introduced into the environment. In this document, the authors explore the occurrence in hospital wastewater and the environmental risks of three relevant pharmaceutical groups: cytostatics, antibiotics, and contrast agents.

Keywords Antibiotics, Antibiotics resistance, Contrast agents, Cytostatics, Hospitals, Risk assessment

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Contents

1 Introduction

The presence of pharmaceutical active compounds (PhACs) in the environment such as antibiotics, analgesics, and psychiatric drugs – among others – is considered a serious threat to water quality [1–9]. As contaminants of emerging concern (CECs), PhACs have attracted the attention of the scientific community all over the world during the last couple of decades. There are just few regulations in force that deal with the discharge of these kinds of micropollutants into the environment. Current efforts are attempting to set new policies to address the issue of increasing PhACs occurrence in the environment and to create a framework for controlling the release of these compounds. The European Union, in the Directive 2008/105/EC under the decision (EU) 2015/495 of 20 March 2015 has recently established a *watch list* of substances for monitoring unionwide; it establishes that those substances found to pose a significant risk should be considered for inclusion in a priority substances list [10]. In the watch list it is possible to find some macrolide antibiotics such as erythromycin or the non-steroidal anti-inflammatory drug (NSAID) diclofenac. A critical assessment on the environmental fate and effects of the PhACs will contribute to the future enforcement of regulations as well as providing a set of best management practices related to water quality.

It is well known that hospitals are important sources of micropollutants (especially pharmaceuticals) to urban wastewater [7, 9, 11–23]. Hospital regularly discharges a large number of compounds right into urban sewers: active principles of drugs and their metabolites, chemicals, heavy metals, disinfectants and sterilants, personal care products, endocrine disruptors, specific detergents for endoscopes and other instruments, radioactive markers, iodinated contrast media, and even illicit drugs [8].

A great number of these pollutants is just partially or even not removed at all from wastewater by the conventional treatment technologies [6, 12, 24–30]. This is a major cause of concern, since they can reach the aquatic environment and pose a

threat to natural life [4, 5, 31]. Whilst industrial sectors such as chemical production, pharmaceutical manufacturing, and metallurgic industry, among others, should include a wastewater treatment system in their facilities before discharging into the urban sewage system, the hospitals are not obliged to have dedicated pretreatment for their effluents. Hospital wastewaters would be considered as toxic and hazardous effluents and consequently they should be treated at local scale before the entrance in the urban sewer system [7].

The occurrence of three important groups of pharmaceuticals commonly occurring in hospital effluents: antibiotics, cytostatics, and contrast agents is presented in this chapter. Not only their presence but also the potential environmental implications, as a result of their disposal into the aquatic environment, are also discussed.

2 Contrast Agents Occurrence

Contrast agents are substances such as iodine, barium, or gadolinium compounds, administered to a patient to increase the contrast when using imaging technology in medical applications. Their basic principle is that these agents should provoke a difference in the absorption of radiation (X-rays in the case of iodinated and barium-type contrasts and radiofrequency, in the case of gadolinium-type contrasts) of target anatomic structures in relation to their surroundings. These substances are widely employed in health care for the visualization of bodily tissues in the course of medical diagnosis, particularly when it is challenging to identify the interface between two adjacent tissues or tissues in contact with blood or other physiological fluids. Contrast agents perform a number of functions, including increase in the computed tomography sensitivity, enhanced differentiation between tissues, provision of specific biochemical information, and evaluation of tissue and organ functional performance [32].

Contrary to pharmaceuticals used for therapeutic (curative) purposes, they are developed as biological inactive substances. Therefore, so far it is being considered that they have little ecotoxicological effect.

2.1 Iodine-Based Contrasting Agent

Iodine-based contrasting agents, since the introduction of tri-iodinated benzene derivatives in the early 1950s, have traditionally been used in larger amount than any other contrast agent [33]. In 1 year basis, more than 600 million X-ray examinations are conducted and approximately 75 million of these procedures are carried out using a contrast agent [34]. The success of this type of molecules in X-ray imaging is mainly based on the unique properties of iodine; the element has a high atomic number and therefore achieves a higher level of X-ray attenuation than that observed for biological tissues. Most ionic iodinated contrast agents are neutral

or negatively charged and exhibit a high tendency to establish interactions with biological structures. Four different groups of iodinated contrast agents are mostly used nowadays [33]:

1. Ionic monomer: single tri-iodinated benzene ring with a carboxylate-containing benzene substituent (iothalamate, diatrizoate).
2. Ionic dimer: 2 linked tri-iodinated benzene rings in which at least 1 carboxylate-containing group is substituted on at least 1 benzene ring (ioxaglate).
3. Nonionic monomer: single tri-iodinated benzene ring without a carboxylate-containing benzene substituent (iohexol, iopromide, ioversol, iopamidol, ioxilan).
4. Nonionic dimer: 2 linked tri-iodinated benzene rings that do not contain a carboxylate functional group within any benzene substituent (iodinaxol).

Despite the large use of these substances in hospital facilities, studies concerning occurrence and discharge remain to date scarce.

Weissbrodt et al. [22] established a mass flow analysis of iodinated X-ray contrast media in a Swiss hospital. The authors concluded that the total emission of contrast media suffered strong inter day variations ranging from 255 to 1,259 g day^{-1}, and exhibited a maximum on the day when the highest radiology treatment occurred. The authors stated that, according to the high administration of iodinated contrast media in hospitals, these kinds of facilities are presumable one of the major point sources and major responsible of contamination of the aquatic environment by these type of substances.

Kuroda et al. [35] developed a model to predict mass flows and concentrations of several pharmaceutical compounds across sewage treatment plants and rivers in Switzerland. The authors established a total consumption in Switzerland of 16,064 kg $year^{-1}$ gathering the consumption of diatrizoate, iobitridol, iohexol, iomeprol, iopamidol, iopromide, and ioxitalamic acid.

2.2 Gadolinium-Based Contrasting Agents

Lanthanide-based contrast agents are commonly used in magnetic resonance imaging (MRI) due to their unique magnetic properties. Among the lanthanide group, the most widely employed element is Gadolinium, Gd^{3+}. This cation is, however, extremely toxic on its free form, partially due to its similarity on the ionic radius of Ca^{2+} (Gd^{3+} 0.99 Å; Ca^{2+} 1.00 Å) [32]. With just 1% difference, Gd^{3+} can compete with Ca^{2+} and affect a variety of biological processes. However, many lanthanides such as Gd form highly stable and non-toxic chelate-type complexes with different polyaminocarboxylic acids [32, 36].

Contrast agent formulations are usually highly concentrated (0.5–1.0 mol L^{-1} Gd) so that on an average, approximately 1.2 g of Gd is applied to a typical MRI patient with each dose. This leads to a very high input of anthropogenic Gd into the

environment [36]. It is worth noting that the literature revised to date points out that the use of Gd as contrast agent in magnetic resonance imaging is by far the most relevant anthropogenic source of this metal to the environment.

A study performed by Kümmerer and Helmers [37] regarding emissions of Gd from a German hospital indicated a total discharge varying from 2.1 to 4.2 kg $year^{-1}$, yielding a theoretical concentration of metal from 8.5 to 30.1 μg L^{-1} in the effluent. The authors, using the number of magnetic resonance tomography instruments in Berlin estimated an environmental release about 67.7 kg. Extrapolation of data from Berlin to the overall population in Germany leads to a total release in the country of 1,355 kg of Gd.

Künnemeyer et al. [36] explored the presence of different Gd chelates in a German hospital wastewater and in the different units of an urban sewage treatment plant. The authors measured the concentration of contrast agent in two different towers where the patients were conveyed after being examined in the radiology department, located in the central building of the hospital. They reported concentrations of 0.10 μg L^{-1} Gd (below the detection limit of the HILIC/ICP-MS method the authors used) and 3.30 μg L^{-1} Gd in the towers. In another study, performed in a hospital in Switzerland, Kuroda et al. [35] estimated a gadolinium discharge of 157 kg $year^{-1}$.

Goullé et al. [13] monitored a variety of metals using ICP-MS techniques in wastewater from a French hospital to quantify the contribution of its discharge to the urban pollution. The authors tracked the metal profile in the wastewater for 29 days and pointed out large differences between working and non-working days. While in the working days, an average concentration of 3.25 μg L^{-1} was measured, in non-working days, the concentration of Gd decreased to 0.21 μg L^{-1} being the average along the 29 days period 2.44 μg L^{-1}. The authors monitored as well the concentration in the wastewater treatment plant and observed that Gd was just poorly removed. Above 88% of the Gd entering in the influent was not removed and resulted into its discharge into the environment via River Seine. With the data gathered by the authors, they concluded that more than 4 kg Gd are yearly discharged into the river.

3 Cytostatics Occurrence

The huge increment of cancer disease in the population has led to an enlargement on drugs consumption and it can be foreseen an even higher discharge of this kind of substances into the environment in the coming years.

Chemotherapy drugs are a specific group of pharmaceutical compounds used to treat cancer diseases. They are often called *anticancer drugs* or *cytostatics* and have been shown to have potent cytotoxic, genotoxic, mutagenic, carcinogenic, endocrine disruptor, and/or teratogenic effects in several organisms, since they have been mainly designed to disrupt or prevent cellular proliferation, usually by interfering in DNA synthesis. Chemotherapy uses powerful chemicals to kill fast-growing cells in the body and can be used alone or combined to treat a wide variety of cancer diseases.

The cytostatics include a large number of compounds which belong to different chemical families. They can be divided into several groups based on factors such as the mode of action, chemical structure, their relationship to another drug, and/or if they come from natural sources. For instance, some anticancer drugs are grouped together because they were derived from the same herbal, although they have different modes of action.

Cytostatics can be classified in ten groups by mode of action based on different health organizations (WHO, SEFH, Mayo Clinic, American Cancer Society, and EACR):

- Alkylating agents (cyclophosphamide, chlorambucil, ifosfamide, cisplatin, carboplatin, dacarbazine, procarbazine, etc.);
- Antimetabolites (cytarabine, tegafur, floxuridine, azatadine, thioguanine, azathioprine, methotrexate, 5-flurouracil, etc.);
- Anti-tumor antibiotics (bleomycin, mitomycin-C, ciprofloxacin, daunorubicin, doxorubicin, epirubicin, etc.);
- Topoisomerase inhibitors (topotecan, irinotecan, etoposide, teniposide, etc.);
- Mitotic inhibitors (vincristine, paclitaxel, docetaxel, etc.);
- Corticosteroids (prednisone, methylprednisolone, etc.);
- Miscellaneous chemotherapy drugs (L-asparaginase);
- Hormone (fulvestrant, tamoxifen, anastrozole, megestrolacetate, etc.);
- Anti-tumor antiretroviral (ritonavir, saquinavir, indinavir, nelfinavir, and atazanavir), and
- Immunotherapy drugs (rituximab, alemtuzumab, thalidomide, lenalidomide, etc.).

There are relevant scientific advances in chemotherapy, based sometimes on more targeted treatments or even on the prevention of the cancer disease (such as the cancer vaccines or use of the genetic profiling to take early preventive measures). However, there are many conventional drugs described along this chapter which are – to date – still necessary based on their well-proven effectiveness in a large number of cancers.

Reports on occurrence of cytostatic compounds in the environment are very recent but still scarce [12, 23, 24, 26, 27, 29, 37–45] and the concentration found in wastewater and natural samples is very low compared to other common pharmaceuticals. To date, most of the studies reported in literature have been performed in wastewater, particularly tackling hospital effluents as relevant potential source of these micropollutants.

Table 1 intends to summarize the data available in the literature regarding the presence of these drugs in hospital effluents. Certainly, there is almost no information of these compounds in surface water, groundwater, and drinking water neither in activated sludge or natural sediments. Only 15 studies have reported incidence of anticancer drugs in hospital effluents. Five of these studies have been performed in Spain, three in Germany, two in China, two in France, one in Switzerland, one in United Kingdom, and one in Austria. Most of the studies have assessed one or two compounds. Yin et al.(2009) had studied up to six compounds in 21 Chinese

Table 1 Literature review about the occurrence of cytostatics in hospital effluents

Cytostatics	Concentration (ng L^{-1})	Location	No. of beds	Reference
Anastrozole	0.3–3.7	China	n.a.	[46]
Azathioprine	15	China	n.a	[47]
	19–187	Spain	400	[24]
	blq-188	Spain	400	[12]
Cyclophosphamide	146	Germany	n.a.	[43]
	19–4,500	Germany	n.a.	[42]
	30–900	France	n.a.	[48]
	5,300	Spain	n.a.	[41]
	6–2,000	China	n.a	[47]
	25–200	Spain	400	[24]
	36–43	Spain	400	[12]
Carboxyphosphamide	TI	Spain	400	[24]
Platinum compounds[a]	3,000–250,000	Austria	n.a.	[18]
	350	France	n.a	[13]
	1,700	Austria	n.a.	[49]
	<30	France	n.a.	[48]
Daunorubicin	<60	Austria	n.a.	[50]
Docetaxel	nd-175	Spain	400	[24]
	nd-79	Spain	400	[12]
Doxorubicin	260–1,350	Austria	n.a.	[50]
Doxorubicinol	<10	China	n.a.	[47]
Etoposide	5–380	China	n.a.	[47]
	110–300	France	n.a.	[48]
	nd-83	Spain	400	[24]
	nd-714	Spain	400	[12]
5-Fluorouracil	8,600–124,000	Austria	n.a.	[51]
	<5.0–27	Switzerland	n.a.	[52]
	20,000–122,000	Austria	n.a.	[50]
2, 2-Difluoro-deoxyuridine(m)	<9.0–840	Switzerland	n.a.	[52]
Gemcitarabine	<0.9–38	Switzerland	n.a.	[52]
Ifosfamide	24	Germany	n.a.	[43]
	6–1,914	Germany	n.a.	[27]
	4–10,647	China	n.a.	[47]
	blq	Spain	400	[24]
	nd-228	Spain	400	[12]
Letrozole	0.20–2.38	China	n.a.	[46]
Methotrexate	1,000	U.K.	n.a.	[53]
	2–4,689	China	n.a.	[47]
	nd-23	Spain	400	[24]
	nd-19	Spain	400	[12]
Paclitaxel	nd-99	Spain	400	[24]
	blq-100	Spain	400	[12]

(continued)

Table 1 (continued)

Cytostatics	Concentration (ng L^{-1})	Location	No. of beds	Reference
Hydroxy-paclitaxel	TI	Spain	400	[24]
	nd	Spain	n.a.	[21]
Procarbazine	<5	China	n.a.	[47]
Tamoxifen	0.2–8.2	China	n.a	[46]
	26–94	Spain	400	[24]
	36–170	Spain	400	[12]
	45–970	Spain	400	[11]
Hydroxy-tamoxifen(m)	blq	Spain	n.a.	[21]
	TI	Spain	400	[24]
4,4-Dihydroxy desmethyltamoxifen(m)	TI	Spain	400	[24]
Vincristine	<20	China	n.a.	[47]
	blq-49	Spain	400	[24]
	blq	Spain	400	[12]

nd not detected, *n.a.* not available, *TI* tentatively identified, *blq* below limit of quantification, *m* human metabolite

[a]This group includes several compounds such as cisplatin, carboplatin, oxiliplatin, and/or lobaplatin very frequently estimated as a total platinum concentration

hospital effluents [47]. Later, Ferrando-Climent et al. [24] studied the occurrence of 10 representative cytostatics at hospital effluents in Spain. With the analytical methodology developed in [24], Ferrando-Climent and colleagues tracked the behavior of 10 of these drugs in an urban system monitoring from hospitals through WWTPs until surface water [12]. Recently, Negreira et al. [21] have evaluated the presence of 13 anticancer drugs and 4 metabolites in municipal and hospital wastewaters in Spain.

Cyclophosphamide and ifosfamide are the most studied anticancer drugs being as well the most consumed according to the National Health System of Spain [54]. Levels of cyclophosphamide ranged from 6 till 143 ng L^{-1} and from 19 until 4,500 ng L^{-1} in urban and hospital wastewaters, respectively (Table 1) [42, 43, 48]. This wide range in occurrence levels can be attributed to the limited number of studies available and it is in accordance with the variability observed in wastewater concentrations for the drugs with relative low consumption. Only in very few cases, some anticancer drugs were detected at relatively high levels. This is the case of 5-fluorouracil detected up to 124,000 ng L^{-1} in a hospital effluent [50]. However, tamoxifen was found in almost all the hospital samples analyzed by Ferrando-Climent et al. in different studies at range of concentration from 26 until 970 ng L^{-1} [11, 12, 24].

Despite it is not the scope of this chapter, it is important to highlight that most of the anticancer drugs have never been analyzed in surface water. Only Ferrando-Climent et al. have studied the occurrence of ten cytostatics in the Ter river at northeast of Spain [12].

Furthermore, there is a huge gap when it comes to information about the presence of human metabolites of cytostatics in the aquatic environment. So far, only three studies have reported the presence of human metabolites in hospital wastewaters. Ferrando-Climent et al. [24] have tentatively identified hydroxy-tamoxifen, 4,4-dihydroxy desmethyltamoxifen, and carboxyphosphamide in the effluent of Trueta Hospital in Girona (Spain). Kovalova et al. reported up to of 840 ng L^{-1} of 2, 2-difluoro-deoxyuridine (human metabolite of 5-fluorouracil) [55]. Also Negreira et al. have reported the presence of paclitaxel and tamoxifen human metabolites in wastewaters [21].

According to up-to-date literature data, it can be concluded that there is a lack of information regarding the sources, fate, and occurrence of anticancer drugs. It becomes a challenging and difficult task identifying whether the main sources of contamination are hospital effluents or urban influents. In fact, there are no studies that comprehensively gather the occurrence of a representative number of anticancer drugs in the whole urban water cycle. The scarcity of information about environmental levels of these compounds is partially explained by the lack of analytical methods suited to environmental applications [24, 47, 52]: the anticancer drugs belong to different chemical families and developing a multi-residue method for all of them is an analytical challenge. Furthermore, the high cost of chemotherapy pharmaceutical reference standards – often produced through expensive synthesis – and their particular health and safety hazards makes the conventional target analysis of these compounds difficult in most of the environmental laboratories. This is mainly due to the special and expensive safety conditions required for their handling (training of analysts for cytotoxic handling, personal protective equipment, biological safety cabinet or similar category hood, specific containers for residues, etc.).

4 Antibiotics Occurrence

Hospital effluents have been pointed out as an important contribution for the entrance of pharmaceuticals into urban wastewaters or even into the aquatic environment [9]. Among these, antibiotics are one of the most frequently detected therapeutic groups in hospital effluents [7, 56, 57], mainly due to their excretion in urine and, in a less extent, in faeces, as metabolites or in the unchanged form.

The presence of antibiotics in hospital effluents will be influenced by different factors such as size of hospital, bed density, number and type of wards and services, number of inpatients and outpatients and their clinical situations, differences in antibiotics prescription habits, country, and seasonality [9, 58, 59]. However, fluoroquinolones, macrolides, sulfonamides, β-lactam antibiotics, and lincosamides are among the most ubiquitous classes of antibiotics found in hospital effluents together with antibiotics like trimethoprim and metronidazole [9].

Usually, they are found at higher concentrations than those reported in urban wastewaters, reaching a few hundreds of μg L^{-1} [60–62].

Several studies have reported the occurrence of antibiotics in hospital effluents all over the world (Table 2), nevertheless most of the available data concerns to

Table 2 Examples of the occurrence of antibiotics in hospital effluents all over the world

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
Macrolides				
Erythromycin	1,350 ± 2,300	USA	250	[59]
	60 ± 40		250	
	20		350–450	
	260 ± 220		350–450	
	80 ± 80		600	
	<5–140	Switzerland	346	[75]
	330–520	Denmark	–[a]	[82]
	<16–1,075	Portugal	1,456	[56]
	n.d.-22.2		350	
	n.d.-913		110	
	47.8–7,545		96	
	60–320	Italy	300	[7]
	80–230		900	
	470	Korea[b]	813–2,743	[73]
	261 ± 12	China	–[a]	[72]
	13 ± 1		–[a]	
	10–30	Spain	75	[78]
	27,000 (max)	Germany	–[a]	[65]
Erythromycin-H_2O[c]	2,160 ± 3,520	USA	250	[59]
	60		250	
	70		350–450	
	20		350–450	
	50 ± 50		600	
	827 ± 47	China	–[a]	[72]
	448 ± 65		–[a]	
	610–840	Denmark	–[a]	[82]
	83,000 (max)	Germany	–[a]	[65]
Azithromycin	20.1–59.9	Spain	400	[68]
	85–113	Spain	400	[66]
	139 ± 156	Switzerland	346	[15]
	110 ± 180	Switzerland	346	[75]
	1,600–2,500	Denmark	–[a]	[82]
	1,227–7,351	Portugal	1,456	[56]
	89.2–4,492		350	
	<25–376		110	
	<25–2,665		96	
	<7.4–110	Italy	300	[7]
	45–1,040		900	

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
Clarithromycin	22 ± 9	Saudi Arabia	300	[83]
	78–498	Spain	1,000	[74]
	167.3–941.1	Spain	400	[68]
	1,420 ± 1,450	USA	250	[59]
	250 ± 230		250	
	630 ± 800		300	
	140 ± 20		350–450	
	10		350–450	
	210 ± 120		600	
	113–973	Spain	400	[66]
	2,555 ± 1,558	Switzerland	346	[15]
	1,280 ± 840	Switzerland	346	[75]
	1,300–1,800	Denmark	–[a]	[82]
	2.56–199	Portugal	1,456	[56]
	n.d.-45.6		350	
	n.d.-960		110	
	n.d.-165		96	
	20–140	Italy	300	[7]
	50–14,000		900	
	2,000 (max)	Germany	–[a]	[65]
Josamycin	<3–12	Italy	300	[7]
	<3–15		900	
Roxithromycin	130–160	Denmark	–[a]	[82]
	23	Switzerland	346	[15]
	<5–140	Italy	900	[7]
	1,180 ± 69	China	–[a]	[72]
	2,189 ± 362		–[a]	
	1,000 (max)	Germany	–[a]	[65]
Spiramycin	200–2,200	Vietnam	220	[62]
	200–1,700		520	
	<2–40	Italy	300	[7]
	<3–110		900	
Lincosamides				
Clindamycin	423 ± 17	Taiwan	–[a]	[76]
	184–1,465	Spain	400	[66]
	24–31	Denmark	–[a]	[82]
	983 ± 945	Switzerland	346	[15]
	1,160 ± 1,180	Switzerland	346	[75]
Lincomycin	7 ± 1	Taiwan	–[a]	[76]
	80	USA	250	[59]

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
	40 ± 10		350–450	
	20 ± 10		600	
	119	Spain	400	[66]
	240–48,400	Korea[b]	813–2,743	[73]
	2,000	USA	–[a]	[69]
	300		–[a]	
	174 ± 18	China	–[a]	[72]
	63 ± 17		–[a]	
(Fluoro)quinolones				
Flumequine	11.2 ± 0.7	Taiwan	–[a]	[76]
Oxolinic acid	62.9 ± 2.0	Taiwan	–[a]	[76]
Ofloxacin	800–7,400	Vietnam	220	[62]
	1,600–19,800		520	
	4,750–14,377.8	Spain	400	[68]
	1,547–4,778	Spain	1,000	[74]
	7,262 ± 1,533	Taiwan	–[a]	[76]
	2,978–10,368	Spain	400	[66]
	48–660	India	350	[67]
	26–230		570	
	3,135–24,811	Portugal	1,456	[56]
	1,986–12,865		350	
	n.d.-662		110	
	13,000–22,000	Italy	300	[7]
	3,300–37,000		900	
	4,240 ± 221	China	–[a]	[72]
	3,440 ± 429		–[a]	
	2,340 ± 365		–[a]	
	1,600 ± 225		–[a]	
	25,500	USA	–[a]	[69]
	34,500		–[a]	
	35,500		–[a]	
	4,900		–[a]	
	200–7,600	Sweden	–[a]	[61]
	31,000 (max)	Germany	–[a]	[65]
Ciprofloxacin	46,200 ± 30,600	France	450	[70]
	970–3,390	France	1,100	[84]
	5,600–53,300	Vietnam	220	[62]
	600–40,200		520	
	8,305.1–13,779.7	Spain	400	[68]
	2,730 ± 371	Taiwan	–[a]	[76]
	5,329–7,494	Spain	400	[66]
	259–1,530	India	350	[67]

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
	214–868		570	
	10,000–15,000	Italy	300	[7]
	1,400–26,000		900	
	31,980 ± 14,060	Switzerland	346	[15]
	15,700 ± 8,000	Switzerland	346	[75]
	6,000–7,600	Denmark	–[a]	[82]
	2,259–38,689	Portugal	1,456	[56]
	457–13,344		350	
	120–1,334		110	
	101–2,000		96	
	3,080	Korea[b]	813–2,743	[73]
	136 ± 26	China	–[a]	[72]
	217 ± 41		–[a]	
	11 ± 2		–[a]	
	7,000 ± 100	Vietnam	–[a]	[71]
	10,900 ± 800		–[a]	
	1,200 ± 200		–[a]	
	2,100 ± 100		–[a]	
	1,100 ± 100		–[a]	
	25,800 ± 8,100		–[a]	
	<38–54,049	Norway	1,200	[57]
	<38–39,843		–[a]	
	2,000	USA	–[a]	[69]
	850		–[a]	
	3,600–101,000	Sweden	–[a]	[61]
	51,000 (max)	Germany	–[a]	[65]
Enoxacin	330–480	Italy	300	[7]
	58–450		900	
Levofloxacin	51–750	India	350	[67]
	61–150		570	
Lomefloxacin	190 ± 39	China	–[a]	[72]
	1,162 ± 285		–[a]	
	313 ± 52		–[a]	
Norfloxacin	241 ± 72	Taiwan	–[a]	[76]
	327	Spain	400	[66]
	160	India	570	[67]
	3,140 ± 1,820	Switzerland	346	[75]
	5,933 ± 3,390	Switzerland	346	[15]
	40–100	Italy	300	[7]
	23–510		900	
	303 ± 41	China	–[a]	[72]
	1,620 ± 242		–[a]	

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
	136 ± 28		–[a]	
	15,200 ± 300	Vietnam	–[a]	[71]
	3,400 ± 400		–[a]	
	13,600 ± 300		–[a]	
	8,400 ± 2,500		–[a]	
	44,000 (max)	Germany	–[a]	[65]
Sulfonamides				
Sulfadiazine	9–137	Spain	1,000	[74]
	19.2 ± 1.6	Taiwan	–[a]	[76]
	50 ± 40	USA	300	[59]
	2,330 ± 6,640	Switzerland	346	[75]
	380–630	Denmark	–[a]	[82]
	1,896 ± 4,003	Switzerland	346	[15]
	29–33	Italy	300	[7]
	77–380		900	
	48 ± 2	China	–[a]	[72]
	253 ± 47		–[a]	
Acetyl-sulfadiazine[c]	110–150	Denmark	–[a]	[82]
Sulfamerazine	16.1 ± 1.5	Taiwan	–[a]	[76]
Sulfamethoxazole	200–20,300	Vietnam	220	[62]
	100–18,900		520	
	2,670 ± 354	Taiwan	–[a]	[76]
	190.2–4,816.7	Spain	400	[68]
	970 ± 190	USA	250	[59]
	2,170 ± 970		250	
	490 ± 400		300	
	2,150 ± 1,350		350–450	
	490 ± 770		350–450	
	1,520 ± 380		600	
	65–200	Spain	400	[66]
	21–2,240	India	570	[67]
	3,230 ± 4,700	Switzerland	346	[75]
	12,000–16,000	Denmark	–[a]	[82]
	3,476 ± 4,588	Switzerland	346	[15]
	307–8,714	Portugal	1,456	[56]
	191–5,524		350	
	41.0–1,288		110	
	n.d.-695		96	
	3,000–6,500	Italy	300	[7]
	900–3,400		900	
	613 ± 3	China	–[a]	[72]
	195 ± 42		–[a]	

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
	1,060 ± 178		–[a]	
	12,500–37,300	Brazil	–[a]	[63]
	108–3,840	Korea[b]	813–2,743	[73]
	<4–1,375	Norway	1,200	[57]
	<4–4,107		–[a]	
	800	USA	–[a]	[69]
	2,100		–[a]	
	400		–[a]	
	400–12,800	Sweden	–[a]	[61]
	6,000 (max)	Germany	–[a]	[65]
N-acetylsufamethoxazole[c]	59 ± 14	Saudi Arabia	300	[83]
	455 ± 440	Switzerland	346	[75]
	59–79	Denmark	–[a]	[82]
	2,394 ± 2,261	Switzerland	346	[15]
Sulfapyridine	251	Switzerland	346	[15]
Sulfisoxazole	21.0 ± 1.8	Taiwan	–[a]	[76]
Sulfamethizole	1,500–1,600	Denmark	–[a]	[82]
Sulfamethazine	<2–14	Italy	300	[7]
	<4–30		900	
Tetracyclines				
Demeclocycline	<3–52	Norway	–[a]	[57]
Doxycycline	100–270	Italy	300	[7]
	<15–970		900	
	600–6,700	Sweden	–[a]	[61]
	<5–403	Norway	1,200	[57]
	<5–336		–[a]	
	8,100	Portugal	–[a]	[60]
Tetracycline	332 ± 35	Taiwan	–[a]	[76]
	<7–26	Italy	300	[7]
	<9–33		900	
	<15–1,537	Norway	1,200	[57]
	<15–4,178		–[a]	
	42,200–158,000	Portugal	–[a]	[60]
	54,700		–[a]	
	23,200–29,200		–[a]	
Epitetracycline[c]	17,500	Portugal	–[a]	[60]
	18,900		–[a]	
Oxytetracycline	4.1 ± 0.5	Taiwan	–[a]	[76]
	300–1,300	Italy	300	[7]
	<7–100		900	
	<12–3,743	Norway	1,200	[57]
	<12–2,294		–[a]	

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
Minocycline	317,790	Portugal	–[a]	[60]
	531,700		–[a]	
Chlorotetracycline	20–60	Italy	300	[7]
	<8–94		900	
	222	Korea[b]	813–2,743	[73]
	<6–69	Norway	–[a]	[57]
Iso-chlorotetracycline[c]	17 ± 1	China	–[a]	[72]
	20 ± 5		–[a]	
β-lactams				
Penicillins				
Amoxicillin	<31.6–218	Spain	400	[66]
	33–43	Denmark	–[a]	[82]
Penicillin G	5,200	USA	–[a]	[69]
	850		–[a]	
Oxacillin	986 ± 181	Taiwan	–[a]	[76]
Cephalosporins				
Ceftazidime	2,600–5,000	Vietnam	220	[62]
Cefotaxime	143.7–240.4	Spain	400	[68]
	89	Spain	400	[66]
	0.3 ± 0.1	Taiwan	–[a]	[76]
Cephalexin	2,228 ± 205	Taiwan	–[a]	[76]
Cephradine	166 ± 40	Taiwan	–[a]	[76]
Cefazolin	<49.2–83.4	Spain	400	[68]
	4,905 ± 1,236	Taiwan	–[a]	[76]
Cefuroxime	150–210	Denmark	–[a]	[82]
Other antibiotics				
Trimethoprim	100–4,300	Vietnam	220	[62]
	100–7,100		520	
	1,596–4,791	Spain	1,000	[74]
	83.8 ± 4.4	Taiwan	–[a]	[76]
	136.6–3,826	Spain	400	[68]
	970 ± 540	USA	250	[59]
	1,320 ± 460		250	
	1,060 ± 730		300	
	970 ± 260		350–450	
	380 ± 430		350–450	
	930 ± 210		600	
	50–216	Spain	400	[66]
	3,800–4,900	Denmark	–[a]	[82]
	3,650–11,300	Brazil	–[a]	[63]
	19–95,100	Korea[b]	813–2,743	[73]
	370 ± 370	Switzerland	346	[75]

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
	930 ± 890	Switzerland	346	[15]
	837–3,963	Portugal	1,456	[56]
	30.5–1,182		350	
	12.5–1,089		110	
	n.d.-122		96	
	800–1,800	Italy	300	[7]
	68–860		900	
	174 ± 15	China	–[a]	[72]
	92 ± 36		–[a]	
	61 ± 22		–[a]	
	50–14,993	Norway	1,200	[57]
	<2–11,899		–[a]	
	5,000	USA	–[a]	[69]
	2,900		–[a]	
	10–30	Spain	75	[78]
	600–7,600	Sweden	–[a]	[61]
	6,000 (max)	Germany	–[a]	[65]
Metronidazole	100–16,400	Vietnam	220	[62]
	100–130,400		520	
	66.9 ± 3.1	Taiwan	–[a]	[76]
	67–643	Spain	400	[66]
	6.7–417	India	350	[67]
	9.2–127		570	
	1,860 ± 2,030	Switzerland	346	[75]
	3,388 ± 1,322	Switzerland	346	[15]
	n.d.-12,315	Portugal	1,456	[56]
	<12–1,569		350	
	<12–4,315		110	
	<12–5,008		96	
	330–1,640	Italy	300	[7]
	260–1,100		900	
	1,800–9,400	Spain	75	[78]
	100–90,200	Sweden	–[a]	[61]
Metronidazole-OH[c]	150-887	Spain	400	[66]
	n.d.-11,344	Portugal	1,456	[56]
	n.d.-2,125		350	
	n.d.-523		110	
	n.d.-990		96	

(continued)

Table 2 (continued)

Antibiotic	Concentration (ng L^{-1})	Country	No. of beds	Reference
Chloramphenicol	<9–36	Italy	300	[7]
	<4–10		900	
Nifuroxazide	100–2,560	Italy	300	[7]
	100–330		900	

n.d. not detected
[a]Data not available
[b]Combined data of four hospitals
[c]Metabolite

developed countries (e.g., Europe, USA). Antibiotics like ciprofloxacin, ofloxacin, clarithromycin, sulfamethoxazole, trimethoprim, and metronidazole are among the most frequently detected in hospital effluents (Table 2), reaching levels up to 101 [61], 37 [7], 14 [7], 37.3 [63], 95.1 [63] and 130.4 μg L^{-1} [62], respectively.

Besides antibiotics, some of their metabolites have also been found in hospital effluents as, for instance, *N*-acetylsulfamethoxazole [15, 64], erythromycin-H_2O [59, 65], or metronidazole-OH [56, 66]. Usually, the occurrence of antibiotics in hospital effluents follows a seasonal trend, being detected higher concentrations in the winter than in the summer [7, 67].

4.1 Fluoroquinolones

Fluoroquinolones are one of the most frequently detected classes of antibiotics in hospital effluents. Their presence has been reported in Europe [7, 56, 57, 68–70], North America [69] and Asia [62, 67, 71, 72]. Ciprofloxacin, ofloxacin, and norfloxacin are the most often found, at concentrations ranging between <38 ng L^{-1} [57] and 101 μg L^{-1} [61]; 26 ng L^{-1} [67] and 37 μg L^{-1} [7]; and 23 ng L^{-1} [7] and 44 μg L^{-1} [65], respectively. The presence of enoxacin, levofloxacin, and lomefloxacin has also been reported at levels up to 480 ng L^{-1} [7], 750 ng L^{-1} [67], and 1,162 ng L^{-1} [72], respectively.

4.2 Macrolides

Other class of antibiotics often found in hospital effluents are macrolides. Among these, clarithromycin, erythromycin, and azithromycin are the most frequently detected antibiotics, showing concentrations between 22 ng L^{-1} [56] and 14 μg L^{-1} [7]; <16 ng L^{-1} [56] and 27 μg L^{-1} [65]; <7.4 ng L^{-1} [56] and 7,351 ng L^{-1}, respectively. Besides these macrolide antibiotics, also roxithromycin, spiramycin, and josamycin were found in

hospital effluents at maximum levels up to 15 [7], 2,189 [72] and 2,200 ng L^{-1} [62], respectively.

4.3 Sulfonamides

Sulfamethoxazole is the sulfonamide antibiotic most frequently detected in hospital effluents. It has been found in European [7, 56, 68], North [59] and South American [63], and Asian [62, 73] hospitals wastewaters at concentrations ranging from <4 ng L^{-1} [57] to 37.3 μg L^{-1} [63]. Sulfadiazine is the second most detected sulfonamide antibiotic (9–2,330 ng L^{-1}) [74, 75].

4.4 Tetracyclines

Tetracycline, doxycycline, oxytetracycline, and chlorotetracycline are some of the tetracycline antibiotics found in hospital effluents (Table 2). They have been mainly detected in European countries at concentrations up to 158 μg L^{-1} [60], 6,700 ng L^{-1} [61], 3,743 ng L^{-1} [56] and 222 ng L^{-1} [73], respectively.

4.5 β-Lactam Antibiotics

β-Lactam antibiotics are divided into two groups: penicillins and cephalosporins. This class of antibiotics was only detected in a few countries, namely Spain [66, 68], Denmark [64], USA [69], Taiwan [76], and Vietnam [62]. Although β-lactam antibiotics are among the most consumed antibiotics in many countries [77], they have a low frequency of detection that might be justified by the rapid degradation of the β-lactam ring by enzymes present in bacteria or to their susceptibility to suffer hydrolysis and, subsequently, went for a process of decarboxylation [62, 77]. The maximum concentrations of β-lactam antibiotics detected in hospital effluents were similar for both groups, reaching around 5 μg L^{-1} for penicillins (penicillin G) [69] and cephalosporins (ceftazidime) [62].

4.6 Lincosamides

Lincomycin and clindamycin are the two lincosamide antibiotics most frequently detected in hospital effluents (Table 2). They were found at maximum concentrations of 48.4 μg L^{-1} (Korea) [73] and 1,465 ng L^{-1} (Spain) [66], respectively.

4.7 Other Antibiotics

Besides the above-mentioned classes of antibiotics, there are two other antibiotics that have been often found in hospital effluents. They are trimethoprim and metronidazole. The former is co-administered with sulfamethoxazole; therefore, it is expected that it would be also highly detected in hospital wastewaters, following the same pattern of detection. Trimethoprim was found all over the world, in Europe [15, 61, 68, 74], North [59, 69] and South America [63], and Asia [62, 72]. Concentration of trimethoprim in hospital effluents ranged from <2 ng L^{-1} to around 15 μg L^{-1} [57]. Regarding metronidazole, its presence was reported in hospital effluents of Europe [56, 61, 78] and Asia [62, 67], reaching maximum concentrations of 130.4 μg L^{-1} [62].

Although antibiotics have been detected at high concentrations in hospital effluents, this does not necessarily imply a high contribution to the mass load of antibiotics into urban wastewaters, since the flow rate of the hospital is much lower than those of wastewater treatment plants (WWTPs). In fact, the load of antibiotics into urban wastewaters can widely vary from substance to substance, but for some antibiotics the contribution of hospital effluents can be very important. This is the case of clarithromycin, ciprofloxacin, and metronidazole that several authors showed to have an important hospital contribution [7, 57, 79, 80], with maximum contributions up to 94%, 272%, and 84%, respectively. Nevertheless, a wide range of contributions to the mass load of antibiotics into urban wastewaters is described in the literature. For instance, Santos et al. [56] showed that in Portugal, 41% of the antibiotics found in urban wastewaters were originated in the effluents of four hospitals, while in Norway, depending of the antibiotic, the contribution of hospital effluents varied from less than 1% (sulfamethoxazole and tetracycline) to 272% (ciprofloxacin) [57]. A similar behavior was reported for an Australian hospital, whose contribution to the load of antibiotics varied from less than 5% (cephalexin and sulfamethoxazole) to 56% (roxithromycin) [81]. Similar maximum contributions were found for several antibiotics in Italy [7], Switzerland [80], and Germany [79].

5 Risk Assessment

Hospital effluents are discharged either treated or untreated into receiving aquatic environment and therefore a high proportion of the contaminants present can access water bodies. Hence, besides the occurrence of antibiotics, cytostatics, and contrast agents in hospital effluents, it is also important to evaluate the risk that their presence may pose to aquatic organisms.

As mentioned previously, contrary to pharmaceuticals used for therapeutic purposes, contrast agents are developed as biologically inactive substances. Taking into account this key characteristic, it might be expected then that these substances exhibit a low ecotoxicity. Steger et al. [85] reported no toxicity of iopromide in

short-term studies to concentrations up to 10 g L^{-1} to any of the aforementioned species nor *Vibrio fischeri*. In chronic experiments, no effect was observed for *Daphnia magna* at concentrations up to 1 g L^{-1}. The authors calculated a PEC/PNEC ratio for iopromide lower than 0.0002, considered as an indication of the extremely low environmental risk associated with its use. In another study, Steger-Harmann et al. [86] further characterized the environmental fate of iopromide and demonstrated that the substance undergoes primary degradation in sewage treatment and the primary product (obtained after release of a propanediol residue) showed an even faster photolysis than the parent compound. The authors performed short-term toxicity tests on the primary degradation product and demonstrated the absence of effects in *Daphnia magna* at concentrations as high as 1 g L^{-1}. The toxicity of the same compound against *Scenedesmus subspicatus* was also assessed and the authors reported just a 2% growth rate reduction after 72 h for an initial dose of 500 mg L^{-1}. The primary product of the degradation of the iopromide was concluded then not to be toxic for any of the tested organisms. The authors explored the toxicity of the amine by-product against *Danio rerio* (zebra fish) in acute toxicity tests over 96 h and demonstrated it was not toxic at concentrations about 100 mg L^{-1}.

On the opposite side of contrast agents, it might be found the cytostatics group. As previously mentioned in Sect. 3, the cytostatics are, in general terms, regarded as very hazardous compounds, since they are designed to kill or to provoke severe damage on cells. These processes may cause as side-effects acute disorders and alterations on normal functions of the organisms exposed to them (endocrine system, immunologic system, etc.). Ecotoxicological studies carried out with cytotoxic substances such as 5-fluorouracil have revealed that the lowest observed-effect concentration (LOEC) in algae and bacterial assays was about 10 μg L^{-1}, close to the concentration found in several sewage effluents [87]. In another example, the LOEC obtained for tamoxifen in freshwater fish was 5.6 μg L^{-1} [88]. This concentration is only onefold higher than those found in wastewaters nowadays (about 0.2 μg L^{-1}) [11, 12, 24]. Recent studies have revealed also that mixtures of cytostatics in hospital samples possess an important toxic effect, even higher than the expected by addition of the toxicity of the individual drugs [42, 89]. Therefore, potential synergy should not be neglected when it comes to toxicity of "cocktails" of drugs in water. Furthermore, several authors have pointed out that some pharmaceutical substances, frequently discharged in hospital effluents, might be assessed in regard to their bioaccumulative potential in the aquatic environment. This is the case of one anticancer drug, tamoxifen, which was included in a list of priority substances by Jean et al. [14] due to strong evidences based on its bioconcentration potential (accumulation of a chemical in an organism when the source of chemical is solely water), consumption data, biodegradability, and excretion factor. These authors pointed out the necessity of measuring accumulated dose levels of some PhACs – including tamoxifen – in species at different trophic levels. Finally, Ferrando-Climent et al. [12] found that ciprofloxacin (cytotoxic antibiotic) and tamoxifen posed a potential hazard to the aquatic environment when they reach surface waters, therefore their presence, control, and removal in

previous stages of the urban systems (hospital effluents and WWTPs) are key to keep them away from the natural environment.

Several studies have evaluated the degree of risk that antibiotics detected in hospital effluents might have for aquatic organisms [7, 56, 80, 90], showing that the potential risk is site-specific and depends of factors such as compound concentration in the effluent, compound toxicity, or a combination of both parameters [90, 91].

Antibiotics were identified as the therapeutic group present in hospital effluents that cause the greatest concern and they were pointed out as the main contributors for the high environmental risk of these effluents [7, 74, 91].

The environmental risk assessment of antibiotics in hospital effluents has been evaluated by calculating the hazard quotient (*HQ*) or risk quotient (*RQ*) for the different antibiotics, as the quotient between the Predicted Environmental Concentration (*PEC*) or the Measured Environmental Concentration (*MEC*) and the Predicted No-Effect Concentration (*PNEC*). When *MEC* values are used, a worst case scenario approach is followed and the highest concentration detected in hospital effluent is used. Normally, three different trophic levels are considered (algae, daphnids, and fish). Algae showed to be the most sensitive species to the toxic effect of antibiotics, nevertheless antibiotics might pose risk to all the trophic levels, representing a threat for the entire aquatic ecosystem [56].

Antibiotics like ofloxacin, clarithromycin, and trimethoprim have been frequently identified as substances with high risk for aquatic organisms ($HQ > 1$) [56, 74, 90] as well as erythromycin, sulfamethoxazole, and ciprofloxacin [7, 57, 80]. In fact, Frédéric and Yves [90] reported *HQ* higher than 1,000 for ofloxacin, trimethoprim, norfloxacin, and sulfapyridine, while Mendoza et al. [74] found *HQ* higher than 10 for ofloxacin, trimethoprim, and clarithromycin in a hospital from Valencia (Spain).

A study conducted in a Brazilian hospital that embraced 21 antibiotics belonging to seven different classes of antibiotics (penicillins, cephalosporins, carbapens, aminoglycosides, macrolides, quinolones, and sulfonamides) showed that 14 antibiotics posed a high environmental risk, 15 a medium environmental risk, and only 2 antibiotics showed a low environmental risk (benzilpenicillin and sulfamethoxazole) [92]. Cephalosporins, macrolides, and trimethoprim were among the antibiotics with high environmental risk. Due to their high potential for environmental risk, it was proposed the inclusion of 6 antibiotics (ciprofloxacin, ofloxacin, sulfamethoxazole, azithromycin, clarithromycin, and metronidazole) in a list of 10 pharmaceuticals identified as potentially dangerous for the aquatic organisms and that should be included in future monitoring programmes to be performed in hospital effluents [56].

Finally, it should be kept in mind that antibiotics appear in the aquatic environment as a mixture, either of different compounds belonging to the same class of antibiotics, acting by similar mechanisms, or of different therapeutic groups, which may have synergic or additive effects, showing higher toxicity than single compounds [56, 80, 92].

5.1 Antibiotic Resistance

Another source of risk of hospital effluent, and related to the occurrence of antibiotics, consists in the potential development and release of antibiotic-resistant bacteria (ARB) and genes (ARG) [93]. Overuse and misuse of antibiotics has led to the emergence of ARB, compromising the effectiveness of antimicrobial therapy since the infectious organisms are becoming resistant to commonly prescribed antibiotics [94]. In fact, emergence and spread of antibiotic resistance bacteria has been classified by the World Health Organization (WHO) as one of the three biggest threats to public health in the twenty-first century [93].

Overall a low elimination of both antibiotics [56, 68] and ARB and ARGs [95–97] is observed in conventional wastewater treatment plants (WWTPs). Therefore, WWTPs constitute a source of these emerging pollutants in the environment, contributing to the spread of antibiotic resistance, which can ultimately be transferred to pathogens of fish and other animals, including humans [98, 99].

As it has been reviewed in this chapter, hospitals are contributing highly to the loads of emerging pollutants including antibiotics, ARB and ARGs in sewer systems and eventually in the environment. Many studies have investigated the presence of this type of contamination in the effluents of hospitals and many ARG or ARB with resistance to several antibiotics have been found in effluents of hospitals in the recent years [68, 84, 100–105]. Many of these studies pinpoint hospital wastewater effluents as hot-spots for antibiotic resistance spread. Antimicrobials in hospitals wastewater (present at higher concentration than in urban wastewater) exert a continuous selective pressure on ARB. Antibiotic residues may also induce bacteria to transfer horizontally antibiotic resistance genes for other community members [58, 106]. Hence it seems that hospital wastewater poses a higher risk for the spread of resistance to specific antibiotic molecules than urban wastewater effluents. However, some other studies showed substantial variability in the total ARG concentrations in samples from different hospitals, being total amount of ARB or/and ARGs higher in residential area samples than in hospital samples [68, 100]. In addition, other authors have evaluated the contribution of untreated hospital wastewater to the dissemination of antibiotic resistance in receiving surface water. This is the case of a particular study in Brazil [100], where hospital wastewater was drained into the municipal wastewater system and further discharged untreated into the river. In this study it was shown that although antibiotic resistance was higher among the hospital wastewater strains than in natural impacted environment, the corresponding genetic profiles of investigated strains did not reveal any genetic similarity.

In the near future, the increasing number of studies monitoring antimicrobial drug usage and resistance will allow to identify trends, to assess environmental risk, to establish a linkage between antimicrobial usage and antimicrobial resistance, and to unravel the pathways involved in the spread of ARGs [98, 107]. This will also help to both assess the human and environment potential risks and to prevent antibiotic resistance evolution. In fact, the use of non-conventional wastewater

technologies in the removal and inactivation of ARGs in hospital wastewater have already been studied by some authors [108, 109]. More research efforts in this line are foreseen since wastewater treatment at the source point for this type of effluents has been highly recommended by some authors [93, 110].

6 Conclusion

Pharmaceutical compounds can pose a serious threat to aquatic environments and hospital wastewater can be considered as a primary source of this pollution as it has been pointed out in this chapter. Usually, hospital wastewater does not undergo any special treatment and is disposed into the urban sewer, where is treated following regular treatment schemes of municipals WWTP. Conventional WWTPs are not designed to efficiently remove most of these compounds and therefore, these substances can finally enter the environment through the discharge of the treated effluents.

While contrast agents are engineered as relatively biologically inactive substances, other pharmaceutical groups such as cytotoxics and antibiotics are specifically designed to provoke severe damages in cells and bacteria.

The discharge in the environment of these substances can therefore provoke a variety of adverse effects in a range of organisms at different trophic levels. In fact, some studies have demonstrated that cytostatics compounds can be toxic at levels close to those found in sewage effluents and that their toxicity increases when they occur in mixtures as a result of the synergistic effect. Antibiotics, present in hospital effluents at very high levels, have an inherent biocide capacity against bacteria, which, due to their adaptation potential, can also develop antibiotic resistance. Therefore, antibiotics is the therapeutic group that provokes the greatest concern among those emerging contaminants considered in this chapter. Antibiotics have demonstrated to pose a high risk to all the trophic levels in aquatic ecosystems and, as in the case of cytostatics, their toxicity can be enhanced in mixtures.

In order to assess the environmental risk that hospital effluents pose, a comprehensive and holistic approach should be adopted, which includes all different relevant substances present in such a complex matrix and that addresses synergistic and antagonistic effects of contaminants mixtures. Special attention should be paid to hospital effluents as a vehicle for the development and spread of antibiotic resistance, an issue of increasing relevance, and concern worldwide.

Hospitals can thus be considered as hot-spots of pollution through their wastewater effluents. The implementation of wastewater treatment plants in hospital facilities can very positively contribute to decrease the discharge of these substances into the sewer and, subsequently, minimize their potential to reach and damage the environment.

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Pharmaceutical Concentrations and Loads in Hospital Effluents: Is a Predictive Model or Direct Measurement the Most Accurate Approach?

Paola Verlicchi

Abstract The pharmaceutical concentration and load in a hospital effluent may be known through the adoption of predictive models based on medicament consumption data or through direct measures. Both methods present strengths and weaknesses and advantages and drawbacks. This chapter presents and compares the predicted and measured concentrations and loads found by different authors for a large number of pharmaceuticals in hospital effluents. It then discusses the main factors influencing the predicted values, as well as those affecting measured ones, and estimates the range of variability of each model parameter (pharmaceutical consumption data, excretion factor, and wastewater volume). It then presents the results of the sensitivity analysis carried out for the predicted concentrations and the uncertainty analysis for measured ones (in the latter case, by evaluating the contribution due to sampling protocol, chemical analysis, and flow rate measurement) and discusses the most critical parameters in both strategies. The study concludes with some recommendations for reducing uncertainties in measured and predicted data, thus improving the accuracy and reliability of the results.

Keywords Consumption data, Measured concentrations, Pharmaceuticals, Predicted concentrations, Uncertainty analysis

Contents

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Abbreviations

HWW	Hospital wastewater
ICM	Iodinated contrast media
MEC	Measured concentration
MEL	Measured load
PEC	Predicted concentration
PEL	Predicted load
PhCs	Pharmaceutical compounds
WWTP	Wastewater treatment plant

1 Introduction

In the last 15 years, increasing attention has been paid to improving knowledge of the pollutant content of hospital effluents in terms of conventional pollutants (namely, COD, BOD_5, suspended solids, nitrogen compounds, and phosphorus compounds) and micropollutants (pharmaceuticals, detergents, disinfectants, heavy metals, microorganisms, and viruses) [1–4] in order to evaluate how to

manage them better [5–7], to test the most adequate treatments [8], and to evaluate the environmental risk posed by the residues of PhCs in hospital effluents [9, 10].

Pharmaceuticals are still unregulated compounds with regard to their occurrence in the aquatic environment (surface and ground water, domestic and hospital wastewater). The European Community has recently set a *watch list* including substances which might be included in the list of priority compounds and therefore subject to regular monitoring [11, 12]. The current list includes 17-α-ethinylestradiol, 17β-estradiol, estron, diclofenac, azithromycin, clarithromycin, and erythromycin. The results collected in ongoing and future investigations will lead to the inclusion or exclusion of these compounds in the priority list as well as new proposals for the watch list.

In the United States, the contaminants which might be included in a national priority list are the antibiotic erythromycin and the estrogens 17α-ethinylestradiol, 17β-estradiol, equilenin, estriol, estrone, mestranol, and norethindrone [13].

In Switzerland, investigations carried out during 2006–2010 led to the so-called Micropoll Strategy and to the definition of a list of priority compounds (including 22 pharmaceuticals and two hormones). The main goal consisted of the reduction of the total micropollutant load released by the largest WWTPs (greater than 100,000 inhabitants). They had to guarantee a reduction of 80% of the influent micropollutant load through upgrade, consisting of the adoption of end-of-pipe treatments (namely, ozonation and powdered activated carbon, PAC) [14].

Hospital effluents are quite often discharged into public sewage and co-treated with urban wastewater. A lively debate is ongoing among scientists regarding the environmental risks posed by this practice [6, 15, 16].

It is well known that a deep and exhaustive knowledge of the PhC content in hospital effluents is necessary to better evaluate the most adequate management and treatment method. Chemical characterization may be carried out by two approaches: direct measurements of their concentrations or the adoption of models to predict them.

Both strategies include advantages and drawbacks and strengths and weaknesses. This chapter presents and discusses models commonly used to predict PhC concentrations and loads in hospital effluents. Based on literature data, predicted and measured concentrations are compared for a wide group of PhCs in hospital effluents and the factors affecting the accuracy and reliability of both predicted and measured concentrations are presented, along with an evaluation of their uncertainty. The chapter concludes with suggestions for reducing uncertainty in direct measures and predictions.

2 Models Proposed for Predicting the Concentration and Load of PhCs in Hospital Effluents

Heberer and Feldmann [17] presented a model for predicting the (weekly) load of active pharmaceutical ingredients based on their consumption amounts and pharmacokinetic data. For each compound the weekly load (kg/week) was estimated by Eq. (1):

$$M_{\text{tot week}} = \sum_{i=1}^{n} a_i \times b_i \times m_i \times s_i \left[\left(1 - R_p\right) + R_p\left(x_p + x_c\right)\right]_i \times 10^{-6} \quad (1)$$

where a_i is the number of the dispensed packages per week for each brand or formulation i,
b_i is the number of units per package for each brand or formulation i,
m_i is the content of each active ingredient per unit (expressed in mg) for each formulation or brand,
s_i is the release rate of active ingredients from the individual formulation or brand i,
R_p is the absorption rate which depends on the mode of application of each brand or formulation i,
x_p is the portion of the active compound excreted as a parent compound after its adsorption, and
x_c is the percentage excreted as conjugate.

As R_p, x_p, and x_c are generally reported as a minimum-maximum range, Eq. (1) is refined in Eqs. (2) and (3):

$$M_{\text{tot week [min]}} = \sum_{i=1}^{n} a_i \times b_i \times m_i \times s_i \left[\left(1 - R_{p\ [\max]}\right) + R_{p\ [\max]}\left(x_{p[\min]} + x_{c[\min]}\right)\right]_i \times 10^{-6} \quad (2)$$

$$M_{\text{tot week[max]}} = \sum_{i=1}^{n} a_i \times b_i \times m_i \times s_i \left[\left(1 - R_{p\ [\min]}\right) + R_{p\ [\min]}\left(x_{p[\max]} + x_{c[\max]}\right)\right]_i \times 10^{-6} \quad (3)$$

and the evaluation leads to a minimum-maximum predicted load of each active ingredient in the investigated effluent.

In their investigations, Feldmann and colleagues [17, 18] compared (minimum and maximum) predicted loads for the selected PhCs (diclofenac, carbamazepine, and metamizole) on the basis of the seven values of measured concentrations $c_{d,i}$ (24-h composite water samples, μg/L) and daily sewage flow rate (L/d) as shown in Eq. (4):

$$M_{\text{meas week}} = \sum_{i=1}^{7} c_{d,i} \times V_{d,i} \times 10^{-9} \tag{4}$$

They defined percentage recovery REC (%) as the ratio between the measured and predicted load on a weekly basis:

$$\text{REC}(\%)_{[\text{min}]} = \frac{M_{\text{meas week}}}{M_{\text{tot week}[\text{max}]}} \times 100 \tag{5}$$

$$\text{REC}(\%)_{[\text{max}]} = \frac{M_{\text{meas week}}}{M_{\text{tot week}[\text{min}]}} \times 100 \tag{6}$$

In 2011, Escher et al. [19] made a first evaluation of predicted PhC concentrations in hospital effluents by adopting a simpler predictive model:

$$\text{PEC}_{\text{HWW}} = \frac{M \times F}{Q_{\text{HWW}}} \tag{7}$$

where M is the amount of active ingredients dispensed within the hospital in the reference period,
F is the excretion factor of the unchanged active ingredient in urine and feces, and
Q_{HWW} is the volume of wastewater produced in the hospital in the same reference period.

M is the sum of all the amounts m_i of active ingredient administered in the different formulations or brands; m_i was obtained on the basis of the number of units U_i for each brand or formulation and the amount of active ingredient in each unit $m_{U,i}$ (Eq. 8):

$$M = \sum_{i=1}^{n} m_i = \sum_{i=1}^{n} U_i m_{U_i} \tag{8}$$

This method was preferred to the previous one and used by other authors, as reported in the following sections.

3 Overview of Studies and Investigations on the PEC and PEL of PhCs in HWW

The main studies dealing with both the predicted concentrations and loads of PhCs in hospital effluents and the measured ones are reported in Table 1, along with their main features. This table also includes studies that critically analyze sampling protocols and provides suggestions for estimating uncertainties in PEC and PEL,

Table 1 Main studies referring to PEC, PEL, MEC, and MEL of pharmaceuticals in hospital effluents

Ref	Main contents
Kümmerer and Helmers [20]	This study deals with measured and predicted concentrations of gadolinium (Gd) in the effluent of the Freiburg University Hospital (1,700 beds). MECs were based on time proportional composite water samples – samples were taken from the main hospital drain every 10 min; 12 mixed samples, each covering an interval of 2 h over a 24 h period, were withdrawn. PECs were based on the annual water consumption within the hospital and downscaling the available national hospital consumption data of Gd (referring to 110,000 beds, which are the beds available in German hospitals) to Freiburg hospital (1,700 beds). An excretion factor of 0.9 was assumed for Gd
Heberer and Feldmann [17]	Authors present a model able to predict the *load* of pharmaceuticals in a hospital effluent, based on consumption and pharmacokinetic data. It was applied to a military hospital in Berlin for diclofenac and carbamazepine. PEL was compared to MEL over a time period of 1 week
Mahnik et al. [21]	This study evaluates the concentrations of selected cytostatics in the sewer system of an oncologic inpatient treatment ward of the Vienna University Hospital (Austria) on the basis of the exact dispensed substances in that ward during the observation period. It then compares them to the concentrations measured during the same period in which the monitored substances were dispensed in the ward
Feldmann et al. [18]	This study applies the model described in Heberer and Feldmann [17] for metamizole to the same military hospital and compares PEL and MEL over a time period of 1 week
Weissbrodt et al. [22]	This study was carried out at one of the 10 largest Swiss hospitals (415 beds) and dealt with an investigation on the occurrence of a selection of common cytostatics and iodinated contrast media (ICM) in the hospital effluent. MELs were based on 24-h flow proportional composite water samples. PELs were assessed from the actual consumption levels over 9 consecutive days. A comparison between MELs and PELs leads the authors to establish the quantity of selected compounds excreted on-site, in the hospital sewer network. Fluctuations of the load emitted for the selected compounds are also reported over the day and the whole investigation period
De Souza et al. [23]	The authors evaluated the environmental risk assessment due to intravenous antibiotics dispensed in the intensive care unit of a hospital in Curitiba (Brazil). In this unit (16 beds), antibiotic consumption amounts to 25% of the total consumption within the hospital (160 beds). The authors also presented consumption fluctuations over a year for the class of antibiotics
Ort et al. [16]	The aim of the study is to accurately evaluate the contribution of the PhC load emitted by an Australian hospital (190 beds) to the load in the corresponding WWTP influent (catchment area of about 45,000 inhabitants) for 59 compounds, using direct measurements. This experimental data, which refers to a limited time period is then compared to readily available audit data in order to evaluate if the same kind of information can be used for other locations to make a prediction, without planning specific monitoring campaigns

(continued)

Table 1 (continued)

Ref	Main contents
Ort et al. [24, 25] Ort and Gujer [26] Lai et al. [27]	The first two studies represent reference papers for evaluating uncertainties in the MECs and MELs of PhCs in wastewater. They discuss potential uncertainties in detail and provide guidelines for the proper selection of sampling frequency and sampling mode in order to reduce them. In particular, Table SI_3A and SI_3B (in the Supplementary Information linked to Ort et al. [24]) estimate the increment in sampling errors due to a sampling mode different from the reference one consisting of flow proportional composite sampling. Ort and Gujer [26] discuss sampling mode to obtain representative micropollutant loads in sewer systems. Finally, an interesting discussion is reported in Lai et al. [27] on how to evaluate and reduce uncertainties in direct measurements and predictions with regard to a selection of PhCs in wastewater
Mullot et al. [28]	The study reports the average MECs for 10 PhCs in the effluent of three French hospitals and the PECs for three PhCs with regard to only one hospital (evaluated on the basis of their corresponding daily – when available – or annual consumption data). It then compares PEC and MEC for these three compounds for 14 days, during three sampling campaigns. The study concludes with a comparison between measured and estimated load for the 10 compounds
Escher et al. [19]	This study consists of an evaluation of PEC and PEL for a wide spectrum of compounds emitted by a cantonal hospital and a psychiatric center in Switzerland in order to evaluate the ecotoxicological potential of the top 100 PhCs administered in the two health-care structures for different scenarios (raw hospital effluent, after dilution in the sewer with the urban effluent, and after a common biological treatment by activated sludge process with and without dilution due to mixing with urban wastewater). They assumed that all PhCs administered in the hospital would also be excreted there
McArdell et al. [29]	The authors carried out a comparison of predicted and measured loads in the effluent of a Swiss hospital (346 beds) with regard to the top 30 PhCs and, in particular, to ICM and cytostatics. An analysis was also carried out for disinfectants and metals consumed within the hospital and detected in the hospital effluent
Le Corre et al. [30]	Prediction of the concentrations of PhCs in a hospital effluent represents the first step in the consumption-based approach which is able (1) to assess the contribution of health-care structures to the WWTP influent load of PhCs and (2) to provide a list of critical compounds through the ratio between effect threshold (ET, depending on the acceptable daily intake of each PhC) and PEC for each compound (the so-called margin of exposure MOE = ET/PEC)
Coutu et al. [31]	The study deals with temporal (monthly) variability in consumption of nine antibiotics in the main hospital in Lausanne. These consumptions were then upscaled to all the hospitals located in Lausanne. PECs were evaluated for both hospital and urban settlement wastewater in order to assess the concentration at the entrance of the WWTP
Helwig et al. [32]	Within the European Pills Project, an analysis of the fluctuations in hospital consumption of selected PhCs was carried out, in particular with regard to weekdays and the weekend in psychiatric facilities and

(continued)

Table 1 (continued)

Ref	Main contents
	radiology departments, as well as the laundry effluent (if present). Moreover, a discussion of the annual PhC consumption in six different hospitals located in different countries is provided, with regard to their type and size
Herrmann et al. [15]	PEC and MEC were evaluated for a selection of six psychiatric drugs dispensed in a psychiatric hospital, a nursing home, and a general hospital in Germany. An analysis of the uncertainty in MECs is presented and discussed
Daouk et al. [33]	The study refers to the characterization of the effluent of the Geneva University Hospitals, in Switzerland, in terms of PEC and MEC for 15 PhCs. MECs were based on 24-h time proportional composite water samples; PECs were based on data regarding the annual consumption of the selected PhCs. Moreover, the daily load was also evaluated. In doing this, HWW flow rate was estimated by means of height measure in the pipe and the Kindsvater-Carter equation
Verlicchi and Zambello [34]	The authors compared PEC and MEC in a hospital effluent for 38 PhCs belonging to 11 different therapeutic classes. MECs are based on time proportional water sampling carried out in two different seasons (summer and winter). PECs are based on yearly consumption. Comparisons are reported with regard to the two seasons and the whole year
Klepiszewski et al. [35]	The authors provide an analysis of the importance of a priori accuracy checks in defining the sampling protocol in a PhC monitoring campaign in a hospital sewer

as well as in MEC and MEL. Compounds included in the current study are compiled in Table 2.

4 Model Parameters

According to Eq. (4), the parameters requested by the predictive model are PhC consumption data, PhC excretion factor and the wastewater volume generated within the health-care structure during the period of interest. Figure 1 shows the parameters necessary for the evaluation of PhC load and concentration (left) and their correlation, as well as the parameters that must be set in the case of direct measurement of PhC concentrations and loads (Fig. 1, right). Sampling mode includes continuous mode and discrete mode (namely, grab samples, composite samples based on time, volume or flow proportional mode).

The following paragraphs include a discussion regarding the parameters necessary to evaluate PEC and PEL.

Table 2 Compounds included in this chapter grouped according to their therapeutic class

Analgesics/anti-inflammatories	Acetaminophen, codeine, dexamethasone, diclofenac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, metamizole
Anesthetic	Propofol, thiopental
Antibiotics	Amoxicillin, azithromycin, cefazolin, chloramphenicol, chlortetracycline, cilastatin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, gatifloxacin, metronidazole, moxifloxacin, norfloxacin, ofloxacin, sulfadiazine, sulfamethoxazole, trimethoprim
Anti-diabetics	Glibenclamide
Antihypertensives	Enalapril, hydrochlorothiazide, lisinopril, valsartan
Antineoplastics or cytostatics	5-Fluorouracil, cyclophosphamide, cisplatin, carboplatin, doxorubicin, oxaliplatin, gemcitabine, ifosfamide, tamoxifen
Beta-agonists	Salbutamol
Beta-blockers	Atenolol, metoprolol, propranolol, sotalol, timolol
Contrast agents	Diatrizoate, iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioxitalamic acid
Diuretics	Furosemide
Hormones	Progesterone
Lipid regulators	Atorvastatin, pravastatin
Psychiatric drugs	Amisulpride, carbamazepine, diazepam, doxepin, fluoxetine, gabapentin, levetiracetam, lorazepam, paroxetine, pregabalin, quetiapine
Rare metals	Gadolinium (Gd), platinum (Pt)
Receptor antagonists	Ranitidine

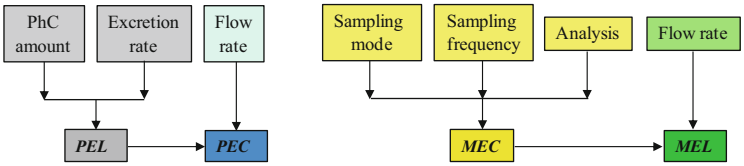

Fig. 1 Main parameters defining predicted and measured concentrations and loads of PhCs

4.1 Consumption Data

The adopted models assume that an even and uniform consumption of each compound occurs over the whole observation period (year, month). Generally, consumption data are available on an annual basis, rarely per quarter, month or shorter periods.

Weissbrodt et al. [22] compared the average estimated consumption of some ICM and cytostatics in a hospital and the exact consumption referred to the observation period of 8 days. They found good agreement for ICM but an overestimation (4.5 times) for cytostatics with respect to the exact consumption. An analysis of the exact daily consumption of ICM highlights that higher consumption occurs on weekdays with respect to the weekend and, on Fridays in particular consumptions are the highest, as the radiology department operates at its highest capacity. During

weekends, only the emergency computer tomography applications are in operation, and the only ICMs used on those days are iomeprol and ioxitalamic acid.

Daouk et al. [33] analyzed the variability of the mean daily loads for a group of PhCs over a week and found that it is in the range of 50–150% of the mean value for compounds widely consumed on a regular basis (namely, acetaminophen, morphine, and ibuprofen). The fluctuations are more pronounced (up to 400%) for less administered PhCs such as diclofenac, mefenamic acid, gabapentin, and carbamazepine. Gadolinium (present in ICM) and platinum (in many cytostatics) exhibited high deviation from the average value during the weekend.

De Souza et al. [23] highlighted that the consumption of PhCs varies among the departments and wards within the structure. They found that in the investigated Brazilian hospital, the intensive care unit contributes more than 25% to the consumption of antibiotics, and monthly fluctuations from the average value are very small and limited to only a few months, whereas fluctuations are more frequent and more pronounced for the whole structure (whose percentage variation varies between −45% and +27%).

Consumption patterns of the different therapeutic classes and of specific compounds have not been thoroughly investigated and results are not always comparable. de Souza et al. [23] reported the profile in terms of the number of units of antibiotics used in the Brazilian hospital and in intensive care units, whereas Coutu et al. [31] reported the monthly fluctuations of antibiotic sales for a hospital normalized to the annual mean.

Analysis of the consumption profiles over the year are available for the group of antibiotics, and for some specific active ingredients, namely, cefazolin and carbamazepine, for some case studies referring to the whole hospital. They are reported in Table 3 as the percentage variation with respect to the monthly average consumption.

Table 3 Percentage variation of the monthly consumption with respect to the average monthly value of some active pharmaceutical ingredients and the whole class of antibiotics

Month	Variation for antibiotics (%)	Variation for carbamazepine (%)	Variation for carbamazepine (%)	Variation for cefazolin (%)
January	3.9	−34	−0.61	−3
February	−12.2	87	−75	24
March	−7.0	−48		26
April	0	−20		−14
May	5.3	14	−66	−16
June	−8.9	−72	−0.61	−3
July	4.4	4	128	30
August	12.8	38	−65	−6
September	16.8	97	38	−36
October	2.7	7	3.53	−3
November	−19.9	−45	38	13
December	2.2	−27		−11
	[36]	[36]	[37]	[37]

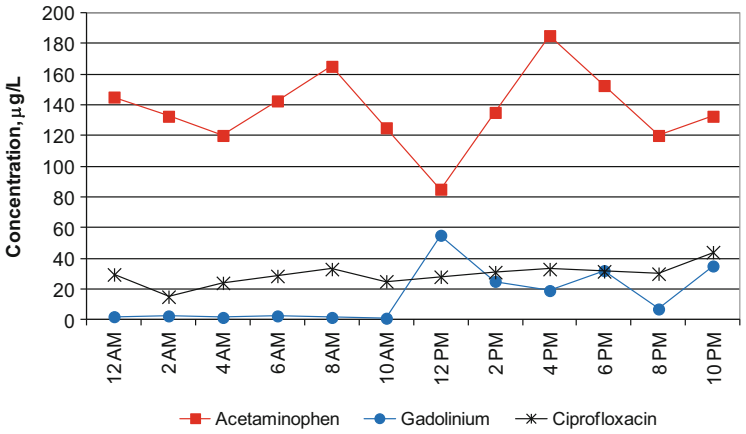

Fig. 2 Hourly fluctuations in concentrations of acetaminophen, gadolinium, and ciprofloxacin in hospital effluents. Data from [20, 39, 40]

Lenz et al. [38] highlighted no consistent difference in the consumption of the cancerostatic platinum compound CPC (namely, cisplatin, carboplatin, oxaliplatin, and 5-fluorouracil) over 18 months.

With regard to consumption in different years, Coutu et al. [31] reported a slight variation for most of the investigated antibiotics, whereas in the analysis carried out by Le Corre et al. [30], based on Australian hospitals, the year-to-year variability amounts from 22 to 44%, depending on the PhCs.

As discussed in Verlicchi and Zambello [34], consumption patterns in healthcare structures differ from those observed in urban settlements. With regard to antibiotics, fluctuations are more evident in urban consumption, with typical seasonal peaks, while in hospitals fluctuations exist, but are less pronounced and in any case, they are site-specific. These considerations lead to the supposition that antibiotic use in hospitals is disconnected from nonhospital use, perhaps due to different protocols and the types of diseases treated with them.

It is difficult yet possible to obtain daily consumption patterns for some compounds. It is important to remember that PhCs are dispensed over the day to patients and the resulting concentration presents fluctuations over the day. Profiles of hourly variation of PhC concentrations (MEC) in a *typical day* are compound-specific and available only for a limited number of active ingredients. Figure 2 reports some of these with regard to hospital effluents. Profiles referring to other substances are reported and discussed in [2].

Weissbrodt et al. [22] report daily profiles for concentrations of some ICM and cytostatics, as well as for hospital effluent flow rates and highlights that the maximum concentrations do not always correspond to maximum load (concentration $\times$ flow rate), and this must be kept in mind in order to have a representative sample in the case of MEC, or to decide when sampling to obtain the maximum occurrence (for environmental risk assessment) or to evaluate the daily load (hourly contributions may differ).

4.2 Excretion Factor

The excreted amount of a specific compound depends on many factors, mainly related to administration routes, human health and metabolism. This is confirmed by the different values reported in literature by many authors for each compound. With regard to the selection of substances considered in this study, the observed ranges are reported in Fig. 3.

In predicting concentrations of PhCs based on their consumption, the assumed value of excretion may greatly influence the resulting concentration, as remarked by Weissbrodt et al. [22]. Suggestions are available in literature – for instance,

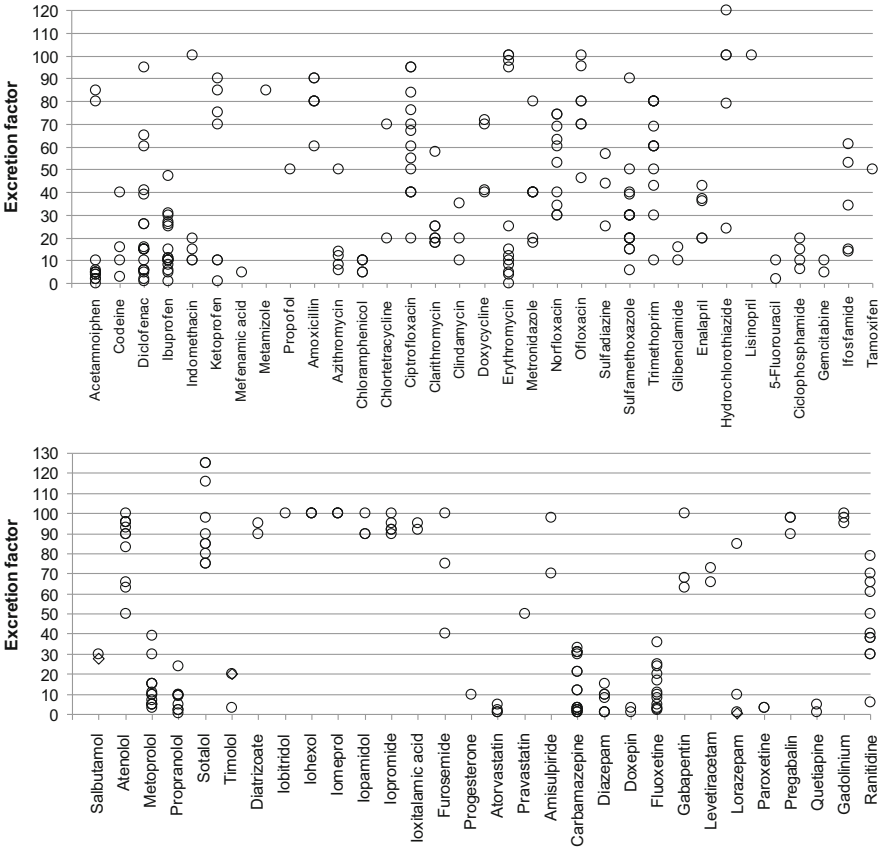

Fig. 3 Range of variability of the excretion factors reported in literature for the selected compounds. Data from: [2, 7, 10, 15, 17, 18, 22, 28, 31–33, 41–52; http://www.bioagrimix.com/hacpp/html/tetracyclines.htm; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC90863; http://www.ncbi.nlm.nih.gov/pubmed/3557734; http://www.medsafe.govt.nz/profs/datasheet/Daoniltab.pdf; http://www.medsafe.govt.nz/profs/datasheet/b/Buventolinhalpwd.htm; http://dmd.aspetjournals.org/content/3/5/361; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1428960/pdf/brjclinpharm00307-0061.pdf; www.torrino.medica.it]

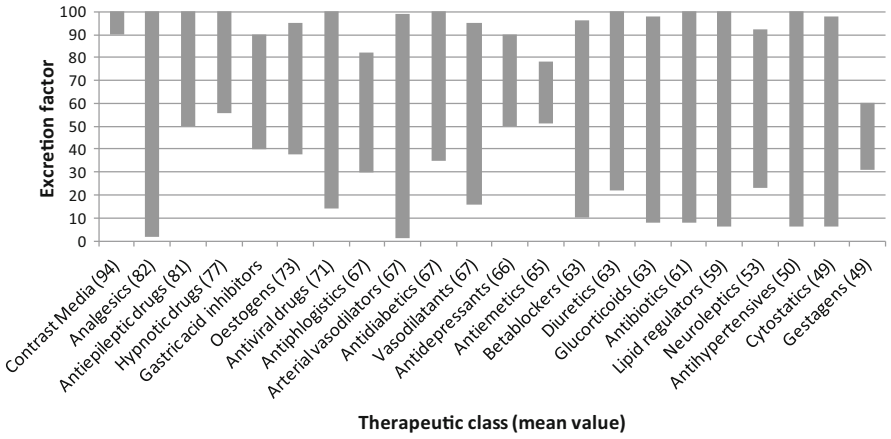

Fig. 4 Range of variability of percentage excretion factors for therapeutic classes. The number in brackets after each compound corresponds to the mean value based on collected data. Data from: [46]

Escher et al. [19] assumed an excretion of 75–100% for active ingredients being used as creams, since wash off from the skin is also a source of water contamination without undergoing metabolism in the human body. Lienert et al. [47] provide rules for evaluating excretion data in case of uncertainties and inconsistencies regarding the fraction excreted via urine and feces. Other researchers used the values they evaluated considering excretion of the parent compound in urine as well as feces, others assumed a literature value, without discussing the criteria used for its selection. In their investigation, Verlicchi and Zambello [34] assumed that the excretion factor was equal to the average value defined on the basis of a collection of literature data, with the intention of accounting for different scenarios in terms of formulation, administration route, metabolism and gender.

Lienert et al. [46] provided an interesting panorama of the variability ranges of excretion factor for some therapeutic classes, as well as the corresponding average values. In Fig. 4 the intervals are reported for 22 groups of compounds and the suggested average value is reported in brackets, after the name of the group.

It is worth noting that there are compounds, such as iodinated contrast media and cytostatics, that are largely excreted by human beings, but they are not completely released into the internal sewer network. In fact, most of them are administered to outpatients, who spend a period of time in hospital which is shorter than the typical excretion time. Weissbrodt et al. [22] found that only 49% for ICM and 5.5% for cytostatics are released in the hospital effluent.

4.3 Flow Rate Prediction

The hospital wastewater flow rate was evaluated based on hospital specific water consumption and hospital size (namely, number of beds) that is the water volume per bed per day. It is known that there is not a clear correlation between hospital size and water consumption [2], and that specific consumption is related to many factors, including water availability and geographical conditions. Values found worldwide are between 200 and 1,200 L/ (bed d), but generally those adopted vary between 400 and 800 L/ (bed d).

Authors have sometimes assumed a fraction of the estimated water consumption, which is generally 0.65–0.85 [53, 54].

Altin et al. [55] estimated water usage amounts for some hospitals in Turkey on the basis of the different kinds of user (personnel, beds, guests, laboratory, laundry and cafeteria). They found that this theoretical value was in good agreement with 80% of the average flow rate consumption resulting from 24-h flow measurements at different times for a medium-size hospital. They remarked that 20% of the consumed water was used for irrigation and cleaning.

In [34], the average daily flow rate results from a mass balance at the investigated hospital, considering water consumption (provided by the internal technical service), inlet contributions due to water bags used in surgery rooms, human excreta due to inpatients, outpatients, staff and visitors and also water losses due to an old water distribution system. The water balance is carried out on an annual basis and, as a consequence, it assumes that every day water consumption and wastewater production follow the same corresponding flow rate pattern.

This may lead to discrepancies with respect to the real wastewater flow rate generated during a specific day in a different period of the year. This concept is clearly shown in the graphs of Fig. 5, which refer to the daily flow rate measured in the Indonesian hospital (538 beds, 1,225 staff) investigated by [56] over three months (March, April and May).

It emerges that the percentage variation compared to the average daily flow rate ranged between −12% and +13%. This could be explained by the fact that during the weekend, laboratory and diagnosis activities and outpatient presence within the hospital are reduced.

Consistent variations were also found with regard to the *monthly* flow rate over the whole year. Figure 6 refers to two medium-size Italian hospitals discussed in [34] where the flow rate was regularly measured and recorded at the end of each month for a whole year. The percentage variation varied between −41% and +72% with respect to the average monthly value. The highest flow values occurred during the hot season. It is also important to observe that although the investigated hospitals had a similar size, the profile of wastewater was different in the two structures.

An analysis of flow rate variation over the year will lead to the definition of an expected range of flow rate variability on an annual basis, for a general hospital. This will be useful in carrying out a sensitivity analysis of the prediction model.

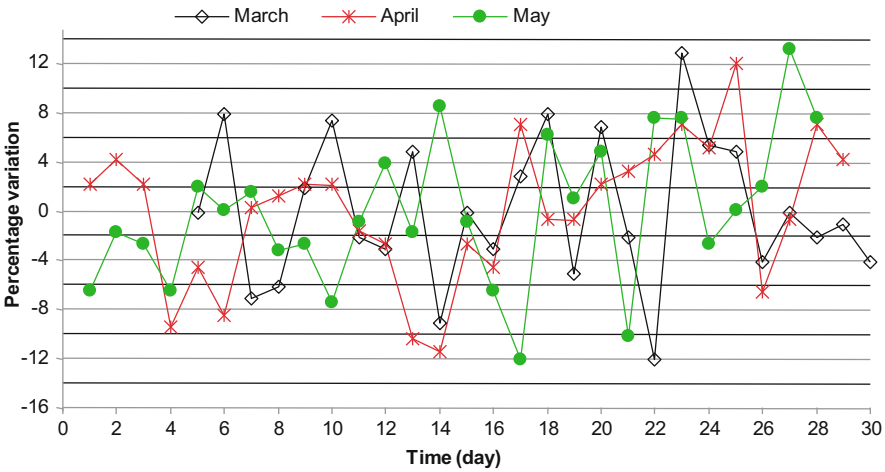

Fig. 5 Percentage variation of the daily flow rate over 3 months in an Indonesian hospital

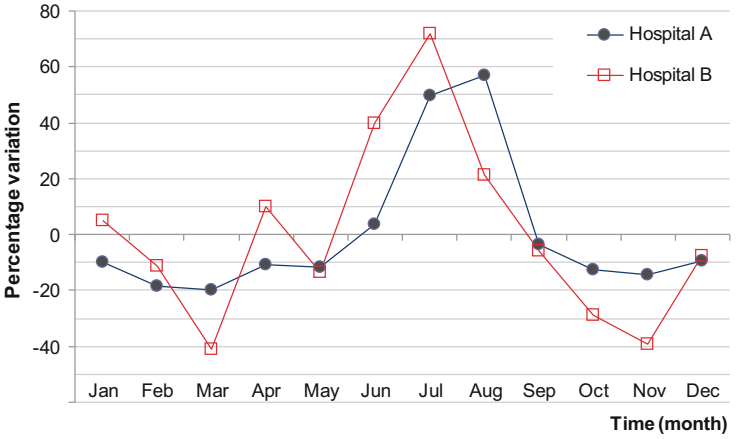

Fig. 6 Percentage variation of the monthly flow rate with respect to the monthly average value in two Italian hospitals: Hospital A: 450 beds, 9,407 m^3/month. Hospital B: 400 beds, 9,960 m^3/month

The analysis of the observed variation of the flow rate concludes with the analysis of the profiles of the percentage variation with respect to the hourly flow rate. Figure 7 refers to three profiles observed in medium-sized hospitals in a *typical day*. In France the hospital has 655 beds and an average hourly flow rate of 27.3 m^3/h [1], in Mauritius the hospital has 535 beds and an average flow rate of 23.3 m^3/h [57] and in Turkey, 324 beds with an average flow rate of 7.8 m^3/h [55].

Due to these *hourly* variations, a (24-h) composite *flow* proportional water sampling mode is preferable with respect to grab samples, as in this way, analysis

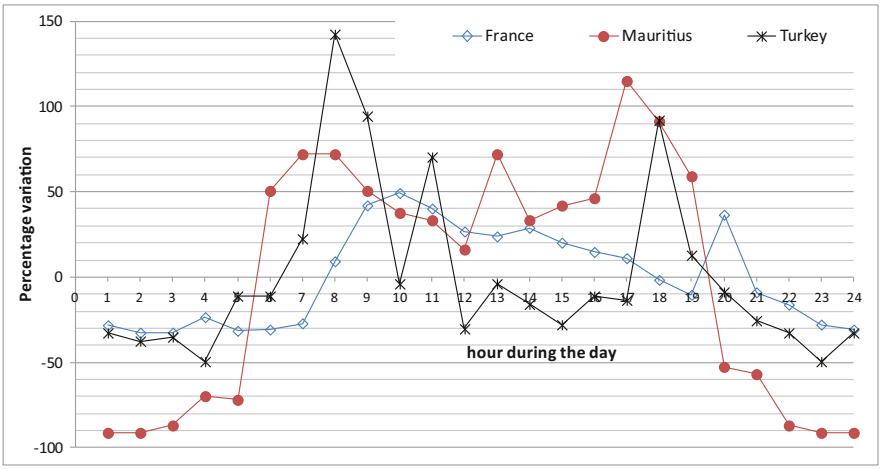

Fig. 7 Percentage variation of the hourly flow rate with respect to the average daily flow rate in three hospitals [1, 55, 57]

of the resulting water samples will weight variations both in occurrence and in flow rate and samples will be more representative of the real conditions (this will result in lower uncertainty, as discussed by [24, 27, 35].

5 Comparison Between Measured and Predicted Concentrations and Loads

Table 1 briefly reports studies and investigations that have dealt with predicted and measured concentrations and loads for a selection of PhCs in hospital effluents. The data discussed in these studies are reported in Fig. 8 in terms of the ratio between PEC and MEC for each compound.

The accuracy evaluation criteria followed in this chapter is that proposed by Ort et al. [58] and already applied in Daouk et al. [33], Verlicchi et al. [51], and Verlicchi and Zambello [34]. It sets that:

- If $0.5 \leq \text{PEC/MEC} \leq 2$, then PEC is acceptable.
- If $\text{PEC/MEC} < 0.5$, then PEC is unacceptably low.
- If $\text{PEC/MEC} > 2$, then PEC is unacceptably high.

As remarked in Verlicchi and Zambello [34], although these criteria are labeled for accuracy evaluation, MECs are not considered a priori more accurate and reliable than PECs, or vice versa, and the criteria are applied to evaluate how different the results of the two approaches are.

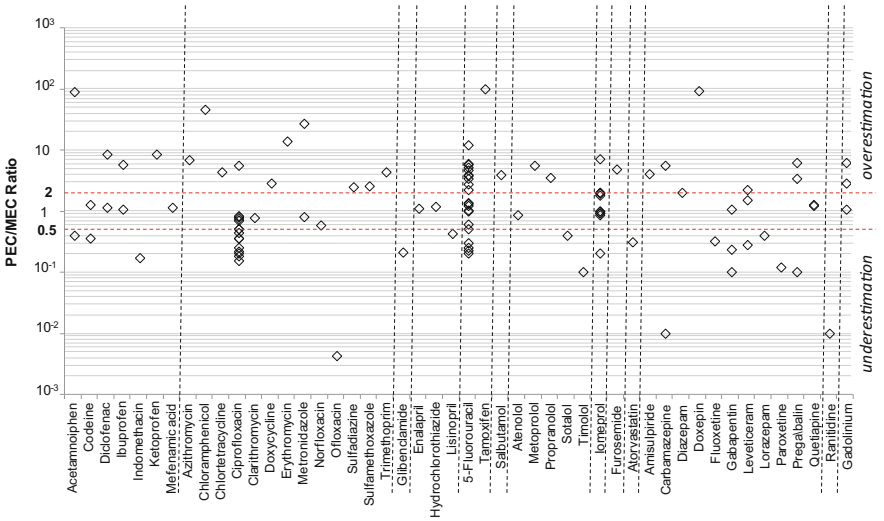

Fig. 8 Ratio between PEC and MEC for a selection of compounds grouped according to their therapeutic class. *Horizontal dotted lines* (corresponding to PEC/MEC equal to 0.5 and 2) define overestimation and underestimation regions as well as good accordance according to the criteria suggested by Ort et al. [58]. Data from: [15, 20, 21, 28, 33, 34]

An analysis of the dispersion of data in Fig. 8 in the three regions defined by the criteria shows that 32% of the data is in the acceptable interval and, for the remaining 64% of data, PEC is too high or too low.

The discussion reported in Sect. 4 regarding the choices necessary in order to define the parameters requested in PEC and PEL model application may be useful in explaining overestimation or underestimation with respect to the direct measures of concentrations. An in-depth analysis of the potential factors influencing the accuracy and reliability of PECs, PELs, MECs, and MELs will be carried out in Sects. 6 and 7.

A good level of accordance was found by [21, 38], who compared PEC and MEC for cytostatics in the effluent of the (only) oncologic inpatient treatment ward of the Vienna University Hospital (18 inpatients), considering minimal excretion rates for the investigated compounds ($E = 0.02$). In particular, Lenz et al. [38] provided MECs and PECs for a group of cytostatics, called cancerostatic platinum compounds (CPCs) including cisplatin, carboplatin, oxaliplatin, and 5-fluorouracil, whereas Mahnik et al. [21] mainly investigated 5-fluorouracil and doxorubicin (an anthracycline). This trend was confirmed by McArdell et al. [29], who compared MEL and PEL for cyclophosphamide in the effluent of the oncologic ward of a 346-bed hospital in Baden, Switzerland.

The same authors [29] investigated predicted and measured loads of a wider spectrum of compounds (the top 11 dispensed in the hospital in Baden) and also found good accordance for ICM in the effluent of the radiologic ward; for many of the most administered active ingredients, they found a ratio PEL/MEL of about

0.33. The loads of valsartan measured were 6 times higher than predicted, which was justified by the fact that other angiotensin receptor blockers may transform to valsartan and contribute to the load being higher than expected. Seasonal variations could also account for higher loads (predictions were based on annual consumption data of PhCs). PELs which were significantly higher than corresponding MELs were found for azithromycin (23 times), cilastatin (25 times), cyclophosphamide (7 times), dexamethasone (14 times) diclofenac (6 times), erythromycin (28 times), and thiopental (41 times). These discrepancies could be due to the fact that annual consumption figures are not representative for the measurement period (summer), as a seasonal fluctuation is expected for most of them.

With regard to cytostatics and ICM, consistent discrepancies were found between measured and predicted values by Weissbrodt et al. [22] who compared PEL and MEL in the effluent of a medium-sized hospital. These differences can be attributed to the fact that most of these compounds are administered to outpatients (70% for cytostatics and 50% for ICM) and therefore only a part of the dispensed amount is excreted within the hospital. Predicted values were in general much higher than measured ones.

Mullot et al. [28] compared MEL and PEL for a selection of compounds in three different French hospitals and found that the ratio between the average values of measured and predicted load was in the range 0.7–1.1 for atenolol, sulfamethoxazole, ciprofloxacin, 5-fluorouracil, and ketoprofen. For cyclophosphamide, the ratio was 0.67 and for propofol it was equal to 0.12.

The authors recognize that the evaluation of this ratio minimizes the fluctuations. In fact, if it is evaluated for a specific hospital, it varies in a wider range – for ifosfamide it becomes 0.30 and for iobitridol 2.1.

Ort et al. [24] remarked that pollutant loads are in general underestimated when flow and concentrations are positively correlated.

Discussion regarding discrepancies between predictions and direct measurements of PhC concentrations and loads has to consider different factors, depending both on the compound itself and the investigated point.

According to Mullot et al. [28], a strong correlation exists for PEC and MEC mainly for those compounds with short elimination half-lives and a weak human metabolism. For other PhCs, prediction of concentrations should also consider various parameters, including outpatient use, pharmacokinetic data, and molecule stability in wastewater.

The prevailing opinion is that predictive models could be extremely useful tools, but intrinsic uncertainties are unavoidable due to the necessary adoption of default or literature values, which should be carefully evaluated case by case in order to reduce the inaccuracy of the estimation. Direct measurements provide a snapshot of a particular situation and time of occurrence and load of PhCs. The main problem consists of evaluating how representative of the situation and time these values could be. As many factors affect PEC and MEC and PEL and MEL, an in-depth analysis was carried out discussing the specific characteristics.

6 Potential Factors Influencing PEC and PEL

6.1 Inaccurate Estimation of PhC Consumption Within the Hospital

PEC values are estimated on the basis of (annual) PhC consumption. This datum generally contains all the PhCs dispensed by the hospital structure to inpatients and outpatients.

In predicting PhC concentrations, the following factors should be kept in mind:

- PEC corresponds to an average value based on consumption and does not consider potential fluctuations of patients treated in the hospital over the year.
- Drug packages may not be completely consumed (and only occasionally packages may be returned to the hospital pharmacy in the case of discharged or deceased patients).
- Inpatients may take their usual medicaments with them from home to the hospital when they are hospitalized. Therefore, these compounds are not considered in the hospital consumption data.
- Day-hospital patients staying in the hospital for only a few hours a day for analyses or therapy requiring specific agents, such as cytostatics, or diagnosis agents or outpatients do not totally excrete the administered compounds in the structure [19, 22, 28]. Escher et al. [19] underlined that a large quantity of PhCs are consumed within the hospital but excreted at home by outpatients. They stated that it is difficult to estimate the fraction released into the internal sewage. Weissbrodt et al. [22] found that only 49% of ICM and not more than 5.5% of cytostatics were excreted there, the remaining percentage was carried home.

  With regard to the effluent of the oncological ward investigated by Lenz et al. [38], it was found that only 27–34% of the total administered platinum (occurring in the dispensed cancerostatic platinum compounds CPC: cisplatin, carboplatin, and oxaliplatin), is excreted in the internal sewage network which can be explained by the short length of time spent in hospital in comparison to the biological half-life of CPC. Lower still is the percentage of the administered amount of 5-fluorouracil (0.5–4.5%) and doxorubicin (0.1–0.2%) released in the structure:
- Lack of patient compliance may be of great importance – Bianchi et al. [59] found that for antipsychotics the mean adherence to therapy was 64%.
- In addition, the hospital pharmacy provides PhCs to discharged patients or outpatients for starting or continuing their treatment at home. This is the case, for instance, for antineoplastics and psychiatric drugs [2, 59]. These substances are neither administered nor excreted in the hospital. Antivirals may be prescribed and delivered in the hospital but are likely to be excreted at home by outpatients [33].
- Where laundry is an internal service, it is in operation during the week and on Saturday morning, not on Sundays. This could lead to higher concentrations of

PhCs as laundry water consumption was estimated to be around 33% of the entire hospital consumption [60].

- Finally, pharmacy consumption data may differ from real consumption data due to lack of patient compliance, as well as due to outside consumption for leaving patients [61].

6.2 Variation in Consumption Over the Year

As highlighted in Sect. 4.1, there are classes of compounds with seasonal variability in consumption (for instance antibiotics), whereas for other classes fluctuations are not pronounced. Consumption data referring to the whole year does not provide information about the real consumption pattern. PEC and PEL will provide an average value on an annual basis.

6.3 Differences Between Pharmacy Consumption Data and Effective Administration

It should be noted that the consumption data in the hospital database correspond to the amounts supplied by the pharmacy to individual wards and not to the amounts effectively administered within each ward or department. Some unused drugs for inpatients may be collected on the wards and returned to the pharmacy for reuse or proper disposal. It is generally not hospital policy to discard drugs in the (solid or liquid) waste system, both for financial and environmental reasons. Hence, these drugs do not contribute to the load in the hospital effluent. Ort et al. [16] remarked that these amounts are generally very limited. Moreover, there could be a lag time between delivery to the ward and actual consumption.

6.4 Inaccuracy in the Excretion Factor Assumed for the Evaluation of PEC

The excretion factor varies according to the kind of formulation, as well as characteristics of the individual who assumed the PhC. The estimated value should consider the excretion data of a large set of individuals as the variations of a small number of patients are not significant.

As discussed in Sect. 4.2, for a given active ingredient, literature quite often provides ranges of excretion factors, resulting from different studies and investigations, showing the minimum-maximum observed range. In many cases, excretion factors refer to investigations carried out some decades ago [7, 45] and do not

consider that new generation PhCs (i.e., gatifloxacin and moxifloxacin) are designed to provide better therapeutic effects, improving the human absorption rate and, at the same time, reducing the excretion rate [62].

It is questionable whether it is still correct, from a scientific view point, to assume existing (and old) literature data for these compounds. This could lead to an overestimation of the predicted concentrations.

When adopting the excretion rate for a given compound, particular attention must be paid to the correct value as it may refer to the unchanged compound or to the corresponding metabolites [47]. If both are considered for the evaluation of the predicted concentrations, an overestimation will occur. Moreover, attention is required regarding the application mode of the active pharmaceutical ingredient, resulting in different excretion rates [17, 19].

In addition, another difficulty is to accurately evaluate the fraction of the sorbed drug which is eliminated unchanged during each of the subsequent days [28]. However, their selected PhCs are mainly polar and not subject to a significant adsorption on suspended matter.

Le Corre et al. [30] suggested considering the total excretion of each PhC to counterbalance other uncontrolled parameters (i.e., improper disposal or unused PhCs). In this way there could only be an overestimation and false negative results would be prevented.

With regard to application mode, Heberer and Feldmann [17] identified dermal application as the main source for the occurrence of diclofenac residues in the hospital effluent, as a low absorption rate is reported for this type of application. For this reason, high excretion values (75–100%) are generally recommended for creams and ointments but, paradoxically, this assumption could also lead to a high level of inaccuracy. A low recovery of these active ingredients could be found as they may be absorbed by clothes or bandages. If a laundry is present within the hospital, part of these compounds might be found in its effluent. If the laundry is not present, this contribution will not be accounted for.

A proper assumption of excretion factor should weigh the administered amount of each active ingredient by considering the contributions of application mode of the different formulations containing the same pharmaceutical.

6.5 Wastewater Flow Variations

The hospital effluent flow rate is often assumed equal to hospital water consumption [19, 33], sometimes as a fraction of water consumption: 65–85% [53], 75% [54], and 80% [55]. Verlicchi and Zambello [34] evaluated the hospital wastewater flow rate on the basis of a water balance at the investigated structure, taking into consideration potable water consumption and the contributions due to water bags used in surgery rooms, wastewater produced by staff, inpatients, outpatients and visitors, as well as estimated losses due to leakage in the old water distribution system within the structure. As discussed in Sect. 4.1, this flow rate presents hourly,

daily, and monthly fluctuations. Uncertainties in the estimation of flow rate may greatly affect the predictions. Moreover, it is important to consider that PEL is strictly correlated to flow rate as well as the dispensed amount of the selected PhC in the same period, and uncertainties depend on both factors, as discussed later.

6.6 *Improper Disposal of Unused Medicines (in Household Waste or via the Toilet)*

Improper disposal of unused medicines, i.e., by flushing them down the toilet or throwing them out with the household waste rather than returning them to the internal pharmacy will also affect prediction accuracy [34]. In the case of a hospital, this factor could be of minor importance compared to investigations carried out for urban wastewater, as the disposal of medicaments is managed by the personnel of the structure, who should return the waste PhCs to an authorized supplier or reverse distributor.

For registered entities such as hospitals, there are no clear guidelines for the disposal of PhCs in the USA [63], but any such disposal must be done in accordance with local environmental regulations. Usually, the US Drug Enforcement Administration (DEA) may dispose of controlled substances by returning them to the manufacturer, by transferring them to a reverse distributor, or by destroying them using a procedure specified by federal regulation (to date, no such procedures exist). Authors remarked that liquids are more frequently discharged than those dispensed in tablet form. In particular, they found that 50% of dispensed acetaminophen and codeine were wasted in the analyzed academic center hospital.

6.7 *Biodegradation/Biotransformation or Adsorption Processes Occurring in the Sewage System Before the Sampling Point*

Within the internal sewer system, PhCs occurring in the wastewater may be subjected to a biodegradation process, as remarked by Weissbrodt et al. [22] with regard to cytostatics.

According to Lai et al. [27] the effect of biodegradation should be considered more or less constant within a given sewer system and over a short sampling period (i.e., days) and that inter-day variability should be negligible. This may not hold true when data among different locations or within a location over a longer time span (i.e., year, seasonal effects) are compared.

Compounds with a high sorption potential, like azithromycin, may be affected by desorption processes as they may sorb onto sludge and particles present in the

sewer and can also be released at a later time depending on environmental conditions [51].

7 Factors Affecting MEC and MEL

7.1 Sampling Protocols

A PhC mainly reaches the internal hospital sewer through toilet flushes. Not all the toilet flushes may contain the dispensed active ingredients. This depends on the human metabolism and, in particular, on the half-life of the compound. It could be assumed that in a day there are 5 toilet flushes for each individual staying within the structure all day. Real short-term variations, expected and observed in a sewer, will depend on the total number of toilet flushes containing the compound of interest discharging into the sewage network. As a consequence, the occurrence of PhCs may vary greatly throughout the day, exhibiting the so-called short-term variations, and therefore it is crucial to plan and adopt a proper sampling protocol, namely, sampling frequency and mode, which is able to provide *representative* wastewater samples for the specific compound [24, 64].

Researchers may choose between different sampling *modes*: they may collect grab samples from one side and time, flow, or volume proportional composite water samples from the other side. Generally, automatic sampler devices are used to collect a number of discrete samples over a 24 h period. According to Ort et al. [24] the continuous flow proportional sampling mode is the most accurate (true and precise) sampling mode for loads of dissolved compounds.

Depending on the dynamic of a PhC in the sewer, the adoption of a specific sampling protocol will lead to different levels of uncertainty. In the study by Ort et al. [24], an in-depth analysis and comparison of the resulting sampling uncertainties are carried out with regard to three active ingredients presenting very different behavior: ranitidine, carbamazepine, and iopromide. The main results are that sampling errors increase with a decreasing number of wastewater pulses per day (i.e., toilet flushes containing the specific compound under study) containing the compound of interest and also with decreasing sampling frequency.

Selection of the most appropriate sampling *frequency* is discussed in Ort and Gujer [26] in order to contain sampling errors. Moreover, in Ort et al. [24, 25] a method for evaluating sampling uncertainties is presented through the discussion of some case studies, referring to compounds of different behavior (gadolinium, ranitidine, iopromide, and carbamazepine). The method is based on sewer type (gravity or pressurized, separate, or combined) and wastewater packets of the compound of interest. The latter parameter considers the number of total pulses reaching the sewer based on the PhC administered amount and daily defined dose and total number of toilet flushes. Examples of applications of this theory are available in [34, 51, 65, 66].

Suggestions for the selection of an accurate sampling protocol resulting in representative water samples and "quite accurate" MECs are provided in [24, 25].

When sampling we can find real variation (due to the pattern consumption of PPCPs) and additional variation due to analytical error (including transport preservation, storage, preparation, and instrumental errors). This uncertainty may become a dominant source of error if not managed.

A continuous flow proportional sampling mode is conceptually the most accurate (true and precise) sampling mode when sampling for loads of dissolved compounds [16, 24]. However, it is not always economically and technically sustainable. It is sometimes recommended to plan sampling periods over several weeks, as done in [17, 21].

To reduce the uncertainties, a precautionary high sampling frequency (<5 min) is recommended by Ort et al. [24, 25] if the dynamics for the substances of interest are not well known or not properly assessed, or to take into account different composite sampling modes, considering that the choice is highly dependent on the site-specific boundary conditions.

For the compounds that have great variation throughout the year, it is very important to decide the most adequate sampling campaign. Measuring only in one season may imply an over- or underestimation of the yearly load. In calculating PEC, the consumption should be considered on a monthly basis for compounds that have a strong seasonal variation.

For estimating the environmental risk posed by PhCs in water, a grab sample in the hour of maximum discharge may be a better choice, since acute toxicological aspects are not only related to the load and even the maximum concentration must be considered. Ort et al. [24, 25] have discussed the main aspects to be considered to ensure the reliability of the measured data and reduce relative uncertainty.

7.2 Analytical Errors

Instrumental and human errors should be considered when calculating the uncertainties related to chemical analysis. These kinds of errors may cause high uncertainties, especially for those compounds detected at very low concentrations (some ng/L) [34, 51]. Johnson et al. [64] measured different subsamples of the same sample in different laboratories, reporting that the PhC concentrations did not guarantee accurate results with these compounds as the standard deviation ranged up to 60%.

With regard to analytical methods, it should be underlined that they only analyze the compound dissolved in the water phase. For the compounds with high sorption potential, a fraction might have sorbed to suspended solids phase and consequently is not analyzed in the water samples.

7.3 Sewer Layout and Fluctuation of the Concentration Throughout the Day and the Week

In planning a monitoring campaign, it is essential to obtain data on the sewer type and layout (gravity or in pressure, combined or separate, potential infiltration contributions, network framework) and also to be aware of the potential fluctuations of the different PhCs throughout the day [24, 25]. In fact, for some compounds (namely, Gd, contract media, cytostatics, and Pt), MECs remain quite low during the night and exhibit several peaks in the morning as well as in the afternoon, following different consumption and excretion patterns [20, 22]. Interesting analyses are reported in [21] with regard to the dynamic of concentrations of 5-fluorouracil in a week, [28] referring to iomeprol, 5-fluorouracil, and ciprofloxacin over 14 days, and [22] with regard to ICM and cytostatics over the day and a week.

These discrepancies with respect to the corresponding daily average value confirm that analytical investigations on PhCs must be performed on 24-h composite water samples in order to measure the average concentrations for the different compounds which would better represent the potential impact of the hospital wastewater [2].

7.4 Flow Rate Measurement

In order to estimate hospital flow rate, Daouk et al. [33] measured the water height in the sewer pipe (by means of a sharp-crested rectangular weir and an ultrasonic flow meter device upstream of the weir) every 2 min (accuracy checking every 2 weeks) and evaluated flow rate on the basis of the Kindsvater-Carter equation [67]:

$$Q = C_e \frac{2}{3} \sqrt{2g} b_e (h_e)^{1,5} \tag{9}$$

where Q is the discharge (m^3/s), C_e the discharge coefficient ($m^{0.5}/s$), g is the gravity acceleration (m/s^2), b_e is the effective width (m), and h_e is the effective height (m).

Heberer and Feldmann [17] continuously measured flow rate using a flow meter device calibrated with a magnetic inductive flow meter. Weissbrodt et al. [22] and Ort et al. [16] routinely measured the flow rate at a high temporal resolution during the test phase. Verlicchi and Zambello [34] instead evaluated the daily flow rate by means of a mass balance, as described in Sect. 6.5.

7.5 Degradation Processes During Sampling and Transportation

As highlighted in Sect. 6.7, biodegradation and biotransformation may occur within the discharge point and the sampling point, as well as during the transportation of the withdrawn samples. In the latter case there could also be photodegradation processes leading to a lower MEC.

8 Uncertainties in Predicted and Measured Concentrations and Loads

Both predicted and measured concentrations and loads are affected by unavoidable uncertainties due to intrinsic fluctuations of the parameters discussed above (Sects. 6 and 7).

8.1 Uncertainties in Concentration and Load Predictions

The magnitude of uncertainty in PEL and PEC was determined by literature (excretion factor), by internal staff (flow rate), or a combination of both approaches (PhC consumption).

Uncertainty in flow rate – Lai et al. [27] assumed a conservative uncertainty estimate equal to ±20% in the case of a gravity sewer network, appearing reasonable on the basis of other studies (among them [68]).

Verlicchi and Zambello [34] assumed a wider range of variability for the hospital flow rate (between −51% and +81%) resulting from literature data (regarding specific hospital flow rates in two medium-size hospitals and throughout the year, as well as weekdays and weekends).

Uncertainty in excretion factor – The assumed uncertainty is compound-specific and very different ranges were found for different PhCs, as remarked by Herrmann et al. [15] who set ±100% for doxepin and quetiapine and ±4% for pregabalin and Verlicchi and Zambello [34] who considered 38 compounds belonging to different therapeutic classes. The ranges they reported are extremely different, starting from ±3% for salbutamol and arriving at ±99 for lorazepam.

Uncertainty in PhC consumption – Verlicchi and Zambello [34] found a modest uncertainty for analgesics and anti-inflammatories (±15%), a slightly higher uncertainty for antibiotics (−36 to +30%), and much higher uncertainty for carbamazepine (−75 to +120%). For compounds whose fluctuations were not clear, a default uncertainty range was assumed equal to ±50%.

With regard to the neurological drugs investigated by Herrmann et al. [15] in psychiatric hospitals and nursing homes, very different uncertainty ranges were

found for the same compound in different structures. This underlines the importance of carrying out site-specific studies and being careful when considering results obtained in other investigations or referring to different health-care structures to be valid.

On the basis of the reported sensitivity analysis of adopted models for PEC and PEL, it emerges that E always has a great influence on PEC and PEL values for most compounds. In addition, in Verlicchi and Zambello [34], wastewater flow rate has a more consistent influence than drug consumption, whereas in Herrmann et al. [15] the consumption amount highly influences the results. Unfortunately, consumption patterns are scarce and only available for a few compounds, mainly antibiotics and carbamazepine. This underlines the need for further investigations to improve knowledge of consumption trends in hospitals over the year and to better evaluate the influence of PhC consumption on PEC uncertainty.

8.2 Uncertainties in Concentration and Load Measurements

The evaluation of the total uncertainty in MELs and MECs is carried out using Eq. (9):

$$U_{\text{total}} = \sqrt{U^2_{\text{Sampling}} + U^2_{\text{Analysis}} + U^2_{\text{Flow rate}}} \tag{10}$$

which considers the contributions due to sampling, chemical analysis and flow rate measurement (the latter parameter has to be considered only for uncertainty in MEL, as remarked in Fig. 1).

Sampling Uncertainties These are often correlated with toilet flushes and the adopted average sampling interval as suggested by [24, 25]. To have an idea of how toilet flushes may influence sampling uncertainty, the evaluation made by Weissbrodt et al. [22] in the case of an average sampling interval of 8 min and different toilet flushes could be useful:

- In the case of 1 or 2 toilet flushes (this is the case of a patient who received the treatment in the hospital and then excreted part of the administered PhC also at home), a sampling uncertainty between −100% and +130% was evaluated.
- For 18 flushes (corresponding to 2–5 patients per day with 4.5 toilet flushes per patient) the sampling uncertainty is ±50%.
- In the case of 50 toilet flushes, the uncertainty reduces to ±30%.

A continuous flow proportional sampling will result in the lowest uncertainty interval (theoretically equal to 0%). Kovalova et al. [69] adopted continuous flow proportional sampling and sampling was synchronized with the real-time potable water consumption at the investigated hospital and assumed U_{sampling} equal to

0. Although Lai et al. [27] adopted a continuous flow proportional mode for their 24-h composite wastewater samples, they assumed an uncertainty of 5% to account for unknown or unforeseen uncertainties.

This sampling protocol is time and money consuming. Different sampling modes (time proportional and grab samples) as well as frequency (discrete samples over a day) may be selected, but the associated sampling uncertainties may consistently increase. An estimation of the increment in the uncertainty ranges is provided in the supplementary data by [24].

Weissbrodt et al. [22] adopted a flow proportional composite water sampling mode and estimated a sampling uncertainty equal to 30–40% for the most administered ICMs (iomeprol, iohexol and ioxitalamic acid) and between 120 and 130% for the investigated cytostatics 5-fluorouracil and gemcitabine. This higher value was explained by the authors with the fact that there is a high chance that toilet flushes containing cytostatics are missed during the sampling.

The sampling uncertainty evaluated by Verlicchi and Zambello [34] in their investigations based on 24-h time proportional hospital effluent sampling varies from 25% to over 100%, depending on the compound (its related consumption amount and expected toilet flushes).

Chemical Analysis Uncertainty due to chemical analysis was estimated from the relative recoveries, intraday instrumental precision, and other uncertainty factors (see Eq. 11), as discussed in [27, 51, 65, 69].

$$U_{\text{Analysis}} = \sqrt{U^2_{\text{recovery}} + U^2_{\text{precision}} + U^2_{\text{other}}} \tag{11}$$

In the investigations by Ort et al. [16] uncertainties due to analysis were estimated equal to 20% for all compounds, in Herrmann et al. [15] U_{Analysis} was evaluated between 5 and 24% for neurological drugs, and in Verlicchi and Zambello [34], it varied between 4 and 16% for all 38 compounds. In Kovalova et al. [69] for 35% of the investigated compounds it was estimated less than 14%, for 32% between 15 and 29%, for 25% between 30 and 100%, and for the remaining 7% greater than 100%.

Uncertainty in Flow Rate Flows in completely filled pressurized pipes may be measured in more accurate way than flows in a gravity sewer. Ort et al. [16] assumed an uncertainty for flow rate measurement of 6% in the case of pressurized pipes, whereas Lai et al. [27] assumed a conservative uncertainty estimate equal to 20%, appearing reasonable on the basis of other studies (i.e., [68]) and considering the gravity flow.

More accurate evaluations were carried out by Daouk et al. [33], whose measurement methods were described in Sect. 7.4 and who assumed an uncertainty equal to 5%.

Le Corre et al. [30] assumed an uncertainty of 50% to account for the seasonal or day-to-day variability of dry weather wastewater volumes and flow measurement

errors. Herrmann et al. [15] evaluated a maximum uncertainty interval in flow rate equal to −19% and +14%. Finally, Verlicchi and Zambello [34] assume a wider range of variability for the hospital flow rate (between −51% and +81%) resulting from literature data (regarding specific hospital flow rates in two medium-size hospitals and throughout the year as well as on weekdays and at the weekend).

An analysis of the different contributes appearing in Eq. (9) highlights that the parameter which contributes the most to the total uncertainty for MEC is the sampling mode, with only a few exceptions. If a flow proportional sampling mode was adopted, the sampling uncertainty would be at the most 25–30% for pharmaceuticals with more than 50 pulses per day. For those with around only 10 pulses per day, the sampling uncertainty would be around 75%.

9 Conclusions and Perspectives

The analysis carried out above has highlighted that each strategy (prediction models and direct measurements) presents strengths and weaknesses. The advantage of one approach is often the disadvantage of the other, so it is recommended to use them both in a complementary manner.

The use of PECs is advised to reduce the cost of sampling campaigns, which are however necessary when greater precision is required. The predicted approach can be used with some confidence for substances where no analytical method exists to experimentally determine concentrations and loads or where the limit of quantification is not low enough [24], in situations where it would be hard to sample wastewater due to complex and inaccessible sewer systems around the hospital, and, finally, in cases where the collection of representative samples is impossible [24, 30].

The PEC approach could be useful in the phase of identifying priority compounds and during an initial attempt to assess environmental risk with regard to the effluent of the whole health-care structure or of a specific wing [23]. It is worth noting that predicted data do not identify strong fluctuations and, instead, result in average values [32].

Only predicted models could be used to assess new marketed PhCs, whereas MECs can only be used for the risk management of substances that are already marketed. For estimating environmental risk, a grab sample in the hour of maximum discharge may be a better choice, as acute toxicological aspects are not only related to load, and even the maximum concentration must be considered.

To sum up, citing the words by [70], it should be noted that:

- Great efforts have been made in assessing the occurrence of PhCs in hospital effluents (*known known*).
- More needs to be done (*unknown known*), as for some compounds analytical methods are not yet available or not yet validated.
- Future efforts are required to improve our knowledge (*unknown unknown*).

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Contribution of Hospital Effluents to the Load of Micropollutants in WWTP Influents

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Abstract Hospital effluents cause growing interest, as they may be an important contamination source of micro- and macropollutants to WWTP influents. These effluents are usually characterised by higher concentrations and greater diversity of pollutants compared to urban wastewater. However, in certain cases, hospital effluents may represent only a small fraction of the total WWTP influent. Several recent studies report that their contribution to WWTP influents is limited and they are only one of the important sources of micropollutants in the environment. Nevertheless, specific micropollutants may exhibit relatively high hospital contribution, which may cause environmental risks. Several other important sources of micropollutants (chronic medication, nursing home, outpatients, cattle, etc.) are released in urban wastewaters. These sources should not be neglected, because they represent an important load that may impact aquatic environments.

Actual loads and characteristics of hospital effluents remain difficult to determine, as they strongly depend on several factors such as the characteristics of the hospital, regional and seasonal variations, variety of molecules and metabolites, load estimation uncertainties and others.

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The SIPIBEL observatory enables an unique comparison of hospital and urban untreated and treated effluents, due to parallel processing. Monitoring data obtained over the years demonstrated that despite higher concentrations, the hospital contribution to the total load of contaminants is lower than the urban one, considering both wastewaters and treated effluents. However, specific releases from healthcare facilities deserve attention and require awareness of stakeholders to determine strategies and regulations adapted to protect environmental and human health.

Keywords Aquatic pollutants, Hospital contribution, Hospital wastewater, Micropollutants, Pharmaceuticals, Urban wastewater, WWTP

Contents

Abbreviations

HC	Hospital contribution
HTE	Hospital treated effluent
HWW	Hospital wastewater
ICM	Iodinated contrast media
LOQ	Limit of quantification
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCA	Principal component analysis
UC	Urban contribution
UTE	Urban treated effluent
UWW	Urban wastewater
WWTP	Wastewater treatment plant

1 Introduction

In the last decades, hospital wastewater (HWW) has been receiving an increasing amount of attention, although it generally presents a small fraction (less than 10%) of the total volume in the WWTP influent [1]. HWW is composed of the effluents of all hospital activities both medical (operations, emergency and first aid, laboratories, diagnosis, radiology, etc.) and non-medical (toilets, kitchens, laundry activities, etc.) [2]. Specific medical discharges are produced by healthcare, analysis and research activities. Therefore, HWW has particular composition that may be very different from conventional urban wastewaters (UWW). Compared to UWW, HWW may contain higher concentrations of macropollutants [3], as well as higher concentrations and greater varieties of micropollutants (4–50 times higher than in UWW) such as pharmaceutical residues (parent compounds and their degradation products), iodinated contrast media (ICM), heavy metals, detergents and other substances. They may be harmful for environmental and consequently for human health (e.g. [4, 5]).

Some of these hazardous substances have regulatory status and are disposed of accordingly (e.g. dental amalgam). However, for most of them (such as antibiotic residues, drugs and specific pathogens), no regulations exist [2]. Furthermore, besides the pharmaceutical parent compounds, degradation products produced by metabolic processes in the body, or by other physicochemical degradation processes that may take place through sewage networks, are released in wastewaters. All these compounds are often discharged with the HWW into sewage systems and then co-treated with UWW in the nearest wastewater treatment plant (WWTP) without specific pretreatments [3].

Conventional WWTPs are usually designed to eliminate nutrients with domestic origin. Hence, they are not completely effective in the removal of specific hospital pollutants [4]. Consequently, hazardous HWW pollutants and their by-products may be potentially released in the environment, endangering both environmental and human health. To improve the removal of those pollutants, diverse technologies (i.e. mainly oxidation process or activated carbon used in additional treatments) or separate treatments have been developed and applied on HWW [6]. However, the treatment effectiveness of each technique varies depending on the targeted compound. Moreover, regular and ubiquitous implementation of advanced treatment technologies is limited because of related spatial, energy and financial costs. It is also worth noting that the technologies involving advanced oxidation processes may lead to the production of oxidation and photodegradation compounds which could demonstrate toxic effects [6].

Recent works raise also the question of the effectiveness of separate treatment of HWWs regarding the limitation of the spread of bacterial resistance to antibiotics [7]. Indeed, a high fraction of prescribed antibiotics (more than 75% in Germany) are used outside hospitals; therefore, high abundance of resistant bacteria may occur in UWW as well [7]. Following these considerations, it is important to correctly estimate the hazardous nature and risk of HWW for environmental and

human health, in order to decide on their optimal management and ways of treatment.

Several publications have reported on higher overall concentrations of micropollutants in HWW compared to UWW or WWTP influents [3, 4]. However, these concentrations may change significantly according to the available hospital services (e.g. laundry, kitchen, etc.), the systems preventing water wastage, the sewage collecting system (combined or separated) and the management of stormwaters. Furthermore, the discharge of HWW is usually several times lower than that of UWW [8], which means that, despite higher concentrations of micropollutants, the HWW may contribute less to the environmental load of pollutants than the UWW. Therefore, an essential question is how significant the hospital contribution (HC) is to the total pollutants load and how hazardous this quantity is for the environment [9]. Assessment of pollutant fluxes originating from hospitals in addition to the concentrations of micropollutants in HWW is very important [1]. However, most of the existing publications that discuss HC are limited to a small number of molecules, and there is a lack of data on emission of pharmaceuticals from health institutions other than hospitals [10].

Here we aim to characterise the HC, to discuss the factors that influence it and to summarise the advantages and drawbacks of methods used for the investigation of HC. Furthermore, we present a short summary of results on HC of wastewaters and treated effluents produced by the SIPIBEL observatory (France).

2 Characteristics of Hospital Contribution (HC)

A number of recent studies report that despite higher concentrations of micropollutants in HWW, their HC to WWTP influent is generally lower than the urban contribution (UC). According to Kümmerer and Henninger [11], 25% of the antibiotics used in Germany were administered in hospitals. In Switzerland, the percentage is lower – 18% of the top-100 active compounds were sold for use in healthcare facilities [12]. Considering antibiotics only, hospital prescription principally accounted for around 5–20% of the total use in Europe [13], 30% in UK [14] and 25% in the USA [15].

However, HC may strongly vary depending on the study site and the compound. Thomas et al. [16] and Langford and Thomas [9] found that for most of the studied pharmaceuticals, HC to the WWTP influent is only around 2% or even less. Trimethoprim (ca. 4% HC) and paracetamol (ca. 12% HC) were the only two molecules exceeding these values. In contrast, several other studies reported that HC of pharmaceuticals is around one third of the total WWTP input and that specific molecules may exhibit much higher HC, which may cause environmental

hazard [10]. Beier et al. [17] found that around 34% of prescribed pharmaceuticals in their studied area (Germany) were originating from the investigated hospital. This contribution was molecule-specific and it reached 94% for clarithromycin. Based on consumption data, Escher et al. [18] concluded that HC was around 38% (as UC was around 62%). Daouk et al. [19] reported HC of 29% for the Geneva canton (Switzerland), which ranged between 1.2 and 77%, except for molecules that were exclusively consumed in the hospital (piperacillin, cisplatin and gadopentetic acid). HC of certain analgesics (codeine and morphine) and antibiotics (metronidazole and sulfamethoxazole) was relatively important.

Several other studies reported that HC for the most molecules remains below 15% [1, 3, 8]. Ort et al. [8] found that HC is relatively low and constant – less than 5% for 17 compounds and between 5 and 15% for 11 compounds. HC of trimethoprim and roxithromycin reached 18% and 56%, respectively. Verlicchi et al. [3] found that HC was less than 5% for 32 substances, between 5 and 15% for 18 compounds and higher than 15% for 12 molecules (7 antibiotics, 2 receptor antagonists, 1 analgesic, 1 diuretic and 1 lipid regulator). They found relatively high HC for ofloxacin (67% HC), azithromycin (67% HC), clarithromycin (53% HC), ranitidine (52% HC) and metronidazole (45% HC). Le Corre et al. [1] also showed that 63–84% of the investigated molecules have HC smaller than 15%. Nevertheless, between 10 and 20% of the pharmaceuticals consumed in hospitals were hospital-specific substances, which are likely to exhibit high HC. Based on national consumption data, Herrmann et al. [10] reported that in general hospitals, the consumption of pharmaceuticals affecting the alimentary tract and the cardiovascular system was 10–500 times lower than outside hospitals. However, the hospital consumption of the antibiotic cefuroxime, the antipsychotic clomethiazole and the carbonic anhydrase inhibitor acetazolamide was similar to their urban consumption. Santos et al. [20] also found that HC may strongly vary (from 3.3 to 74%) depending on the compound: HC of antihypertensives, psychiatric drugs or lipid regulators was relatively low (<10%), but for analgesics, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) (one of the most consumed therapeutic classes), HC was much higher (HC of 51, 41 and 32%, respectively).

An overview of the literature points out that HC can be determined by the use of different sampling strategies and methods, which makes the direct comparison of results between studies difficult [8]. However, studies that apply different methods (mass balance or consumption-based contribution) came to similar conclusion that in general HC of pharmaceuticals to the WWTP input is lower than UC. Nevertheless, numerous studies concluded that hospitals are still relatively important source of pollutants, especially according to the most consumed therapeutic classes of pharmaceuticals like antibiotics, analgesics and others. Furthermore, HC of micropollutants is strongly dependent on multiple factors (e.g. type of healthcare facility, hospital bed density, wastewater treatment, location, season, etc.).

3 Factors Influencing the Hospital Contribution of Micropollutants

3.1 Compound-Specific HC

As mentioned above, HC depends on the compound. It may vary strongly from <0.1 to 100% [19, 21]. Compounds predominantly or exclusively administered in hospitals may demonstrate higher HC. Vancomycin [4], oxytetracycline, chlorotetracycline, demeclocycline, cyclophosphamide and ifosfamide [16], for example, were detected in HWW, but not in urban samples. Ort et al. [8] also could quantify ciprofloxacin, desmethyl citalopram, indomethacin, lincomycin and sertraline in HWW only. However, it is worth noting that for concentrations close to the limit of quantification (LOQ), higher dilution of the UWW may be the reason why certain compounds could not be quantified [8].

Pharmaceuticals predominantly administered in hospitals, but mainly consumed by outpatients, are often excreted outside healthcare facilities (e.g. ICM and cytostatics). Weissbrodt et al. [12] reported that 70% of cytostatics and 50% of ICM were administered to outpatients and only 1.1–3.7% and 49% of their excreted amounts, respectively, were found in the HWW. Lenz et al. [22] also reported that only a small fraction of the amounts administered in the hospital was found in its effluent (i.e. 0.1–0.2% for doxorubicin, 0.5–4.5% for 5-fluorouracil and 27–34% for total platinum). Hence, actual HC of pharmaceuticals may be significantly lower than HC evaluated from the amount of administered drugs in hospitals. Further decrease is expected, as increased outpatient treatment is predicted in the future [12].

3.2 Healthcare Facility- and Region-Specific HC

HC of pollutants depends on the characteristics of the healthcare facility: hospital size and age, presence of general services (kitchen, laundry, etc.), number and types of medical sections, management policies, etc. [5]. Larger hospitals with higher number of beds and diversity of wards have more intense activity and exhibit therefore higher HC of pollutants to the total WWTP influent compared to smaller hospitals [1, 20]. Recently built hospitals possess improved sewage collection network. Hence, their HC of micropollutants may increase due to reduction of losses caused by sewer leakage. Moreover, each hospital provides specific medical services which require the use of different compounds, depending on the applied techniques and therapies. Escher et al. [18] reported that the top-100 pharmaceuticals used in general and psychiatric hospitals differed distinctly and only 37 pharmaceuticals were overlapping. Santos et al. [20] found that analgesics, NSAIDs and diuretics were present in higher concentrations in paediatric and maternity hospitals, than in university and general ones, while iopromide (an X-ray contrast agent)

and antibiotics were present in higher concentrations in the university hospital. Herrmann et al. [10] reported that anticonvulsants, psycholeptics and psychoanaleptics were more consumed in psychiatric hospitals and nursing homes (74% and 65%, respectively) than in general hospital.

Consumption patterns (and consequently HC) may vary strongly between countries or regions, even when hospitals are of similar size and are equipped with similar wards and diagnosis activities [23]. HC is often country-specific and varies depending on the socio-economical and geographical environment. For example, the lists of pharmaceuticals suggested for the treatment of specific diseases differ strongly between countries, because of local availability and prescription habits [20]. Molecules that are prescribed together are expected to be found in similar ratios (e.g. trimethoprim and sulfamethoxazole) [8]. Some therapeutic classes may exhibit geographical and/or seasonal applications. In mountain regions, for example, the use of anti-inflammatories in hospitals may increase in winter, due to frequent sport traumas [24].

After all, the hospital bed density of medical facilities remained to be one of the most important factors related to the HC [25]. Hospital bed density of 4.4 beds per 1,000 inhabitants is a typical value for developed countries [8]. Heberer and Feldmann [25] investigated drainage area with a high hospital bed density of 24.7‰ and found relatively higher HC of carbamazepine and diclofenac (26% and 17%, respectively) compared to other studies [8]. However, despite such high bed density, HC remained lower than the UC. After comparison of several studies, Verlicchi et al. [3] concluded that highest HC values were reported in the study of Beier et al. [17] where the bed density was the highest (33.5‰). Santos et al. [20] reported that higher HC of pharmaceuticals was observed in university hospital with bed density of 3.4‰, while lower HC was observed together with lower variety of molecules (less than 1% of all the therapeutic groups) in maternity hospital with bed density of 0.2‰. Herrmann et al. [10] found that areas with higher medical cases per citizen (0.33‰) exhibit higher HC than the national average (0.22‰ for Germany). Hence, hospitals in such environments may be seen as point sources for specific compounds.

Considering these regional-specific differences, the performance of analyses on local scale is important for the determination of the most accurate HWW management and treatment and for the insuring of good environmental protection [3].

3.3 Temporal Changes

HC may also be influenced by seasonal changes [3]. In cold seasons, occurrence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water may increase [24]. Such seasonal fluctuations and temporal changes of pollutants are strongly dependent on the pathologies. In UWW, seasonal fluctuations are typical for compounds prescribed for airway infections and throat, nose

and ear infections, unlike for compounds prescribed for long periods or whole life (e.g. beta-blockers, diuretics, etc.) [23].

In HWW, changes according to the season are less evident [26]. However, certain compounds may exhibit daily or weekly fluctuations due to variations in their application and in water consumption [16]. Goullé et al. [27], for example, reported drastic reduction in release of the heavy metals gadolinium and platinum in nonworking days (94% and 87%, respectively). Compounds administered to treat specific diseases and infections (e.g. azithromycin, metronidazole, norfloxacin, ofloxacin and clindamycin) in hospitals exhibit rather short-term usage-related fluctuations, according to the occurrence, intensity and duration of corresponding disease outbreaks. The ratio between peak consumption and average consumption of these compounds may vary from 0.2 to 5; therefore, their HC may significantly change over short time periods [23]. Due to such short-time temporal fluctuations in HWW, adequate sampling frequency is essential for the obtaining of representative HWW samples. HC of largely used pharmaceuticals like ciprofloxacin is rather stable [23]. Ort et al. [8] reported fairly constant loads for atenolol, gabapentin, paracetamol and trimethoprim as well.

4 Uncertainties Related to the HC Estimation Method

HC of pollutants can be estimated with direct measurements or consumption data. Both methods have their benefits, but also drawbacks that may lead to under- or overestimation of HC, as discussed in details in another chapter of the book.

4.1 Direct Measurements

The following challenges concern the direct measurements of HC of micropollutants:

- *Sampling mode* – Defining appropriate composite flow-proportional water sampling with sufficient frequency (preferably over several weeks) is essential to obtain representative samples. This can be time-consuming and complex and it may result in severe artefacts if not done in a proper way [8].
- *Compound-specific analytical methods* – The huge variety of compounds and their metabolites released in wastewaters requires a broad spectrum of analytical methods. At present we are limited by the existing methods that do not cover all compounds, by their complexity and financial costs.
- *Limit of quantification (LOQ)* – Depending on the molecule and the matrix interferences, compounds exhibit different LOQ. Concentrations under the LOQ can hardly be taken into account, which may be especially problematic for molecules in concentrations close to the LOQ [8].
- *Instrumental and human errors* – These may also cause high uncertainty, especially for compounds measured at very low concentrations [23].

4.2 Consumption Data

Calculation based on consumption data can be applied independently from the analytical methods, and no effort to obtain representative samples is required. It also gives the possibility of considering longer periods of time, but several drawbacks may lead to uncertainties in the prediction [19, 23]:

- *Data precision* – consumption is site-specific. Hence, ideally, calculation should be based on the consumption of the targeted healthcare facility and the sales of the pharmacies that are located in the catchment area of the WWTP. However, data is often available in terms of *sales* data, generally on an annual and national/regional basis, comprising different healthcare facilities [10, 28], which makes it difficult to depict regional variations and short-term usage-peaks [6].
- *Inappropriate disposal* – unwanted or expired compounds which are directly flushed down toilets may lead to uncertainties. Analysis of consumption data is more robust when investigating regularly consumed compounds with high detection frequency [19].
- *Drugs administered to outpatients* – compounds, almost exclusively administered in hospitals, but taken by outpatients, may be mainly excreted in private homes and released with UWWs [12]. As they may be especially harmful for the environment (e.g. cytostatics are carcinogenic, mutagenic and toxic for reproduction), their release in urban wastewaters should not be neglected [18].
- *Regularly taken medicines* – when being hospitalised, patients may take their previously prescribed medicine with them (e.g. beta-blockers or lipid regulators) [17].
- *Over-the-counter medicines* – sales of easily accessible medicines (e.g. ibuprofen) are not always considered [8].
- *Urban visitors' consumption* – drugs may be sold to patients who leave the catchment area, or visitors may come with their own medicine (this consideration is especially important for touristic regions).
- *Metabolism and excretion rates* – excretion rates strongly depend on gender, age, health status and concurrent consumption of other pharmaceuticals [28]. Moreover, for many compounds, values found in the literature are highly variable, which may refer only to excretion by urine, faeces or both [23].

Pharmaceuticals are likely to form transformation products that have to be considered for the correct estimation of HC. Langford and Thomas [9] estimated HC of carbamazepine, tamoxifen and ketoprofen parent molecules as less than 2%. However, in the treated WWTP effluent, their concentrations were higher than in the influent, which means that they were probably excreted as conjugates. Degradation and sorption onto the sewage should also be considered. Ciprofloxacin, for example, significantly partitions onto the suspended matters within the WWTP [16].

As a result of these uncertainties, Verlicchi and Zambello [23] found agreement of actual measurements and consumption data for limited number of compounds. Daouk et al. [19] reported agreement for one third and Ort et al. [8] for three

quarters of the investigated molecules. Herrmann et al. [10] reported that differences between predicted and measured concentrations were lower than one order of magnitude and, therefore, they concluded that the application of consumption data may be appropriate to assess patterns of pharmaceuticals in HWW.

5 Environmental Risk of Hospital Effluents

Potential toxic effects of HWW to the aquatic environment and presence of drug-resistant bacteria in HWW have been highlighted in different studies. Weissbrodt et al. [12] mentioned that the toxicity of HWW is 5–15 times higher than that in domestic wastewater. Verlicchi et al. [3] found nine substances that pose potential ecotoxicological risk in HWW and four of them (antibiotics) in the influent/effluent of the WWTP. Santos et al. [20] also suggested that according to the environmental risk, attention should be payed mainly to antibiotics (such as ciprofloxacin, ofloxacin, sulfamethoxazole, azithromycin and clarithromycin). In comparison, Daouk et al. [19] found that, when taking into account WWTP dilution and removal efficiencies, the fraction of ciprofloxacin and sulfamethoxazole coming from the hospital only showed a risk for the aquatic environment, according to their Predicted No-Effect Concentrations. Nevertheless, when considering the total urban consumption, five more compounds appeared to be important regarding their environmental risk: gabapentin, piperacillin, ibuprofen, diclofenac and mefenamic acid [19]. Le Corre et al. [1] also reported that only a small percentage of compounds originating from hospitals may be of concern. Hence, pharmaceuticals administered in hospitals may contribute to the mixture risk quotient, but usually their contribution alone is rarely a predictor of environmental risk [18]. However, in regions with high hospital bed density, healthcare facilities can be seen as point sources of pharmaceuticals that may lead to higher HC and pose environmental risks [10].

Further data is required for the assessment of potential impacts of HWW. According to the compound and its specific effect, appropriate ecotoxicological tests should be applied to evaluate their potential environmental toxicity in order to develop relevant environmental toxicity thresholds [29]. To date, few field studies have been implemented in order to compare the environmental impact of hospital and urban treated effluents. Recently, Chonova et al. [4] showed that microbial communities from natural biofilms may be affected differentially by hospital treated effluents (HTE) and urban treated effluents (UTE), depending on the nutrient and pharmaceutical loads in these effluents.

Most studies cannot provide experimental comparison of the complete treatment process of UWW and HWW and of their treated effluents, because the two wastewaters are usually treated together. Such comparison is essential to comprehend the removal efficiency during treatment of HWW and UWW and to evaluate the danger of the resulting treated effluents. Since 2013, the French observatory of SIPIBEL has been monitoring influents and effluents (concentrations and fluxes) of

completely separated parallel treatments of urban and hospital wastewaters in a common WWTP. Data collected in this observatory allow direct comparisons of the two parallel processes [4]. SIPIBEL unique data on HC of micropollutants are synthetised here, in order to better apprehend HC for further optimising of management and treatment of HWWs.

6 Case Study SIPIBEL: Separate Management of Hospital Effluents in an Urban WWTP

6.1 The SIPIBEL Observatory: Study Site and Monitoring

The study site SIPIBEL (Site Pilote de Bellecombe, Scientrier, France) is a pilot WWTP that treats HWW from the general hospital CHAL (Centre Hospitalier Alpes Léman, 450 beds) and UWW from a catchment area of 21,000 inhabitants. HWW and UWW are processed in separate basins applying the same treatment procedure that includes filtration, grit and grease separation, conventional biological treatment with activated sludge (aerobic and anoxic) and final clarification [4]. This particular configuration gives the opportunity to investigate the HC of micropollutants to the total wastewater, but also to analyse the effectiveness of the treatment and to calculate the HC to the treated effluent discharged into the aquatic environment.

The SIPIBEL observatory performed regular monitoring of several micro- and macropollutants in both wastewaters (HWW and UWW) and their treated effluents. Once a month, 24-h composite flow-proportional water samples were collected (a total of 200 subsamples for each location, 100 mL each). Analyses were done as described in SIPIBEL report [30] and Wiest et al. [31]. Here, we present the HC of wastewaters (between March 2012 and December 2015) and treated effluents (between March 2012 and April 2014) for four groups of pollutants that include 27 parameters:

- *8 metals* (arsenic, cadmium, chrome, copper, gadolinium, lead, nickel and zinc)
- *12 pharmaceuticals* (atenolol, carbamazepine, ciprofloxacin, diclofenac, econazole, ibuprofen, ketoprofen, paracetamol, propranolol, salicylic acid, sulfamethoxazole, vancomycin)
- *4 nutrients* (NH_4^+, NO_2^-, NO_3^- and PO_4^{3-})
- *3 families of surfactants* (anionic surfactant, cationic surfactant and non-ionic surfactant)

Mass loadings were obtained by multiplying the concentrations of each compound by the mean daily flow of the respective location. Wastewater discharge was 37 times higher for UWW compared to HWW which resulted in a more than 5 times longer hydraulic retention time and higher oxygenation in the hospital basin. Mean HC (calculated as mean of HC for each compound) in wastewater and treated

effluent and mean removal efficiencies (calculated as mean of removal efficiency for each compound) were calculated for each group of pollutants over all samplings. Principal Component Analyses (PCA) were performed with all groups of pollutants to visualise the main tendencies in concentrations and loads of urban and hospital wastewaters and treated effluents. This was done with R software (3.3.0, R Development Core Team) using the ade4 package [32].

6.2 *Pollutant Concentrations in Urban and Hospital Wastewaters*

General trends of concentrations of the investigated pollutant groups in hospital and urban wastewaters and their separately treated effluents are presented in Fig. 1a, b.

In both cases, urban and hospital samples are placed oppositely on the first axis, showing very different composition of pollutants according to the wastewater origin. The overlapping of HTE and UTE, visible on Fig. 1b, shows that these differences become weaker after treatment. Both HWW and HTE are characterised by higher total concentrations of pharmaceuticals and surfactants (compared to UWW and UTE, respectively) as a result of their regular use in healthcare facilities.

Removal efficiency of pharmaceuticals depends on several parameters such as operational conditions, treatment process, physicochemical processes as well as the substance properties (hydrophobicity, charge and biodegradability) [33–35].

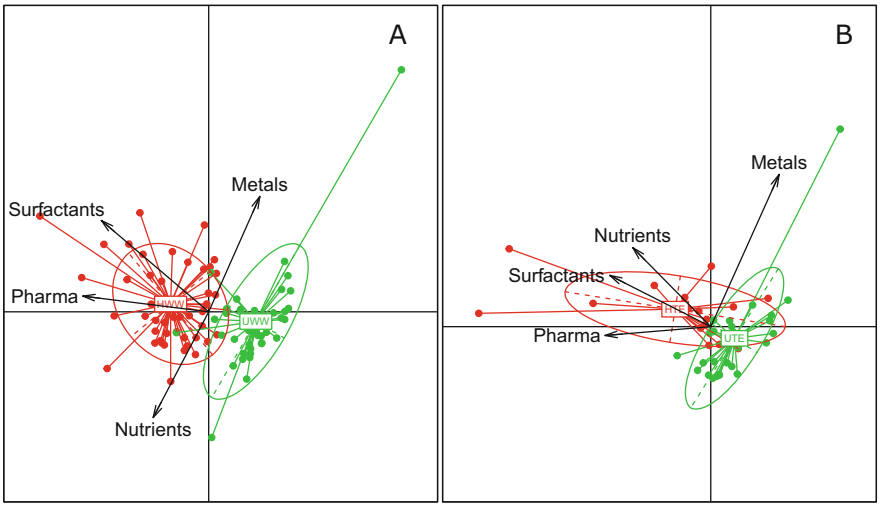

Fig. 1 Two-dimensional plots of PCA based on concentrations of metals, pharmaceuticals, nutrients and surfactants in hospital (*red*) and urban (*green*) (**a**) wastewaters and (**b**) treated effluents. The first two axes explained 63.9% and 68.6% of the variability of (**a**) and (**b**), respectively

Therefore, removal efficiencies can vary significantly between compounds, between WWTPs and even within the same WWTP between time periods [36]. Pharmaceuticals showed clearly higher overall removal in the hospital basin probably influenced by the longer hydraulic retention time which is known to improve the removal of certain molecules (e.g. ibuprofen) [37]. Despite this, their overall concentrations in the HTE remained higher than in the UTE.

6.3 *Pollutant Loads and Contributions in Urban and Hospital Waters*

When taking into account the high discharge of the UWW, the relative importance of pollutant loads according to their wastewater origin drastically changes for both wastewaters (Fig. 2a) and treated effluents (Fig. 2b). Urban waters are characterised by higher load of pollutants. The variability between urban samples is much higher, which may be explained by the larger variation of contamination sources and stronger seasonal fluctuations.

The UWW contributed more to the total discharge of pollutants than the HWW (Fig. 3a). Pharmaceuticals are one of the most important hospital-specific pollutants. Their HC was higher than for other pollutants (approximately 27%), which is in agreement with other studies [19]. HC of surfactants was 9% and of metals and nutrients only 6% and 5%, respectively. Detailed contributions of each of the molecules can be found in the literature [31]. Several other studies on hospital

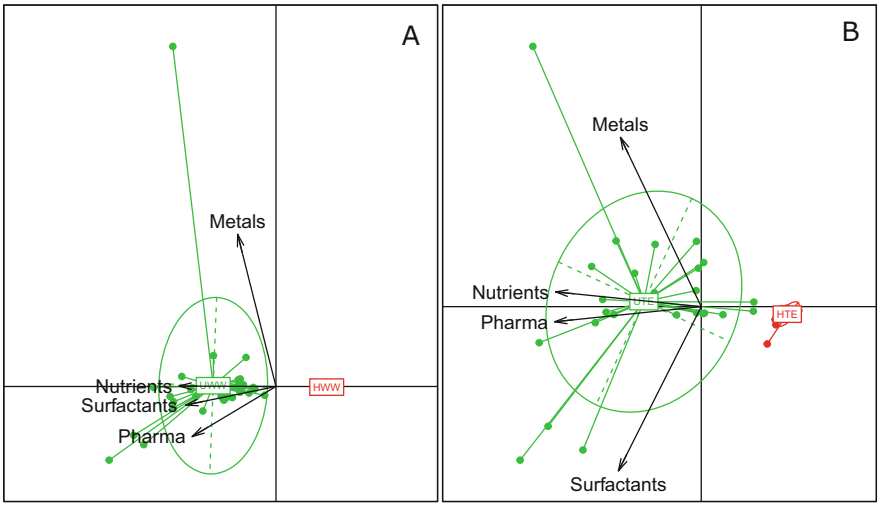

Fig. 2 Two-dimensional plots of PCA based on loads of metals, pharmaceuticals, nutrients and surfactants in hospital (*red*) and urban (*green*) (**a**) wastewaters and (**b**) treated effluents. The first two axes explained 81.8% and 77.5% of the variability of (**a**) and (**b**), respectively

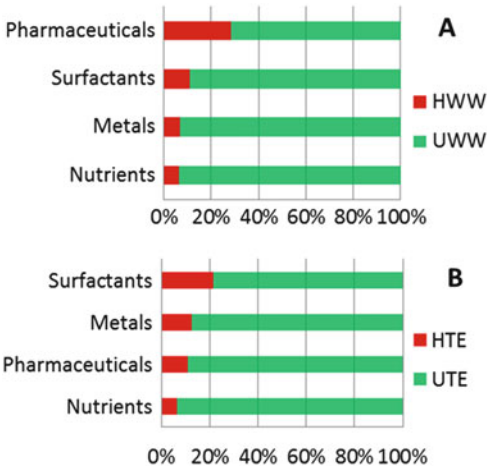

Fig. 3 Hospital (*red*) and urban (*green*) contributions to total WWTP input of metals, pharmaceuticals, nutrients and surfactants in (**a**) wastewaters and (**b**) treated effluents

loads of French hospitals have reported the presence of pharmaceuticals and diagnostic products as well as anaesthetics and disinfectants [38–40].

After treatment, HC of pollutants in the recipient river remained much lower than UC for all groups of pollutants (Fig. 3b). The higher removal of pharmaceuticals in the hospital basin led to the decrease of their HC to less than 13%. In contrast, surfactants were better removed in the urban basin, and consequently their HC in treated effluents was twice higher than in wastewaters. HC of nutrients and metals in the treated effluents also increased to 16% and 9%, respectively.

The monitoring data of the SIPIBEL observatory offers an unique opportunity to compare urban and hospital wastewaters before and after treatment. Although HWW displays higher initial concentrations in micro- and macropollutants, its contribution to the total load of pollutants is lower than contribution of UWW due to the differences in the discharge. After treatment, the overall HC in the treated effluents remains lower than the UC. However, HC of specific compounds may still be relatively high and it should not be neglected.

7 Conclusion

Hospital effluents are a particular case of anthropogenic pollutants. Loads of pollutants transferred from hospital to municipal WWTPs strongly depend on several factors, such as the number of hospitals, bed density, industrialisation level and population density.

Although there are several uncertainties related to the estimation of the HC, most studies highlight that in general HC of micropollutants to the WWTP input is lower than UC. Many pharmaceuticals are taken on a regular basis at home. Furthermore, the increasing short hospitalisations and treatments of outpatients will lead to increased releases of many compounds to UWW [1]. Drugs may be released into

the environment through several other ways as well, such as livestock treatment, aquaculture, pet care or pharmaceutical manufacturing [16, 41].

However, releases from healthcare facilities are specific and deserve attention. Higher concentrations of pharmaceuticals and detergents have often been underlined, due to their intensive and regular use. Depending on the situation, HC may reach around 30% of the total load of pharmaceuticals in the WWTP input [17–19]. In regions with high hospital bed density, hospitals may be seen as a point source for pharmaceuticals' emission. Molecules predominantly or even exclusively used in hospitals are often identified in hospital effluents. They may exhibit significantly high HC that may cause environmental hazards. Hospital waste management requires awareness of stakeholders to determine regulations and to better comprehend the hospital activities and their specific potential releases and environmental impact.

In order to decrease HC of micropollutants, different strategies are applied worldwide. Awareness about eventual environmental risks should be raised, and unnecessary prescription of drugs in hospitals should be avoided. For example, the inappropriate use of human antibiotics was estimated at 20–50% of the consumption [42]. Further reduction of HC can be achieved by improving stocks organisation to avoid waste and by proper disposal of leftover pharmaceuticals [11]. Finally, wastewater discharge may be reduced through separate collection of rain water or application of strategies limiting water consumption [4]. This will result in lower quantities of HWW, which will require less energy and financial costs for the application of additional pretreatments [6].

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Lessons Learned from European Experiences and Presentation of Case Studies

Silvia Venditti, Kai Klepiszewski, and Christian Köhler

Abstract The present work aims to give an overview about the current state of adopted treatment trains for hospital wastewater in the European countries. Hospital effluent is considered as a point source of micropollutants such as pharmaceutical residues (antibiotics in particular) and anti-resistant bacteria in a municipal sewer system with the surface water as ending point.

The changes in the legislation (i.e. WFD, EU 2015/495) forced researchers, administrators and stakeholders to debate about possible technical solutions to implement. Starting with studies on fate and pathways of pharmaceuticals compounds and their metabolites, the European scientific community assessed removal of micropollutants in conventional activated sludge (CAS) systems and their possible upgrade with tertiary treatments. The solution was then compared with decentralized one at point source according to different methodologies such Life-Cycle Assessment (LCA). These considerations drove to the implementation of different solutions according to policy decisions of the individual countries. Switzerland is the first European country that cast in the necessity of a post-treatment step in national legislative mould. In other European countries, such as Germany, reduction measures of pharmaceutical loads are decided on regional level.

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Contents

1 Introduction

Contamination by human pharmaceutical compounds has received increasing attention in recent years, as it may constitute a potential risk for aquatic and terrestrial ecosystems. These micropollutants in general originate from urban environments, arrive in the wastewater catchment and its connected treatment system and may finally reach the aquatic environment. These residues are typically found at very low concentrations and are unlikely to affect human health. However, their release into the environment leads to a number of negative effects such as anomalies in the reproduction system of fish due to hormones [1, 2], which are already evaluated and discussed in Environmental Risk Assessment (ERA) studies [3–5]. Concerns have also been raised over increased bacterial resistance to antibiotics released into the environment.

Due to numerous investigations of the international scientific community, the European Commission decided to include six pharmaceuticals in a so-called *watch list* (Commission Implementing decision (EU) 2015/495 of 20 March 2015), namely the contraceptive 17α-ethinylestradiol (EE2), the hormone 17β-estradiol (E2), the non-steroidal anti-inflammatory drug diclofenac (already present in the Directive 2013/39/EU) and the macrolide antibiotics erythromycin, clarithromycin and azithromycin. The list entails proposed detection limits of 0.035, 0.4, 10 and 90 ng/L, respectively. Substances of the *watch list* are proposed to be monitored to provide representative data for risk assessments, which will support the identification of priority substances.

The inclusion in the list of priority substances will further require an impact assessment. Currently, there are 45 aquatic pollutants (including heavy metals, polycyclic aromatic hydrocarbons, chlorinated compounds and pesticides) covered under the list of priority substances which provides environmental quality standards in surface waters (Directive 2013/39/EU of the European Parliament and the council of 12 August 2013).

The action of the European Commission enhanced the interest in numerous institutions, stakeholders and authorities moving from the isolated activities of an individual research group, specialized in a specific technique, to large multidisciplinary projects that coordinate the activities of multiple researchers, expert

in different areas, into a multipronged approach to the topic. POSEIDON (EVK1-CT-2000-00047, funded under FP5-EESD, call for proposal: 2000), NEPTUNE (036845, funded under FP6-SUSTDEV, call for proposal: 2005), PILLS and noPILLS (INTERREG IVB NWE programme, call for proposal: 2007 and 2012, respectively) involved the actors of the so-called medicinal product chain examining the problem across all scales and have provided knowledge about fate and removal options during treatment processes of emerging xenobiotics with focus on pharmaceuticals and personal care products.

The findings of these projects are essential for the definition of mitigation strategies to be implemented in the community. Stakeholders and authorities participate as members of the Advisory Board to anticipate possible legislation restrictions.

2 Conventional Management of Hospital Wastewater: Centralized Treatment

As starting point, POSEIDON and NEPTUNE projects investigated above all existing wastewater and drinking water treatments with respect to their efficiency in removing pharmaceuticals.

The main point source of some pharmaceuticals in urban wastewater systems is in fact hospital wastewater, together with retirement homes and some dedicated infrastructures. Generally, hospital wastewater is co-treated with domestic (and industrial) wastewater in conventional Wastewater Treatment Plants (WWTPs). Since existing WWTPs are not designed to remove pharmaceuticals, parent compounds and their metabolites are subsequently released into the environment as a result of low pharmaceutical elimination efficiencies [6] (Table 1).

The difficulties in removing pharmaceuticals from wastewater are firstly due to their physico-chemical properties, in terms of solubility, volatility, polarity, influencing absorbability, biodegradability and stability. Compounds of the same therapeutic class can have quite different chemical and physical properties resulting in different behaviour during treatment processes. This may explain why they are not subject to similar removal efficiencies. Secondly, concentrations of those pharmaceuticals (range 10^{-3}–10^{-6} mg/L) are much smaller than those of common macropollutants (e.g. BOD_5, COD, nitrogen and phosphorus compounds, range of 10^{-1}–10^{3} mg/L). Finally, it is difficult to correlate physical properties of pharmaceuticals to their corresponding removal efficiency achieved during conventional wastewater treatment, as operating parameters such as biomass concentration, Sludge Retention Time (SRT), Hydraulic Retention Time (HRT), pH, temperature, configuration, type of plant but also wastewater influent characteristics regarding the quality can contribute to it.

In general, sorption of pharmaceuticals on sludge depends on the lipophilicity and acidity of the compound as well as the ambient conditions such as pH, ionic strength, temperature, the presence of complexing agents and the properties of the

Table 1 Removal rate of common pharmaceuticals after conventional WWTs [7–9]

Group	Compound (CAS-Reg.)	Octanol–water partitioning Log K_{ow} [10]	Sorption constant K_d (l/kg SS)	pK_a (strongest basic) [10]	Degradation rate constant k_{biol} (l/kg SS)	Removal[a]
Antibiotics	Amoxicillin (26787-78-0)	−2.3	1.06 [11]	7.43	<0.13 [12]	L
	Ciprofloxacin (85721-33-1)	−0.57	20,000 [11]	8.68	0.55 [13]	M-H
	Clarithromycin (81103-11-9)	3.18	260 [11]	8.38	<0.5 [12]	M
	Erythromycin (114-07-8)	2.37	160 [14]	8.38	<0.12 [12]	M
	Sulfamethoxazole (723-46-6)	0.79	200–400 [14]	1.97	5.9–7.6 [12]	H
Anaesthetics	Lidocaine (137-58-6)	2.44	n.d.	7.75	n.d.	L
Analgesics	Diclofenac (15307-86-5)	4.5	16 [12]	−2.1	< 0.02 [15]	L
	Naproxen (22204-53-1)	3.18	n.d.	−4.8	0.08 [15]	M
	Paracetamol (103-90-2)	0.51	n.d.	−4.4	58–80 [12]	VH
Anticonvulsant	Carbamazepine (298-46-4)	2.54	<8 [15]	−3.8	<0.005 [15]	L
Cytostatics	Cyclophosphamide (50-18-0)	0.8	n.d.	−0.57	n.d.	L
	Fluorouracil (51-21-8)	−0.89	n.d.	−8	n.d.	L
X-ray contrast media	Iodixanol (92339-11-2)	−2.9	n.d.	−3.2	n.d.	L

[a]L: low (i.e. <40%), M: medium (i.e. between 40 and 60%), H: high (i.e. between 60 and 85%) and VH: very high (i.e. over 85%) removal efficiencies

sludge itself. Sorption occurs via absorption (hydrophobic interactions characterized by the octanol–water partition factor, Log K_{ow}) and adsorption (electrostatic interactions characterized by the dissociation constant, pK_a) and can be estimated by the K_d value (sorption coefficient for activated sludge), i.e. the ratio of the compound's concentration in the solid and aqueous phase at equilibrium conditions. Compounds with high Log K_{ow} (hydrophobic) have intuitively more affinity for the solid fraction.

As an example, fluoroquinolone antibiotics were generally found to be highly removed by sorption onto activated sludge which is in strong contrast to general 20% of removal accounting for most of the compounds of this therapeutic group. The high hydrophilicity (low K_{ow} value) of this antibiotic class suggests actually a very limited absorption behaviour. However, the overall sorption tendency is fairly considerable (high K_d value) due to the electrostatic interactions (high pK_a) of this compound with activated sludge. Anticonvulsant and analgesic pharmaceuticals are persistent and difficult to degrade. Generally, carbamazepine was not removed at all in conventional sludge treatments [15] while diclofenac showed a more differentiated behaviour in the treatment plants. It is assumed that the difficulties in removing carbamazepine and diclofenac from wastewater can be attributed to their hydrophobic character (log K_{ow} of 2.54 and 4.51, respectively) and low biodegradability. The more hydrophilic substance paracetamol is normally totally degraded. Cytostatics and X-ray contrast media are all known to be hardly removed.

Given the global limited removal efficiency with classical treatment processes, conventional treatment plants could be upgraded with technologies specifically developed to achieve high removal rates. In this context, post-treatment of the activated sludge process, e.g. advanced oxidation processes and activated carbon sorption, is being investigated. Each process bears its individual advantage and disadvantage.

Ozone is a strong oxidizer and produces hydroxyl radicals in its decomposition. As post-treatment, it was reported to degrade most of the organic micropollutants under study [16, 17]. However, ozonation leads to the formation of undesired by-products. This is the case when xenobiotics are only partly oxidized and when matrix components are reacting with ozone. By-products can cause even higher toxic effects than their parent compounds [18]. These transformation products are usually of lower molecular complexity and can partially be separated from water by biological post-filtration [18, 19]. Ozone can also be combined with hydrogen peroxide dosage which initiates ozone decay associated with the formation of OH-radicals and consequently contributes to the enhanced efficiency of the oxidation mechanism [20]. This advanced oxidation process can also cause negative effects on the degradation efficiency of xenobiotics. Due to their structure, some components rely exceptionally on ozone reaction and compete with hydrogen peroxide radicals that can act as scavengers of ozone molecules [20, 21].

UV irradiation is another oxidation process where organic micropollutants are degraded either by direct photolysis or by chemical oxidation, i.e. the dosing of hydrogen peroxide and the subsequent oxidation through OH-radicals as advanced oxidation process [22, 23]. As every investigated oxidation process, UV irradiation leads to the formation of partially oxidized products bearing environmental risks and

requires therefore a post-treatment similar to ozone. Moreover, compared to the latter, UV lamps were found to demand for considerable electrical energy [23].

Activated carbon binds micropollutants by adsorption to its highly specific surface area. Efficiencies with granulated activated carbon as filtration step after biological treatment have been studied on several treatment plants with satisfying results [8, 24]. Main cost factor is the concentration of organic matter in the effluent of the biological process. It competes with xenobiotics for the active surface area of the carbon and highly influences therefore the consumption of the costly carbon. The production and regeneration of activated carbon requires a lot of electrical energy for heat. Powdered activated carbon has been proposed to be more efficient compared to granulates [9] with an overall micropollutant removal rate of more than 80%. It would nevertheless require an additional tank to separate the powder from the treated water.

After all, the upgrading of WWTPs with advanced treatment processes will undoubtedly result in large financial costs as well as in undesirable increases in energy consumption and therewith in greenhouse gas emissions.

Recent pilot studies demonstrate the high electrical energy demands of advanced treatment. The energy consumption of a UV module to remove pharmaceuticals caused 1.1 kWh/m^3 of treated wastewater from a pilot-scale plant treating hospital sewage [23]. Hence, most focus lies on more energy efficient ozone and activated carbon treatment. Ozonation as post-treatment for WWTPs with large capacities (>10,000 PE) resulted in a specific energy need between 0.03 and 0.035 kWh/m^3 [19]. This implies still 12% of the total energy consumption (0.3 kWh/m^3) of a typical nutrient removal plant. A sand filter requires around 13% of the total WWTP energy consumption [25] and is necessary to remove oxidation by-products downstream the ozonation. Thus, the overall contribution of the ozone post-treatment sums to 25%.

The high-energy demand of advanced treatment technologies shows the need to invest in finding appropriate solutions to minimize their application as much as possible.

3 Is a Decentralized Treatment an Option?

Another solution as alternative to the ineffective treatment of large hydraulic loads of centralized plants could involve the pharmaceutical removal of highly concentrated wastewater, namely at point sources (in particular hospitals). This would have the additional positive effect of reducing pollutant emissions from combined sewer overflows during heavy rain events.

The concept is not new. In the 1980s, there was found the need to separate urine of patients exposed to radiotherapy in order to effectively reduce the radioactivity before the discharge. Some hospitals decided to implement dedicated WC to collect the contaminated urine and reduce the radioactivity with time to safe level in the effluent.

The PILLS project (INTERREG IVB) in particular focussed on this decentralized treatment approach as an effective precautionary approach compared to the

centralized treatment option with its disadvantages, i.e. dilution with other municipal wastewaters.

The project deeply investigated both approaches, i.e. centralized and decentralized, by applying several technological solutions in both pilot and full scale. Strengths and weaknesses of centralized and decentralized solutions were identified based on environmental, economic, technical and sanitary criteria via the understanding of the substance flows of pharmaceuticals in urban wastewater systems (see Fig. 1).

During the operation of the treatment systems, the partners (i.e. Emschergenossenschaft (D), Eawag (CH), Waterschap Groot Salland (NL), Glasgow Caledonian University (UK), Université de Limoges (F) and CRP Henri Tudor (L)) were investigating a wide range of pharmaceuticals which were chosen considering those known to be excreted in the highest amount and with the highest ecotoxicity and related to the individual use on the country.

As an example, approximately 23 kg of antibiotics were used in the CHEM hospital in Luxembourg in 2013 only. Fluoroquinolones, which include ciprofloxacin, represent the largest fraction of antibiotics accounting for approximately 16 kg. They are followed by macrolides (4.9 kg), penicillins (1.7 kg) and finally sulfonamide (73 g). For other partners, the penicillins group with amoxicillins in front was the most used one. Other pharmaceuticals are also subject to the market trend. As X-ray contrast media the hospital in Luxembourg was mainly using iohexol in 2012 and iobitridol in 2015. Changes in medication, due to pharmacological advances or administrative and regulatory decisions, are important to capture when mass flows are analysed over a certain period.

Four case studies, two of which pilot scale (Table 2), were examined and compared in the frame of the PILLS project. In all cases, a close collaboration with the hosting hospital was crucial to retrieve the amount and type of the applied pharmaceuticals on a chronological basis.

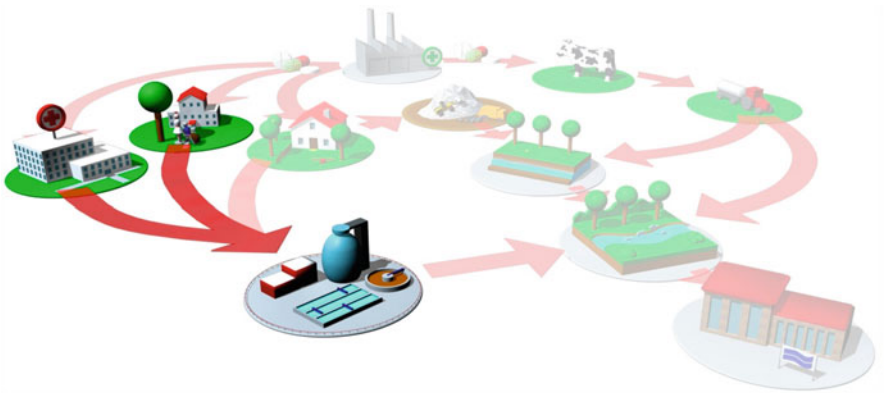

Fig. 1 Substance flows of pharmaceuticals in urban wastewater systems and focus of the PILLS project [26]

Table 2 Case studies (PILLS)

Partner/Hospital/Size of the hospital	Decentralized treatment[a]				Discharge
	m^3/day	Pretreatment	Biological step	Advanced treatment	
Pilot scale					
Eawag (CH) Cantonal hospital of Baden 346 beds	1.2	Mechanical screening	MBR	O_3 + SF PAC + SF	Water body
LIST, former CRP Henri Tudor (L) Centre Hospitalier Emile Mayrisch (CHEM) 640 beds	1.5	Mechanical screening	MBR	RO O_3/H_2O_2 UV/H_2O_2	Sewer
Full scale					
Waterschap Groot Salland (NL) Isala 1,076 beds	240	Mechanical screening	MBR	O_3 + GAC GAC + UV/H_2O_2 + GAC	Sewer
Emschergenossenschaft (D) Marienhospital Gelsenkirchen 50 beds	200	Mechanical screening	MBR	PAC O_3 + MBB UV/TiO_2 + MBB	Surface water

[a]*MBR* Membrane BioReactor, *PAC* Powder Activated Carbon, *MBB* Moving Bed Reactor, *GAC* Granulated Activated Carbon, *SF* Sand Filtration

All pilot plants are characterized by a combination of technologies, which has the objective of eliminating the largely persistent residues of medicinal products in addition to the biodegradable substances and nutrients.

Each design entailed as core technology a *membrane bioreactor* (MBR) followed by advanced physical–chemical (UV, ozone, activated carbon, advanced oxidation processes and reverse osmosis) treatment methods. The performance of the pilot installations was evaluated in terms of removal efficiencies of pharmaceutical substances, the "classical" parameters (COD, BOD, N and P) as well as the energy consumption.

The MBR provided a good effluent quality in terms of COD, nutrients and bacteria removal which remained stable throughout the operation time. Concerning pharmaceutical removal, MBR treatment showed the highest elimination efficiencies for compounds with high biodegradability (e.g. paracetamol) and low efficiencies for most of the other compounds. The elimination efficiencies generally agreed with other studies [6, 11]. Furthermore, for some pharmaceuticals (e.g. antibiotics) it could be shown that the investigated MBR systems provide higher pharmaceutical elimination rates than conventional activated sludge (CAS) systems. However, the majority of the pharmaceutical mass flow was in the MBR permeate.

Regarding **ozonation** as post-treatment option, the major part of the pharmaceutical mass flow was oxidized during an ozone dosage of 15 mgO_3/L resulting in a

dosage of 1.28 gO_3/g DOC according to the Luxembourgish case study. Lowest elimination was observed for cyclophosphamide, iodixanol and naproxen (58%, 78% and 88%) which are known for reacting slower with ozone ($k''(O_3,app) < 50\ M^{-1}\ s^{-1}$) as already described in the literature [27, 28]. Tests were also done to evaluate the benefit of adding hydrogen peroxide into the ozone reactor influent, accelerating the decomposition of ozone and partially increasing the amount of OH-radicals in aqueous solution. Under these conditions, the elimination of slow O_3-reactive micropollutants should increase. This approach could theoretically have economic benefits since the use of a lower dosage of O_3 is resulting in less electrical energy demand. However, the hydrogen peroxide dosage resulted in a removal decrease of fast O_3-reactive pharmaceuticals. It was assumed that a part of the ozone was "consumed" by OH-radicals [20]. The lack of ozone resulted in an insufficient reaction with these type of pharmaceuticals. It is therefore crucial to find the optimum ratio of O_3/H_2O_2. Apart from the type of pharmaceuticals, this is influenced by the water matrix as well. The presence of few scavenger species (i.e. carbonate ions, pH and organic matter DOC) in the treated water can in fact result in a significant reduction of the treatment efficiency [20].

The pH was monitored over the experiments and it was found constant also with high H_2O_2 dosage. This result suggests that the generated intermediates and the acids become increasingly important scavengers of hydrogen radicals [29] especially when the supplied H_2O_2 dose is above the optimum value at which H_2O_2 tends to accumulate in the water. During ozonation, the probable formation of by-products (i.e. bromated) has also to be considered. Bromate is a potential human carcinogen [20] that forms during ozonation of bromide-containing waters. Levels of bromide in the source water above 50 µg/L can turn into a problematic bromate concentration [30]. In the Luxembourgish MBR permeate, a high concentration of Br^- (220.6 ± 7.5 µg/L) was measured together with a relatively high transferred ozone dose. To keep bromate formation relatively low, it was therefore suggested to not exceed an O_3 dosage range between 0.48 and 1.28 gO_3/g DOC. The Swiss partner of the PILLS project found similar results, i.e. an overall elimination of 80% with 0.5 gO_3/g DOC (except for cyclophosphamide, ifosfamide and the X-ray contrast media diatrizoate, iopamidol and iopromide).

Regarding the use of **PAC**, the Swiss partner stated an optimal dosage of 20 mgPAC/L (except for sulfamethoxazole and the X-ray contrast media diatrizoate and iopamidol).

The cost–benefit analysis for the **UV technology** has revealed 70% higher energy efficiency when using the LP UV lamp compared to the MP UV lamp. The best results for both configurations were gained as AOP operation when dosing 1.11 g/L H_2O_2 [23]. UV/H_2O_2 applying a fluence of more than 47,250 J/m^2 was effective to remove >77% of all the analysed pharmaceuticals.

Activated carbon filtration led to the elimination rates of >95% for all compounds with a fresh **GAC** filter. High elimination could also be achieved with reverse osmosis (RO).

With respect to the **energy consumption** of the treatment train, the following findings were made. For first step, i.e. the mechanical treatment (upstream the

bioreactor), 0.3–0.6 kWh/m^3 of electricity were estimated. The demand for the MBR was calculated with 0.9 kWh/m^3. During the regeneration process of activated carbon, the energy demand was found to be higher for PAC (0.45 kWh/m^3 including sand filtration) than for GAC (0.2 kWh/m^3). The energy consumption of the UV treatment amounted between 0.5 and 1.0 kWh/m^3 which is higher than ozonation ranging from $<$0.2 to 0.9 kWh/m^3. Energy consumption of RO was more than 1.0 kWh/m^3.

However, the centralized/decentralized treatment solution of pharmaceuticals was not only substance specifically discussed in the PILLS project. Performances in reducing **ecotoxicological effects** and in mitigating the propagation of antibiotic resistant genes were examined together with an energy cost evaluation. The biological treatment in the MBR decreased the potential toxic effects of the raw hospital wastewater. However, MBR permeate was still toxic to some organisms. Advanced treatments could not completely reduce the presence of toxic compounds and in some bioassays an increasing toxicity was even measured after the oxidation processes by ozonation or UV treatment. A post-treatment, such as sand filtration, of the oxidation processes could reduce the adverse effects of the oxidation significantly but not remove it satisfyingly. Only GAC filtration was found to efficiently remove the adverse effects of the UV treatment effluent.

In the context of advanced treatment of wastewater, the effects of treatments on antibiotic resistance are of important interest. Accordingly, quantification of the rRNA 16S encoding gene was performed together with monitoring of integrons as biomarker of **antibiotic resistance dissemination**. Antibiotic resistant genes were mostly removed during membrane filtration subsequent to the activated sludge process with a pore size of 0.04 μm. The effect of ozone or activated carbon on the reduction of the resistant integrons and their relative abundance in wastewater was negligible compared to the efficiency of the MBR.

Life-Cycle Assessment (LCA) methodology was used to holistically assess all the mentioned aspects (treatment type and its impact on the environment) and to conclude a preferable treatment approach. LCA normally considers three steps of the life cycle: the construction, the operation phase and the dismantling. In this particular case, because this LCA aims at comparing scenarios having similar infrastructures, the first and the last phases of the life cycle can be neglected. Only the indirect pollutant emissions due to the operation of the plant, i.e. those generated by energy and raw materials consumption and production, are considered. The environmental impact is calculated for many impact categories (global warming potential, acute and chronic ecotoxicity in water, carcinogenic effects and others) to broaden the possibility of comparison. LCA results showed that pharmaceuticals have a negligible impact compared to other pollutants such as phosphorus or heavy metals. From this perspective, an additional post-treatment has no advantage, neither in a centralized nor in a decentralized WWTP. The post-treatments generate significant additional impacts (related to energy and chemical consumption), for a relatively poor gain. If a decentralized treatment is implemented at a hospital, LCA gives a preference to ozonation or activated carbon treatment as compared to UV. It

is to highlight, however, that the results suffer from high uncertainties due to the assessment models of the toxicity of xenobiotics in LCA [31].

3.1 Other Relevant European Cases

Consequently, to the actions of the European Commission, more European countries started to test possible technical solutions for pharmaceutical removal with respect to the national and local requirements.

This accounts especially for building new hospitals or expanding activities of existing ones where administrations started to concretely consider treating wastewater at point source. Table 3 summarizes the characteristics of other relevant cases of decentralized applications excluding those of the PILLS project (already illustrated in Table 2).

The implementation of a full-scale WWTP to treat hospital wastewater has been first realized in 2008 in Germany at the Kreiskrankenhaus (hospital) Waldbröl [32–34], according to the authors' knowledge. Besides the aim to reduce pharmaceutical emissions, the hospital's objective was also to reduce the costs in terms of high charges that were raised by the receiving municipal WWTP operator due to the hospital loads of total organics and nitrogen.

Table 3 European cases (excluding PILLS applications) for full-scale decentralized treatments

Country	Main investigator	Location/Size of the hospital	Description
Germany [32–34]	RWTH Aachen University	Kreiskrankenhaus (hospital) Waldbröl Max 340 beds	Implementation of a WWTP with MBR process with O_3 post-treatment Nano-filtration, reverse osmosis and activated carbon filtration were "only" tested on pilot scale
Denmark [35, 36]	Grundfos BioBooster A/S	Herlev Hospital Max 825 beds	Two sequences are being tested: (1) MBR followed by O_3, GAC and/or H_2O_2 and UV (2) MBR followed by GAC and UV The test phase was completed in 2016
France [37]	Le GRAIE	Bellecombe, Scientrier, Haute-Savoie, France	The study site SIPIBEL included the pilot WWTP Bellecombe that has been implemented with separate treatments of hospital and urban wastewater, since a new hospital (Centre Hospitalier Alpes Léman, CHAL) was opened in February 2012
Italy [38]	University of Ferrara	Cona Hospital, Ferrara 900 beds	The plant comprised an MBR equipped with UF membranes followed by O_3 and UV
Netherlands [39]	Stowa	Reinier de Graaf Gasthuis (hospital) in Delft	The "Proof-of-principle" of Pharmafilter was tested full scale. Modular treatments can be combined and summed

Another treatment application was built in the frame of the expansion of Herlev Hospital medical specialties. The Danish government decided to take the opportunity of complying with the Environmental Protection Act's regulations concerning the use of the Best Available Techniques (BAT) for the treatment of wastewater. A full-scale plant that combines membrane technology with state of art advanced treatment (i.e. GAC, UV and O_3) was built to treat up to 560 m^3/day. Results were recently published [36] showing the excellent quality effluent with interest compounds concentrations below their PNEC.

An antecedent case was adopted in France with the concept of a separate treatment for wastewater contaminated by micropollutants. Here, the local administration of the commune Bellecombe decided for this approach in perspective of the construction of a new hospital [37]. The study site SIPIBEL (Site Pilote de Bellecombe, http://www.graie.org/Sipibel/), located at Scientrier, Haute-Savoie, France, comprised the pilot WWTP that was implemented with separated treatments, i.e. one for the hospital and one for the urban wastewater. Hospital effluents are led without special pretreatment into a collecting system, which routes them directly to the WWTP. The separated urban sewer network of the WWTP connects around 20,850 inhabitants. The assessment of both treatment lines (hospital wastewater and urban wastewater) was done by taking into account the treatment efficiency and the environmental response of the effluents. It was found that hospital wastewater treated with activated sludge removed more efficiently pharmaceuticals than equally treated urban wastewater. Antibiotics and analgesics were, anyway, still highly concentrated in the effluent of the hospital wastewater because of their high initial concentration.

Similarly in Italy, the question of treating the wastewater coming from the new complex hospital of Ferrara was raised due to the inadequate capacity of the receiving local WWTP of Gualdo, designed for a capacity of 1,000 PE. The case of study [38] benefits from a solid pilot-scale investigation about an appropriate MBR design that, upgraded with advanced treatments (i.e. O_3 and UV), is able to reduce the impact of the effluent in the environment. The comprehensive study considered technical aspects such as footprint and operating costs in order to guide decision makers.

More innovative product related solutions were also differently applied. In the Netherlands, the Pharmafilter installation [39] was tested producing a clean high quality effluent with no observable traces of pharmaceuticals suitable for reuse based on the parameters measured.

In Belgium, the scientific discussion [40] led to the founding of the ongoing Medix Project backed by the Walloon Region and its Greenwin competitiveness centre (for sustainable development) in partnership with national (Cebedeau, Liège University and Balteau SA) and international (Luxembourgish Institute of Science and Technology) institutions. The project aims at the development a system for the treatment of medicinal residues in wastewater. Results are not disclosed yet due to an intellectual properties agreement.

Apart from the above cases, the general trend of treatment installations indicates towards the centralized approach. However, technologies involving activated carbon or ozone are by far not attractive for rural areas with very small treatment plants from an economical but also holistic environmental point of view. Therefore, the

planning and implementation of large-scale tertiary treatment currently focusses on bigger WWTPs in urban areas which are significant point sources in the river basins they are located in. The strategy in this context is to update a limited number of individual treatment plants following a priority list to achieve the best reduction of micropollutant emissions possible for relevant surface waters.

In this context, Switzerland was the first country that decided on national level to upgrade municipal WWTPs. Based on plant capacity, effluent/dry-weather stream flow relation and sensitivity criteria, the Swiss government identified 100 out of 700 WWTPs that will be upgraded with a post-treatment step such as activated carbon or ozone within the next years [27, 41]. Currently, there are six plants in Switzerland with a post-treatment step either in operation or in planning phase. The majority, i.e. two-thirds, are applying ozone while the rest is equipped with PAC to remove organic micropollutants.

Also in Germany, considerable progress has been done within the last few years. This involves several regional studies to identify upgrading WWTPs candidates from an emission and related effects in the receiving water and to put this knowledge into action. For example, in the German federal state of Baden-Württemberg, 12 upgraded WWTPs are meanwhile in operation, two are in construction and three are planned to be upgraded [42]. The state of North Rhine-Westphalia counts seven upgraded WWTPs in operation while two are in construction and ten more are planned for upgrading. Over 99% of the concerned WWTPs offer capacity of more than 10,000 PE. PAC has a share of 63% and is therefore the favourite tool to reduce xenobiotic emissions. This is followed by GAC (21%) and ozone (16%). However, the decision for the one or the other treatment technology, that is normally done based on the local situation, appears not be evenly distributed over the regions since ozone is not all applied in Baden-Württemberg [42].

Considering the legislative development and the progress in measures that have "already" been undertaken, let us assume that the count of WWTPs, being able to reduce organic micropollutants to levels of no concern, will drastically increase within the upcoming years in Europe.

4 Alternative Actions to the Technical Solutions

The results achieved in the PILLS project strongly contributed to build the technical knowledge necessary to face pharmaceutical pollution. The impact on the scientific community was enormous and involved more and more actors of the "medicinal product chain". A natural consequence of the debate was the follow-up project European cooperation project noPILLS (INTERREG IVB) [43] which aimed to provide further information on the fate of pharmaceutical residues in the aquatic environment and alternative solutions to reduce emissions into surface waters. The core of the project was to address practical experience on the identification of potential and actually implemented technical and social intervention points across the "medicinal product chain". The focus was especially on consumer behaviour,

wastewater treatment and multi-stakeholder engagement. The project introduced and tested a separate collection of urine in the routine treatment of patients in radiology departments. Although with very low PNEC (potential no effect concentration), the X-ray contrast media were used as main tracer to evaluate the feasibility of such a methodology [44]. The separate collection and disposal of urine from ambulant patients only (Luxembourg) and from ambulant and stationery patients together (Germany) resulted both in a detectable reduction of emissions at the hospital but also and most importantly on catchment level, i.e. at the WWTP influent [25]. Moreover, separation at source and separate disposal is an efficient measure to avoid emissions of metabolites of pharmaceutical substances. Once implemented, it solves also the problem of pharmaceuticals based on new active ingredients of unknown behaviour in urban wastewater systems and risk for aquatic ecosystems. Key for the efficiency of a separation campaign is the active involvement of the medical staff (for the motivation and engagement of patients). Another important outcome was the clear need to inform and partly educate the medical staff about the environmental effects of pharmaceutical residues in the environment to increase the awareness and understanding.

5 Conclusions

The efficiency of conventional WWTPs in removing micropollutants – in particular pharmaceuticals and their metabolites – is relatively poor. Thus, a further treatment is required on centralized or decentralized level.

It was demonstrated that advanced treatments can effectively remove pharmaceuticals but at high energy and investment costs. However, decentralized treatment solutions at point sources did not show significant gain whereas no conclusive assessment was performed. It is to point out that, apart from pharmaceuticals, a centralized solution has the considerable advantage to tackle other organic micropollutants such as herbicides, fungicides, etc. as well that would otherwise reach the aquatic environment.

Nowadays, several countries in Europe started to take some action individually following their national policy. Few upgraded WWTPs are already existing. The majority of the upgraded plants is featured with PAC as post-treatment. With respect to the legislative progress, the aggregated scientific knowledge and the positive experiences from field studies, much more upgrading actions are expected in the near future on large treatments plants. A challenge, however, will be to find appropriate solutions for small treatment plants with decisive xenobiotic impact on sensitive water bodies and their ecosystem, i.e. generally rivers with low hydraulic rate.

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Hospital Wastewater Treatments Adopted in Asia, Africa, and Australia

Mustafa Al Aukidy, Saeb Al Chalabi, and Paola Verlicchi

Abstract This chapter provides an overview of the current management and treatment of hospital wastewater in Asia, Africa, and Australia. Twenty peer reviewed papers from different countries have been analyzed, highlighting the rationale behind each study and the efficacy of the investigated treatment in terms of macro- and micro-pollutants. Hospital wastewaters are subjected to different treatment scenarios in the studied countries (specific treatment, co-treatment, and direct disposal into the environment). Different technologies have been adopted acting as primary, secondary, and tertiary steps, the most widely applied technology being conventional activated sludge (CAS), followed by membrane bioreactor (MBR). Other types of technology were also investigated. Referring to the removal efficiency of macro- and micro-pollutants, the collected data demonstrates good removal efficiency of macro-pollutants using the current adopted technologies, while the removal of micro-pollutants (pharmaceutical substances) varies from low to high removal and release of some compounds was also observed. In general, there is no single practice which could be considered a solution to the problem of managing HWWs – in many cases a number of sequences are used in combination.

Keywords Antibiotic resistant bacteria, Hospital wastewater, Pharmaceuticals, Removal efficiency, Wastewater treatment

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Contents

1 Introduction

Hospital wastewater (HWW) is the wastewater discharged from all hospital activities, both medical and non-medical, including activities in surgery rooms, examination rooms, laboratories, nursery rooms, radiology rooms, kitchens, and laundry rooms. Hospitals consume consistent quantities of water per day. The consumption in hospitals in industrialized countries varies from 400 to 1,200 L per bed per day [1], whereas in developing countries this consumption seems to be between 200 and 400 L per bed per day [2].

HWWs are considered of similar quality to municipal wastewater [3, 4], but may also contain various potentially hazardous components which mainly include hazardous chemical compounds, heavy metals, disinfectants, and specific detergents resulting from diagnosis, laboratory, and research activities [5–9]. Higher concentrations of pharmaceutical compounds (PhCs) were found in hospital effluents than those found in municipal effluents [10, 11]. According to recent literature [8, 12–14], HWWs may be considered a hot spot in terms of the PhC load generated, prompting the scientific community to question the acceptability of the general practice of discharging HWWs into public sewers [8], where they are conveyed to municipal wastewater treatment plants (WWTPs) and co-treated with urban wastewaters (UWWs) [8, 13, 15, 16].

HWWs represent an important source of PhCs detected in all WWTP effluents, due to their inefficient removal in the conventional systems [17–20]. Indeed, HWWs may have an adverse impact on environmental and human health through the dissemination of antibiotics and antibiotic resistant bacteria in rivers [21–24]. The correct management, treatment, and disposal of HWWs are therefore of increasing international concern.

In European countries efforts are being made to improve the removal of PhCs by means of end-of-pipe treatments, and different full scale WWTPs have already been constructed for the specific treatment of hospital effluents [25].

In order to highlight this area of research in the rest of the world, this chapter provides an overview of the current management and treatment of HWWs in Asia, Africa, and Australia.

2 Treatment Scenarios of HWWs

Different treatment scenarios are applied in different countries for the treatment of HWWs. Table 1 lists all the treatment scenarios applied, with the corresponding references. Hospital effluents are usually discharged into the urban sewer system, where they mix with other effluents before finally being treated in the sewage treatment plant (co-treatment). This practice is common in Australia, Iran, Egypt, India, Japan, South Africa, and Thailand. However, in many other developing countries, such as Algeria, Bangladesh, Congo, Ethiopia, India, Nepal, Pakistan, Taiwan, and Vietnam, hospital effluents can represent a major source of toxic elements in the aquatic environment since the effluents are discharged into drainage systems, rivers, and lakes without prior treatment. According to Ashfaq et al. [41], no hospital, irrespective of its size, has installed proper wastewater treatment facilities in Pakistan. In Taiwan, some hospitals discharge their wastewaters

Table 1 Treatment scenarios of hospital effluents in different countries

Country	Treatment	Reference
Algeria	Direct disposal into the environment	[26]
Australia	Co-treatment	[14, 27]
Bangladesh	Direct disposal into the environment	[23]
China	Specific treatment	[10, 28–30]
Congo	Direct disposal into the environment	[31]
Egypt	Co-treatment	[4]
Ethiopia	Direct disposal into the environment	[32]
India	Direct disposal into the environment/co-treatment/specific treatment	[11, 31, 33]
Indonesia	Specific treatment/direct disposal into the environment	[34]
Iran	Specific treatment/co-treatment	[3, 35–37]
Iraq	Specific treatment	[38]
Japan	Co-treatment	[39]
Nepal	Direct disposal into the environment	[40]
Pakistan	Direct disposal into the environment	[21, 41]
Republic of Korea	Specific treatment	[42]
South Africa	Co-treatment	[43]
Taiwan	Direct disposal into the environment	[44]
Thailand	Co-treatment	[45]
Vietnam	Direct disposal into the environment	[6]

(legally or illegally) directly into nearby rivers with scarce treatment at all [44]. Of 70 governmental hospitals from different provinces of Iran, 48% were equipped with wastewater treatment systems, while 52% were not. Fifty-two percent of the hospitals without treatment plants disposed their raw wastewater into wells, 38% disposed it directly into the environment and the rest into the municipal wastewater network [35]. Comparison of the indicators between effluents of wastewater treatment systems and the standards of Environmental Departments shows the inefficiency of these systems and, despite recent improvements in hospital wastewater treatment systems, they should be upgraded.

In Indonesia, only 36% of hospitals have a WWTP and 64% of wastewater is discharged directly into receiving water bodies or using infiltration wells. Mostly, Hospital Wastewater Treatment Plants (HWWTP) use a combination of biological-chlorination processes with the discharge often exceeding the quality standard, such as Pb, phenol, ammonia free, ortho-phosphate, and free chlorine. The low quality of discharges into HWWTPs, especially of toxic pollutants (Pb and phenol), can be caused by not yet optimal biological-chlorination process [34].

An interesting investigation was carried out in 2004 in Kunming city, a large city in the southwest of China. Of 45 hospitals there were 36 with wastewater disinfection equipment. In the same year, the wastewater treatment facilities of 50 hospitals were investigated in Wuhan city, which is the biggest city in the central southern part of China. It showed that there were 46 hospitals with wastewater treatment facilities, and for only about 50% of them, the effluent quality from wastewater treatment facilities accorded with the national discharge standard [29, 46, 47].

In Iraq, most of the hospitals have their own treatment plant, but they are not capable of meeting Iraqi standards, especially in terms of nutrient and pathogen removal [38]. The scenario of hospital wastewater treatment is more stringent in countries like China, Indonesia, and the Republic of Korea, where HWW is treated onsite (specific treatment).

An effective, robust, and relatively low-cost treatment was used to disinfect HWWs during Haiti cholera outbreak occurred after the earthquake of January 2010. Two in-situ protocols were adopted: Protocol A included coagulation/flocculation and disinfection with hydrated (slaked) lime ($Ca(OH)_2$) by exposure to high pH and Protocol B using hydrochloric acid followed by pH neutralization and subsequent coagulation/flocculation, using aluminum sulfate. This approach is currently being adapted by non-governmental organizations (NGOs) to help managing human excreta in other emergency settings, including the outbreaks of Ebola and other infectious diseases in west Africa, Philippines, and Myanmar [48].

3 Overview of the Included Studies

The main characteristics of the studies included in this chapter referring to the specific treatment of hospital effluents are reported in Table 2. The main reason for research in European countries is generally an awareness of the potential risks

Table 2 List of the studies included in the overview together with a brief description of the corresponding investigations and rationale

Reference	Main characteristics of experimental investigations and treatment plants	Rationale	Investigated parameters
[6]	Investigation into the occurrence and behavior of fluoroquinolone antibacterial agents (FQs) in HWWs in Hanoi, Vietnam. A specific hospital CAS treatment plant was also investigated for the removal of FQs	The potential environmental risks and spread of antibacterial resistance among microorganisms	Ciprofloxacin and norfloxacin
[10]	Investigation carried out in Beijing (China) for the quantification of 22 common psychiatric pharmaceuticals and their removal in two psychiatric hospital WWTPs (CAS)	Potential impact of PhCs on ecosystems and human health	22 psychiatric pharmaceuticals
[11]	Investigation undertaken to identify the presence and removal of selected PCs in four STPs located in South India. The treatment process that treats HWWs is an extended aeration activated sludge process	The risk associated with the presence of pharmaceuticals in the environment	7 PhCs
[17]	Investigation carried out at the hospital located in Vellore, Tamil Nadu (India), by means of a lab-scale plant consisting of coagulation (by adding $FeCl_3$ up to 300 mg/L), rapid filtration, and disinfection (by adding a bleaching powder solution) steps	Options for hospital effluent pretreatment before discharge into public sewage	Conventional parameters: COD, BOD_5, SS, and P
[35]	Investigation carried out in Iran to analyze the hospital wastewater treatment system of 70 governmental hospitals from different provinces	Control of the discharge of chemical pollutants and active bacteria contained in hospital wastewater	Conventional parameters: TSS, BOD_5, COD
[34]	Investigation on a pilot-scale plant consisting of an aerated fixed film biofilter (AF2B reactor) coupled with an ozonation reactor fed by the effluent from Malang City hospital in Indonesia	Pollution and health problems for humans being caused by the discharge of HWWs	Conventional pollutants: BOD, phenols, fecal coliform, and Pb
[28]	Investigation carried out at Haidian community hospital (China), where a full scale submerged hollow fiber MBR was installed	Efficiency and operation stability of MBR equipped with microfiltration membranes in treating HWWs	Monitored pollutants were COD, BOD_5, NH_4, turbidity, and *Escherichia coli*

(continued)

Table 2 (continued)

Reference	Main characteristics of experimental investigations and treatment plants	Rationale	Investigated parameters
[29]	Investigation carried out in China on the operating conditions and MBR efficiency in treating hospital effluents	Attempts to avoid the spread of pathogenic microorganisms and viruses, especially following the outbreak of SARS in 2003	Conventional parameters: COD, BOD_5, NH_3, TSS, bacteria, and fecal coliform
[30]	A combination process of biological contact oxidation, MBR, and sodium hypochlorite disinfectants was applied to treat HWWs in Tianjin (China)	To meet the requirements of the Chinese discharge standards of water pollution for medical organizations	Conventional parameters: SS, BOD_5, COD, NH_3, total coliforms, fecal coliform
[40]	Analysis of the removal performance in a full scale two stage constructed wetland (CW) designed and constructed in Nepal to treat hospital effluent (20 m^3/d). The system consists of a three chambered septic tank, a horizontal flow bed (140 m^2), with 0.65–0.75 m depth, and a vertical flow bed (120 m^2) with 1 m depth. The beds were planted with local reeds (*Phragmites karka*)	Transferring CW technology to developing countries to reduce pollution in aquatic environments	Conventional parameters: TSS, BOD_5, COD, NH_4, PO_4^{2-}, total coliforms, *E. coli*, streptococci
[42]	Investigation carried out at two hospital WWTPs located in Korea to assess the occurrence and removal of selected pharmaceutical and personal care products. The wastewater treatment plants consist of (1) flocculation (FL) + activated carbon filtration (AC); (2) flocculation + CAS	Potential risks of anthelmintics on non-target organisms in the environment and their resistance to biodegradation	33 pharmaceutical and personal care products
[45]	Investigation carried out in Bangkok, Thailand, on the pretreatment of hospital effluents by using a lab-scale photo-Fenton process	Improvement in the biodegradability of hospital effluents by using the photo-Fenton process as a pretreatment	Conventional parameters: COD, BOD_5, TOC, turbidity, TSS, conductivity, and toxicity
[49]	Investigation carried out in Taiwan on the disinfection by continuous ozonation of the hospital effluent and in particular of the effluent from the kidney dialysis unit and on the increment of hospital effluent biodegradability	Disinfection effect and improvement in biodegradability of hospital effluent by ozonation	Conventional parameters: COD, BOD, total coliforms

(continued)

Table 2 (continued)

Reference	Main characteristics of experimental investigations and treatment plants	Rationale	Investigated parameters
[50]	Investigation carried out in India on a pilot plant consisting of preliminary and primary treatments, a conventional activated sludge system, sand filtration, and chlorination	Investigation into the microbiological community and evaluation of the risk of multidrug resistant bacteria spread	Different microbiological parameters: total coliforms, fecal enterococci, staphylococci, *Pseudomonas*, multidrug resistant bacteria
[51]	Analysis of the performance of seven WWTPs (CAS + chlorination) in the Kerman Province (Iran) receiving hospital effluents in terms of removal of main conventional parameters and malfunctions	Malfunctions in WWTPs receiving hospital effluents	Conventional parameters: COD, BOD_5, DO, TSS, pH, NO_2^-, NO_3^-, Cl^-, and SO_4^{2-}
[52]	Investigation carried out in Iran on a pilot-scale system consisting of an integrated anaerobic – aerobic fixed film reactor fed with hospital effluent before co-treatment with urban wastewater	Potential reduction of the organic load in hospital effluents by biological pretreatment before co-treatment	Conventional parameters: COD, BOD_5, NH_4, turbidity, bacteria, and *Escherichia coli*

posed by the occurrence of PhC residues in secondary effluents and the need to reduce the PhC load discharged into the environment via WWTP effluents [25]. However, the rationale behind the studies presented in this chapter was to evaluate different options for hospital effluent treatments before discharge into public sewage or into the environment, to improve the biodegradability of hospital effluents, to avoid the spread of pathogenic microorganisms, viruses, antibiotic resistant bacteria, pharmaceuticals, and chemical pollutants, to reduce the organic load and finally, to meet the requirements of discharge standards in different countries. Of all the studies, only four deal with the occurrence of PhCs in hospital effluents, while the remaining studies take into consideration pathogenic bacteria and conventional pollutants like COD, BOD, and SS.

4 Antibiotic Resistant Bacteria in HWWs

Although antibiotics have been used in large quantities for some decades, the existence of these substances in the environment has received little attention until recently. In the last few years a more complex investigation of antibiotics has been undertaken in different countries in order to assess their environmental risks. It has been found that the concentrations of antibiotics are higher in hospital effluents than in municipal wastewater, which has higher concentration levels than different

surface waters, ground water, and sea water [53]. HWWs could be a source of antimicrobial-resistant bacteria which are excreted by patients. The HWWs either flow into a hospital sewage system or directly into a municipal wastewater sewer, before being subsequently treated in a WWTP. After treatment in a WWTP, the effluent is discharged into surface waters or is used for irrigation. Studies have shown that the release of wastewater from hospitals was associated with an increase in the prevalence of antibiotic resistance. A study conducted in Australia by Thompson et al. 2012 [27] revealed evidence of the survival of antibiotic resistant strains in untreated HWWs and their transit to the STP and then through to the final treated effluent. The strong influence of HWWs on the prevalence of antimicrobial-resistant *E. coli* in Indian WWTPs has been revealed by Alam et al. [24] and Akiba et al. [33]. Untreated hospital and municipal wastewaters were found to be responsible for the dissemination of antibiotics and antibiotic resistant bacteria in the rivers of Pakistan [22].

In Bangladesh, a study was conducted by Akter et al. [23] concerning the effects of hospital effluents on the emergence and development of drug-resistant bacteria. They concluded that hospital and agricultural wastewater is mostly responsible for causing environmental pollution by spreading un-metabolized antibiotics and resistant bacteria. Analyses of the results obtained from South Africa indicated that HWWs may be one of the sources of antibiotic resistant bacteria in the receiving WWTP. The findings also revealed that the final effluent discharged into the environment was contaminated with multi-resistant *enterococci* species, thus posing a health hazard to the receiving aquatic environment as these could eventually be transmitted to the humans and animals exposed to it [43, 54].

As a result, hospitals are important point sources which contribute to the release of both antimicrobials and antibiotic resistant genes into surface waters, especially if hospital wastewaters are discharged into the receiving ambient waters without being treated.

5 Treatment Sequences for HWWs Under Review

The sequences adopted for the specific treatment of hospital effluent in different countries are reported in Table 3, along with the corresponding bibliographic reference. As can be seen, treatments differ with a trend towards MBR, followed by CAS. Most of the investigations refer to full scale plants and include the following treatment trains: CAS in China, India, Iran, and Vietnam; MBR, MBR + disinfection in China; Flocculation + Activated carbon, Flocculation + CAS in South Korea; Septic Tank + H-SSF bed + V-SSF bed in Nepal, and Ponds in Ethiopia. Seventy-eight percent of the equipped hospitals in Iran used activated sludge systems and 22% used septic tanks [35].

Several pilot plants were also tested in different countries: CAS + Sand Filtration + Chlorination in India; Aerated Fixed Film Biofilter + O_3 in Indonesia; CAS and Fixed film bioreactor in Iran, and finally preozonation in Taiwan. Lab scales of

Table 3 Treatment sequences for hospital effluents included in the chapter

Country	LAB	PILOT	FULL scale	Reference
China			MBR MBR + chlorination	[29]
China			MBR	[28]
China			CAS	[10]
China			Biological contact oxydization + MBR + sodium hypochlorite disinfection	[30]
Egypt	CAS			[4]
Ethiopia			Ponds	[32]
India		CAS + SF + chlorination		[50]
India	Coagulation + filtration + chlorination			[17]
India			CAS	[11]
Indonesia		Aerated fixed film biofilter + O_3		[34]
Iran		CAS		[36]
Iran			CAS + chlorination	[51]
Iran		Fixed film bioreactor + co-treatment		[52]
Iran			CAS, septic tank	[35]
Iran	Electrocoagulation			[55]
Iraq	MBR			[38]
Nepal			Septic tank + H-SSF bed + V-SSF bed	[40]
Republic of Korea			Floc + activated carbon, Floc + CAS	[42]
Taiwan		Preozonation		[49]
Thailand	Photo-Fenton Photo-Fenton + CAS			[45]
Vietnam			CAS	[6]

Floc flocculation, *SF* sand filtration, *H-SSF* horizontal subsurface flow, *V-SSF* vertical subsurface flow

CAS were tested in Egypt, coagulation + Filtration + Chlorination in India, MBR in Iraq, and Photo-Fenton, Photo-Fenton + CAS in Thailand. Recently, HWWs were also treated by electrocoagulation using aluminum and iron electrodes in Iran [55]. In this study the removal of COD from HWWs was investigated in a lab scale achieving a good removal at pH 3, 30 V, and 60 min reaction time using iron electrodes.

6 Efficiency of the Adopted HWW Treatment Plants

The removal efficiencies of conventional parameters as well as PhCs from HWWs using different systems are discussed below. As previously reported, different technologies were tested for the treatment of HWWs acting as primary, secondary, and tertiary steps.

6.1 Removal Efficiency of Conventional Pollutants

Figure 1 shows the removal efficiency of conventional pollutants obtained from different studies using a primary treatment (Coagulation + filtration + disinfection; Photo Fenton) and secondary treatment (CW; Ponds; CAS; MBR; Biological contact oxidation + MBR + NaClO disinfection; Anaerobic aerobic fixed film reactor, and Aerated fixed film bioreactor + O_3).

Very good removal efficiencies were observed for TSS and BOD_5 (97–99%), COD (94–97%), N–NH_4 (80–99%), total coliform (99.87–99.999%), *E. coli* (99.98–99.999%), and *Streptococcus* (99.3–99.99%) using a septic tank followed by a H-SSF and a V-SSF bed purposely designed for the treatment of HWWs in Nepal [40].

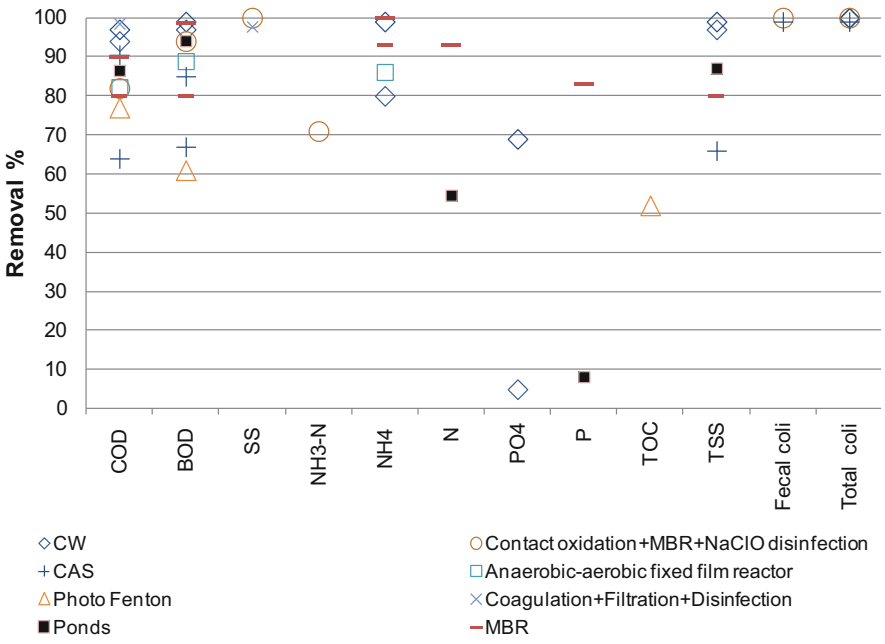

Fig. 1 Removal efficiencies from HWW for conventional pollutants in different primary and secondary treatments. Data from [4, 17, 28–30, 32, 35, 38, 45, 52]

The suitability of a series of facultative and maturation ponds for the treatment of HWWs has been examined in Ethiopia [32]. The percentage treatment efficiency of the pond was 94, 87, 87, 69, 55, 55, and 32 for BOD_5, TSS, COD, Nitrate, Nitrite, Total Nitrogen, and Total Dissolved Solids, respectively, while the treatment efficiency for total and fecal coliform bacteria was 99.74% and 99.36%, respectively. However, the effluent still contains large numbers of these bacteria, which are unsuitable for irrigation and aquaculture.

A pilot-scale system integrated anaerobic–aerobic fixed film reactor for HWW treatment was constructed and its performance was evaluated in Iran [52]. The results show that the system efficiently removed 95, 89, and 86% of the COD, BOD, and NH_4, respectively. COD removal was greater than 70% when 200 mg/L of ferric chloride was added to an Indian raw hospital effluent and removal increased to over 98% if the coagulant was added to settle HWW. A subsequent disinfection step using calcium hydrochloride reduces not only microorganisms, but also COD [17].

Attempts have been made to reduce toxicity and improve the biodegradability and oxidation degree of pollutants in HWWs prior to discharge into the existing biological treatment plant [45, 56]. Using the photo-Fenton process as a pre-treatment method, a significant enhancement of biodegradability was found at the following optimum conditions: a dosage ratio of COD:H_2O_2:Fe (II) of 1:4:0.1 and a reaction pH of 3. At these conditions, the value of the BOD_5:COD ratio increased from 0.30 in raw wastewater to 0.52 for treated wastewater. The toxicity of the wastewater drastically reduced with this process [56].

Nasr and Yazdanbakhsh [35] investigated the treatment efficiency of 70 governmental hospitals from different provinces of Iran, where 78% of them use the CAS system and 22% use septic tanks. The mean removal rates of BOD, COD, and TSS were found to be 67%, 64%, and 66%, respectively. A high removal rate (99–100%) of fecal and total coliforms was obtained using CAS and MBR, followed by disinfection treatment [4, 30].

Figure 1 clearly demonstrates how MBR technology is capable of achieving good removal efficiency (80%) of all the macro-pollutants, with the sole exception of NH_3–N, whose removal was found to be 71%.

In Iraq, local wastewater treatment units in various hospitals are not capable of meeting Iraqi standards, especially in terms of nutrient and pathogen removal. For this reason, a lab scale sequencing anoxic/anaerobic membrane bioreactor system is studied to treat hospital wastewater with the aim of removing organic matter, as well as nitrogen and phosphorus under a different internal recycling time mode [38]. The system produces high quality effluents which can meet Iraqi limits for irrigation purposes for all measured parameters.

Membrane separation plays an important role in ensuring excellent and stable effluent quality. The advantages of MBR systems, such as complete solid removal from effluents, effluent disinfection, high loading rate capability, low/zero sludge production, rapid start-up, compact size, and lower energy consumption, have driven authorities to use them in treating HWWs.

An interesting approach to managing hospital effluents has been established in China, where over 50 MBR plants have been successfully built for HWW treatments, with a capacity ranging from 20 to 2,000 m^3/d (see Table 4). MBR can effectively save disinfectant consumption (chlorine addition can decrease to 1.0 mg/L), shorten the reaction time (approximately 1.5 min, 2.5–5% of the conventional wastewater treatment process), and deactivate microorganisms. Higher disinfection efficacy is achieved in MBR effluents at lower doses of disinfectant with fewer disinfection by-products (DBPs). Moreover, when the capacity of MBR plants increases from 20 to 1,000 m^3/d, their operating costs decrease sharply [29].

The performance of a submerged hollow fiber membrane bioreactor (MBR) for the treatment of HWW was investigated by [28]. The removal efficiencies for COD, NH^{4+}–N, and turbidity were 80%, 93%, and 83%, respectively, with the average effluent quality of COD <25 mg/L, NH^{4+}–N <1.5 mg/L, and turbidity <3 NTU. *Escherichia coli* removal was over 98%. The effluent was colorless and odourless.

A combination process of biological contact oxidation, MBR, and sodium hypochlorite disinfectants has been applied to treat HWWs in Tianjin (China). The obtained results showed that the main parameters meet the requirements of the Chinese discharge standards of water pollution for medical organizations [30].

6.2 Removal Efficiency of PhCs

Figure 2 reports all collected data regarding the removal of PhCs in hospital effluents using a full scale CAS system operating in different countries (Vietnam,

Table 4 Application of MBR in hospital wastewater treatments in China (Adopted from [29])

Treatment train	Membrane area (m^2)	Membrane material	Membrane pore (μm)	Capacity (m^3/d)	HRT (h)	Commissioned
MBR	96	Hollow fiber membrane (PE)	0.4	20		2000
MBR + $NaClO_3$			0.2	100		2004
MBR				140	6	2004
MBR		Organic membrane	1.3	200	5	2002
MBR				200		2004
MBR + NaClO	900	PVDF	0.22	400	7.5	2005
MBR + ClO_2	2,000	PVDF	0.22	500	7	2003
MBR + NaClO	4,000	Hollow fiber membrane (PVDF)	0.22	1,000	5	2005
MBR + ClO_2	8,000	Hollow fiber membrane (PVDF)	0.4	2,000	5.4	2008

PVDF poly vinyldene fluoride, *PE* polyethylene

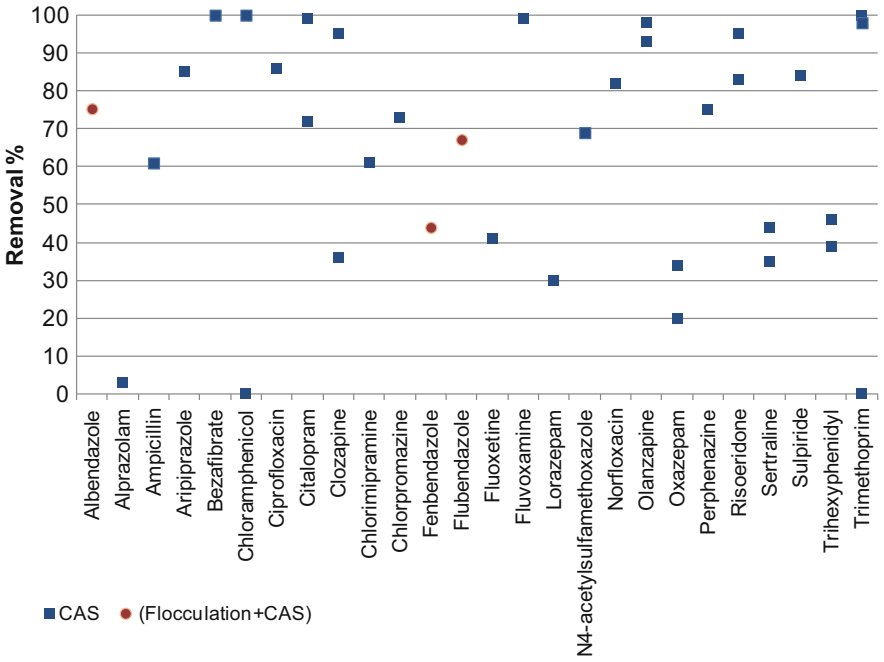

Fig. 2 Removal efficiencies from HWW for selected PhCs in CAS system. Data from [6, 10, 11, 42]

India, South Korea, and China). High removal efficiencies (>80%) were observed for bezafibrate, chloramphenicol, trimethoprim, aripiprazole, clozapine, fluvoxamine, olanzapine, risperidone, sulpiride, and citalopram. Albendazole, ampicillin, N4-acetylsulfamethoxazole, chlorpromazine, chlorimipramine, flubendazole, and perphenazine were moderately removed (60–80%), whereas low removal (less than 50%) was observed for alprazolam, oxazepam, sertraline, trihexyphenidyl, clozapine, fluoxetine, lorazepam, and fenbendazole.

Negative removals of sulfamethoxazole, chloramphenicol, erythromycin, naproxen, bezafibrate, and ampicillin in sewage treatment plants treating hospital effluents in South India were also observed [11].

The results achieved by Yuan et al. [10] showed that a secondary treatment of a psychiatric hospital was more effective in removing the majority of target compounds [e.g., olanzapine (93–98%), risperidone (72–95%), quetiapine (>73%), and aripiprazole (64–70%)] than treated municipal wastewater.

The overall removal values of ciprofloxacin and norfloxacin in a small HWWTP consisting of a CAS+ anaerobic biological treatment system situated in Vietnam were found to be 86% and 82%, respectively [6].

7 Regulation

As previously reported, HWWs are often considered similar to urban wastewater. As a result, they are usually co-treated with urban wastewater in the WWTP. Moreover, in many developing countries, they are directly discharged into the environment along with urban wastewater.

There is no regulation in most of the studied countries that imposes authorities to treat HWWs as special waste, with the exception of China where, in July 2005, the Chinese authorities published the "Discharge standard of water pollution for medical organization," a document outlining comprehensive control requirements for HWWs [30]. Recently, a new law regarding environmental protection has been presented in Vietnam (No. 55/2014/QH13, article 72) [57]. This law obliges hospitals and medical facilities to collect and treat medical wastewater in accordance with environmental standards.

On a global scale, the only existing guidelines concerning hospital effluents management and treatment were published by the World Health Organization (WHO) in 1999: "Safe Management of Wastes from Health-Care Activities" [58] and updated in 2013 [59]. This publication describes basic methods for the treatment and disposal of health-care wastes and in particular recommends a pretreatment of effluents originated from specific departments as discussed in [60] of this book. These guidelines could be a reference in the management and treatment of HWWs mainly for developing countries in order to preserve the environment.

8 Conclusions

Hospitals are important point sources contributing to the release of both PhCs and antibiotic resistant bacteria into surface waters, especially if hospital wastewaters are discharged without treatment into the receiving ambient waters. This problem is more severe in developing countries because no wastewater treatment facility is available in most of the cases. Hospital wastewaters are subjected to different treatment scenarios in the studied countries (specific treatment, co-treatment, and direct disposal into the environment). Due to the lack of municipal wastewater treatment plants, the onsite treatment of hospital wastewater before discharge into municipal sewers should be considered a viable option and consequently implemented. Where applicable, the discharge of HWWs into municipal wastewater collection systems is an alternative for wastewater management in hospitals. Upgrading existing WWTPs and improving operation and maintenance practices through the use of experienced operators are recommended measures.

In general, there is no single practice which could be considered a solution to the problem of managing HWWs. Indeed, in many cases, a number of sequences are used in combination. Each practice has its own strengths and weaknesses. More

effective disinfection processes coupled with membrane filtration should be adopted for better removal of harmful bacteria and PhCs.

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Full-Scale Plants for Dedicated Treatment of Hospital Effluents

Sara Rodriguez-Mozaz, Daniel Lucas, and Damià Barceló

Abstract Hospital effluents are usually discharged in the municipal sewer system without any previous pretreatment. However, hospital wastewater contains a complex mixture of hazardous chemicals and harmful microbes, which can pose a threat to the environment and public health. Therefore, some efforts have been carried out in the last years with the objective of treating hospital wastewater effluents on-site before its discharge either in the sewer system or into the receiving natural water body. Several initiatives and case studies of full-scale wastewater treatment plants (WWTPs) implemented in hospitals are gathered together in this chapter. Different treatment train types were considered and reviewed, and the most common and efficient primary, secondary, and tertiary treatments applied were discussed. Several water quality parameters were monitored in the 23 studies comprised in this chapter for the performance assessment of the hospital wastewater treatment plants (HWWTPs). Special attention was paid to specific contaminants that are present at relatively high levels in hospital effluent such as antibiotics. In line with this, the spread and dissemination of antibiotic resistance from hospital and HWWTPs was considered an important topic to be addressed in this chapter.

Keywords Dedicated wastewater treatment, Full-scale WWTPs, Hospital effluents, On-site treatment, PhACs

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Contents

1 Introduction

Hospital wastewater is comparable with ordinary domestic wastewater plus a very special mixture of different pollutants such as pharmaceutical active compounds (PhACs), heavy metals, detergents, X-ray contrast media, and disinfecting agents [1] along with pathogenic microorganisms such as viruses, bacteria, fungi, protozoans, and helminthes [2, 3]. Hospital sewage can thus represent a threat to public health due to its potential toxicity, highly infectious potential, and its role in pathogen dissemination and in antibiotic resistance spread into the environment. Mixing between these effluents and drugs can indeed promote a selective pressure, capable of inducing innate microorganisms to a rapid adaptation to these fluctuating conditions through genome rearrangement [4]. Despite of this, hospital wastewater has long been treated along with urban wastewater, with the conventional wastewater treatment processes, which are designed for the removal of BOD (biological oxygen demand) and SS (suspended solids), but not for pathogens [5] or other micropollutants [6, 7].

There is not a specific directive or guideline for the management of hospital wastewater effluents in Europe, so member states apply their own legislation, evaluation, and selection criteria for hospital wastewater (HWW) quality and its management. However, national legal regulations, quite rarely, define how to manage and treat hospital wastewaters before its disposal (discharge in public sewage for treatment at a municipal WWTP or discharge into a surface water body) [8, 9]. In some countries (e.g., Spain and France), hospital facilities are considered industrial and therefore HWW should comply with certain characteristics before being discharged in the municipal wastewater treatment plant (WWTP), and very often a pretreatment is required. In some other countries (e.g., Italy), HWW can be directly discharged in the public sewer and conveyed to the municipal WWTP if it complies with specific characteristics established by the WWTP authority. Otherwise, it has to be pretreated. In contrast, in other countries (e.g., Germany) hospital wastewater is considered to be domestic or communal, and neither authorization nor specific characteristics are required [10]. The contribution of hospital facilities to the total volume uploaded in the municipal WWTP depends on many factors but can range between 0.2 and 2% of the total discharge treated in a municipal WWTP as calculated by Carraro et al. based on several studies worldwide [10]. However, in some occasions, a hospital can deliver up to 68% of total

domestic WWTP influent, as reported in a hospital in Italy [11]. In China, the total number of hospitals has raised almost double in two decades, and in 2008 the volume of hospital wastewater generated corresponded to approximately 1% of total municipal wastewater [12].

Indicators required for assessment of hospital effluents quality are usually physicochemical parameters, macropollutants (NH_4, NO_x, oil and grease, tensioactives, phosphorous, chlorines, and others), and, in some rare cases, microbiological indicators (typically *E. coli*). However, a concern has emerged in the last years regarding substances and microorganisms that do not have a regulatory status such as antibiotic residues and specific pathogens, and none of them have a specific limitation before discharge in WWTPs or in surface water [10]. The common practice of co-treating hospitals and urban wastewaters jointly at a municipal WWTP is considered as an inadequate solution for the removal of compounds such as PhACs [13, 14] by many authors, because dilution of the hospital effluents would occur; it has been demonstrated that wastewater dilution is detrimental for the biological removal by conventional activated sludge (CAS) of some micropollutants such as PhACs [15, 16]. Therefore, the use of alternative wastewater treatments at the source point for this kind of effluents has been highly recommended by many authors [9, 13, 14, 16, 17]. Extensive research has been performed in the last year in the development of appropriate decentralized treatment for the hospital effluents as it has been reviewed lately by Verlicchi et al. [13]. However, the application of full-scale dedicated treatment of the effluents in hospitals has been only implemented in a limited number of places. The objective of this chapter is to review the existing studies about on-site full-scale hospital wastewater treatment plants. Trends concerning the most applied treatment train types, parameters monitored, geographical differences, as wells a future research trends are discussed in this chapter.

2 Discussion

In a recent review by Verlicchi et al. on the management of treatment hospital effluent, an overview of 48 peer-reviewed papers is presented assessing the efficacy of different treatment steps of hospital wastewater, comprising lab, pilot, and full-scale approaches [13]. Most of the investigations referred to pilot/lab scale plants (69%) and the remaining 31% to full-scale dedicated facilities; hence, there is still many research efforts dedicated to the optimization of the most appropriate treatment for each hospital. Aspects to take into account in the design and implementation of full-scale treatments are the wastewater characteristics (type and concentration of pollutants), environmental conditions, further use of treated wastewater, and technical and economic feasibility of the treatment.

Table 1 gives an overview of several research works reporting about full-scale dedicated treatments of hospital wastewater effluents. A total of 23 studies performed since 2004 till 2016 are listed in Table 1, which also provides

Table 1 Literature review about dedicated full-scale hospital wastewater treatment plants

Country	Hospital characteristics		Treatment train				Receiving system	Quality parameters evaluated	Reference
	Flow rate (m^3/day)	Patients (beds)	Primary treatment	Secondary treatment	Tertiary treatment	Disinfection			
Denmark	360–500	691		MBR MBR	GAC + O_3/H_2O_2 GAC	UV UV	Water body and sewer system	PhACs, antibiotic resistance, and pathogens	[18]
Germany	768	340		MBR			n.i.	PhACs (8)	[19]
Germany	768	340		MBR			n.i.	Conventional parameters: COD, TOC, AOX, NH_4, total P, *E. coli*, and *Enterococci*	[1]
Germany	768	340		MBR	O_3		n.i.	Endocrine activity	[20]
Germany	200	580		MBR	O_3 + PAC + sand filtration PAC + sand filtration		Water body	Micropollutants (including PhACs), integrons, toxicity	[21]
Netherlands	240	1,076		MBR			Sewer system	Micropollutants (including PhACs), integrons, toxicity	[21]
Netherlands				MBR	O_3 + GAC		Sewer system	PhACs, endocrine activity, microbial parameters, and conventional parameters	[22]

Italy		900		MBR	O_3	UV	n.i.	Conventional parameters: COD, BOD5, NH_4, turbidity, and *Escherichia coli*	[11]
Greece		800		CAS		Chlorination	UWWTP through sewer system	Conventional parameters: COD, BOD5, NO3, PO4 and TSS, and PhACs	[23]
Ethiopia	143	305	Septic tank	Oxidation ponds			Lake	Conventional parameters: COD, BOD5, P, PO4, total nitrogen, NH3, NO3, NO2 TSS, TDS, Cl, S2, total coliforms, and fecal coliforms	[24]
Saudi Arabia	904 622	300 215		CAS	Sand filtration	Chlorination	n.i.	PhACs	[25]
Iran		255–1,073		CAS		Chlorination	n.i.	Conventional parameters: COD, BOD5, DO, TSS, pH, NO2, NO3, PO4, Cl, and sulfate	[26]
India	50	319		CAS		Chlorination	Water irrigation of gardens of hospital	Genotoxicity and mutagenicity	[27]

(continued)

Table 1 (continued)

Country	Hospital characteristics		Treatment train				Receiving system	Quality parameters evaluated	Reference
	Flow rate (m^3/day)	Patients (beds)	Primary treatment	Secondary treatment	Tertiary treatment	Disinfection			
Nepal	20		Septic tank	Constructed wetlands				Conventional parameters: TSS, BOD5, COD, NH_4, PO4 2−, total coliforms, *E. coli*, *Streptococci*	[28]
China				MBR MBR		Chlorination		Conventional parameters: COD, BOD5, NH3, TSS, bacteria, and fecal coliform	[7]
China	20			MBR			n.i.	Conventional parameters: COD, BOD5, NH_4, turbidity, and *Escherichia coli*	[29]
China		500–2,410		MBR Anaerobic oxic Oxidation ditch			n.i.	Antibiotics and corresponding ARGs	[30]

Vietnam[a]		220 520	Filtration Physical and chemical (not specified)	CAS CAS		Not specified	 Environment (not specified)	Antibiotics	[31]
Republic of Korea			Flocculation Flocculation	 CAS	Activated carbon		River water and seawater	PPCPs	[32]
Brazil	190		Septic tank		Anaerobic filter		Water stream	Psychiatric drugs (5)	[33]
Brazil			Septic tank		Anaerobic filter		Water stream	Antibiotics (ciprofloxacin)	[34]
Brazil	219 432	2,000 patients 22,000 patients		UASB CAS	Anaerobic filter	 Chlorination	Bay Lagoon	Enteric viruses and hepatitis A	[35]
Brazil	220	320		CAS		Chlorination	River and seawater through the rainwater network	Antibiotic resistance profiles of *Pseudomonas aeruginosa*, pH, conductivity, turbidity, dissolved oxygen, temperature, salinity, and chlorine	[3]

(continued)

Table 1 (continued)

Country	Hospital characteristics		Treatment train				Receiving system	Quality parameters evaluated	Reference
	Flow rate (m^3/day)	Patients (beds)	Primary treatment	Secondary treatment	Tertiary treatment	Disinfection			
Brazil	220	320		CAS		Chlorination	River and seawater through the rainwater network	*Pseudomonas aeruginosa* isolates and β-lactam-encoding genes	[36]

UASB upflow anaerobic sludge blanket, *PAC* powdered activated carbon, *GAC* granulated activated carbon, *CAS* conventional activated sludge, *MBR* membrane bioreactor, *PPCPs* pharmaceuticals and personal care products, *PhACs* pharmaceutical active compounds, *n.i.* not indicated

[a]Detailed description of the wastewater treatment plants was not available

information about the country where the study was conducted along with several details such as the size of the hospital, the treatment type applied in each case, as well as quality parameters considered to evaluate the efficiency of the treatment. Full-scale WWTPs for the treatment of hospital effluents have been implemented all over the world being Brazil, with seven manuscripts, the country with the highest number of studies about the topic, followed by China and Germany with three studies each, and the Netherlands with two. In other countries such as Denmark, Greece, Italy, Iran, Taiwan, Korea, Ethiopia, Saudi Arabia, India, Nepal, and Vietnam, just one study was reported in each of them. Most of the studies were carried out in developing countries, where for urban wastewater usually only basic sewage systems are operating, and, therefore, dedicated treatments are necessary to guarantee a safe treatment and disposal of hospital effluents. In addition, in the case of countries experiencing epidemics of enteric diseases, the on-site treatment, or at least pretreatment, of the wastewater before discharge into the municipal sewerage system should be considered to prevent and avoid the spread of disease outbreaks due to pathogens [10]. In contrast, in European countries, implementation of dedicated treatments and research efforts on the topic are driven by the awareness of the potential risk posed by hospital effluents and the need of reduce the load of emerging pollutants such as PhACs, which are present at higher concentrations in hospital effluents [9, 37]. In general, if the hospital is not connected with a public wastewater treatment, the facility should have an efficient on-site wastewater treatment [10]. Water scarcity and the need of water reuse for various requirements is another major reason for the performance of on-site treatment of hospital effluents in both developed and low- and middle-income developing countries.

2.1 Wastewater Treatment Trains Implemented in Hospitals

Typical treatment steps in a hospital wastewater treatment plant (HWWTP) include preliminary treatments such as clarification, followed by a secondary biological treatment and by a polishing treatment before its disposal in the sewer system or in the receiving natural environment.

2.1.1 Primary Treatment

Preliminary treatments are generally adopted with the aim of removing rough and coarse material from raw wastewater, thus protecting mechanical and electrical parts in the downstream treatment steps [13]. A septic tank was applied in three HWWTP locations: in Brazil, Nepal, and Ethiopia [24, 28, 33]. In a septic tank, by means of slowing down the wastewater flow, part of the solids settle to the bottom of the tank while the floatable solids (fats, oil, and greases) rise to the top. Up to 50% of the solids retained in the tank decompose; the rest accumulate as sludge at

the tank bottom and need to be removed periodically by pumping the tank. Another example of primary treatment is chemical flocculation, the treatment applied in the dedicated full-scale HWWTP in Korea with the aim of removing suspended solids and colloids from wastewater that do not settle spontaneously [32]. In the recent study of Lien et al., both filtration and other physicochemical processes were applied as preliminary treatment before CAS in HWWTPs in two different hospitals in Vietnam [31].

2.1.2 Secondary Treatment

Conventional Sludge (CAS) and Membrane Biological Reactor (MBR) systems are the most used approaches for secondary treatment within the 23 studies covered in this chapter (Table 1). Traditionally, CAS processes have been the most representative technology at full-scale WWTPs, but such systems require a final settling step in order to separate the biological sludge from the effluent. In contrast, MBR combine the biological process with a membrane filtration step within one process unit, overcoming clarification and producing a high-quality effluent [38]. Moreover, passage through ultrafiltration membranes guarantees a better disinfection of the wastewater, thus reducing the risk of spread of pathogenic bacteria and of multidrug-resistant bacteria [13]. Finally, the absence of suspended solids in the MBR effluent makes it suitable for further tertiary treatment using advanced technologies such as NF and advanced oxidation processes (AOPs), since suspended solids can interfere with their removal performance [13]. Unfortunately, operating expenditures of MBR are still the main drawback that prevents their implementation, mainly due to aeration costs, membrane permeability loss, and hence need of regular membrane replacement [39]. Therefore, MBR systems applied for HWW treatment are investigated and implemented basically in European countries (seven studies) [1, 11, 18–22] and in China (three studies) [7, 29, 30] whereas nine studies in countries all over the world report about CAS treatments [1, 3, 23, 25–27, 31, 32, 35, 36], which are considered in general a more affordable treatment than MBR. The broad implementation of MBR systems for the treatment of hospital effluents in China is quite remarkable. Over 50 MBR plants were built for hospital wastewater treatment during the decade 2000s so that higher disinfection efficacy is achieved in MBR effluents at lower dose of disinfectant with less disinfection by-product (DBPs) formation [7]. Four case studies where MBR is applied to the treatment of hospital wastewaters were investigated by Liu et al. [7], five by Li et al. [30] and one by Wen et al. [29]. Concerning the type of membranes employed in MBR systems, ultrafiltration membranes were investigated in Italy [11], Netherlands [22], Denmark [18, 40] and at the Swiss, German, and Dutch units within the PILLS project [21], whereas microfiltration membranes were only used at the studies in Germany and China [19, 29]. Concerning the removal of PhACs in MBR systems, Verlicchi et al. reviewed the performance of several MBR systems for the treatment of hospital wastewater not only in full-scale but also pilot and lab scale treatments and observed that the aspects that greatly contributes to the

removal of PhACs is the combination of higher biomass concentration in the aerated basin, the development of different bacterial species within the biomass, the smaller sludge flocks (that may enhance sorption on the surface of different contaminants), the higher SRTs, and the higher removal of suspended solids [13].

The performance of CAS treatment was assessed in nine studies for conventional parameters [26], PPCPs [23, 25, 31, 35], *Pseudomonas aeruginosa* [3, 36], enteric viruses and hepatitis A [35], and genotoxicity and mutagenicity [27]. In almost all cases, CAS treatment is followed by a disinfection step (chlorination). Only Sim et al. do not consider further treatment after CAS [32], whereas Lien et al. do not specify the type of disinfection step applied in their study [31]. Conventional parameters of seven WWTPs (CAS + chlorination) in Kerman Province (Iran) receiving hospital effluent in terms of removal of main conventional parameters was evaluated in the study by Mahvi et al. [26]. Disinfection is mandatory in Iran in case of disease outbreaks and in critical periods (in the summer and autumn due to reduced river water flow) [26]. Authors encountered that the most common malfunctions are due to operator inexperience at the WWTP and negligent WWTP management by the authorities. Chemical flocculation followed by a CAS process represents an efficient barrier for anthelmintic drugs (albendazole and flubendazole) considering that overall removal is in the range of 67–75% in a CAS-based treatment in Korea [32]. Finally, in the research by Kosma et al., removal efficiencies were provided for ten PhACs after CAS + chlorination (tertiary treatment) in Greece [23].

Other Biological Systems

Other biological systems applied for HWW treatment include ponds, constructed wetlands, and anaerobic treatment. Investigation was carried out at Hawassa University Referral Hospital (Ethiopia) to examine the suitability of a series of waste stabilization ponds (2 facultative ponds, 2 maturation ponds and 1 fish pond covering an area of about 3,000 m^2 with a total retention time of 43 days) for the treatment of hospital effluents [24]. The treatment was considered efficient in the removal of most of the general contaminant indicators, including total and fecal coliform (higher than 99.4%). However, final concentrations do not fulfill WHO recommendations for restricted and unrestricted irrigation, and the application of constructed wetlands was foreseen as a feasible option to comply with it. In fact, constructed wetlands (CW) are a feasible technology to be applied in developing countries for the treatment of wastewater. A two-stage CW after a septic tank is applied in Nepal to treat hospital effluent and consists in a horizontal subsurface flow bed (H-SSF bed) and a vertical subsurface flow bed (+V-SSF bed) planted with local reeds (*Phragmites karka*) [28]. Very good removal efficiencies were observed for TSS, BOD_5, COD, $N\text{-}NH_4$, as well as for total coliform (99.87–99.99%), *E. coli* (99.98–99.99%), and *Streptococcus* (99.3–99.99%). Finally, application of anaerobic treatment was also considered in some investigation carried out in Brazil on

the removal of enteric viruses and hepatitis A [35] and in the removal of antibiotics and antibiotic resistance genes in China [30].

As regards to biological treatment of wastewater, special attention must be paid to evaluate the potential inhibition effect on the biological activities of pollutants such as PhACs, heavy metals, disinfectants, and detergents that occur at higher concentrations in HWW rather than in UWW; thus, the risk that they could negatively affect the degradation processes of microcontaminants has to be assessed [13]. Adequate pretreatment is extremely useful particularly in membrane bioreactor (MBR) configurations to avoid clogging of membranes and thus guarantee their continuous operation.

2.1.3 Tertiary Treatment

The tertiary treatment is the final cleaning process applied after secondary treatment to remove remaining residual organic matter, inorganic molecules, and remaining microorganisms. Tertiary treatment is necessary to remove in source points such as hospitals, those compounds that are not efficiently removed in conventional biological treatment, and also those particularly relevant from ecotoxicological point of view. In the dedicated treatments reviewed in this chapter, filtration through activated carbon both as powdered activated carbon (PAC) [21] and granulated activated carbon (GAC) [18, 22] as well as non-specified activated carbon [32] was the tertiary treatment more often used as well as ozone treatment [11, 18, 21, 22], followed by anaerobic filtration in three studies of Brazil [33–35] and sand filtration [25].

Tertiary treatment was applied either alone or in combination with other polishing treatment, including final disinfection with chlorine (up to nine studies) [3, 7, 23, 25–27, 30, 31, 35, 36] or UV irradiation [11, 18]. The disinfection of wastewater is particularly required if the wastewater is discharged into any water body used for recreational activities or as a source of drinking water (including aquifers) or if it is discharged into coastal waters close to shellfish habitats, especially if the dietary habits of local people include eating raw shellfish [10]. In these cases, disinfection will always be applied at the end of treatment train, just before discharge in the environment. Concerning PhACs, an overview of the global removals obtained with different strategies applied as tertiary treatment of hospital effluents is provided by Verlicchi et al.: being PAC, UV, and AOPs the ones achieving up to 90% removal of most PhACs groups considered, whereas PhACs removal percentages obtained through chlorination and coagulation ranged between 20–70% and 20–40%, respectively [13]. In the study carried out in a HWWTP in the Netherlands, none of the PhACs (32 different compounds) were detected in the effluent after tertiary treatment based on GAC + ozone [21]. Regarding the fate and use of treated HWW, in most of the 23 studies gathered together in Table 1, treated effluent was discharged into a natural water body, i.e., river streams, lake, or marine environment nearby, whereas only in four cases in the Netherlands, Greece, and Denmark treated hospital wastewater was discharged into

the sewer system [18, 21–23] and further directed to the urban WWTP. Only in the case study of India the treated hospital wastewater was used as reclaimed water: treated wastewater was collected from the outlet of the treatment plant applied (CAS + chlorination) and further used for irrigating the gardens of the hospital [27].

2.2 Water Quality Parameters

Researchers can evaluate the performance of the HWW treatment on the basis of water quality parameters of the raw and treated water. The most common monitored parameters are COD, BOD_5, P, PO_4, total nitrogen, NH_3, NO_3^-, NO_2^-, TSS, TDS, Cl^-, total coliforms and fecal coliforms, as well as other microbial parameters. These are conventional parameters that provide the data necessary to assess if water meets minimal requirements for their disposal directly into the environment or in the sewer systems. However, other parameters have been attracting a lot of attention in the last years, e.g., the presence of emerging pollutants in hospital wastes. Among them, the occurrence and removal of pharmaceutical active compounds (PhACs) have been monitored in WWTPs worldwide in the last 20 years and hence also in HWWTP. PhACs are tackled in 9 out of the 23 studies listed in Table 1 [19–21, 23, 25, 30–34]. The high concentrations encountered in the HWW for many of these compounds as well as their potential environmental impact are the main reasons for their investigation in so many articles. As in the case of conventional WWTPs, treatments applied on-site in HWWTPs are not effective enough to degrade PhACs either, and thus WWTPs are considered the primary source of these compounds in the environment [6].

2.2.1 Antibiotics

Antibiotics are one of the PhACs classes with higher and increasing usage and consumption worldwide driven mainly by rising demand in low- and middle-income countries [41]. The most concerning effect of the antibiotics in the environment is the selective pressure they might exert in aquatic microbes, favoring the spread of antibiotic resistance genes (ARGs) and antibiotic resistance bacteria (ARB) [42, 43].

Hospital effluents have been reported to present a high load of antibiotics, among other pharmaceutical compounds, and thus discussion on the suitability of some source treatment has rose among the scientific community [11, 37, 44]. Antibiotics were studied specifically in three studies in on-site HWW treatment [30, 31, 34]. No apparent removal of the antibiotic ciprofloxacin (CIP) was observed after the treatment of HWW with a septic tank followed by an anaerobic filter in Brazil, with an average concentration in the treated effluent of 65 μg/L [34]. HWWTPs based on CAS treatment in Vietnam resulted in better removal values (21–91%) and thus lower concentrations of the studied antibiotics (metronidazole,

sulfamethoxazole, trimethoprim, ceftazidime, ciprofloxacin, ofloxacin, and spiramycin). However, significant concentrations of these compounds were still present in the hospital effluents after the treatment (up to 53.3 μg/L of CIP) [31]. Ciprofloxacin was also found at high concentrations in various studies in hospital effluents [37, 44, 45]. These high levels might be related to its medical consumption, as these fluoroquinolones are frequently used in hospital practice to treat infections [46] and to its low biodegradability. CIP at a residue level as low as 25 μg/L can cause modification in bacterial strains and have genotoxic effects [47]. Removal efficiency of antibiotics in several HWWTPs based on MBR and CAS (all followed by a chlorination step) ranged from 72.4 to 79.3%, 36.0 to 52.2%, and 45.1 to 55.4% for tetracyclines (oxytetracycline, chlortetracycline, demeclocycline, and tetracycline), sulphonamides (sulfamethazine, sulfaonomethoxine pyridazine, and sulfadiazine), and quinolones (norfloxacin, enrofloxacin, ofloxacin, and ciprofloxacine), respectively [30]. In this case none of the antibiotics were above 1 μg/L in the treated effluent.

2.2.2 Antibiotic Resistance

As WWTPs are among the main sources of antibiotics' release into the environment, many studies have evaluated the fate of ARGs in WWTPs [48, 49]. As it happens with PhACs, conventional WWTPs are not designed to eliminate these pollutants, and therefore the efficiency of different nonconventional wastewater technologies in the removal and inactivation of ARGs has been studied by several authors in alternative WWTPs [50] and also in dedicated hospital WWTPs [3, 30, 36], the latest listed in Table 1.

Many authors even pointed out hospital wastewater treatment systems as contributors to the spread of antibiotic-resistant bacteria into the environment [5, 51]. Moreover, the diversity of gene cassettes is lower in hospital wastewater than in municipal wastewater, but the proportion of multiresistant bacteria (measured by integrons) in the bacterial community is higher in hospital wastewater than in municipal wastewater [21].

In developing countries, hospital effluents are often drained into municipal wastewater systems, and discharged into water bodies, frequently without any treatment aimed at reducing public health risks [3]. Therefore, the application of dedicated treatment for hospital wastewater would allow to minimize potential risk of hospital effluents on-site. Both the quantity of antibiotic-resistant integrons (representing the importance of antibiotic resistance in an environment independently of the quantity of bacteria) and the proportion of bacteria harboring a resistant integron in the same sample (the relative abundance) were investigated in two HWWTPs based on MBR followed by a specific tertiary treatment in the frame of PILLS project [21]. The efficiency of these advanced treatments to remove antibiotic-resistant integrons was between 1 and 5 log, mostly due to the elimination efficiency in the MBR (with ultrafiltration membranes of pore sizes of

0.03–0.04 μm) rather than the almost negligible effect of advanced treatment with ozone or activated carbon (tertiary treatment in the plant in Germany).

A study in China by Li et al. aimed to determine the contamination levels not only of ARGs but also of antibiotics and to analyze the relationships among them in hospital wastewater [30]. This study concluded that the relationships between the contamination level of ARGs and the concentrations of antibiotics should be further explored because the majority of ARGs showed weakly correlated levels of antibiotics. However, the study pointed out HWWTPs as a major reservoir for the evolution and dissemination of antibiotics and ARGs [30].

The diversity of *Pseudomonas aeruginosa* (a multidrug-resistant pathogen that has been suggested to be used as a microbial indicator of water biological quality) as well as its relatedness with β-lactams resistance mechanisms was investigated in the two studies performed in a HWWTP based on CAS followed by a chlorination step in Brazil [3, 36]. Authors concluded that treatment facilities for hospital wastewater can stimulate the increase of antimicrobial resistance bacteria and genes and thus calls for an improvement of water treatment to avoid the spreading of resistance genes in aquatic ecosystems.

In another study performed in Brazil, the contamination by viruses responsible for acute gastroenteritis and hepatitis derived from HWWTPs was confirmed as the systems investigated (UASB and three serial anaerobic filters and CAS system followed by a chlorination tank), which turned out not suitable for removal of the studied viruses present in the hospital wastewaters [35].

2.2.3 Toxic Effect

The analytical detection of pharmaceuticals or other micropollutants in concentrations lower than a few ng L^{-1} does not allow for a conclusion about possible toxic effects of single substances or about the effects of a mixture of compounds on the environment [21]. The toxic effects could involve endocrine disruption, genotoxicity, or antibiotic effects. Therefore, toxicological tests were used in several studies in Europe in order to assess the ecological risk of tested water [20, 21, 27].

A broad battery of ecotoxicity tests was applied for the evaluation of advanced wastewater treatments applied in one hospital in Germany and in the Netherlands such as in vitro screening tests for the assessment of specific effects (e.g., cytotoxicity or endocrine disrupting effects) and general toxicity to bacteria and algae as well as in vivo tests on organisms like snails, worms, water fleas, or fish. The biological treatment in the MBR decreased the toxic effects in raw hospital wastewater although MBR permeate was still toxic to some organisms like bacteria, algae, and snails. The treatment by activated carbon or ozone had in general decreasing effects on the toxicity. However, in some processes by ozonation, an increase of toxicity was observed presumably due to the formation of by-products [21]. The endocrine disturbing activity of the wastewater of a HWWTP (MBR + O3 + GAC) in the Netherlands was determined using four different

parameters: ER, AR, GR, and PR-calux assay for substances able to bind to estrogen, androgen, glucocorticoid hormones, and progesterone receptors, respectively [22]. The various hormone disturbing parameters were no longer detectable in the treated wastewater filtrate [22]. ER calux as well as another estrogen activity test, lyticase yeast estrogen screen (LYES), and the H295R steroidogenesis assay (H295R) was applied for the monitoring of HWW treated by an on-site MBR system followed by ozone treatment in Germany [20]. Overall, treatment of sewage by use of MBR successfully reduced estrogenicity of hospital effluents as well as substances that are able to alter sex steroid production. However, although ozonation was an efficient method (based on the tests applied) to remove most of estrogenic activity, further investigation should be undergone regarding the formation of endocrine active metabolites [20].

Monitoring of the genotoxic and mutagenic potential of the effluent from a hospital in India were carried out using a *Salmonella* fluctuation assay and the SOS chromotest. Untreated raw HWW revealed their highly genotoxic nature, whereas treated WW through CAS treatment followed by chlorination did not exhibit that type of toxicity [27].

3 Conclusions and Future Prospects

Hospital wastewater can represent a chemical and biological risk for environmental and public health due to the presence of several types of hazardous substances. Certain contaminants are in fact present in much higher amounts in hospitals than in municipal effluents. On-site HWWTPs offer the opportunity to eliminate high amounts of these specific contaminants before they can be released and impact the environment. While the need to implement such dedicated treatments in hospital is still under discussion, several initiatives and case studies in full-scale HWWTPs have been applied all over the world and were reviewed in this chapter.

The most suitable approach for hospital wastewater would consist of a pretreatment, a main biological treatment, an advanced treatment, and a posttreatment. In Asian countries, a conventional secondary biological treatment (CAS) followed by chlorination was considered an adequate treatment but only based on the analysis of conventional contaminants and without considering the presence of micropollutants or ecotoxicological values. In a broad set of studies in Europe and China, MBR technology was raised as an appropriate treatment for hospital wastewater. However, in both cases (CAS and MBR), biological treatment of hospital wastewater does not provide a sufficient elimination of some compounds such as pharmaceuticals and some pathogenic microbes. Only additional advanced steps like ozonation, activated carbon, or AOPs will enable a better elimination of these compounds.

Other critical factors need to be investigated when evaluating the performance of dedicated full-scale WWTPs. For instance, the evaluation and monitoring of wastewater losses between entry points (sinks, toilets, drains) and the on-site treatment

plant or tank or discharge point into a municipal sewage [10]. Decoupling of the rainwater drainage system can also led to a more efficient treatment of the hospital wastewater [1]. On the other hand, sewer overflows from municipal sewer systems may lead to discharge of hospital wastewater into the receiving waters, a potential risk of spreading resistant bacteria and pathogens as well as other chemical contaminants [21]. To this respect, antibiotic resistance is a topic of increasing environmental concern and hospitals, hospital effluents, and even HWWTPs are under the spotlight regarding their critical role in the spread of antibiotic resistance in the environment.

Finally, in accordance with the environmental relevance of the emerging pollutants, and based on the studies performed in the last years, some of these emerging pollutants are currently being considered for environmental legislation in different countries. In the case of the European Union, the anti-inflammatory drug diclofenac and three macrolides antibiotics (erythromycin, clarithromycin, and azythromycin) have been included in the so called "watch list" of priority substances under the Water Framework Directive (WFD) for the "specific purpose of facilitating the determination of appropriate measures to address the risk posed by these substances" [52]. In United States, the Environmental Protection Agency (EPA) has included the antibiotic erythromycin and five synthetic hormones to a list of contaminants that must be controlled, the Drinking Water Contaminant Candidate List [53]. Finally, in 2008 the Global Water Research Coalition (GWRC) published a report in which a large number of PhACs were classified in several classes: high, medium, and low priority compounds. This report identifies compounds that are most likely found in water supplies and that may have significant impacts on human and environmental health [54]. Future regulation of these compounds and the establishment of specific limit values in water would definitely affect the management of hospital effluents as they are significant sources of many of these compounds. In this scenario, the increase in the number of dedicated full-scale HWWTPs can only be foreseen, and therefore further efforts need to be devoted to research in the field.

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Overview on Pilot-Scale Treatments and New and Innovative Technologies for Hospital Effluent

Marina Badia-Fabregat, Isabel Oller, and Sixto Malato

Abstract In this chapter, pilot-scale studies and some innovative lab-scale investigations on hospital wastewater (HWW) treatment are presented. Pilot-scale systems usually consist of a first biological treatment to remove organic matter, nutrients, and some pharmaceutically active compounds (PhACs) followed by a physicochemical treatment to increase removal of PhACs and other micropollutants (MPs). Biological treatments are usually advanced treatments such as membrane bioreactors (MBRs), which allow longer residence time of microorganisms, and thus, more suitable conditions for the removal of micropollutants such as PhACs. Moreover, membranes also sanitize the effluent, retaining the pathogenic microorganisms and reducing release of antibiotic resistance genes (ARG). On the other hand, ozonation and activated carbon (AC) are the most common alternatives chosen as a polishing step. Research is actively working on innovative treatments, such as photocatalysis, to reduce the treatment cost, which is the major drawback for implementation of dedicated (in situ) degradation treatments of PhACs in HWW.

Keywords Advanced oxidation processes, Hospital wastewater, Membrane biological reactor, Photocatalysis, Pilot plants

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Contents

Abbreviations

AC	Activated carbon
AOP	Advanced oxidation processes
ARG	Antibiotic resistance genes
BOD	Biological oxygen demand
CAS	Conventional activated sludge
COD	Chemical oxygen demand
DGGE	Denaturing gradient gel electrophoresis
DOC	Dissolved organic carbon
EDDS	Ethylenediamine-*N*,*N*′-dissucinic acid
EDTA	Ethylenediaminetetraacetic acid
GAC	Granulated activated carbon
HRT	Hydraulic residence time
HWW	Hospital wastewater
LC/MS	Liquid chromatography-mass spectrometry
LYES	Lyticase Yeast Estrogen Screen
MBBR	Moving bed biofilm reactor
MBR	Membrane bioreactor
MLSS	Mixed liquor suspended solids
MPs	Micropollutants
MWW	Municipal wastewater
NDMA	*N*-nitrodimethylamine
NF	Nanofiltration
PAC	Powder activated carbon
PhACs	Pharmaceutically active compounds
qPCR	Quantitative polymerase chain reaction
RO	Reverse osmosis
SRT	Sludge residence time
WWTP	Wastewater treatment plant

1 Introduction

Hospital wastewater (HWW) physicochemical parameters are usually similar to municipal wastewater (MWW). The main differences in legislated HWW effluent parameters are its slightly higher dissolved organic carbon (DOC) and chemical oxygen demand (COD) as well as higher biological oxygen demand (BOD), suspended solids and chlorides. However, on a micropollutant level, a much higher concentration of pharmaceutically active compounds (PhACs) and disinfection products are found in HWW than MWW [1, 2]. PhACs are organic micropollutants of growing concern due to (1) their widespread presence in the environment because of their generally low biodegradability in conventional wastewater treatments and (2) their associated risks, such as carcinogenicity, mutagenicity, and endocrine disruption [3]. So far, there is still no legislation on the maximum individual or total PhAC concentration in urban or hospital wastewater discharge. Release of pathogenic microorganisms and spreading antibiotic resistance genes (ARG) are issues of special concern as well [4].

The main issue, as mentioned above, is that wastewater treatment plant (WWTP) technologies, such as conventional activated sludge (CAS) systems, are not effective in removing many of those PhACs, which are therefore released into the environment. Therefore, new specifically designed or adapted treatments for PhACs degradation are being developed [2, 5–7]. There is some discussion in the scientific literature about whether HWW should be treated separately at source to take advantage of their higher concentrations, or discharged to urban WWTP and treated with municipal wastewater. According to Joss et al. [8], pseudo first-order kinetics have been observed in biological degradation of PhACs. Therefore, treatment at the source point might be the best choice to avoid dilution of PhACs concentration. In fact, in the last few years, research on separate treatment of the HWW has increased significantly [2, 9, 10].

HWW treatments usually consist firstly of a pretreatment step to separate the solid fraction, followed by a biological treatment to remove most DOC, nutrients, and some PhACs, and finally include a physicochemical treatment to completely degrade PhACs and sanitize the effluent. An exhaustive review of hospital effluent management and treatment experiments has recently been published [11]. This chapter compiles the most recent relevant pilot-scale studies for the treatment of hospital wastewater, with a brief discussion of the main advantages, drawbacks, and limitations of each technology. Moreover, innovative fungal and enzymatic treatments, moving bed biofilm reactors (MBBR), photo-Fenton, and solar photocatalysis, not yet specifically implemented at pilot scale for hospital wastewater treatment, are also described.

2 Biological Wastewater Treatments

Biological HWW management technologies have been widely explored in recent years. In fact, biological reactors are the main treatment for removal of DOC, nutrients, and micropollutants in pilot plants for HWW management. Conventional treatments, such as CAS, are reportedly rather ineffective in the degradation of most recalcitrant PhACs [12]. The main reason seems to be lower sludge age and the challenging acclimation of biomass compared to other treatments which allow higher sludge residence time and thus biomass adaptation, such as membrane bioreactors (MBR) or MBBR [6]. Therefore, as described in Sect. 2.1, most biological reactors tested at pilot scale are MBRs. However, HWW treatment technologies should be, above all, cost-effective. Today most alternatives are costly (i.e., investment and operating costs of membrane modules) and, for some PhACs, not totally effective yet. Therefore, innovative systems being developed at laboratory scale using specific microorganisms, such as fungal treatment or enzymatic treatments which take advantage of the specific activity of some isolated enzymes, are also promising alternatives. The studies presented in this chapter were performed at lab scale or pilot scale depending on the maturity of the technology.

2.1 Pilot-Plant Treatments

2.1.1 Conventional Activated Sludge

Some short studies have dealt with CAS treatment of HWW. There is only one recent pilot-scale study by Chonova et al. [13], in which two parallel CAS bioreactors were constructed to treat MWW and HWW and compare the two types of wastewater at the SIPIBEL (Site Pilote Bellecombe) study site in Haute-Savoie (France). However, due to the different wastewater flow rates of each (140 $m^3\ d^{-1}$ hospital effluent and 2,200 $m^3\ d^{-1}$ urban effluent), HRTs in the two pilot plants were different, 1.3 days in the urban pilot plant and 9.3 days in the hospital plant. Aerobic and anoxic/anaerobic conditions were applied in CAS reactors to allow nitrification and denitrification processes. In general, higher degradation of PhACs was observed in the hospital WWTP than in the urban WWTP, although concentration in the effluent after biological treatment was still higher in the hospital WWTP than in urban WWTP because of the higher influent concentration.

2.1.2 Membrane Bioreactors

During the last few years, some pilot plants have been built to demonstrate the feasibility of degrading PhACs in hospital wastewater. MBR is the preferred technology for pilot hospital wastewater treatment plants because of its lower

footprint, more efficient PhACs removal, and significant hygienization of the effluent compared to CAS.

MBR is usually chosen as an aerobic pretreatment for the removal of COD, nutrients, and some PhAC before a physicochemical polishing treatment to remove the remaining PhAC and transformation products (TPs) generated during biological treatment [2, 10, 11, 14]. The most common physicochemical treatments are ozonation [9, 10, 15, 16], granulated activated carbon (GAC) [9, 10, 15], UV/H_2O_2, and reverse osmosis (RO) [9], which can be applied alone or as part of a train of treatments. Langenhoff et al. [9] concluded that ozonation and RO were the most effective post-treatments for the removal of diclofenac, a poorly degradable PhAC, and Nielsen et al. proposed ozonation as the best cost-effective treatment for polishing [10]. A detailed discussion of the performance of physicochemical treatments may be found in Sect. 3.

The most important MBR operating parameters for controlling bioreactor performance are the hydraulic residence time (HRT) and sludge residence time (SRT), but for PhACs removal the last is of crucial importance. Higher SRT achieved by membrane retention of solids allows the adaptation of specific microorganisms, able to degrade recalcitrant compounds, that might have slower growth rates [11]. Moreover, configuration of aerobic, anoxic, and anaerobic compartments should allow for different degrees of nutrient removal. The type of membrane may also strongly affect MBR effluent quality. Membrane construction materials may be polymeric or ceramic and their configuration tubular, flat sheet, or hollow fiber. Moreover, membranes might be disposed in external modules or be submerged membranes. However, the most important classification for membranes is done depending on their pore size. Therefore, microfiltration membranes are those with pore sizes of around 0.2–0.4 μm and, for ultrafiltration membranes, pore size is usually between 0.03 and 0.06 μm. Smaller pore size is not only important for better removal of some wastewater components but it is also crucial for the hygienization of the effluent (although, e.g., viruses removal cannot be achieved even with ultrafiltration membranes due to its small size) and the obtainment of a clarified effluent suitable for the next polishing treatments. Therefore, disparity of MBR membrane configurations makes the comparison difficult [17].

An exhaustive analysis of PhACs was conducted in the Swiss European PILLS Project pilot plant, where 68 micropollutants were monitored with automated online SPE-HPLC-MS/MS analysis [2]. In that study, removal of the total compound load was found to be only 22%, despite the high SRT (30–50 days). The main reason was the low percentage of iodinated contrast media degradation, which accounted for over 80% of the total load. MBR configuration was designed for nitrogen removal, thus consisting of an anoxic tank of 0.5 m^3 followed by a 1 m^3 aerobic compartment with submerged ultrafiltration flat sheet membranes. HRT in the MBR was calculated to be <1 day taking into account that the inlet flow rate was 1.2 m^3/day.

In the DENEWA project, 80% average removal of the 40 PhACs analyzed and 100% removal of fecal bacteria was achieved in the effluent of the MBR pilot plant at Antonius Hospital in Sneek (Netherlands) [15]. In another study in Denmark,

PhACs removal results showed variable percentages, and therefore, further polishing treatment was recommended [10]. MBR consisted only of an aerobic compartment treating 2.2 m^3/day. HRT and SRT were calculated to be approximately 4 h and 35 days, respectively. On the other hand, microbial content showed a decrease of over 99% for *E. coli*, total coliforms, and total Enterococci after ceramic ultrafiltration of 0.06 μm of pore size [10]. Maletz et al. [16] also monitored the degradation of several endocrine disruptors and total estrogenicity by means of the Lyticase Yeast Estrogen Screen (LYES) and ER-CALUX® assays. Significant original estrogen activity of untreated wastewater was almost completely eradicated after treatment by MBR. Cytostatics were also highly removed in an MBR pilot plant treating wastewater from the oncologic ward of a hospital in Vienna. In this case, the MBR was an aerobic tank with a volume of 150 L and working at an HRT of 20–24 h [18]. However, it has to be taken into account that, sometimes, removal can be mainly due to adsorption on the biomass instead of biodegradation, as Lenz et al. [19] found for cancerostatic platinum compounds in the same MBR pilot plant. SRT varied between 42 and >300 days; however, PhACs concentration adsorbed in the biomass increased during the experimental period despite the SRT. Recently, a study of Prasertkusak et al. [20], testing PhACs removal under low HRT (3 h) on an MBR pilot plant of 1.3 m^3 treating the effluent of a hospital in Thailand, found that main removal of some compounds was due to adsorption on the colloidal particles as well. Therefore, purged sludge destination should be carefully determined in order to avoid PhACs spreading in the environment.

Summarizing and considering the overall results in the pilot plants above, MBR treatment might be insufficient to completely eliminate micropollutants. Nonetheless, it is still a necessary step for DOC elimination before a physicochemical process to improve their performance (e.g., ozonation, activated carbon, photodegradation) and a suitable method for wastewater hygienization and possible reduction in spreading antibiotic resistance genes (ARG).

The main drawback of the MBR technology is its cost. Kovalova et al. [21] calculated that HWW treatment with MBR followed by ozone or PAC would cost 2.4 and 2.7 € m^{-3}, respectively. Nielsen et al. [10] also calculated the investment in an MBR + ozone treatment system for a 900-bed hospital to be approximately 1.6 million € with operating costs of 1 € m^{-3}. In this case, the technology, with 0.2 μm-pore rotating ceramic membrane discs, could take up to 60 g L^{-1} of MLSS at an average flow rate of 50 L h^{-1} m^{-2}. This was further developed by the Grundfos Biobooster company in a public–private consortium for the construction of the full-scale wastewater treatment plant at Herlev Hospital (Denmark) [22].

2.1.3 Other Configurations

CAS treatment modifications have improved PhACs degradation. For example, Mousaab et al. [6] achieved better removal of poorly biodegradable PhACs in HWW by using a biofilm support in an activated sludge reactor due to the increase in biomass concentration and SRT and/or sorption of some PhACs on the biofilm.

Moreover, negative effects of biomass on the following ultrafiltration step were reduced (i.e., less membrane fouling and more stable transmembrane pressure).

An anaerobic–aerobic fixed-film reactor operating in a sequential batch configuration also significantly removed pathogenic bacteria in a simple low-energy consumption operation and maintenance configuration according to the authors [23]. However, PhACs removal was not monitored.

2.1.4 Lab-Scale Experiments Complementing Pilot-Plant Results

Lab-scale monitoring or study of specific aspects of pilot-plant performance is useful to broaden knowledge of the biological technologies. Respirometric tests, from which important parameters such as biomass inhibition can be obtained, are a clear example. González-Hernandez et al. used respirometric analysis to show how the sludge from a pilot MBR treating hospital wastewater adapted to PhACs much better than the sludge from a municipal WWTP [24]. In another study, addition of cytostatics in an MBR treating MWW strongly affected microorganisms, increasing their endogenous respiration and decreasing the exogenous respiration due to toxicity [25]. However, degradation rates were still high because of the old sludge age in the MBR.

Molecular analysis is a good tool for determining the microbial communities inside the bioreactors. Chonova et al. [13] studied the effect of the treated effluents of two CAS pilot plants, one treating MWW and the other HWW, on the microorganisms in each bioreactor. They compared the bacterial communities which developed on sterilized stones placed in the two treated effluent pipes by means of denaturing gradient gel electrophoresis (DGGE) analysis. The origin of the wastewater had a clear effect on the microbial community: less biofilm and lower bacterial diversity was found for the treated hospital effluent.

2.2 Innovative Lab-Scale Treatments

There are some reviews in the literature dealing with lab-scale treatment studies for hospital wastewater [11, 14]. Section 2.1 of this chapter describes the PhACs removal technologies most studied including pilot-plant study results. Therefore, this section focuses only on the most innovative technologies tested at lab scale and some studies which might help to improve existing pilot plants or future design of new studies and full-scale plants.

2.2.1 Fungal Treatments

The use of fungi, and especially ligninolytic fungi, for degrading recalcitrant compounds has been studied for a long time. Promising results have been found

for the degradation of many individual PhACs [26, 27] and recently, for treatment of real hospital and veterinary hospital wastewater, even under nonsterile conditions [5, 28].

Although use of many fungi has been reported for the degradation of emerging contaminants (i.e., *Phanerochaete chrysosporium*, *Pleurotus ostreatus*, *Bjerkandera adusta*, and *Irpex lacteum*) [27], the one most studied for the treatment of hospital wastewater is the white-rot fungus *Trametes versicolor*. *T. versicolor* was grown in pellet form, an efficient type of self-immobilization of the biomass inside the bioreactor. Treatments have been performed in air-pulsed glass fluidized-bed bioreactors in both batch and continuous operating modes. Several PhACs including recalcitrant anticancer drugs [29], antibiotics, and ARG [30] have been degraded. Hazard quotients in HWW treatments were lower than in CAS treatment, mainly due to the strong reduction in antibiotic concentration [31].

One point that still needs to be optimized is competition with indigenous microorganisms in the effluent to be treated. Recently, molecular tools have found that not only the growth of bacteria inside the bioreactor might be detrimental to treatment performance as often reported, but also the growth of fungi other than the one inoculated [32]. Therefore, operating strategies such as nutrient addition (e.g., source of nutrients, addition rates, C/N ratio) need to be addressed to increase survival of the inoculated fungus. Pretreatments such as coagulation–flocculation seem to benefit long-term performance of the treatment [33].

2.2.2 Innovative MBR Treatments

As mentioned above, MBR is the technology most investigated for pilot-scale hospital wastewater treatment. This is because of its significant advantages over CAS, such as higher-quality effluent, lower space requirements, higher biomass concentration, and less sludge production. However, some drawbacks, such as membrane fouling, which leads to higher operating costs, also need to be considered. Therefore, more lab studies still need to be performed to improve MBR performance, especially long-term.

An innovative variation of MBR treatment is the submerged sponge-membrane (sponge-MBR), a type of hybrid MBR. This configuration enabled Nguyen et al. to achieve similar COD removal, higher total nitrogen removal, and lower fouling rates than conventional MBR [34]. PhACs were not analyzed in this study. The main reason for the improvement in performance was claimed to be the entrapment of 60% of the biomass in the sponges, which led to simultaneous nitrification and denitrification and reduction of cake formation in the membranes, especially at low flow rates (i.e., 2 L h^{-1} m^{-2}). The experiments were performed in an MBR with a working volume of 22 L and PDVF hollow-fiber membrane modules with a 0.5 m^2 surface area and 0.2 μm pore size. The cubic polyethylene sponges were 2 × 2 × 2 cm with a porosity of 98%.

An Iraqi lab-scale study in a sequencing anoxic/anaerobic membrane bioreactor focused on improvement of nutrient removal (*N* and *P*) in HWW through different recirculation rates [35]. However, no analyses of PhACs were performed.

2.2.3 Moving Bed Biofilm Reactors

A moving bed biofilm reactor consists of a bioreactor in which biomass grows suspended in the liquid phase and also attached to carriers. Sludge is usually older when microorganisms are grown in the form of a biofilm and treatment performance is generally improved.

Andersen et al. [36] compared the performance of two types of MBBR, a pure one and an Integrated Fixed-Film Activated Sludge technology called HYBAS, where carriers are inserted in the activated sludge basin. Two or three sequential bioreactors were needed to obtain an effluent with the required quality. The MBBR system performed better than CAS for the removal of PhACs, especially the semi-degradable compounds.

Marjeta et al. achieved 59% and 35% removal of the cytostatic compounds, cyclophosphamide and ifosfamide, respectively, in real HWW [37]. Experiments were performed in aerated glass bioreactors with the biomass attached to polyethylene carriers (Mutag Biochip™).

2.2.4 Other Treatments and Studies

Prayitno et al. showed high BOD and fecal coliform removal in an aerated fixed-film biofilter. However, an additional ozone reactor was needed to completely remove phenol and Pb [38]. Those were the only micropollutants monitored in the study; PhACs were not analyzed.

Enzymatic treatment was studied in the ENDETECH project. Novel membranes with immobilized fungal laccase on the surface were synthetized and the correlation between attached enzymes and tetracycline removal was observed [7]. However, results of real wastewater treatment are still unpublished [39].

Aside from this, as mentioned above, hospital effluents show high concentrations of opportunistic pathogens, antibiotic-resistant bacteria, and ARG. The relationship between antibiotic resistance profiles of bacteria in hospital effluents before and after treatment is complex. ARG are spread by horizontal transfer between bacteria through genetic elements such as plasmids, transposons, and integrons. These genetic elements often include more than one ARG, conferring multidrug resistance. Stalder et al. studied the differences in biomass between two CAS systems treating HWW and MWW [40]. They concluded that separate treatment of hospital effluents increases the risk of dissemination of pathogenic bacteria and antibiotic resistance genes. Live/dead assays, DGGE analyses, pyrosequencing, and quantitative PCR (qPCR) for Class I resistance integrons allowed them to monitor the biomass structure, bacterial diversity, and antibiotic

resistance determinants in addition to overall performance. Relative abundance of Class I resistance integrons increased 3.5-fold in the HWW treatment reactor. The authors related that increase to the in situ development of bacteria with those genetic elements (*Pseudomonas* and *Acinetobacter* genera) rather than with horizontal transfer. Therefore, attention should be given to downstream treatments and soil application of sludge from HWW treatment.

3 Physicochemical Wastewater Treatments

As described in the section above, despite the positive results with advanced biological treatments for HWW pollutant removal [12, 41], their inefficiency for complete removal of some hazardous substances, such as some PhAC [42], has been well demonstrated. Several studies have particularly demonstrated that these substances can also affect the operation of conventional WWTPs [43]. Therefore, advanced treatment technologies such as adsorption on activated carbon (AC), membrane separation, and advanced oxidation processes (AOPs) may be advisable for the removal of many pollutants present in HWW even after an advanced biological treatment system. In fact, physicochemical treatments are usually assigned as tertiary treatments for polishing a biological treatment effluent after the majority of the organic carbon load has been removed.

3.1 Physicochemical Separation

3.1.1 Adsorption

Activated carbon (AC) for removal depends largely on carbon dose and the octanol/water partition coefficient (K_{ow}). AC filtration very often fails, as drugs are readily protonated or deprotonated in neutral water depending on their pK_a. Therefore, carbon adsorption alone does not seem suitable for proper removal [44]. Moreover, AC regeneration or disposal is necessary after carbon saturation, leading to other environmental risks which may be similar or even worse than the trace micropollutants in HWW. Therefore, life cycle assessment of different alternatives is necessary when contaminants are not eliminated but simply removed from water by AC. This method is suitable for wastewater with DOC <20 mg L^{-1}, because higher concentrations would interfere with adsorption of microcontaminants (MCs), the main goal of HWW treatment.

Removal by adsorption onto activated carbon has been studied as an advanced wastewater treatment stage in bench, pilot, and full-scale operation [45] in numerous applications [46, 47]. Powdered AC (PAC) can be adopted as a tertiary treatment or dosed directly into the biological stage of the treatment [46, 48]. Due to its smaller particle size, PAC adsorption kinetics are typically superior

and might therefore be more efficient compared to granular AC (GAC) [45]. PAC shows a general preference for hydrophobic compounds like many MCs in HWW. For example, benzotriazole, carbamazepine, and diclofenac were almost completely removed in a full-scale PAC application [46]. In a pilot-scale comparison with PAC (12 mg L^{-1}), over 90% carbamazepine was removed and benzotriazole removal was very efficient [47]. Similar results were reported for post-treatment of HWW, with complete removal of carbamazepine, bezafibrate, diclofenac, and iomeprol [48].

3.1.2 Membrane Filtration

Physical treatments such as membrane nanofiltration (NF) and reverse osmosis (RO) have been shown to be promising technologies for removing MCs usually present in HWW [49, 50]. Although nanofiltration applied to MC separation has been studied, some authors have focused on the separation mechanisms as a function of MC physicochemical properties [51, 52], while others have studied how fouling affects pharmaceutical rejection [53, 54], and still others have concentrated on membrane operating conditions (flow rate, pressure, temperature, pH, water characteristics, etc.) and their influence on pollutant separation [55]. However, information on membrane treatment of real HWW is very limited, especially for evaluating micropollutant removal in the ng L^{-1} and μg L^{-1} ranges.

Data from pilot and full-scale facilities operating with advanced treatment trains for MC removal show varying behavior. Although RO and NF membrane rejection is quite high (>85%), it is very dependent on the type of membrane and only in some cases removal achieved was >98% [56–58].

Membrane processes do not degrade MCs, but concentrate the pollutants in a waste stream with a smaller volume, which requires appropriate treatments for safe disposal into the environment. Rejection can account for 35% of the influent flow and is four to ten times more concentrated. This approach has been addressed in pilot-scale experiments at the Plataforma Solar de Almería, Spain, in the last few years, and economic figures are already available [59]. Since the most significant RO operating problems are severe membrane fouling and high energy consumption, NF may be a good low-pressure alternative with comparable efficiency for MC removal from HWW [60]. Another approach for HWW treatment tested at pilot scale is combining ultrafiltration membranes and bioreactors with biofilms on support media, which can lower the concentration of proteins and polysaccharides (the main cause of clogging in membranes) and improve membrane functioning, thereby lowering costs [6].

3.2 Oxidation

Since traditional oxidation methods (e.g., Cl_2, HClO, H_2O_2, $KMnO_4$, etc.) are ineffective against MCs, only advanced oxidation processes (AOP) are considered in pilot and full-scale applications. AOP removal performance is better than traditional oxidation methods due to the stronger oxidant power of free radical compounds, mainly hydroxyl ($HO^{\cdot}$). Second to fluorine (3.03 V vs standard hydrogen electrodes (SHE)) the hydroxyl radical is the strongest known oxidant, with a potential of 2.8 V vs SHE. These radicals are able to oxidize almost any organic molecule yielding CO_2 and inorganic ions. Rate constants for most reactions in aqueous solutions are usually in the range of 10^6–10^9 M^{-1} s^{-1}. Hydroxyl radicals are generated by direct photolysis of oxidants like H_2O_2, O_3 or water with high energy UV radiation, Fenton and photo-Fenton techniques, heterogeneous photocatalysis with semiconductors, electrochemical techniques, and cavitation techniques [61]. The most common AOPs (listed in Table 1) used at pilot scale and/or with HWW use irradiation or ozonation. Recent research concentrates on the two AOPs which can be powered by solar radiation ($\lambda > 300$ nm), heterogeneous photocatalysis with UV/TiO_2, and homogeneous catalysis with Fe^{2+}/H_2O_2/UV or photo-Fenton.

Applied in wastewater and drinking water treatment, AOPs are a powerful way of removing contaminants. One remarkable advantage of AOPs is that they are environmentally friendly, which means that they do not transfer pollutants from one phase to another like extraction, activated carbon adsorption, filtration, or reverse osmosis, nor do they produce large amounts of hazardous sludge and waste. However, AOPs applied to water treatment may produce harmful degradation by-products, and therefore, these applications must be optimized, not only economically, but also for their safety.

Ozonation is the dark oxidation method most used in the removal of MCs. Photocatalysis and UV/H_2O_2 are the photooxidation methods most used to degrade MCs with removal rates over 98% [58]. Although AOPs for removal of contaminants from HWW may seem costly, the growing scarcity of water and concerns about this specific contamination in many parts of the world would seem to be sufficient reason for their application to HWW. HWWs are heavily contaminated

Table 1 AOPs using radiation for the generation of hydroxyl radicals

AOP	Key reaction	Wavelength (nm)
UV/H_2O_2	$H_2O_2 + h\nu \rightarrow 2HO^{\cdot}$	$\lambda < 300$
UV/O_3	$O_3 + h\nu \rightarrow O_2 + O(^1D)$ $O(^1D) + H_2O \rightarrow 2HO^{\cdot}$	$\lambda < 310$
UV/H_2O_2/O_3	$O_3 + H_2O_2 + h\nu \rightarrow O_2 + HO^{\cdot} + HO_2^{\cdot}$	$\lambda < 310$
UV/TiO_2	$TiO_2 + h\nu \rightarrow TiO_2(e^- + h^+)$ $TiO_2(h^+) + HO_{ad}^- \rightarrow TiO_2 + HO_{ad}^{\cdot}$	$\lambda < 390$
Fenton Photo-Fenton	$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\cdot} + HO^-$ $Fe^{3+} + H_2O + h\nu \rightarrow Fe^{2+} + H^+ + HO^{\cdot}$	$\lambda < 580$

with pharmaceutical substances, which can also lead to the development of antibiotic resistance mechanisms in any bacteria present in it. Smaller-scale AOP treatment systems for such effluents could transform any recalcitrant compounds, greatly facilitating their subsequent treatment within municipal wastewater treatment plants.

3.2.1 Ozonation

HWW treatment with ozone as the oxidizer is one of the chemical treatment technologies most studied in Europe. Ozone oxidizes MCs directly or indirectly on HO hydroxyl radicals ($HO^{\cdot}$). Ozone molecules react selectively with compounds containing double chain bonds (C=C), certain functional groups (e.g., –OH, $–CH_3$, $–OCH_3$), and N, P, O, and S anions, however, oxidation by $HO^{\cdot}$ is nonselective. Under alkaline conditions, the indirect reaction predominates due to the extremely rapid and nonselective nature of $HO^{\cdot}$ (10^9 M^{-1} s^{-1}). One of the first studies, on removal of diclofenac from wastewater, was published by Ternes et al. [62]. The authors employed ozone concentrations of 5.0–15.0 mg L^{-1} to find out its removal efficiency in WWTP effluents, and found it to be >96%. During recent years, some WWTPs in Switzerland and Germany have been upgraded with ozone oxidation.

Although it has been found that ozonation mainly transforms pollutants into unknown oxidation products with unknown toxicity [63, 64], in general, such transformation products are in low concentrations, and have insignificant estrogenic and antimicrobial activities compared to the parent compound [65]. Furthermore, the ozone reaction with the organic matter dissolved in such effluents could also produce toxic compounds, such as formaldehyde, ketones, phenols, nitromethanes, and carcinogenic substances, like bromates and N-nitrodimethylamine (NDMA) [66]. Blackbeard et al. [67] observed formation of atrazine by-products (atrazine desisopropyl and atrazine desethyl), an increase in NDMA (from 15.3 to 31.4 ng L^{-1}), and especially, a 40× amplification of bisphenol A.

A pilot-scale HWW treatment plant consisting of a primary clarifier, membrane bioreactor, and five post-treatment technologies, including ozone, was operated to test its elimination efficiency for 56 MCs [21]. Elimination required 1.08 mg O_3/mg DOC. As a general rule, more dissolved organic carbon (DOC) increased the ozone dose required for removal of a pharmaceutical in HWW, and the ozone dose required for removal of a pharmaceutical is compound specific. Results recently presented by Hansen et al. for HWW pretreated in an MBR showed that doses varied as much as 0.50–4.7 mg O_3/mg DOC [68]. They also found that efficiency was clearly affected by pH, as at low pH the ozone's lifetime increased drastically from less than 1 min at pH close to 8 to over 10 min at pH near 5. Efficiency (mg O_3 required for removal of MCs) in HWW was also lower at a higher pH of 5–9. A larger reaction tank at lower pH would be needed to avoid releasing ozone into the environment from the treatment plant.

The main drawback of this technology is that ozone production is very energy-intensive and its conversion efficiency is low (0.01–0.015 kWh m^{-3} of pure oxygen

produced) and 1 kg of O_3 produced from oxygen requires 12 kWh [69]. About 85% of the energy consumed is wasted as heat which must be eliminated to prevent the reactor from overheating. The investment cost of upgrading a small to medium-scale WWTP, such as those specifically designed for HWW, with a retrofitted ozonation stage could increase by 20–50%, and energy consumption 5–30% higher [70].

3.2.2 UV/H_2O_2

To date, UV/H_2O_2 is the most popular large-scale UV-driven AOP [43]. H_2O_2 is more stable than O_3 and it can be stored for a long period of time prior to use, but residual H_2O_2 must be removed before discharging. $HO^{\cdot}$ degradation efficiency is significantly affected by the presence of natural organic matter and inorganic anions. The UV/H_2O_2 process is a powerful removal technology for MCs in HWW, however, degradation efficiency depends on the characteristics of the water matrix, such as turbidity and alkalinity, among others. Studies of MC degradation under different UV/H_2O_2 conditions have found that UV doses differ as much as 40–1,700 mJ cm^{-2} for treatment of carbamazepine, diclofenac, or triclosan [71–74] in different waters including HWW, pointing out the necessity of pilot-scale testing for proper design of any specific treatment. The UV/H_2O_2 irradiation technology was recently explored as a membrane bioreactor (MBR) post-treatment in a HWW pilot treatment plant [75]. Efficiency was assessed by examining 14 MCs (antibiotics, analgesics, anticonvulsants, beta-blockers, cytostatics, and X-ray contrast media). The main output was a holistic life cycle assessment (LCA) comparison of different scenarios. The study revealed 70% higher energy efficiency with low-pressure UV lamps than medium-pressure UV lamps, and 1.11 g L^{-1} H_2O_2 as the best operating condition.

3.2.3 Photocatalysis

Pilot-scale results have shown that photocatalysis with TiO_2 is very inefficient in terms of treatment time and accumulative energy compared to photo-Fenton and ozonation [76]. We have not found any successful MC treatment results with TiO_2 in any real effluent from hospitals or other sources like municipal wastewater effluents.

On the other hand, due to the photochemistry of many Fe^{3+} species, irradiation with UV or UV/Vis light can lead to a series of photochemical reactions which invariably reduced to its Fe^{2+} state, continue the Fenton process indefinitely, as long as the system remains illuminated (reacting again with H_2O_2). This photoreduction process can be described as

$$\mathrm{Fe(III)(L)_n} + \mathrm{hv} \rightarrow [\mathrm{Fe(III)} - \mathrm{L}]^* \rightarrow \mathrm{Fe(II)(L)_{n-1}} + \mathrm{L_{ox}^{\cdot}}.$$

In the absence of any organic ligands, Fe^{3+}-hydroxy complexes present in acidic solutions (mainly $Fe[(H_2O)_5OH]^{2+}$) absorb the most in the UV/Vis region. This enables sustainable regeneration of Fe^{2+} to continue indefinitely as long as the system is illuminated. This variant of the Fenton process, called photo-Fenton, has much higher degradation kinetics than dark Fenton [77]. Fe^{3+} can also form complexes with many organic ligands, especially those acting as polydentate ligands, as described below. Photo-Fenton is economically competitive with ozonation for treating MCs, and is also used for treating membrane rejection effluents containing high concentrations of MCs [59].

However, the main shortcomings of this process (e.g., frequent pH adjustment of the water matrix, disposal of the final sludge, high cost due to H_2O_2, and catalyst consumption) still limit its broader full-scale application [78]. Nevertheless, many variations of the Fenton process have arisen in the last few years, suggesting intensified future use of the classic Fenton process with radiation. Photo-Fenton represents a promising AOP for the removal of a wide variety of MCs present in HWW due to its environmentally friendly application and the prospect of operating under natural solar irradiation, which lowers operating costs considerably. Photo-Fenton efficiency in degrading MCs is derived from several operating parameters, such as reagent dose (H_2O_2 and iron), iron type (ferrous or ferric iron), pH, and organic/inorganic content of the wastewater matrix. Recently, in a comprehensive review, Wang et al. [79] described the main process parameters affecting Fenton/photo-Fenton efficiency for the removal of various MCs dissolved in water or wastewater. In this case, it is unnecessary to separate soluble iron species from the treated wastewater to comply with regional regulatory limits for effluent discharge.

The majority of studies have demonstrated that the optimum pH for photo-Fenton is 2.8. However, Fe^{3+} can form complexes with higher molar absorption coefficients in the near-UV and visible regions than the aquo complexes, while also using a larger fraction of the solar radiation up to 580 nm. Formation of chelation complexes with organic ligands is thus an essential part of iron cycling in nature, regulating iron transport, speciation, and availability, especially in sunlit surface waters. This new approach has removed the economic burden associated with the chemical cost for pH rectification, especially for full-scale application. The high photo-Fenton efficiency for treatment of various MCs has prompted its pilot-scale research and development and application of concentrating parabolic solar collectors (CPCs). This use of natural sunlight dramatically lowers the operating cost of the process, and is thus a major step towards full-scale application for small communities.

The addition of chelating agents for increasing the optimal operating pH of the photo-Fenton process applied to MCs shows increased quantum yields at the same time, thereby permitting the use of a wider fraction of the solar spectrum. Carboxylic acids are a special case of chelating agents occurring naturally in photo-Fenton

systems, as they are frequent intermediates prior to mineralization during the oxidative treatment of many contaminants. As they accumulate in solution, the degradation process accelerates. The two ligands, oxalate and citrate, have been thoroughly studied as photo-Fenton additives [80], but would still need to operate at acid pH and require post-treatment neutralization for a kinetically optimized process. Ethylenediaminetetraacetic acid (EDTA) was considered for some time, as it can form soluble complexes in a wider pH range, but it is not biodegradable and is considered a persistent pollutant. One of its isomers, Ethylenediamine-*N*,*N*′-dissucinic acid (EDDS), has been gaining attention recently. It is considered biodegradable and safe for environmental applications. Fe^{3+} is complexed by EDDS with a predominant ratio of 1:1 at pH up to 9, with hydroxylated forms appearing as the pH rises. The 1:1 form is also the most photoactive, and can generate $HO^{\cdot}$ when photolyzed. It has successfully degraded MCs in effluents at neutral pH with low iron and H_2O_2 concentrations at pilot scale [81].

Pilot-scale test results for the complete removal of a plethora of pharmaceuticals typical in HWW, such as antibiotics, nonsteroidal anti-inflammatory drugs, analgesic drugs, hormones, X-ray constant contrast media [82–87], and others, have been quite satisfactory.

Miralles et al. studied pilot-scale photo-Fenton treatment of a real effluent (MWW) for pharmaceuticals in the NF concentrate. They employed LC/MS for realistic evaluation of the kinetics in an economic assessment [88]. NF pretreatment enabled photo-Fenton to be run at lower flow rates and with higher starting MC concentrations, thus substantially reducing photoreactor size and the amount of reagents needed per cubic meter of treated effluent. These results reinforce the idea that treatment of extremely low concentrations of contaminants, such as those found in HWW, requires different operating concepts from the application of AOPs to high-organic-load industrial wastewaters.

4 Concluding Remarks

HWW is an important source of emerging contaminants, such as PhACs and ARG. Therefore, concern about their proper treatment is growing, although still for the most part unregulated. On-site treatment seems to be the most suitable option for HWW to avoid dilution with MWW.

Conventional biological treatments, such as CAS, have been reported unable to remove many of those PhACs. Therefore, alternatives increasing the SRT and thus acclimation of microorganisms to those compounds seems to be the most suitable way to increase degradation. The most common biological treatment under pilot-scale testing is MBR, which also allows disinfection of wastewater because of the passage through (commonly) ultrafiltration membranes. Innovative alternative treatments, such as fungal treatment, are being studied at lab scale. Today's biological treatments are still unable to totally remove some PhACs. Therefore, biological treatments in pilot-scale HWW treatment systems are usually a first step

for the removal of DOC and nutrients before a final polishing step with some physicochemical treatment.

The demand for cost reduction and the need to overcome some disadvantages of well-established polishing treatment methodologies have been promoting the search for new sustainable and economically friendly technologies. Novel approaches employing AOPs and their combination with other processes (e.g., AOP, adsorption, and membrane filtration processes) to improve their efficiency for MCs have arisen as promising options.

In recent years, membrane systems have been shown to be the most promising technologies for MC separation from water, but information on the treatment of the concentrate stream containing MCs which such systems generate is very limited. PAC/GAC has also been tested in some pilot plants with good results. However, the production of a waste steam (used PAC/GAC) and the high energy costs for regeneration make this approach not very sustainable. Ozonation might be considered a cost-effective solution, providing high removal percentages for many PhAC. The main drawback in this case is the generation of transformation products that might be even more toxic than the parent compounds. Finally, photocatalysis, and especially photo-Fenton is a promising technology which uses natural sunlight and can therefore lower the operating costs.

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Final Remarks and Perspectives on the Management and Treatment of Hospital Effluents

Paola Verlicchi

Abstract This final contribution highlights the main findings resulting from past studies on the characteristics, management, treatment and environmental implications of hospital effluents. Milestone investigations have been international projects (among which Poseidon, Pills, Nopills, Neptune, Knappe, ENDETECH, and PharmDegrade) as well as specific studies suggesting adequate treatments for the effluents of new hospital facilities or the upgrade of existing treatment plants with the aim of removing targeted pollutants occurring at extremely low concentrations (ng/L to μg/L). The different strategies in managing (a separate or a combined treatment) have been discussed and the debate on the current best technologies (conventional technologies + end-of-pipe treatments or advanced biological and chemical processes) is outlined through the presentation of specific full scale treatment plants. The new frontiers in the treatment of hospital effluents are shown by presenting ongoing lab and pilot scale investigations in different countries.

What we expect in the near future are new findings regarding the occurrence and removal of new targeted pharmaceuticals, antibiotic resistant bacteria and genes, environmental risk assessment of the mixture of substances and with regard to chronic exposure, improvement in the removal of (well-known and new) targeted compounds by tested treatment trains.

Keywords Ecotoxicity, Hospital effluent, Knowledge gaps, Management, Micropollutants, Research needs, Treatment

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Contents

1 Lessons Learned

This final chapter summarizes the lessons learned from past studies and investigations on the basis of the issues addressed in the different contributions collected in this book.

A huge boost to the debate on the occurrence of pharmaceuticals in hospital effluents, their management and proper options for their treatment as well as the environmental risk assessment posed by their residues, was given by international projects (such as Poseidon, PILLS, Nopills, Neptune, Knappe, ENDETECH, and PharmDegrade), as well as international collaborations among research groups that shared their competences and interests, research in collaboration with Water Cycle Boards, effluent discharge authorization bodies, and hospital technical direction staff, all interested in improving their knowledge of hospital wastewater characteristics, management and treatments.

We know that it is not easy to obtain authorizations to sample hospital wastewater and the influent and effluent of treatment plants receiving hospital effluents, in order to look for compounds that are generally still unregulated. Other challenges that past research has faced are related to the following issues: the monitoring of a representative selection of pharmaceuticals, analysis of uncertainties in direct measurements; acquisition of consumption data of pharmaceuticals within some healthcare facilities as well as in the corresponding catchment area in order to evaluate predicted concentrations and – knowing the flow rate – to make a comparison between the respective load contribution; analysis of the sensitivity of the adopted predictive model investigations on different options of treatment (dedicated or combined); advanced or conventional treatments at a lab and pilot scale; discussion of full scale treatment trains for the specific treatment of hospital effluents; and the environmental risk assessment in terms of risk quotient as well as OPBT (occurrence, persistence, bioaccumulation and toxicity).

Most of this research was carried out in Europe, Australia and in North America, although Asia, Africa and South America were also involved, demonstrating that increasing attention has been paid worldwide to this multi-faceted topic.

Focusing on European experiences, a special reference must be made to the Bellecombe pilot site (reported in many contributions). This is a case study of excellence, located in the Haute-Savoie, France. It involves a hospital (450 beds), which opened in February 2012, a treatment plant with two distinct treatment trains

allowing separate treatment of the hospital effluent and the treatment of the surrounding area (20,850 inhabitants), and a receiving surface body, the Arve river. This site represents an observatory and a support for international research programs, defined by local organizations – dealing with water and hospital management – as well as legislators, industries and scientists [1].

This book collected the results of long, demanding multidisciplinary studies carried out worldwide starting from international projects to national or regional studies related to the necessity of tackling the problem of the pollutant load of a health-care structure effluent or the treatment of the effluent of a new hospital facility in a rural or peri-urban area [8]. It also presented the viewpoint of the different actors involved in the monitoring of pharmaceuticals and other emerging contaminants in hospital effluents, management and treatment of hospital effluents, environmental risk assessment: biologists, epidemiologists, environmental engineers and chemical engineers, legislators, planners and decision makers.

2 Hospital Effluents: Regulated or Unregulated Wastewater?

There is disparity in regulating the effluent of a health-care facility from one country to another. Generally, no regulation exists for this kind of wastewater. It is often considered to be of the same pollutant load as domestic wastewater and only in a few countries is considered an industrial effluent and specific authorizations and periodical monitoring are required. Sometimes local regulations require pre-treatment of the hospital effluent (generally a simple disinfection). It can then be released into public sewage and conveyed to a municipal wastewater treatment plant where it undergoes the same treatments as urban wastewater. A picture of the current available legislations in some European and Asiatic countries is presented and discussed in the book, as well as the guidelines set by the US EPA and World Health Organization for the management of hospital wastewater. In particular, those provided by the World Health Organization in "Safe Management of Wastes from Health-Care Activities" (1999 and their revised version published in 2014) [2] highlight the risks related to liquid chemicals, pharmaceuticals and radioactive substances, recommend pre-treatments of hazardous liquids, a set-up of sewerage systems for health-care structures, minimum treatments (primary, secondary and tertiary, i.e. disinfection) and removal efficiency for selected pollutants (e.g., 95% of influent bacteria). These should be the reference guidelines for a "minimum" and sustainable management and treatment of hospital effluents in each country without specific regulations.

As the number of potential targeted micropollutants occurring in the effluent is extremely high, a selection is advisable. In this context, prioritization methods are useful tools for both regulation and surveillance purposes in the environmental policy of pharmaceuticals and other emerging contaminants. Different approaches

can be used, leading to a different ranking of priority compounds. The book presents and discusses the results obtained, by following (1) an environmental risk assessment based on the risk quotient (the ratio between measured or predicted concentrations in hospital effluents and the corresponding predicted-no-effect concentration) and (2) the occurrence-persistence-bioaccumulation-toxicity (OPBT) approach for the administered pharmaceuticals in different facilities. Differences were observed between different countries and hospitals. Based on the analysis carried out, priority compounds generally include antibiotics (ciprofloxacin, amoxicillin, piperacillin and azithromycin), the anti-inflammatory drug diclofenac, the hormone estradiol and the antidiabetic metformin.

At EU level, there are no regulations concerning micropollutants in hospital effluents, but with regard to pharmaceuticals in water compartments, EU Decision 2015/495 [3] proposes a "watch list" of substances for Union-wide monitoring including the analgesic diclofenac, the hormones estrone (E1), 17-β estradiol (E2), 17-α ethinylestradiol (EE2), and the macrolide antibiotics erythromycin, azithromycin and clarithromycin. This list is periodically revised and the compounds will either be included in or excluded from a priority list of substances to be monitored.

3 Compositions of Hospital Wastewater: What We Know and What Remains Unknown

Conventional pollutants in hospital effluents have been thoroughly investigated in the past and the variability in their concentration is fairly well known. With regard to micropollutants, concentration collection has developed over the years, covering a wider spectrum of substances, but for some of them there is still little available data, due to difficulties mainly in sampling and chemical analysis.

The first review on hospital effluent characterization was published in 2010 [4]. The collected data concerned only 40 emerging contaminants (mainly pharmaceuticals and detergents) whose concentration range was compared to that observed in urban raw wastewater, and resulted higher in hospital effluents than in urban ones for some compounds. Despite the widespread prominence given to detecting the most targeted compounds (the so-called *Matthew Effect* discussed in the volume Preface), in the following years, many other substances have been monitored, as well as some of their metabolites and transformation products. This was the result of the development of new analytical techniques and increasing awareness of enlarging the spectrum of monitored micropollutants in the hospital water sample (and in the water compartment in general). Some classes, such as antibiotics, were more often investigated due to their antimicrobial properties and their role in the propagation of resistance, and to the fact that they are one of the most hazardous pharmaceutical classes for the aquatic environment.

The influence of the sampling mode (grab or composite – and in the latter case flow-, time- and volume proportional in the defined temporal unit) and frequency (number of samples during the observation period) on the reliability and representativeness of direct measures was thoroughly investigated and suggestions for planning the experimental campaign for the monitoring of hospital effluents were provided. Another approach has been suggested to avoid the many difficulties associated with the sampling of hospital water (authorization to take samples, definition of sampling mode and frequency, sample conservation and analysis): the adoption of predictive models based on pharmaceutical consumption data, human excretion factor and water volume used within the health-care facility. In this case, other challenges must be tackled: data acquisition for pharmaceutical consumption, human excretion, and consumed water. Again, uncertainties affecting these data should be estimated in order to evaluate the accuracy level of the predicted concentrations.

An interesting issue addressed in the book is the ecotoxicity of hospital effluents, strictly related to the wards, diagnostic activities and services (laundry, kitchen) within the health-care facility. It was found to be higher than in an urban effluent, varying during a day and a full year of activity. With regard to the environmental risk posed by the hospital effluent, a "single substance" approach was often used by researchers and, more recently they investigated the so-called cocktail effect linked to the occurrence of a mixture of substances in the effluent which may exhibit additive, synergic and antagonist effects. Future research will concentrate on more in-depth investigations of hospital effluent ecotoxicity and will consolidate the methodologies of ecotoxicological risk assessment adopted so far.

In this context, occurrence and environmental implications were given for three classes of compounds largely administered in hospitals: contrast media, antineoplastics and antibiotics. The first group includes biologically inactive substances, with a high excretion factor and low ecotoxicity. The second one regards extremely hazardous compounds, designed to kill or to cause severe damage to cells. It emerged that mixtures of anticancer drugs in hospital samples possess an important toxic effect, even higher than that expected by the addition of the toxicity of the individual drugs [5]. Finally, the focus on antibiotics highlights that the group includes compounds with a high worldwide frequency of occurrence in hospital effluents and the potential development and release of antibiotic-resistant bacteria (ARB) and genes (ARG) [6]. According to the WHO, the emergence and spread of ARBs has been classified one of the biggest threats to public health in the twenty-first century.

In the near future, studies monitoring anitimicrobial drug usage and resistance will allow the identification of trends and improve the environmental risk assessment, in order to establish a link between anitimicrobial usage and antimicrobial resistance and to unravel the pathways involved in the spread of ARGs [7]. Moreover, efforts will be required in investigating the chronic effects of the mixture of compounds on the environment.

4 Management and Treatment: What Is Sustainable and Correct?

The selection of a separate treatment of the hospital effluent or a combined treatment with the local urban wastewater (due to the hospital surrounding area) is strictly related to the contribution of hospital and urban settlements to the hydraulic and pollutant loads (in terms of macro- and micropollutants) [8].

The presentation of case studies allows identification of the best practices in designing and managing a hospital facility: separate collection of rain water, adoption of strategies aiming to limit water consumption within the hospital, smart organization stocks of pharmaceuticals to avoid waste, and the correct disposal of left-over (and expired) pharmaceuticals. These will result in a lower quantity both of water and pollutant load, which will require less energy and lower financial costs for the adoption of additional treatments.

Technologies adopted in full scale plants for the specific treatment of hospital effluents are always multi-barrier plants including pretreatments, membrane bioreactors and advanced oxidation processes (mainly O_3, O_3/UV and granular activated carbon GAC). Due to the high variability in the chemical, physical and biological properties of the targeted compounds, different removal mechanisms have to occur, in order to promote their removal. The book provides an overview of the current full scale treatment plants in operation in European countries, resulting from complex pre-tests aiming to identify the most adequate technologies, as well as their operational conditions to optimize removal efficiency. This selection was also influenced by local legal, economic and environmental constraints.

It is important to observe that in some European countries, centralized treatments are preferred and in a few cases, moves to upgrade the existing ones have been planned and are underway. In this context, Switzerland was the first country that decided on a national level to upgrade municipal wastewater treatment plants. Based on plant capacity, effluent/dry-weather stream flow relation and sensitivity criteria, the Swiss government identified 100 out of 700 wastewater treatment plants that will be upgraded with a post treatment step, such as activated carbon or ozone within the next few years. Currently, there are six plants in Switzerland with a post-treatment step either in operation or at a planning phase. The majority, i.e. two-thirds, apply ozone, while the others are equipped with PAC to guarantee an average removal of organic micro-pollutants of 80% (according to the so-called Micropoll strategy).

With regard to hospital effluent management and treatment outside Europe, conventional technologies are nearly always adopted, mainly including pretreatments, activated sludge processes, and chemical disinfection. In Brazil, anaerobic reactors are used in different cases, as well as an aerobic biofilter as a tertiary treatment. In China, after the SARS outbreak, activated sludge systems were replaced by membrane bioreactors (equipped with ultrafiltration membranes) in many plants, in order to guarantee greater removal of microorganisms. Treatment is completed by chlorine disinfection.

In some countries, less effective treatments are still present, including ponds and other natural systems (constructed wetlands).

Innovative treatments are under investigation on a lab or a pilot scale and are based on the use of fungi grown in pellet form, or particular membranes: membranes with immobilized fungal laccase, submerged sponge ones, membranes for nanofiltration or reverse osmosis and seem to be quite promising in removing targeted compounds. Increased interest towards advanced technologies can be seen in Brazil where they have been testing photo Fenton applications.

More recently, attention has also been paid to the removal of ARG and ARB from the hospital effluent [9]. The Pills project highlights that the risk of the spread of resistance to specific antibiotic molecules is higher in hospital effluents than in urban wastewater. The efficiency of advanced biological and chemical processes varies in the range of 1–5 log units. Ultrafiltration membrane bioreactors guarantee a consistent reduction of this risk, whereas a following step including ozonation, sand or powder active carbon filtration does not contribute to a further reduction [10].

In the near future, planning proper measures able to manage and treat hospital facility effluents will guarantee good removal of a wide spectrum of compounds with extremely different characteristics, as well as an abatement of ARG and ARB; the adoption of sustainable and economically friendly methodologies; reliable and tested technologies and containment of investment and operational costs. These actions are strictly related to the development of technologies currently under investigation and the results of more complex environmental risk assessments combining the different aspects previously discussed. Environmental risk assessment studies must also consider the risks of long-term exposure to sub-acute levels, as well as the risks of cocktails of pollutants in the aquatic environment and also their metabolites and transformation products.

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